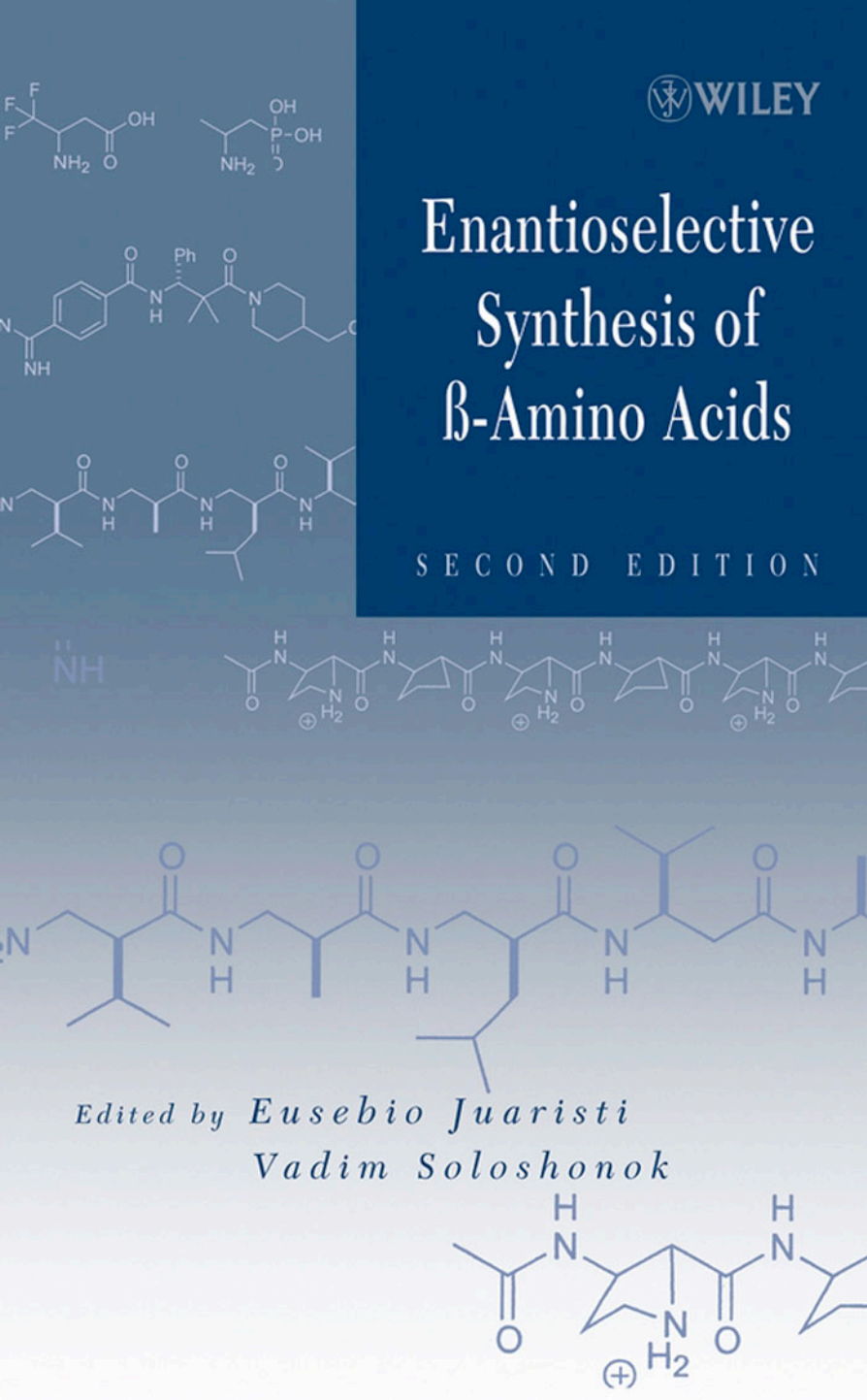

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Enantioselective Synthesis of ß-Amino Acids

SECOND EDITION

Edited by Eusebio Juaristi
Vadim Soloshonok

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PREFACE

From the date of the publication of the first edition of this book, the synthesis and application of enantiopure β-amino acids have continued to emerge as very important and challenging synthetic endeavors. Indeed, whereas only 5 pertinent literature entries on this subject are registered prior to 1980 and 11 for the period 1980–1990, more than 500 reports have appeared during 1991–2004.

Much of the work related to enantioselective synthesis of chiral β-amino acids published before 1996 was reviewed in the first volume of this series; nevertheless, the unprecedented growth in the field of asymmetric synthesis of β-amino acids prompted the preparation of a second volume that not only updates the reviews included in the first volume but also covers novel developments in the field. In particular, several chapters are dedicated to discuss exciting advances in the synthesis of β-peptides and comparison of their structural features and physical and biological properties with those of the natural α-peptides. De novo design and synthesis of β-amino acids–based oligomers currently are the driving force for the development of new methods allowing preparation of structurally varied, tailor-made β-amino acids. In accord with growing demand for synthetic efficiency and practicality of organic synthesis, many newly developed methods feature operationally convenient conditions and high chemical and stereochemical yields.

An important new addition in the reviews to be presented in the second volume of *Enantioselective Synthesis of* β*-Amino Acids* is that most contributing authors included some general and practical experimental procedures for the preparation of β-amino acids, according to the particular method described in the chapter. We believe that this combination of comprehensive monograph and guidebook will be attractive to the readers. As was the case in the first volume, most contributions were written by the original developers of these important methods of synthesis.

Of interest to both academic and industrial chemists, introductory overviews on the structural types of relevant β-amino acid targets and on salient β-amino acids present in natural products are followed by a discussion of the most important methods that have been recently developed for the asymmetric synthesis of cyclic and open-chain β-amino acids. Particular attention is given to novel organocatalysts and organometallic catalytic procedures. Also included is a report on the preparation of libraries of enantiopure β-amino acids using combinatorial approaches as well as reviews on the asymmetric synthesis of fluorine-containing and phosphonic analogs

of β-amino acids. As indicated above, two chapters are dedicated to the synthesis and analysis of the secondary structure and the biological activity of β-peptides.

We hope that the relevance and timeliness of the topics discussed in this book will render it of interest to a broad group of chemists in universities and the pharmaceutical and related industries.

EUSEBIO JUARISTI and VADIM A. SOLOSHONOK

PREFACE TO THE FIRST EDITION

β-Amino acids, although less abundant than their α-analogues, are also present in peptides and in other natural products, and in free form they show interesting pharmacological effects. Furthermore, β-amino acids are synthetic precursors of β-lactams, which are potentially biologically active and of current interest. Although several methods for the synthesis of racemic β-amino acids have been developed, only recently has the preparation of enantiomerically pure compounds emerged as an important and challenging synthetic endeavor.

Following introductory overviews of the relevance of β-amino acids in pharmaceutical sciences, this book presents a discussion of the most important methods that have been developed for the asymmetric synthesis of β-amino acids. Each important method is described by the original leader chemist who developed it, and thus each chapter is written with authority and firsthand knowledge.

I hope that the relevance and timeliness of the topics discussed in this book—the first comprehensive monograph in the area—will render it of interest to a broad group of chemists in universities and in the pharmaceutical and related industries.

EUSEBIO JUARISTI

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CHAPTER 1

Structural Types of Relevant β-Amino Acid Targets

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1.1 INTRODUCTION

The simplest β-amino acid is β-aminopropionic acid (β-alanine, **1**), which is not a proteinogenic amino acid, but it is an essential component of many relevant, biologically active compounds, such as vitamin B_3 (pantothenic acid, **2**).[1] Furthermore, chiral derivatives of β-amino acid are useful precursors of chiral, enantiomerically pure β-amino acids; see, for example, β-alanine derivatives **3**–**6**.[2–5] (Scheme 1.1).

There are three general types of *open-chain* chiral β-amino acids, depending on whether the substitution takes place at the carbon bearing the carboxyl group (α-position), the carbon bearing the amino group (β-position), or at both positions (α,β-disubstitution) (Fig. 1.1*a*).[6] In addition, *cyclic* β-amino acids may present the amino acid and the carboxylic groups as substituents of a carbocyclic ring or may incorporate the amino group in a heterocyclic ring (Fig. 1.1*b*).

Recently, Seebach and co-workers[7,8] proposed the terms β^2- and β^3-amino acid, where the numbers indicate the position of the side chains, in order to distinguish positional isomers (Scheme 1.2).

The following sections in this chapter are arranged following the Seebach β^2/β^3 convention and present illustrative examples of relevant β-amino acids in each category. No attempt is made to include an exhaustive list of compounds or contributing authors.

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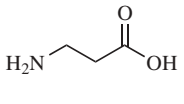
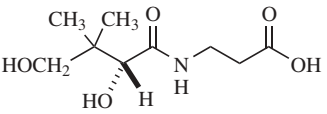
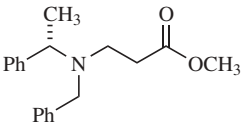


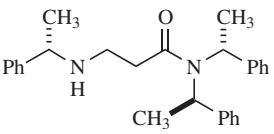
β-Alanine, **1**



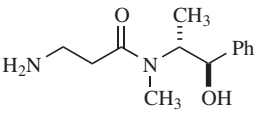
(*R*)-(+)-Pantothenic acid, **2**



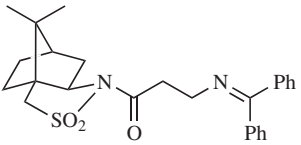
3, ref 2



4, ref 3

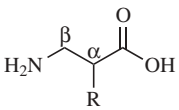


5, ref 4

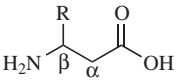


6, ref 5

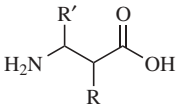
Scheme 1.1



α-substituted

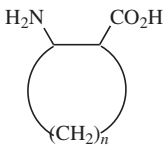


β-substituted

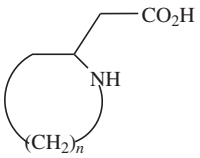


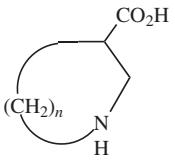
α,β-substituted

(a) Linear β-amino acids



carbocyclic

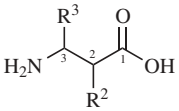




heterocyclic

(b) Cyclic β-amino acids

Figure 1.1



β^2-amino acid, $R^3 = H$

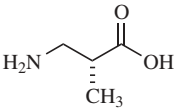
β^3-amino acid, $R^2 = H$

cyclic β-amino acid, $R^2–R^3 = (CH_2)_n$

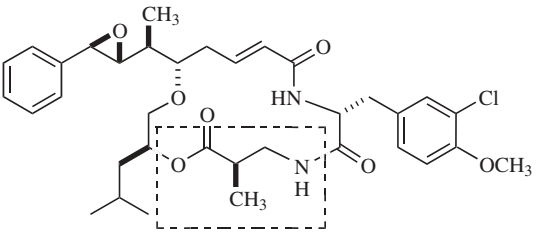
Scheme 1.2

1.2 β²-ALKYL-β-AMINO ACIDS

(*R*)-2-Methyl-3-aminopropionic acid (*R*)-**7** is a prototype of β²-alkyl-β-amino acids and is a residue present in cryptophycin 1 (**8**), a potent antitumor depsipeptide[9] (Scheme 1.3).



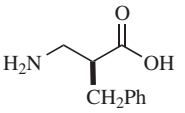
(*R*)-**7**



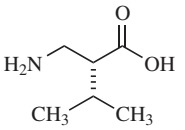
Cryptophycin, **8**

Scheme 1.3

Enantiopure β²-phenylalanine (*S*)-**9** and β²-homovaline (*R*)-**10** were recently synthesized by Gellman and co-workers[10] to provide access to new β-peptides with specific conformations and particular functions (Scheme 1.4).



(*S*)-β²-Phenylalanine, (*S*)-**9**

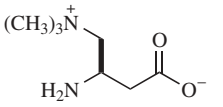


(*R*)-β²-Homovaline, (*R*)-**10**

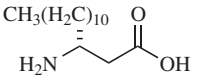
Scheme 1.4

1.3 β³-ALKYL-β-AMINO ACIDS

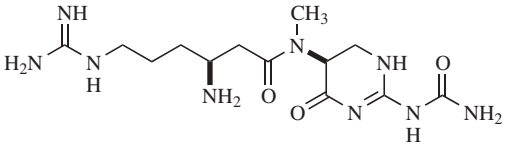
Among β-amino acids that exhibit interesting pharmacological properties in free form, emeriamine (*R*)-**11** has shown activity as a hypoglycemic and antiketogenic agent[11] (Scheme 1.5). In this context, iturinic acid (*R*)-**12** is a component of biologically relevant peptide iturin,[12] and synthetic antibiotic TAN-1057 A (**13**) is a dipeptide containing a β³-argenine fragment[13] (Scheme 1.5).



Emeriamine, (*R*)-**11**



Iturinic acid, (*R*)-**12**

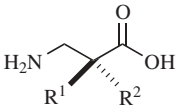


TAN-1057 A, (*S,S*)-**13**

Scheme 1.5

1.4 $\beta^{2,2}$-DISUBSTITUTED β-AMINO ACIDS

α,α-Dialkylated derivatives of proteinogenic amino acids are efficient inhibitors of those enzymes that metabolize the natural substrates.[14] Furthermore, synthetic peptides incorporating α,α-dialkylated α-amino acids adopt modified backbone conformations,[15] exhibiting increased lipophilicity[16] and increased resistance to both enzymatic and chemical hydrolysis.[17] It may be anticipated that incorporation of α,α-disubstituted β-amino acids into unnatural peptides will confer peculiar conformational and chemical properties. Not surprisingly, several reports describing the enantioselective synthesis of $\beta^{2,2}$-dialkylated β-amino acids have recently appeared,[18–20] and Scheme 1.6 presents four examples taken from Ref. 19.



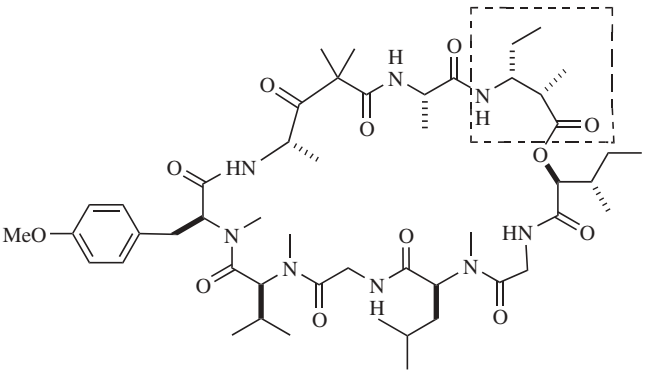
(*R*)-**14**, $R^1 = CH_3$; $R^2 = n\text{-}C_4H_9$
(*S*)-**14**, $R^1 = n\text{-}C_4H_9$; $R^1 = CH_3$
(*R*)-**15**, $R^1 = CH_3$; $R^2 = CH_2Ph$
(*S*)-**15**, $R^1 = CH_2Ph$; $R^2 = CH_3$

Scheme 1.6

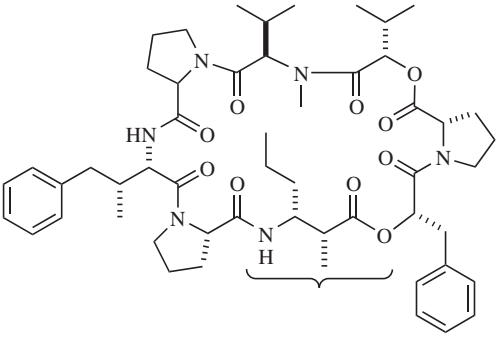
1.5 $\beta^{2,3}$-DISUBSTITUTED β-AMINO ACIDS

Dolastatin 11 (**16**) is a natural product which exhibits activity against lymphocytic leukemia and contains a 2-methyl-3-aminopentanoic acid reside within a cyclic depsipeptide.[21] (Scheme 1.7). Majusculamide C is a related depsipeptide which is cytotoxic and exhibits fungicidad activity against several plant pathogens.[22] Very recently, Kimura and co-workers[23] reported the isolation and structural

elucidation of kulokekahilide-1 (**17**), a cytotoxic cyclic bidepsipeptide which contains the $\beta^{2,3}$-disubstituted β-amino acid residue 3-amino-2-methylhexanoic acid (Scheme 1.7).



Dolastatin 11, **16**



Kulokekahilide 1, **17**

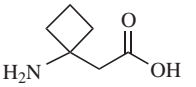
Scheme 1.7

The relevance of $\beta^{2,3}$-dialkyl-β-amino acids is not limited to their biological occurrence, as several cases have proved their usefulness in the development of sheet-forming β-peptides.[24]

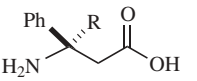
1.6 $\beta^{3,3}$-DISUBSTITUTED β-AMINO ACIDS

While oligomers of the achiral $\beta^{2,2}$-gem-disubstituted β-amino acids 1-(aminomethyl)cyclopropane and 1-(aminomethyl)cyclohexane carboxylic acid have already been shown to form 8- and 10-membered hydrogen-bonded rings,[25] significant work is presently being conducted with analogous peptides containing $\beta^{3,3}$-disubstituted β-amino acids.[20,26]

Scheme 1.8 presents the structures of achiral $\beta^{3,3}$-cyclobutane aminocarboxylic acid **18**[26] and chiral open-chain compounds **19** and **20**[27] as illustrative examples of this type of β-amino acid.



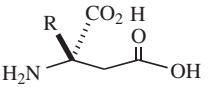
18, ref 26



(*S*)-**19**, R = CH_3, ref 27
(*S*)-**20**, R = *n*-Bu, ref 27

Scheme 1.8

$\beta^{2,3}$-Alkylated aspartic acids **21**–**24** are both α,α-disubstituted α-amino acids and β,β-disubstituted α-amino acids[28] (Scheme 1.9). Aspartic acid derivatives such as **21**–**24** are specially interesting subjects for study owing to their relevant biological properties.

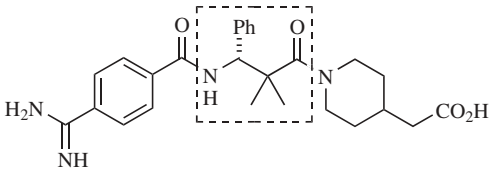


(*S*)-**21**, R = CH_3
(*S*)-**22**, R = CH_2CH_3
(*S*)-**23**, R = *n*-C_4H_9
(*S*)-**24**, R = CH_2Ph

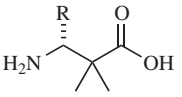
Scheme 1.9

1.7 $\beta^{2,2,3}$-TRISUBSTITUTED β-AMINO ACIDS

(*R*)-(+)-3-Amino-3-phenyl-2,2-dimethylpropionyl derivative NSL-95301, (*R*)-**25**, is a novel trisubstituted β-amino acid exhibiting potent inhibition of platelet aggregation, which makes it a promising antithrombotic agent[29] (Scheme 1.10). From the synthetic point of view, both catalytic enantioselective[30] and stoichiometric diastereoselective[31,32] procedures afford $\beta^{2,2,3}$-amino acids **26**–**28** in good enantiomeric excess (Scheme 1.10).



(+)-NSL-95301, (*R*)-**25**

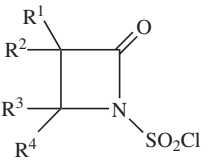


(*R*)-**26**, R = Ph
(*R*)-**27**, R = 1-naphthyl
(*R*)-**28**, R = C_6H_{13}

Scheme 1.10

1.8 β2,2,3,3-TETRASUBSTITUTED β-AMINO ACIDS

Tetrasubstituted $\beta^{2,2,3,3}$-amino acids may be capable of acting as secondary-structure breakers when incorporated into β-peptides. β-Lactamas **29** and **30** are two examples of suitable precursors of $\beta^{2,2,3,3}$-amino acids[33] (Scheme 1.11).

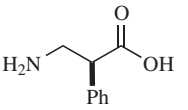


29, $R^1 = R^2 = R^3 = R^4 = CH_3$
30, $R^1 = R^2 = (CH_2)_5$; $R^3 = R^4 = (CH_2)_5$

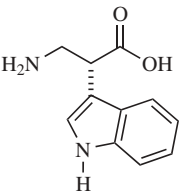
Scheme 1.11

1.9 β2-ARYL-β-AMINO ACIDS

(*S*)-3-Amino-2-phenylpropionic acid, (*S*)-**31**, is an α-aryl-β-amino acid present in the side chain in the structure of penicillin betacine, whereas its ethyl ester derivative has neurological activity.[34] Tryptophan analog (*R*)-**32** has recently been synthesized by Arvanitis and co-workers[35] (Scheme 1.12).



(*S*)-**31**



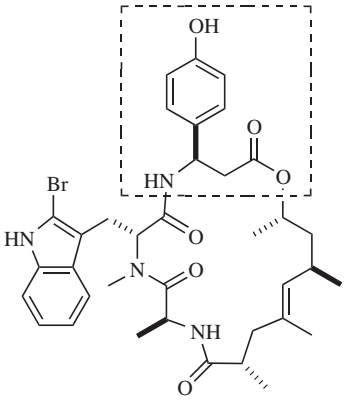
(*R*)-**32**

Scheme 1.12

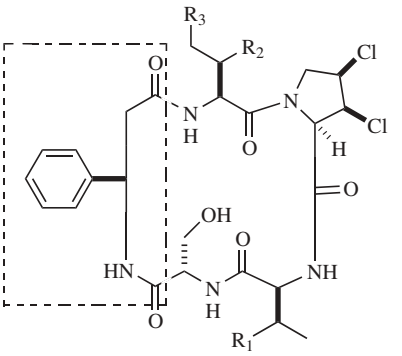
1.10 β3-ARYL-β-AMINO ACIDS

β-Tyrosine is a β-aryl-β-amino acid present in jasplakinolide (**33**), a sponge metabolite of considerable interest because of its insecticidal, anthelminthic, and

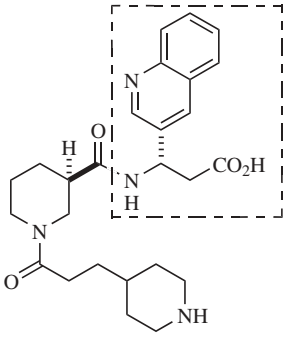
antifungal properties.[36,37] Similarly, (*R*)-3-amino-3-phenylpropionic acid is present in cyclic peptide astins **34**–**36**, natural products with antitumor properties[38] (Scheme 1.13).



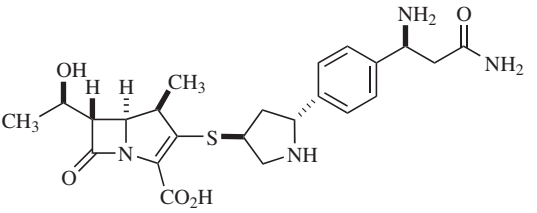
Jasplakinolide, **33**



34, R_1 = H, R_2 = OH, R_3 = H
35, R_1 = OH, R_2 = H, R_3 = H
36, R_1 = H, R_2 = H, R_3 = H



RWJ-53033, **37**



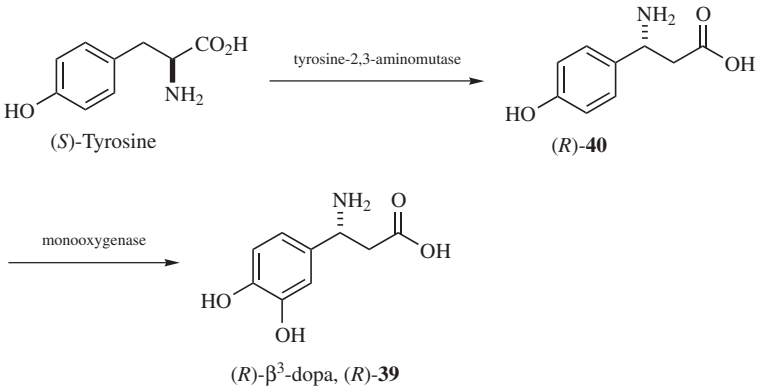
38

Scheme 1.13

More recently, β^3-quinoline-β-alanine derivative RWJ-53033 (**37**) was considered for development as a potent nonpeptide integrin antagonist,[39] whereas para-substituted 3-aryl-3-aminopropionic acid derivative **38** is actually a broad-spectrum carbapenem drug[40] (Scheme 1.13).

Recently, von Nussbaum and co-workers[41] discovered the new natural β^3-amino acid (*R*)-β-(3,4-dihydroxyphenyl)-β-alanine [(*R*)-β^3-Dopa, (*R*)-**39**] in the mushroom

Cortinarius violaceus. Actually (*R*)-**39** is present in the mushroom as the Fe(III) complex, which gives the fruit its peculiar blue-violet color. (*R*)-β^3-Dopa was also obtained by enzymatic conversion of tyrosine via β^3-(4-hydroxyphenyl)-β-alanine precursor (*R*)-**40**[42] (Scheme 1.14).



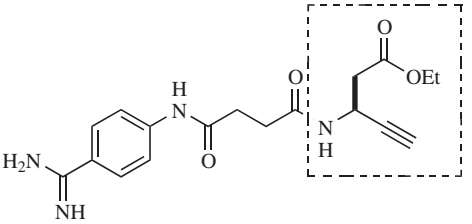
Scheme 1.14

1.11 OLEFINIC AND ALKYNYL-β-AMINO ACIDS

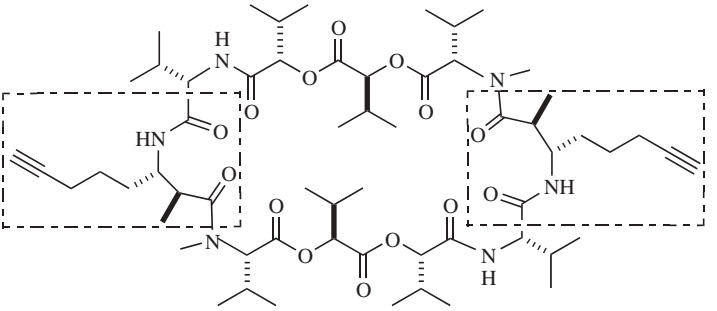
α,β-Unsaturated β-amino acid derivatives have found widespread use in the synthesis of naturally occurring compounds such as alkaloids[43] and antibiotics,[44] and they have also been employed as precursors to derivatives with relevant pharmacological properties.[45] Furthermore, unsaturated (3*S*)-aminopentynoic acid is the key pharmacophore in the antithrombotic agent xemilofiban (**41**).[46] Two interesting natural products containing unsaturated β-amino acids are onchidin (**42**)[47] and mutoporin (**43**).[48] Onchidin is a potent protein phosphatase-1 inhibitor. Very recently, the novel α,β-unsaturated β-amino acid–containing molecule CJ-15,801 (**44**) was reported as an inhibitor of multiple-drug-resistant *Staphylococcus aureus* strains[49] (Scheme 1.15).

γ-Unsaturated β-amino acids represent an interesting subclass of compounds. For example, unsaturated α-methyl-β-amino acid ADDA (**45**) is present in the antibiotics cyanovirifin RR, nodularin, and microcystin LR.[50] Very recently, Lurain and Walsh have developed a method for the enantioselective synthesis of γ-unsaturated β-amino acids such as **46**–**49**[51] (Scheme 1.16).

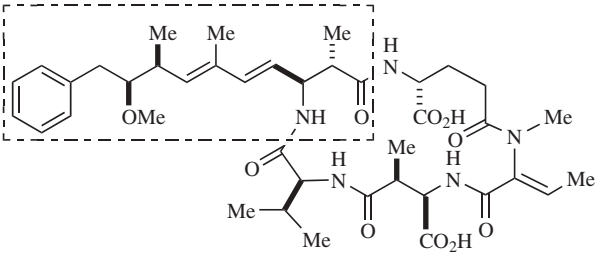
Special mention deserves also the synthetic procedure recently developed by Adam et al.[52] that provides a route to α-methylene-β-alkyl-β-amino acids **50** and **51** (Scheme 1.16).



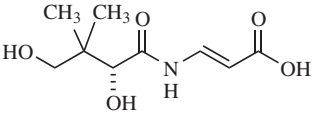
Xemilofiban, **41**



Onchidin, **42**

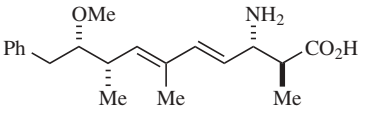


Motuporin, **43**

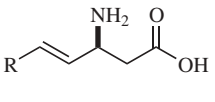


CJ-15,801 (**44**)

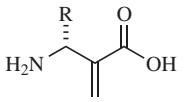
Scheme 1.15



ADDA, **45**



46, R = Ph
47, R = cyclohexyl
48, R = isobutyl
49, R = C_8H_{17}

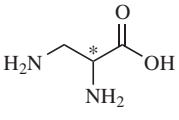


(*R*)-**50**, R = CH_3
(*R*)-**51**, R = *i*-Pr

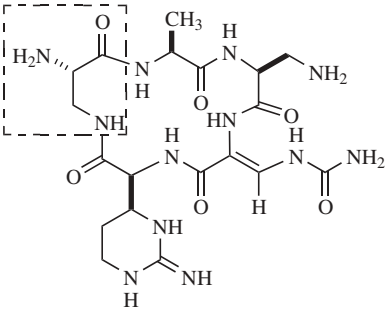
Scheme 1.16

1.12 α,β-DIAMINO ACIDS

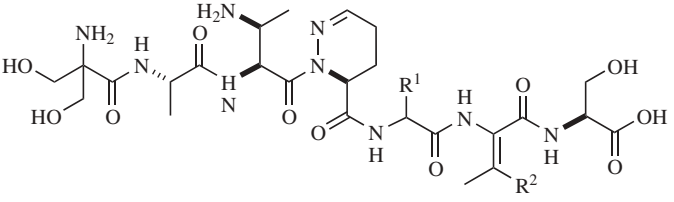
α,β-Diaminopropionic acid (**52**) is the prototype for this type of β-amino acids. This diamine is a structural component of several natural products, such as bleomycin,[53] sulfazecin,[54] and capreomycin (**53**).[55] By the same token, (2*S*,3*S*)-diaminobutanoic acid is a common component of the linear heptapeptide antibiotics antrimycins (**54a**–**h**)[56] (Scheme 1.17). Modified taxol side chain **55** has been coupled to the taxane ring system to increase water solubility of the corresponding taxol analogs.



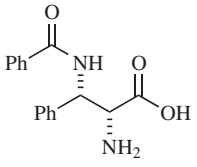
52



Capreomycin IIB, **53**



54a, R^1 = R^2 = Me
54b, R^1 = Et, R^2 = Me
54c, R^1 = *n*-Pr, R^2 = Me
54d, R^1 = *i*-Bu, R^2 = Me
54e, R^1 = Me, R^2 = Et
54f, R^1 = R^2 = Et
54g, R^1 = *n*-Pr, R^2 = Et
54h, R^1 = *i*-Bu, R^2 = Et

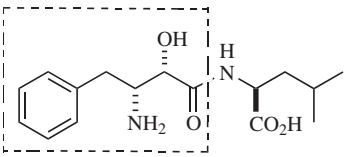


55

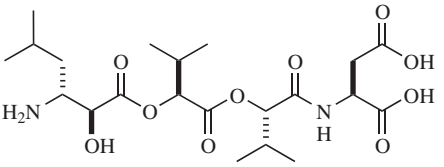
Scheme 1.17

1.13 α-HYDROXY-β-AMINO ACIDS

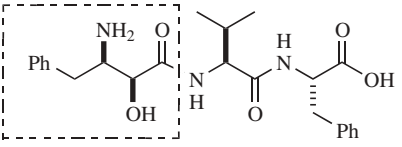
α-Hydroxy-β-amino acids are probably the most important members of the β-amino acid family. They are the essential moiety of many well-known natural products endowed with significant biological activity. The best known example is the potent neoplastic agent taxol[57,58] but also remarkable are bestatin (**56**), a well-known immune response modifier containing (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid,[59] aminopeptidase inhibitors amastatin (**57**)[60] and phebestin (**58**),[61] and microginin (**59**),[62] which inhibits angiotensin-converting enzyme (Scheme 1.18).



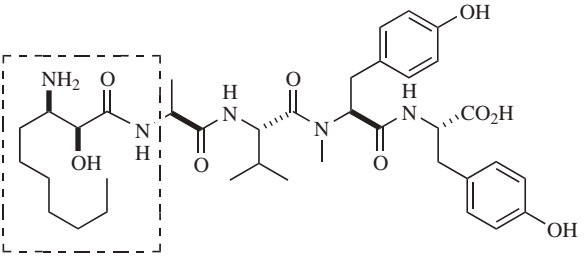
Bestatin, **56**



Amastatin, **57**



Phebestin, **58**



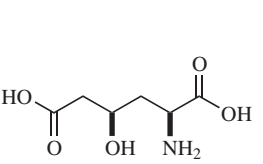
Microginin, **59**

Scheme 1.18

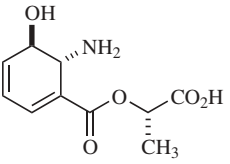
1.14 β-AMINO-γ-HYDROXY ACIDS

β-Amino-γ-hydroxy acids are relevant compounds because they are components of peptides of pharmacological interest.[63] One example is (2*S*,4*R*)-2-amino-4-hydroxy-adipic acid (**60**), which is a constituent of theonellamide F, a powerful cytotoxic

agent against P388 leukemia cells[64] (Scheme 1.19). A second example is the metabolite oryzoxymycin (**61**), isolated in 1968 by Hashimoto et al.[65]



(2*S*,4*R*)-**60**

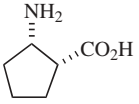


(−)-Oryzoxymycin, **61**

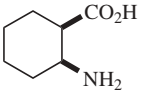
Scheme 1.19

1.15 CARBOCYCLIC β-AMINO ACIDS

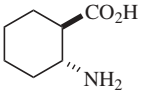
Cispentacin (**62**) is an antifungal antibiotic,[66] whereas other carbocyclic β-amino acids are useful intermediates for the enantioselective synthesis of alkaloids.[67] For example, (2*S*)-amino-(1*R*)-cyclohexanecarboxylic acid (**63**) has found many applications in the synthesis of natural products and peptide mimetics.[68] By contrast, nonnatural cyclic *trans*-cyclohexyl and *trans*-cyclopentyl β-amino acids (**64** and **65**, respectively) have been incorporated into β-peptide foldamers[69] (Scheme 1.20).



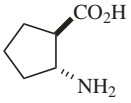
Cispentacin, **62**



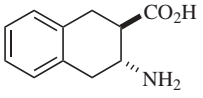
(1*R*,2*S*)-**63**



(1*R*,2*R*)-**64**



(1*R*,2*R*)-**65**



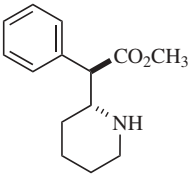
(2*R*,3*R*)-**66**

Scheme 1.20

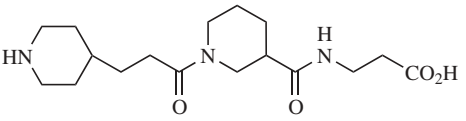
Conformationally restricted peptidomimetics frequently exhibit increased biological activity as well as enhanced stability. Incorporation of cyclic β-amino acids into such unnatural peptides confers the desired rigidity characteristics.[69–71] A salient example of conformationally constrained β-amino acids is phenylalanine analog **66**[72] (Scheme 1.20).

1.16 HETEROCYCLIC β-AMINO ACIDS

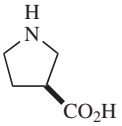
Methylphenidate (**67**) is the most frequently used medication for the treatment of hyperactive children with attention-deficit disorder.[73] RWJ-50042 (**68**) is an effective antagonist of the platelet fibrinogen receptor, containing a nipecotic acid scaffold[74] (Scheme 1.21).



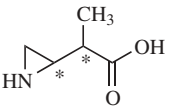
Methylphenidate, **67**



RWJ-50042, **68**



(*S*)-**69**



70

Scheme 1.21

β-Proline **69** (3-carboxypyrrolidine) has been synthesized in both enantiomeric forms and used to study structure–activity relationships between receptors and natural amino acids.[75] Also interesting is the recent synthesis of all four stereoisomers of β-amino acid **70** containing an aziridine heterocycle[76] (Scheme 1.21).

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CHAPTER 2

β-Amino Acids in Natural Products

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2.1 INTRODUCTION

2.1.1 Importance of β-Amino Acids in Natural Products

Contrary to proteinogenic α-amino acids that are constituents of all enzymes which control the metabolism in living matter and are thus an essential prerequisite for life, most β-amino acids only occur as constituents of distinct natural products, such as peptides, cyclopeptides, depsipeptides, glycopeptides, alkaloids, or terpenoids.[1] Apparently, bacteria, cyanobacteria, fungi, and plants often incorporate β-amino acids into secondary metabolites[1] that serve as tools to secure their survival in competition with other organisms.[2,3] Therefore, these compounds are often characterized by potent biological and physiological activities[4] that are often crucially based on their β-amino acid substructures. As a consequence, many natural products with a β-amino acid moiety are potential lead structures for the development of new drugs.[5]

Moreover, the incorporation of β-amino acids into peptides instead of α-amino acids increases their stability against degradation by mammalian peptidases.[5] This enhanced stability is caused by a lack of enzymes which allow cleavage of peptidic bonds between α-amino acids and β-amino acids.[6] Therefore, β-amino acids are an important tool in the development of drugs capable of withstanding hydrolytic degradation for prolonged periods of time.[5]

This chapter is dedicated to Prof. Heinz G. Floss on the occasion of his seventieth birthday.

Enantioselective Synthesis of β-Amino Acids, Second Edition
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2.1.2 Biological Activities of Selected Natural Products with β-Amino Acid Moiety

Reaching from deleterious toxins to valuable cytostatica, this class of natural products generates many potential lead structures for pharmaceutical and agricultural research that have not yet been investigated extensively.

For instance, microcystins (**241**–**245**), common constituents of blue-green algae growing in water reservoirs, are highly toxic for mammals, since they are potent phosphatase inhibitors.[7] Their deleterious properties are illustrated by a mass intoxication approximately 10 years ago, when 60 hemodialysis patients died after treatment with a hemodialysate prepared from a water supply that was contaminated with cyanobacteria.[8] Along these lines, the disease lathyrism characterized by crippling of bones is caused by consumption of seeds derived from plants such as the grass pea (*Lathyrus sativus*) that contain 3*N*-oxalyl-2,3-diaminopropanoic acid (**174**).[9]

On the other hand, the outstanding cytotoxic effects of the cryptophycins (**94**–**103**)[10,11] or the dolastatins (**106**–**112**)[12] might result in the development of new anticancer drugs. Taxol (**227**)[13,14] and derivatives thereof as well as bleomycin (**178**)[15] have already become important anticancer drugs, whereas penicillins (**181**)[16] and related β-lactams have served for decades as prominent antibiotics.

2.1.3 Scope of This Review

So far, only a very limited number of reviews covering β-*amino acids in natural products* are available.[1] However, some reviews, dealing mainly with the synthesis,[17] biosynthesis,[18] and biological activity[19] of β-amino acids, include also information on their occurrence in nature. In addition, information about some of these compounds can be found in books devoted to natural products in general[20] or in reviews dealing with special classes thereof, for instance, in a review on depsipeptides[4] or marine organisms,[21,22] which have turned out to be rich sources of peptides containing β-amino acids.

This review intends to draw a representative picture of the variety of natural products with a β-amino acid moiety that are known today. Information will be given about their natural source (specification of organism), their biological activity and importance, and, if available, their biosynthesis as well as in part their total synthesis. To present as many β-amino acid core structures as possible, only a limited number of representatives for each β-amino acid will be discussed.

2.1.4 Distribution and Biosynthesis of β-Amino Acids in Different Source Organisms

In general, β-amino acids occur in all five kingdoms of living organisms, that is, in animals, plants, fungi, bacteria, and protista. However, β-amino acids are not equally distributed over all these classes of organisms.[1] Contrary to all other β-amino acids, β-alanine (**1**) and β-aminoisobutrate (**85**) are present in all living organisms, since they are directly involved in primary metabolism.[23] To the best of our knowledge, mammals and, moreover, probably all animals are not able to produce any β-amino acids except **1**, **85**, and derivatives thereof. Reports on the

occurrence of β-amino acids in natural products isolated from animals such as sponges[21] or mollusks[12] are not contradictory to that hypothesis, since it has been demonstrated repeatedly that cyanobacteria living in a symbiotic relationship with sponges (see Sections 2.2.6.4 and 2.8.2.5) or serving as nutrition for mollusks (see Section 2.3.2.1) are the real producers of the β-amino acid in question.

Some plants such as *Taxus brevifolia* have the ability to generate a β-amino acid directly from a proteinogenic α-amino acid by action of a 2,3-aminomutase that catalyzes an α,β-shift of the amino group.[18] However, plant alkaloids with a β-amino acid moiety such as aphelandrine (**57**) are biosynthetically derived from cinnamic acid via Michael-type addition reactions.[24] Various alkaloids, such as cocaine or lysergic acid, only formally possess β-amino acid moieties. They usually do not originate biosynthetically from a β-amino acid building block but are formed for example by Mannich-type condensations or oxidative cyclizations. Several 2,3-diamino acids occur either in free form or as derivatives thereof[25] (see Section 2.6 and 2.6.1). β-Alanine is present in the form of its betaine[26] in some plants.

As in plants, 2,3-aminomutases have been detected in fungi.[27] So far, only such β-amino acids have been found that are related to a proteinogenic α-amino acid counterpart. In fungi, β-amino acids occur in cyclopeptides such as the destruxins (**9**–**20**)[28] as well as in free form.[29] The penicillins and cephalosporins contain formally an α,β-amino acid moiety, since only α-amino acids are involved in their biosynthesis.[30]

Probably the greatest variety of β-amino acids is found in bacteria. Bacteria produce both β-amino acids that are derived from proteinogenic α-amino acids and a considerable number of β-amino acids that have no proteinogenic α-amino acid counterpart. Cyanobacteria are especially capable of producing the latter type of β-amino acids,[21] which are often constituents of peptides, cyclopeptides, and cyclodepsipeptides together with a variety of other unusual amino acids, such as γ-amino acids and D-amino acids. Although we often do not know exactly why bacteria produce such a variety of natural products with β-amino acids, it seems reasonable to assume that they use these compounds as a chemical defense mechanism against predators and competitors.[3,31] Cyclopeptides with unusual amino acids exhibit a variety of activities. Their biosynthesis, however, is performed starting from the monomeric amino acids as building blocks, similar to an assembly line, by a multienzyme complex, a nonribosomal peptide synthase.[32] Bacteria are also masters in the biosynthesis of polyketides which are generated by polyketide synthases that are related to nonribosomal peptide synthases. To provide the necessary variety of amino acid building blocks, bacteria possess both 2,3-aminomutases to generate β-amino acids from α-amino acids and special polyketide synthases that generate β-oxo acids which are transaminated to polyketide-type β-amino acids.[33]

At present, very little is known about natural products in the kingdom of the protista. Nevertheless, also some protista seem to be able to produce β-amino acids.

2.1.5 History

The first β-amino acid detected in nature was β-alanine (**1**), which was isolated in the form of its betaine from Liebigs meat extract[34] in 1909, apparently by

hydrolysis of carnosine, which is abundant in tissue.[35] β-Aminoisobutyrate (**85**), structurally closely related to β-alanine, however, was isolated 40 years later from human urine.[36,37] In 1923, the second β-amino acid, β-phenylalanine (**7**), was detected in form of its *N*,*N*-dimethyl derivative, Winterstein's acid,[38] during attempts to clarify the structures of the taxane alkaloides from *Taxus baccata*, while β-lysine (**3**) was characterized first in 1952 as an isomer of lysine in hydrolysates of the antibiotic viomycin (**206**).[39] Shortly afterward, it was also detected in hydrolysates of streptothricin (**43**).[40] At that time, structures were elucidated by classical chemical degradation methods and confirmed by total synthesis.[40] In the following years, biochemical studies proved that β-lysine was an intermediate in the catabolism of some *Clostridium* species, generated by an aminomutase from α-lysine.[41] Until the early 1980s several other β-amino acids related to proteinogenic α-amino acids, such as β-arginine (**4**) in blasticidin S (**45**),[42] β-tyrosine (**8**) in the edeines (**75–76**),[43] and β-glutamic acid (**5**),[44] have been found in natural products. Their biosynthesis was investigated first by feeding experiments with radiolabeled compounds[45] and later with stable isotopes.[46] Some of the aminomutase enzymes, for example, the lysine 2,3-aminomutase,[41] were purified. Besides X-ray analysis, proton nuclear magnetic resonance (^{1}H NMR) and electron impact mass spectrometry (EIMS) also became important tools for structure elucidation. At that time, the source organisms were mostly plants and terrestrial bacteria. Starting with the 1980s, marine sponges and cyanobacteria became important subjects of investigation. These organisms often contain cyclic and acyclic peptides and depsipeptides with unusual amino acid moieties—structures that were very difficult to elucidate before two-dimensional NMR techniques, fast atom bombardment mass spectrometry (FABMS), chiral high-performance liquid chromatography (HPLC) (Marfey's method[47,48]), and chiral gas chromatography/mass spectrometry (GC/MS) became available.[22] Even today, if no crystal structure is available, the assignment of the absolute configuration is often difficult and requires degradation of the peptides to the monomeric amino acids and a comparison with authentic synthetic samples.[21] Therefore, *several chemical structures* presented in this review *will lack some stereochemical information*.[49,50] The investigation of cyanobacteria, which is still ongoing, resulted in the detection of a huge variety of new β-amino acids that are mostly of polyketidic origin.[1,21,22] In the 1990s systematic efforts to clarify the mode of action of 2,3-aminomutases were undertaken with lysine 2,3-aminomutase as the model enzyme.[51] More recently, isolation of bacterial gene clusters and identification of genes that are responsible for the biosynthesis of β-amino acids have started and some amino-mutases have already been overexpressed.[33,52]

2.1.6 Arrangement of Natural Products and General Remarks

In this review, the natural products will be arranged according to their β-amino acid moiety. First, the natural products with β-amino acids directly derived from proteinogenic α-amino acids will be discussed followed by natural products with other β-amino acid moieties. All β-amino acids that do not have a

direct proteinogenic α-amino acid counterpart will be termed an ''unusual'' β-amino acid.

In a few cases structure drawings in the literature do not match completely with the reported data, especially in respect to their stereochemistry. In those cases the structures are presented according to the experimental data. Ambiguities are mentioned in the corresponding figures. Peptide bonds in chemical structures are drawn regardless to their trans (or cis) amide configuration.

2.2 NATURAL PRODUCTS CONTAINING β-AMINO ACIDS RELATED TO PROTEINOGENIC α-AMINO ACIDS

So far, eight β-amino acids that are directly derived from a corresponding proteinogenic α-amino acid have been discovered in nature either in free form or as a part of a larger molecule: β-alanine (**1**), β-leucine (**2**), β-lysine (**3**), β-arginine (**4**), β-glutamate (**5**), β-glutamine (**6**), β-phenylalanine (**7**), and β-tyrosine (**8**) (Fig. 2.1). Formally, aspartic acid could be regarded both as an α-amino acid and as a β-amino acid; however, it is the α-amino acid functionality that is nearly always used in natural products to form a peptide bond. Some microcystins, however, use aspartic acid as a β-amino acid.[53]

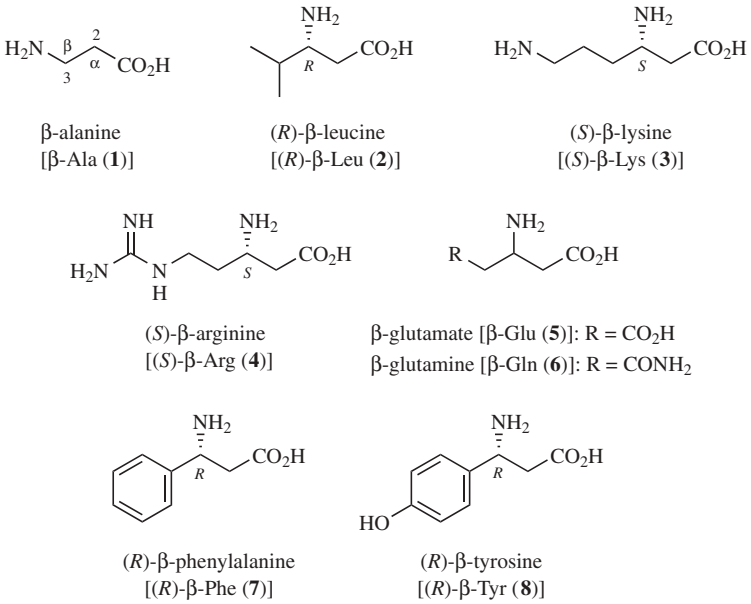


Figure 2.1 β-Amino acids directly derived from proteinogenic α-amino acids.

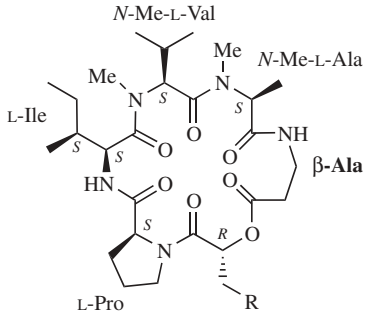
2.2.1 β-Alanine

β-Alanine (**1**) is the most widespread of all β-amino acids. It has been found in animals, plants, fungi, and bacteria because it is incorporated in compounds of the primary metabolism. For example, coenzyme A, an essential cofactor for all living organisms, contains a β-alanine moiety. In mammals, **1** has been found in free form, since it is produced as an intermediate in the catabolism of uracil.[23,54] In Plumbaginaceae, β-alanine betaine (*N*,*N*,*N*-trimethyl-β-alanine) serves as an osmoprotectant[26,55] along with the more common glycine betaine.

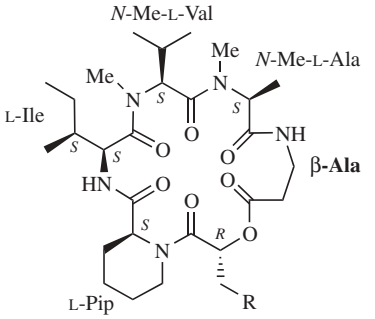
Important natural products containing β-alanine (**1**) are anserine, the barangamides (**32**–**35**), carnosine, some of the cryptophycins (see Section 2.3.1.1), the destruxins (**9**–**20**), leualacin (**21**), the leucinostatins (**22**–**25**), papiliochrome II (**26**), phascoline (see Section 2.3.1.2), the theonellamides C–F (see Section 2.8.2.3), the theonellapeptolides (**27**–**31**), and the yanucamides (**36**–**37**).

2.2.1.1 Anserine and Carnosine In mammals, β-alanine (**1**) is a constituent of carnosine (β-alanyl-L-histidine) and anserine (β-alanyl-3*N*-methyl-L-histidine), which are important scavenger molecules for radicals.[56] Since degradation of carnosine and anserine is required in mammals, they have peptidases able to cleave the peptide bond between L-alanine and L-histidine or *N*-methyl-L-histidine. However, as pointed out above, enzymes are lacking which efficiently hydrolyze peptidic bonds between all other α-amino acids and β-amino acids.[6]

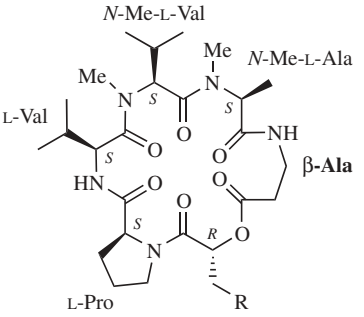
2.2.1.2 Destruxins Following the first detection of destruxins A (**9**) and B (**10**) in the entomopathogenic fungus *Metarrhizium anisopliae* (former name: *Oospora destructor*) in 1961[57] and their structure elucidation,[58,59] a large number of representatives of this class of cyclic hexadepsipeptides have been isolated[28,60] from other fungi, too, such as *Trichotecium roseum* TT103,[61] *Alternaria brassicae*,[62] and *Ophiosphaerella herpotricha*[63] (Fig. 2.2). The structures of **9**[64] and **10**[65] have been confirmed by several stereoselective total syntheses.[28] Also, a variety of analogs have been synthesized[64] and a considerable number of biological studies have been undertaken, since destruxins have turned out to be potent insect pathogens[28] that might be applicable for insect biocontrol. However, the destruxins are not used commercially so far, probably because they are also phytotoxic, especially to *Brassica* species.[2] The phytotoxic effects of the destruxins seem to be directly connected with their ecological role as virulence factors. Destruxin B was identified as the plant pathogenic factor of the fungus *A. brassicae* specifically affecting several *Brassica* species such as *B. napus* and *B. juncea* by conditioning the plant host tissue for an invasion of the parasitic fungi.[2] The destruxins A, B, and E (**12**) are also cytotoxic against P-388 and L1210 leukemia cells.[66] Moreover, the destruxins A and B exhibit suppressive effects on the hepatitis B viral surface antigen[67] and a positive inotropic effect on rat cardiac tissue.[68] The insecticide activity of the destruxins is caused by an initial tetanic paralysis attributed to muscle depolarization by direct opening of the Ca^{2+} channels.[69] Details on the synthesis, biosynthesis, biotransformation, and biological activity of the destruxins are presented in a recent review.[28]



destruxin A (**9**): R = –CH=CH_2
destruxin B (**10**): R = *i*-Pr
destruxin C (**11**): R = –CHMeCH_2OH
destruxin E (**12**): R =



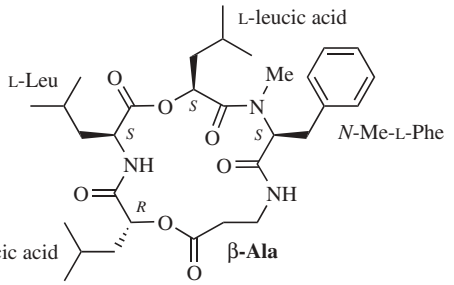
destruxin A_1 (**13**): R = –CH=CH_2
destruxin B_1 (**14**): R = *i*-Pr
destruxin D_1 (**15**): R = –CHMeCO_2H
destruxin E_1 (**16**): R =



destruxin A_2 (**17**): R = –CH=CH_2
destruxin B_2 (**18**): R = *i*-Pr
destruxin C_2 (**19**): R = –CHMeCH_2OH
destruxin D_2 (**20**): R = –CHMeCO_2H

Figure 2.2 Selected destruxins.

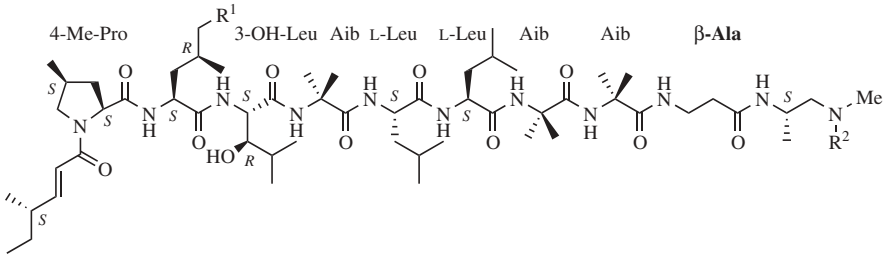
2.2.1.3 Leualacin Leualacin (**21**) is a cyclic pentadepsipeptide[70] isolated from the fungus *Haspidospora irregularis*[71] (Fig. 2.3). Since leualacin is a potent calcium channel blocker probably acting specifically on the dihydropyridine-sensitive Ca^{2+} channel similar to dilitazem,[71] it could be a lead structure for new applications in the treatment of cardiovascular diseases. Therefore, leualacin[72,73] and a few analogs[74] have been synthesized.

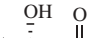


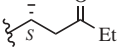
21

Figure 2.3 Leualacin.

2.2.1.4 Leucinostatins The leucinostatins A (**22**),[75,76] B (**23**),[76,77] C (**24**),[78] and D (**25**)[79] (leucinostatin A = P168[80]) are peptide antibiotics produced by cultures of the saprophytic fungi *Paecilomyces lilacinus* A-257[75] and *Paecilomyces marquandii*[76] (Fig. 2.4). Interestingly, leucinostatin A has also been found in an endophytic *Acremonium* sp. of the European yew (*T. baccata*).[81] Their structures have been confirmed by an X-ray analysis of **22** × HCl[82] and by a total synthesis of **25**.[83] Leucinostatin D exhibits activity against some penicillin-resistant gram-positive bacteria (*Staphylococcus aureus* 39/2: MIC 6 μg/mL)[79] as well as fungi and plants and furthermore shows cytotoxic effects against HeLa, KB, and P-388/S (infective dose ID_{50} 1.0 ng/mL) tumor cells.[79] However, the leucinostatins are also highly toxic for mammals, such as mice (oral application of leucinostatin A: lethal dose LD_{50} 5.4 mg/kg).[84]



leucinostatin A (**22**): R^1 =  R^2 = Me

leucinostatin B (**23**): R^1 =  R^2 = H

leucinostatin C (**24**): R^1 = H, R^2 = H

leucinostatin D (**25**): R^1 = H, R^2 = Me

Figure 2.4 Leucinostatins.

2.2.1.5 Papiliochrome II Papiliochrome II (**26**),[85] a yellow wing pigment of the swallowtail butterfly *Papilio xuthus*, is a mixture of two stereoisomers (Fig. 2.5). It is biosynthetically derived from β-alanyl-dopamine and L-kynurenine.[86,87]

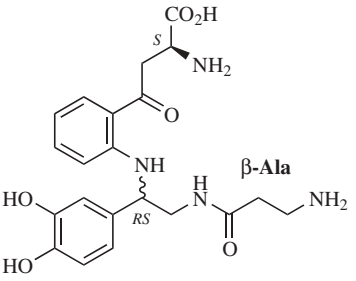


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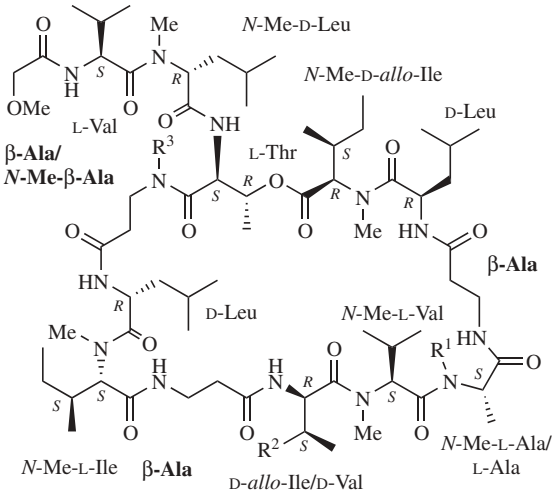
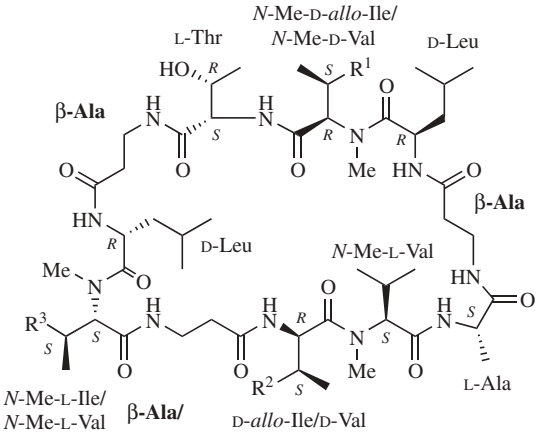
Figure 2.5 Papiliochrome.

2.2.1.6 Theonellapeptolides and Barangamides The theonellapeptolides Ia–e (**27**–**29**),[88] IId (**30**),[89] IIe (**31**),[90] and IIIe[91] are a group of cyclic depsipeptides that have been isolated from an Okinawan specimen of the marine sponge *Theonella swinhoei* (Fig. 2.6). They exhibit moderate cytotoxicity against L1210 tumor cells (theonellapeptolides Ia–e: IC_{50} 1.3–2.4 μg/mL),[92] ion transport activity for Na^+ and K^+ ions,[92] inhibit Na^+/K^+–ATPase (IC_{50} 7 μM),[93] and show immunosuppressive activity.[94]



theonellapeptolide Ia (**27**): R^1 = Me, R^2 = Me, R^3 = H
theonellapeptolide Id (**28**): R^1 = Me, R^2 = Et, R^3 = H
theonellapeptolide Ie (**29**): R^1 = Me, R^2 = Et, R^3 = Me
theonellapeptolide IId (**30**): R^1 = H, R^2 = Et, R^3 = H
theonellapeptolide IIe (**31**): R^1 = H, R^2 = Et, R^3 = Me

Figure 2.6 Selected theonellapeptolides and barangamides.



barangamide A (**32**): R^1 = Et, R^2 = Et, R^3 = Et
barangamide B (**33**): R^1 = Et, R^2 = Et, R^3 = Me
barangamide C (**34**): R^1 = Et, R^2 = Me, R^3 = Et
barangamide D (**35**): R^1 = Me, R^2 = Et, R^3 = Et

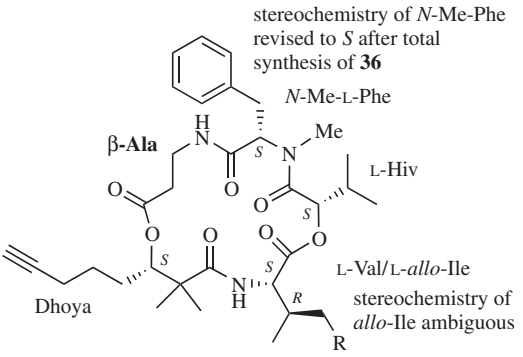
Figure 2.6 (*Continued*).

The barangamides A (**32**)[94] and B–D (**33–35**)[90] isolated from the same species collected on Baranglompo Island, Indonesia, have an isomeric core structure but lack the peptide side chain. Interestingly, despite its similarity to the theonellapeptolides, **32** does not exhibit cytotoxicity against L1210 tumor cells.[90]

2.2.1.7 Yanucamides A and B The yanucamides A–B (**36–37**) are cyclic depsipeptides that have been isolated from an assemblage of the marine cyanobacteria *Lyngbya majuscula* and a *Schizothrix* species[95] (Fig. 2.7). Both yanucamides exhibited strong brine shrimp toxicity (LD_{50} 5 ppm).[95] Recently, a total synthesis of yanucamide A (**36**) led to a revision of the absolute configuration of the *N*-Me-Phe moiety and established the stereochemistry of the 2,2-dimethyl-3-hydroxyoct-7-ynoic acid (Dhoya) residue.[96]

2.2.2 β-Leucine

In the plant *Andrographis paniculata* (*R*)-β-leucine (**2**) is generated by a non-B_{12}-dependent 2,3-aminomutase from L-α-leucine.[97] Reports on the occurrence of a B_{12}-dependent leucine 2,3-aminomutase in bacteria,[98] mammals,[98] and plants[99] have to be doubted, since neither B_{12} has been detected in plants nor could these results be confirmed later.[100]



yanucamide A (**36**): R = H yanucamide B (**37**): R = Me

Figure 2.7 Yanucamides.

2.2.3 β-Lysine

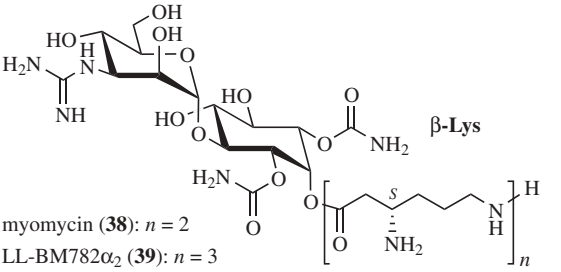
(*S*)-β-Lysine (**3**) has been found in a variety of *Clostridium* species, since it serves as the first intermediate in the catabolism of L-lysine. The *S*-adenosylmethionine (SAM)-dependent 2,3-aminomutase that converts L-lysine to (*S*)-β-lysine was isolated from *Clostridium subterminale* SB4 and its mode of action was investigated in detail.[51] Recently, the corresponding gene was identified and isolated and heterologously expressed in *Escherichia coli*.[52]

In archea, such as *Methanococcus thermolithotrophicus*, *Methanogenium cariaci*,[101] or *Methanosarcina thermophila*,[101] N^{ε}-acetyl-β-lysine serves as an osmolyte. In *M. thermolithotrophicus* N^{ε}-acetyl-β-lysine is the dominant osmolyte at higher NaCl concentrations, while at lower concentrations β-glutamate is also present.[102] In *M. cariaci* N^{ε}-acetyl-β-lysine is biosynthetically derived from α-lysine.[103]

β-Lysine (**3**) is a constituent of albothricin (**44**), the capreomycins IA and IB (see Section 2.7.2), LL-BM782α_{1a}, LL-BM782α_1, LL-BM782α_2 (**39**–**41**), lysinomycin (**42**),[104] myomycin (**38**), streptothricin F (**43**), tallysomycin A[105] (see Section 2.6.1.2), tuberactinomycin O (see Section 2.7.2), and viomycin (see Section 7.2).

2.2.3.1 Myomycin, LL-BM782α$_{1a}$, LL-BM782α$_1$, and LL-BM782α$_2$

Myomycin (**38**)[106] and the closely related glycopeptidic antibiotics LL-BM782α_{1a}, LL-BM782α_1, and LL-BM782α_2 (**39**–**41**)[107] have been isolated from a *Nocardia* sp. (Lederle culture BM782) (Fig. 2.8). LL-BM782α_1 and LL-BM782α_2 are effective in protecting mice against infections with *Mycobacterium tuberculosis*. The structure first proposed for myomycin was later revised.[107] Myomycin itself shows a moderate but broad-spectrum activity against bacteria, since it inhibits the bacterial protein biosynthesis by direct interaction with the 30S subunit of the ribosome.[108]



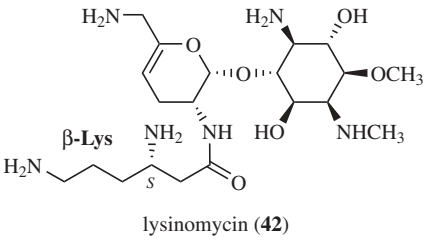


Figure 2.8 Glycopeptide antibiotics with β-lysine moieties.

2.2.3.2 Streptothricins and Albothricin The streptothricins are broad-spectrum peptidyl nucleoside antibiotics which were first isolated from *Streptomyces lavendulae* in 1942[109] (Fig. 2.9). The strepothricins differ only in the number of β-lysine residues. The structure of streptothricin F (**43**) has been confirmed by a total synthesis.[110] Feeding experiments showed that β-lysine is biosynthetically derived from α-lysine,[111] while the heterocyclic β-amino acid streptolidine (**202**) is derived from α-arginine.[112] Although the streptothricins are potent antibiotics, their inherent nephrotoxicity prevents a clinical application.[113] However, streptothricin is used nowadays as a selection marker in molecular

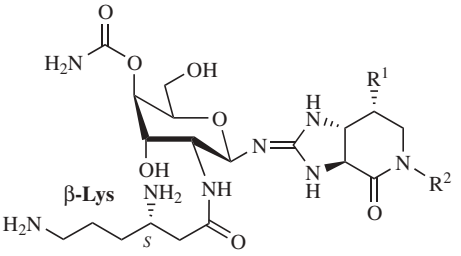
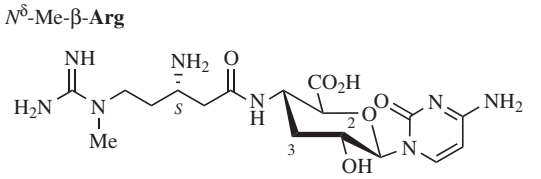
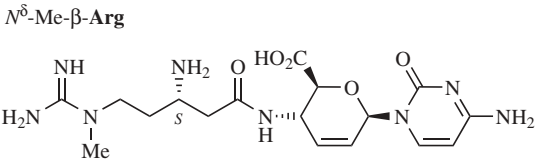


Figure 2.9 Peptidyl nucleosyl antibiotics.



blasticidin H (**45**)



blasticidin S (**46**)

Figure 2.10 Blasticidins.

biology.[114] The streptothricins inhibit the protein biosynthesis similar to myomycin by binding to the 30S subunit of the ribosome.[108] A structurally closely related antibiotic is albothricin (**44**), which was isolated from a soil sample of the unidentified actinomycete SIPI-2985.[115]

2.2.4 β-Arginine and Blasticidins

β-Arginine (**4**) has been found as a constituent of the blasticidins (**45**–**46**) and of LL-BM547β (see Section 2.7.2) (Fig. 2.10). Blasticidins H (**45**)[116] and S (**46**)[117] are peptidyl nucleosides isolated from *Streptomyces griseochromogenes*. The structure of **46**[42,118] has been confirmed by X-ray analysis.[119] Blasticidin S is effective in protecting rice plants from infection by the fungus *Pyricularia oryzae*, which causes rice blast disease. Therefore, it was produced on a large scale for agricultural use. Blasticidin S acts through binding to the 50S ribosomal subunit, resulting in an inhibition of protein biosynthesis in procaryotes and eucaryotes.[120] It is also highly toxic for mammals. More recently, blasticidin S is used as selection marker in combination with a blasticidin S deaminase resistence gene for the introduction of cloned deoxyribonucleic acid (DNA) sequences in mammalian cells.[121] Its biosynthesis has been studied by feeding experiments[122,123] and isolation, characterization, and expression of the gene cluster from *S. griseochromogenes* in *Streptomyces lividans*.[124] The (*S*)-β-Arg moiety in blasticin S is generated by a 2,3-aminomutase from L-α-arginine.[122]

2.2.5 β-Glutamate and β-Glutamine

β-Glutamate (**5**) is accumulated as an osmolyte in archea such as *M. thermolithotrophicus*[125] and *Methanohalophilus portucalensis*.[126] The biosynthetical origin of **5** is still obscure. However, a direct origin from glutamate seems unlikely.[103] *N*-Methyl-β-glutamate has been found as a free amino acid in extracts from

Prochloron didemnii (Lewin),[44] a procaryotic algal symbiont associated with certain didemnid ascidians. The halophilic methanogen *M. portucalensis* uses β-glutamine (**6**) as an osmolyte when grown in media containing more than 2 M NaCl.[126] The glutamine synthase of *M. portucalensis* is also capable of accepting β-glutamate as substrate, suggesting that β-glutamine is derived, in this organism, from β-glutamate.[126]

2.2.6 β-Phenylalanine and β-Tyrosine

β-Phenylalanine (**7**) is a constituent of andrimid (**47**), the astins (**58–63**, **65–67**), cyclochlorotine (**64**), some of the edeines (**77–78**), γ-L-Glu-L-β-Phe-β-Ala isolated from the Azuki bean (*Phaseolus angularis*),[127] the moiramides (**48–50**), (*S*)-periphylline (**51**), the taxines A (**229**) and B (see Section 2.8.1.2), and (*S*)-verbascenine (**53**). β-Tyrosine (**8**) occurs in aphelandrine (**57**), the chondramides A–D (**71–74**), some of the edeines (**75–76**), the geodiamolides H–I (**68–69**), and the jaspamides (**70**).

2.2.6.1 Andrimid and Moiramides A–C Andrimid (**47**) was first isolated from cultures of an *Enterobacter* sp., which is an intracellular symbiont of the brown planthopper, *Nilaparvata lugens*.[128] Compound **47** shows potent activity against *Xanthomonas campestris* pv. *oryzae* NIAES 1225 (MIC 0.1 μg/mL), the pathogen responsible for causing bacterial blight in rice plants.[128] Andrimid and the closely related moiramides A–C (**48–50**) have also been isolated from cultures of a marine isolate of the bacterium *Pseudomonas fluorescens*[129] (Fig. 2.11). It turned out that both andrimid and moiramide B (**48**) exhibit potent in vitro antibacterial activity against methicillin-resistant strains of *S. aureus* (**47**: MIC 2 μg/mL; **48**: MIC 0.5 μg/mL).[129] Structure–activity relationship studies with synthetic andrimid (**47**) and analogs thereof suggest that the acylsuccinimide moiety with a 4*S*-methyl substituent is required for antimicrobial activity against *X. campestris* pv. *oryzae*[130] and that the central lipophilic β-amino acid is essential for antibacterial activity against *S. aureus* and *Haemophilus influenzae*.[131]

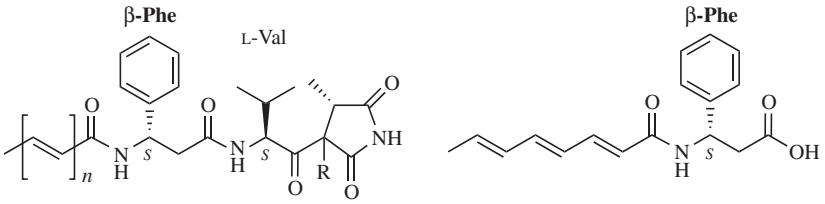
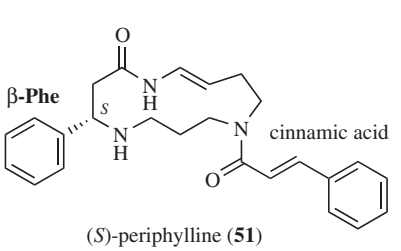


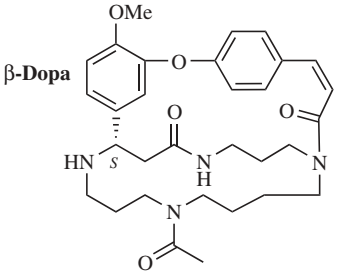
Figure 2.11 Andrimid and moiramides.

2.2.6.2 Aphelandrine, Chaenorhine, Periphylline, and Verbascenine

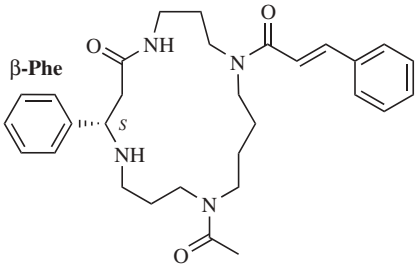
Some spermine alkaloids such as periphylline (**51**),[132] verbascenine (**53**),[133,134] aphelandrine (**57**),[135,136] and chaenorhine (**52**),[137,138] isolated from plants, possess a β-Phe, a β-Tyr, or a β-Dopa moiety (Fig. 2.12). However, these alkaloids are probably not biosynthetically derived from a β-amino acid but are derived from cinnamic acid that reacts with spermine in a Michael addition step. This hypothesis was confirmed in recent investigations on the biosynthesis of aphelandrine in *Aphelandra squarrosa*, showing that prelandrine (**55**) is a key intermediate.[24]



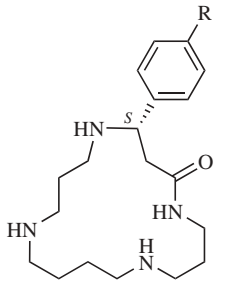
(*S*)-periphylline (**51**)



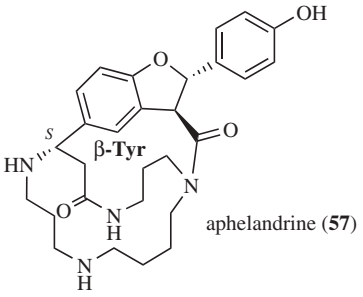
(*S*)-chaenorhine (**52**)



(*S*)-verbascenine (**53**)



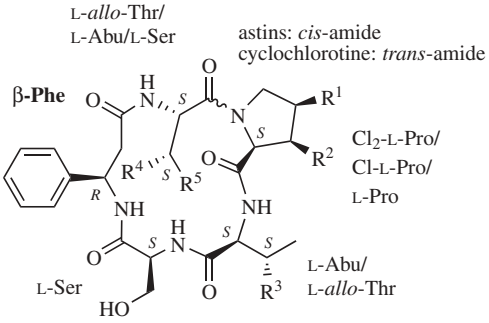
protoverbine (**54**): R = H
prelandrine (**55**): R = OH
buchnerine (**56**): R = OMe



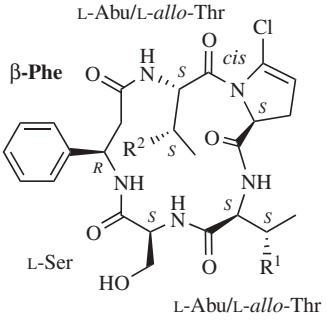
aphelandrine (**57**)

Figure 2.12 Spermine alkaloids.

2.2.6.3 Astins and Cyclochlorotine The astins A–B (**58–59**),[139] C (asterin, **60**),[140] and D–I (**61–63**, **65–67**)[141] are cyclic pentapeptides isolated from biologically active extracts of the roots of *Aster tataricus*, a plant that is used in Chinese medicinal teas. The structure of astin G has been confirmed by a total synthesis.[142] The astins are structurally closely related to cyclochlorotine (**64**)[143] (islanditoxin[144]) (Fig. 2.13), a toxic metabolite from the rice mold *Penicillium islandicum*, whose ingestion causes a severe health hazard, since it induces hepatocellular injury and liver cirrhosis.[145] In mice, the LD_{50} values are at 0.40 mg/kg for an intravenous (i.v.) and at 7.0 mg/kg for oral application.[146] Astins A–C exhibit antitumor activity against sarcoma 180 ascites in mice, while astins D–I were inactive, suggesting that the Cl_2-Pro residue is important for their activity.[141] A crystal structure determination as well as conformational studies by



astin A (**58**): R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = OH, R^5 = Me
astin B (**59**): R^1 = Cl, R^2 = Cl, R^3 = OH, R^4 = H, R^5 = Me
astin C (**60**): R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = H, R^5 = Me
astin F (**61**): R^1 = H, R^2 = Cl, R^3 = H, R^4 = H, R^5 = Me
astin G (**62**): R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = Me
astin I (**63**): R^1 = Cl, R^2 = OH, R^3 = H, R^4 = H, R^5 = Me
cyclochlorotine (**64**): R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = OH, R^5 = H

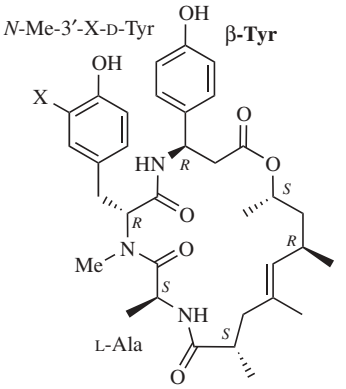


astin D (**65**): R^1 = H, R^2 = H
astin E (**66**): R^1 = OH, R^2 = H
astin H (**67**): R^1 = H, R^2 = OH

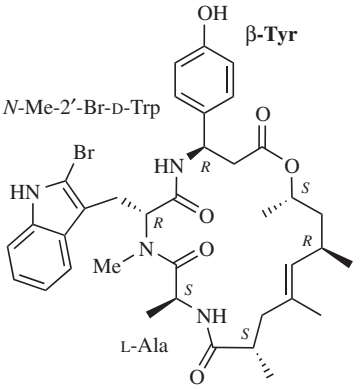
Figure 2.13 Astins and cyclochlorotine.

two-dimensional NMR of **59** and of **64** revealed that the proline amide bond is cis configured in the astins, while it is trans configured in cyclochlorotine.[147]

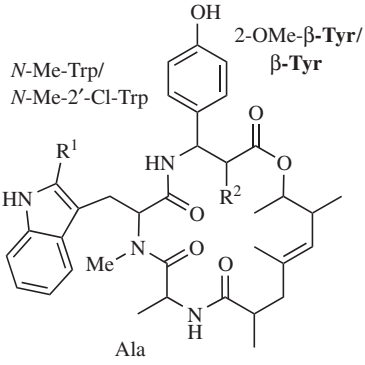
2.2.6.4 Chondramides A–D, Geodiamolides H–I, and Jaspamides The chondramides A–D (**71**–**74**)[148] isolated from the myxomycete *Chondromyces crocatus* are cyclodepsipeptides[149] that are structurally related to the jaspamides and geodiamolides (Fig. 2.14). The chondramides are highly active against *Candida albicans* and human cancer cell lines, such as cervical carcinoma KB-3-1 cells (IC_{50} 2–7 ng/mL) and leukemia K-562 cells (IC_{50} 3–6 ng/mL),[148] by disruption of the organization of the actin cytoskeleton.[150]



geodiamolide H (**68**): X = I
geodiamolide I (**69**): X = Br



jaspamide (jasplakinolide, **70**)



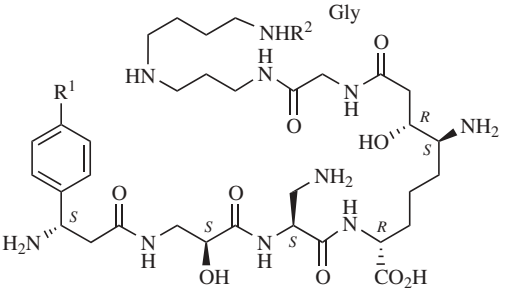
chondramide A (**71**): R^1 = H, R^2 = OMe
chondramide B (**72**): R^1 = Cl, R^2 = OMe
chondramide C (**73**): R^1 = H, R^2 = H
chondramide D (**74**): R^1 = Cl, R^2 = H

Figure 2.14 Geodiamolides, jaspamide, and chondramides.

Among the cyclopeptidic geodiamolides A–R[151] isolated from a variety of sponges belonging to taxonomically distant orders, only the geodiamolides H–I (**68**–**69**)[152] isolated from a *Chymbastela* species collected in Papua New Guinea possess a β-tyrosine moiety. Geodiamolide H exhibits in vitro cytotoxicity against a number of human cancer cell lines (ovarian cancer OV Car-4: GI_{100} 18.6 nM) similar to the geodiamolides A–F in an in vitro experiment with L1210 cells (LD_{50} 2–39 ng/mL),[153] while geodiamolide I was inactive. Therefore, the β-Tyr moiety lacking in the geodiamolides A–G and K–R seems to be no prerequisite for their cytotoxic activity. Jaspamide (**70**)[154,155] (jasplakinolide[156]) has been isolated from the different marine sponge genera *Jaspis* (c.f. *johnstoni*, *J. splendens*), *Auletta constricta*, and *Hemiasterella minor*,[157] and its structure has been confirmed by several total syntheses.[158–160] The structurally closely related jaspamides B and C have been isolated from *J. splendens*.[161] Jaspamide exhibits antifungal,[154] anthelminthic,[155] cytotoxic (P-388: IC_{50} 0.04 ng/mL),[156] antimicrobial, insecticidal (*Heliothis virescens*: LC_{50} 4 ppm),[154] and ichthyotoxic activities. The antiproliferative activity of **70** against the human leukemia cell line HL-60 is caused by a disruption of the organization of the actin cytoskeleton, as also shown for the geodiamolides.[162]

The isolation of structurally closely related compounds from a variety of sponges and from a myxomycete indicates that symbionts in the sponges are the real producers of jaspamide and the geodiamolides.

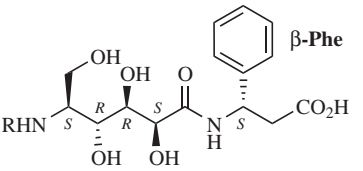
2.2.6.5 Edeines A_1,B_1,D_1,F_1 The edeines A_1–B_1 (**75**–**76**),[163] D_1 (**77**),[164] and F_1 (**78**)[165] are antibiotic oligopeptides that were first detected in cultures of *Bacillus brevis* Vm4 in 1959[166] (Fig. 2.15). The structure of edeine D_1 (**77**) has been confirmed by a total synthesis.[167] Apart from the (*S*)-isoserine moiety, the edeines also contain two more β-amino acids, Dap (**167**) and β-Tyr or β-Phe, respectively. The edeines exhibit a broad spectrum of antimicrobial activity. However, the edeines have little clinical relevance, since these universal antibiotics inhibit



edeine A_1 (**75**) R^1 = OH, R^2 = H edeine B_1 (**76**): R^1 = OH, R^2 = NH, NH_2

edeine D_1 (**77**): R^1 = H, R^2 = H edeine F_1 (**78**): R^1 = H, R^2 = NH, NH_2

Figure 2.15 Edeines.



pyloricidin A (**79**): R = H-L-Val-L-Val-L-Leu-
pyloricidin A_1 (**80**): R = H-L-Val-L-Ile-L-Leu-
pyloricidin A_2 (**81**): R = H-L-Val-L-Leu-L-Leu-
pyloricidin B (**82**): R = H-L-Val-L-Leu-
pyloricidin C (**83**): R = H-L-Leu-
pyloricidin D (**84**): R = H

Figure 2.16 Pyloricidins.

nonspecifically the protein biosynthesis in all phylogenetic kingdoms.[168] The edeines interact with the small 30S ribosomal subunit and inhibit the initiation phase of the translation.[169] Feeding experiments to clarify the biosynthesis of the edeines A_1 and B_1 revealed that the β-Tyr moiety is generated from α-tyrosine probably via *p*-hydroxycinnamic acid as an intermediate, since a [^{15}N]-labeled amino group is lost during the course of the reaction.[45]

2.2.6.6 Pyloricidins A–D The pyloricidins (**79**–**84**) are peptides with a C-terminal (*S*)-β-Phe (**7**) moiety[170] (Fig. 2.16). They have been isolated recently from cultures of the strains *Bacillus* sp. HC-70 and *Bacillus* sp. HC-72 and exhibit a selective antibiotic activity against *Heliobacter pylori*,[171] a bacterium that is associated with peptic ulcers and the provocation of gastric cancer in humans. Pyloricidin B (**82**) is active against *H. pylori* (MIC_{50} 63 ng/mL), while it does not disturb the normal gastrointestinal microflora, since it is inactive against common anaerobic bacteria. The pyloricidins A–C have already been synthesized.[172] Structure–activity relationship studies with derivatives therof show that the N-terminal L-Val moiety in **82** is important for its anti–*H. pylori* activity.[173]

2.3 NATURAL PRODUCTS CONTAINING UNUSUAL ALIPHATIC β-AMINO ACIDS

A variety of unusual aliphatic β-amino acids, many of them originating from cyanobacteria, are known. They differ in respect to their chain length and possess, in some cases, additional methyl groups or a terminal triple bond (Fig. 2.17). From a biosynthetic point of view, this class of β-amino acids can be divided roughly into β-aminoisobutyric acid (β-Aib, **85**), polyketide-type β-amino acids, and long-chain fatty acid–type β-amino acids. β-Aib occurs in nature also in free form, while the polyketide-type and fatty acid-type β-amino acids can, in general, be found only as constituents of peptidic natural products. This is not surprising, since the biosynthesis of nonribosomal peptides and depsipeptides as well as the biosynthesis of the

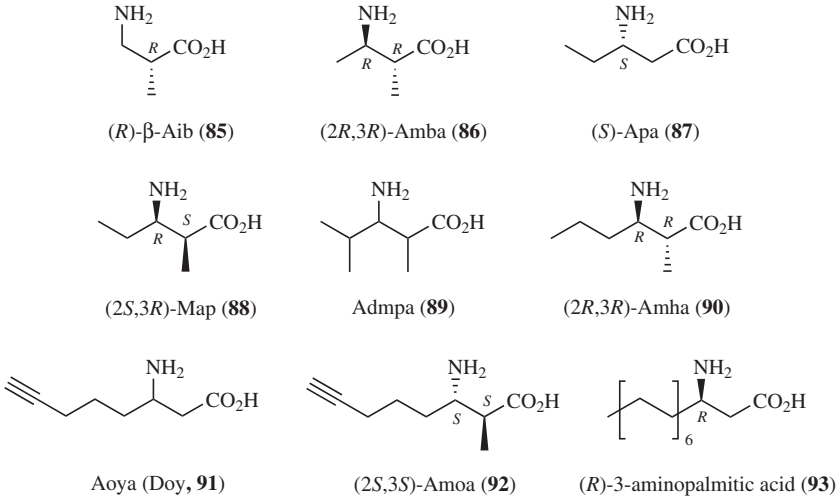


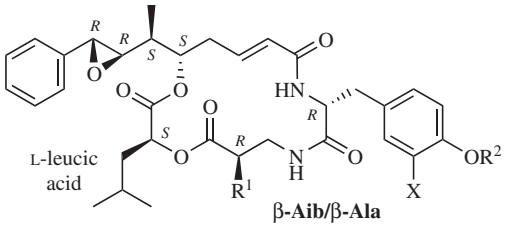
Figure 2.17 Selected unusual aliphatic β-amino acids.

unusual polyketide-type and fatty acid–type β-amino acids occurs in common in a multienzyme complex that does not release biosynthetic intermediates.[32]

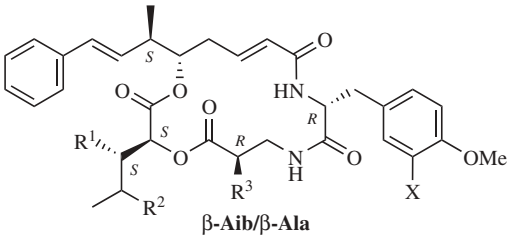
2.3.1 β-Aminoisobutyric Acid

Like β-alanine, (*R*)-β-aminoisobutyric acid [(*R*)-β-Aib, **85**] is widespread, since it is involved in the catabolism of thymine.[174,175] Both stereoisomers of β-Aib occur in nature. Free (*R*)-β-Aib has been found in mammals and in plants such as *Lunaria annua*[176] or *Iris tingitana*.[177] It is also a constituent of the cryptophycins (**94**–**103**) and phascolosomine (**105**). Free (*S*)-β-Aib occurs in mammals as a catabolite of L-valine.[178]

2.3.1.1 Cryptophycins The cryptophycins (**94**–**103**), reviewed recently[179–181] due to their potent antitumor activity, are cyclic and acyclic depsipeptides isolated from the terrestrial cyanobacteria *Nostoc* sp. American Type Culture Collection (ATCC)53789[182] and *Nostoc* sp. GSV 224[183,184] (Fig. 2.18). Cryptophycin 24 (arenastatin A) has also been isolated from the Okinawan sponge *Dysidea arenaria*.[185] Several representatives of the cryptophycins show remarkably high activity against drug-resistant and drug-sensitive tumor cell lines. For example, cryptophycin 1 (**94**) is active against KB cells (IC_{50} 0.0092 nM) and against LoVo cells (IC_{50} 0.01 nM).[183] In mice, **94** is very active against transplanted solid tumors of murine origin such as colon, mammary, and pancreatic adenocarcinomas, or DMS-273, a highly invasive metastatic human lung cell tumor.[183] The activity of the cryptophycins 1 (**94**)[186,187] and 52 (**99**)[188,189] is caused by an irreversible inhibition of the microtubuli assembly. Due to their promising properties, several cryptophycins[180,190] and also synthetic analogs[191] have been synthesized. Structure–activity relationship (SAR)



cryptophycin 1 (**94**): R^1 = Me, R^2 = Me, X = Cl
cryptophycin 2 (**95**): R^1 = Me, R^2 = Me, X = H
cryptophycin 16 (**96**): R^1 = Me, R^2 = H, X = Cl
cryptophycin 21 (**97**): R^1 = H, R^2 = Me, X = Cl
cryptophycin 24 (**98**): R^1 = H, R^2 = Me, X = H
cryptophycin 52 (**99**, *synthetic*): R^1 = Me_2, R^2 = Me, X = Cl

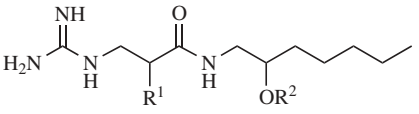


cryptophycin 3 (**100**): R^1 = H, R^2 = Me, R^3 = Me, X = Cl
cryptophycin 4 (**101**): R^1 = H, R^2 = Me, R^3 = Me, X = H
cryptophycin 18 (**102**): R^1 = Me, R^2 = H, R^3 = Me, X = Cl
cryptophycin 29 (**103**): R^1 = H, R^2 = Me, R^3 = H, X = Cl

Figure 2.18 Selected cryptophycins.

studies[181] show that the intact macrolide ring, the methoxy and chloro group, the presence of the epoxide or chlorohydrine, and the methyl group of the (*R*)-β-aminoisobutyric acid (β-Aib) moiety are necessary for the in vivo activity against transplanted tumors in mice.[183] Accordingly, cryptophycin 21 (**97**) containing β-alanine instead of β-Aib is inactive in the mouse experiment, even if it still exhibits cytotoxicity in vitro. It is assumed that the methyl group protects the ester bond from in vivo cleavage.[183] Therefore, a synthetic analog, cryptophycin 52 (LY355703), with the synthetic 3-amino-2,2-dimethylpropanoic acid moiety that prevents ester hydrolysis even better than β-Aib, has been evaluated for the treatment of solid tumors and has reached clinical phase II.[192,193]

2.3.1.2 Phascolosomine and Phascoline Phascoline (**104**) and phascolosomine (**105**) are guanidine derivatives of β-Ala and β-Aib, respectively, that have been isolated from the sipunculid worm *Phascolion strombi*[194] (Fig. 2.19). They have negative chronotropic effects on rat cardiac cells in culture.[195,196]



phascoline (**104**): R^1 = H, R^2 = H
phascolosomine (**105**): R^1 = Me, R^2 = Me

Figure 2.19 Phascoline and phascolosomine.

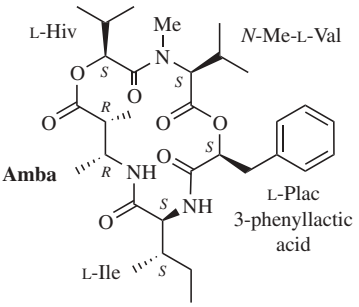
2.3.2 Aliphatic Polyketide-Type β-Amino Acids in Natural Products

3-Amino-2-methylbutanoic acid (Amba, **86**) is part of dolastatin D (**106**) and guineamide B (**114**), while (*S*)-3-aminopentanoic acid (Apa, **87**) has been identified in obyanamide (**115**). 3-Amino-2-methylpentanoic acid (Map, **88**) occurs as a constituent of the dolastatins 11 (**107**) and 12 (**108**), guineamide A (**113**), and majusculamide C (**109**). 3-Amino-2,4-dimethylpentanoic acid (Admpa, **89**) is present in dolastatin 16 (**110**) and homodolastatin 16 (**111**). 3-Amino-2-methylhexanoic acid (Amha, **90**) is more common, since it has been identified as a constituent of guineamide D (**122**), kulokekahilide-1 (**124**), malevamide B (**125**), and the ulongamides A–F (**116–120**). β-Amino acids with an alkyne group are 3-amino-7-octynoic acid (Aoya, Doy, **91**), a constituent of dolastatin 17 (**112**), and 3-amino-2-methyl-7-octynoic acid (Amoa, **92**), a component of guineamide C (**121**), malevamide C (**126**), onchidin (**127**), and ulongapeptin (**123**).

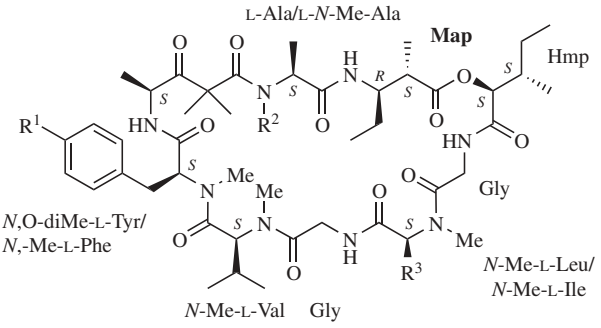
2.3.2.1 Dolastatins 11, 12, 16, 17, D, Homodolastatin 16, and Majusculamide C The dolastatins are peptides that have been discovered after efforts ongoing since 1972 to isolate the antitumor active principles from extracts of the sea hare *Dolabella auricularia*.[12] So far, a variety of structurally not closely related peptides have been isolated. Among the dolastatins, only dolastatins 11 (**107**),[197] 12 (**108**),[197] 16 (**110**),[198] 17 (**112**),[199] and D (**106**)[200] contain a β-amino acid moiety (see Section 2.3.2 and Fig. 2.20). Total syntheses of dolastatins 10,[201] 11,[202] 15, and D[203] have confirmed their structures.

The dolastatins are found in extremely low concentrations in the mollusk *D. auricula*; 1600 kg of wet sea hares yielded 43.6 mg dolastatin 11.[12] On the other hand, some representatives such as dolastatins 3,[204] 12,[205] and 16,[206] as well as compounds closely related to certain dolastatins like homodolastatin 16 (**111**)[207] and majusculamide C (**109**),[208] have been found in the marine cyanobacterium *L. majuscula*. These findings strongly suggest that the real producers of the dolastatins are cyanobacteria, as the marine mollusk consumes the cyanobacteria with its diet.

Several of the dolastatins, especially dolastatins 10 and 15,[209] but also dolastatins 11, 12 and 16, show promising activity against a broad set of cancer cell lines. Interestingly, dolastatin 16 exhibits a strong inhibitory activity against human cancer cell lines such as colon KM20L2 (GI_{50} 1.2 ng/mL), brain SF-295 (GI_{50} 5.2 ng/mL), lung NCI-H460 (GI_{50} 0.96 ng/mL), and melanoma SK-MEL-5 (GI_{50} 3.3 ng/mL),[198] while homodolastatin 16 showed only very weak activities against



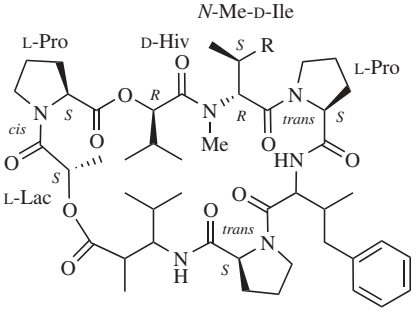
dolastatin D (**106**)



dolastatin 11 (**107**): R^1 = OMe, R^2 = H, R^3 =

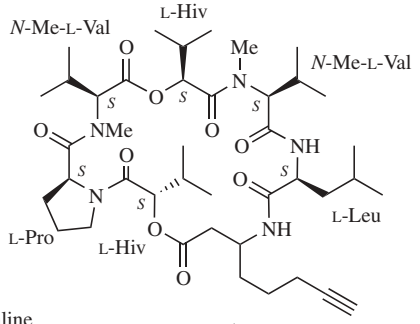
dolastatin 12 (**108**): R^1 = H, R^2 = Me, R^3 =

majusculamide C (**109**): R^1 = OMe, R^2 = H, R^3 =



dolastatin 16 (**110**): R = Me
homodolastatin 16 (**111**): R = Et

(Stereochemistry of Lac ambiguous)

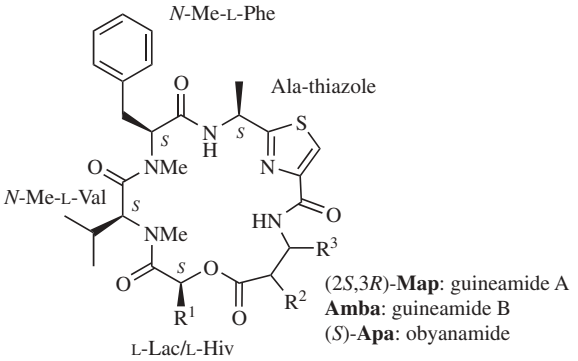


dolastatin 17 (**112**)

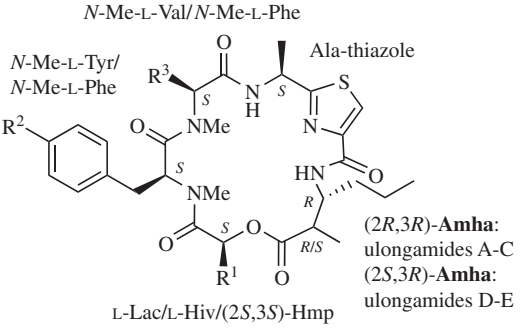
Figure 2.20 Selected dolastatins and majusculamide C.

esophageal and cervical cancer cell lines ($IC_{50} \sim 10$ μg/mL).[207] In general, the activity of the dolastatins is based on the inhibition of the microtubuli assembly during mitosis.[210] Some of the dolastatins, especially dolastatin 10, are already in phase II of clinical trials.[211] Majusculamide C was found to inhibit the growth of a number of fungal plant pathogens such as *Phytophtora infestans*, the dreaded inducer of tomato and potato late blight.[208]

2.3.2.2 Guineamides A–D, Obyanamide, Ulongamides A–F, and Ulongapeptin The guineamides[212] are cyclic depsipeptides isolated from the marine cyanobacterium *L. majuscula*, while obyanamide (**115**)[213] has been obtained from *Lyngbya coniferoides* (Fig. 2.21). The cyclic depsipeptides

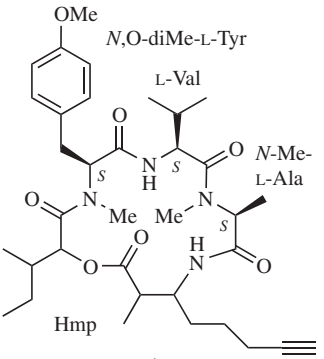


guineamide A (**113**): R^1 = Me, R^2 = Me, R^3 = Et
guineamide B (**114**): R^1 = *i*-Pr, R^2 = Me, R^3 = Me
obyanamide (**115**): R^1 = Me, R^2 = H, R^3 = Et

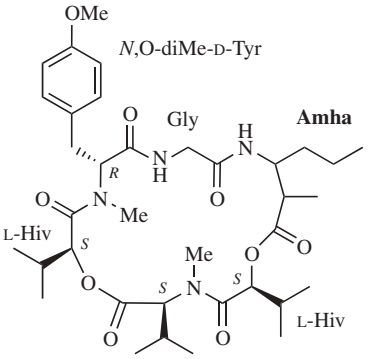


ulongamide A (**116**): R^1 = Me, R^2 = H, R^3 = *i*-Pr
ulongamide B (**117**): R^1 = Me, R^2 = OH, R^3 = *i*-Pr
ulongamide C (**118**): R^1 = Me, R^2 = OH, R^3 = Bn
ulongamide D (**119**): R^1 = *i*-Pr, R^2 = OH, R^3 = *i*-Pr
ulongamide E (**120**): R^1 = CHMeEt, R^2 = OH, R^3 = *i*-Pr

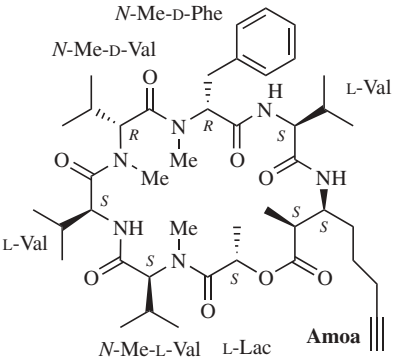
Figure 2.21 Selected guineamides and related natural products.



guineamide C (**121**)



guineamide D (**122**)

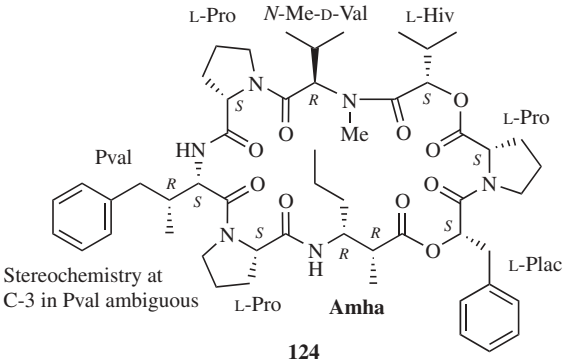


ulongapeptin (**123**)

Figure 2.21 (*Continued*)

ulongamides A–E (**116–120**), F,[214] and ulongapeptin (**123**)[215] have been isolated from a Palauan collection of a *Lyngbya* species. The chemical structures of the guineamides A–B, obyanamide, and the ulongamides A–F are closely related to each other. Guineamides B (**114**) and C (**115**) exhibit weak cytotoxity (IC_{50} 15 μM) to a mouse neuroblastoma cell line, while guineamide A (**113**) showed no activity at 10 μg/mL.[212] Obyanamide[213] and ulongopeptin[215] are moderately active against KB cells (IC_{50} 0.6 μg/mL). Ulongamides A–E exhibited weak cytotoxicity against KB and LoVo cells (IC_{50} 1–5 μM), while ulongamide F, distinguished from ulongamide E only by an exchange of the *N*-methyltyrosine moiety by L-Val, was inactive at <10 μM.[214]

2.3.2.3 Kulokekahilide-1 Kulokekahilide-1 (**124**), isolated from the marine mollusk *Philinopsis speciosa*, is a cyclic octadepsipeptide[216] (Fig. 2.22). It is weakly active against P-388 murine leukemia cells (IC_{50} 2.1 μg/mL).

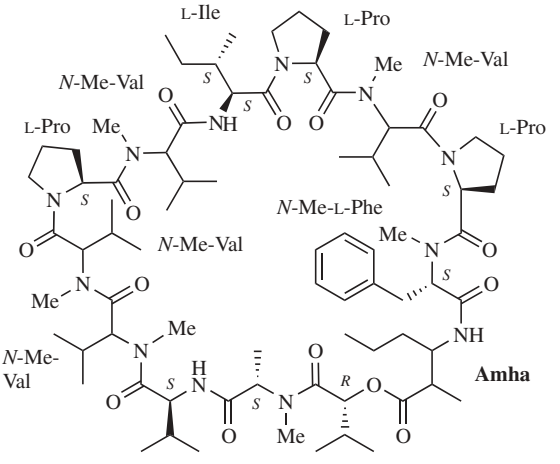


124

Figure 2.22 Kulokekahilide-1.

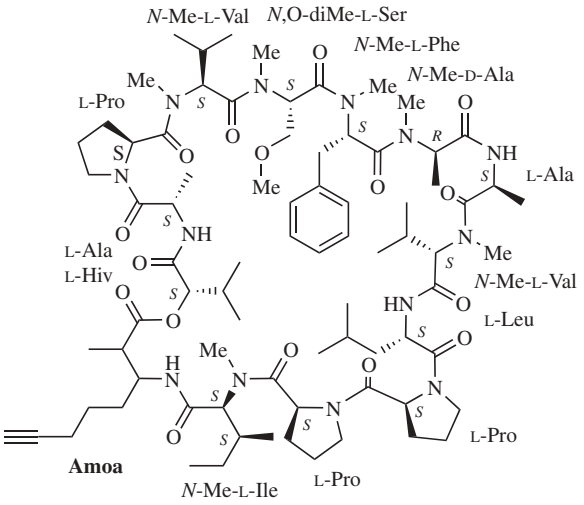
2.3.2.4 Malevamides B–C Malevamides B (**125**) and C (**126**) isolated from the marine cyanobacterium *Symploca laete-viridis* are cyclic depsipeptides[49] (Fig. 2.23). However, **125** is structurally not related to **126**. The malevamides B and C were inactive against P-388, A-549, and HT-29 cancer cell lines at a concentration of 2 μg/mL.

2.3.2.5 Onchidin Onchidin (**127**) is a C_2-symmetric cyclodepsipeptide isolated from a pulmonate mollusk *Onchidium* species[217] (Fig. 2.24). The absolute configuration of the β-amino acid (2*S*,3*S*)-Amoa (**92**) has been confirmed by a synthesis.[218] Onchidin is weakly active against P-388 murine leukemia (IC_{50} 8 μg/mL) and KB cells.



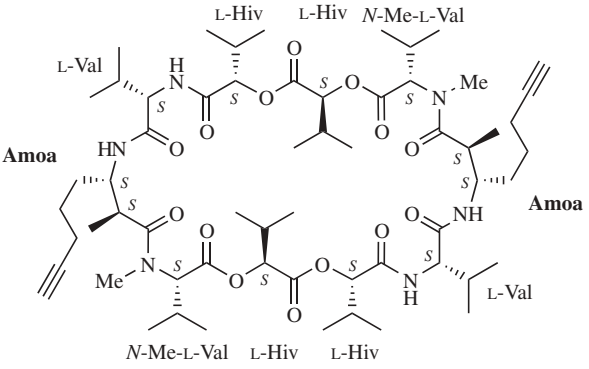
(*S*)-*N*-Me-Val/(*R*)-*N*-Me-Val: 3:1
malevamide B (**125**)

Figure 2.23 Malevamides with a β-amino acid moiety.



malevamide C (**126**)

Figure 2.23 (*Continued*).



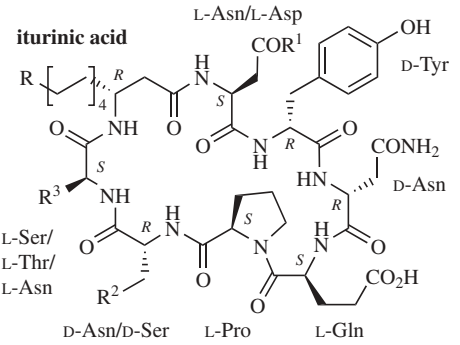
127

Figure 2.24 Onchidin.

2.3.3 Natural Products Containing Long-Chain β-Amino Acids

Long-chain β-amino acids such as (*R*)-3-aminopalmitic acid (**93**) occur as constituents of the bacillomycins (**130**), iturins (**128–129**), mycosubtilin (**131**), and rhodopeptins (**132–136**).

2.3.3.1 Iturins The iturins[219] are a group of cyclooctapeptides including the iturins A (**128**)[220] and C (**129**),[221] bacillomycins D,[222,223] F (**130**),[224] and L,[222] and mycosubtilin (**131**)[225] isolated from cell cultures of *Bacillus subtilis*[226] (Fig. 2.25). The iturins A2–A8 were also found in *Bacillus amyloliquefaciens* RC-2.[227] Each iturin occurs in nature as a mixture of congeners, distinguished in the long-chain



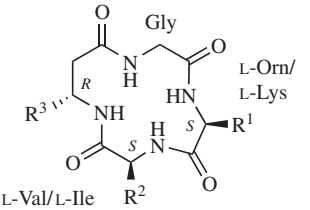
iturin A (**128**): $R^1 = NH_2$, $R^2 = CONH_2$, $R^3 = CH_2OH$
iturin C (**129**): $R^1 = OH$, $R^2 = CONH_2$, $R^3 = CH_2OH$
bacillomycin F (**130**): $R^1 = NH_2$, $R^2 = CO_2NH_2$, $R^3 =$ HO *R*
mycosubtilin (**131**): $R^1 = NH_2$, $R^2 = OH$, $R^3 = CH_2CONH_2$

# 1: R = Et	# 5: R = Bu
# 2: R = Pr	# 6: R = $(CH_2)_2$*i*-Pr
# 3: R = CHMeEt	# 7: R = $(CH_2)_4$Me
# 4: R = CH_2*i*-Pr	# 8: R = $(CH_2)_2$CHMeEt

Figure 2.25 Selected iturins and related natural products.

β-amino acid moiety. Therefore, for example, several different iturins A named as iturin A1, iturin A2, and so on, are known. The structure of iturin A2 has been confirmed by total synthesis.[228] Especially iturin A (**128**) shows antifungal activity (*Penicillium chrysogenum*: GI_{100} 5 μg/mg). Clinical trials have shown that iturins could be valuable drugs due to their broad antifungal activity combined with low toxicity and low allergic effect.[229] The presence of the long-chain β-amino acid is essential for their activity and increases with the chain length. Analogs with β-Asp or β-Ala instead of the long-chain β-amino acid are inactive.[228] The operons encoding the biosynthesis of iturin A and mycosubtilin have been sequenced and characterized.[230] Therefore, it is known that the biosynthesis of the long-chain β-amino acid involves fatty acid synthetases and an amino acid transferase.

2.3.3.2 Rhodopeptins The rhodopeptins (**132–136**) are cyclic tetrapeptides[231] isolated from *Rhodococcus* sp. Mer-N1033[232] (Fig. 2.26). They exhibit high antifungal activity[232] against *C. albicans* (MIC 1.25–5 μg/mL) and *Cryptococcus neoformans*. The structure of rhodopeptin B5 (**136**) has been confirmed by synthesis and the stereochemistry of the β-amino acid moiety has been determined to be R.[233]



rhodopeptin C1 (**132**): $R^1 = -(CH_2)_3NH_2$, $R^2 = i$-Pr, $R^3 = -(CH_2)_6CH(Me)Et$

rhodopeptin C2 (**133**): $R^1 = -(CH_2)_3NH_2$, $R^2 = -CH(Me)Et$, $R^3 = -(CH_2)_6CH(Me)Et$

rhodopeptin C3 (**134**): $R^1 = -(CH_2)_3NH_2$, $R^2 = i$-Pr, $R^3 = -(CH_2)_8$-i-Pr

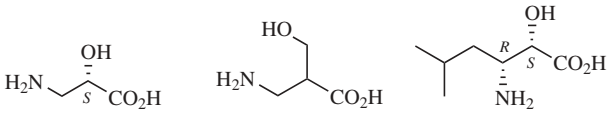
rhodopeptin C4 (**135**): $R^1 = -(CH_2)_3NH_2$, $R^2 = i$-Pr, $R^3 = -(CH_2)_8CH(Me)Et$

rhodopeptin B5 (**136**): $R^1 = -(CH_2)_4NH_2$, $R^2 = i$-Pr, $R^3 = -(CH_2)_9$-i-Pr

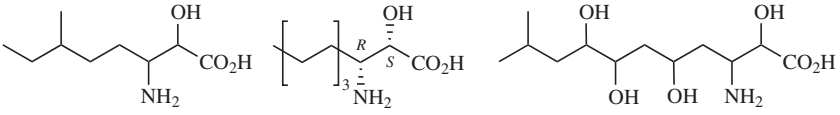
Figure 2.26 Rhodopeptins.

2.4 NATURAL PRODUCTS CONTAINING ALIPHATIC HYDROXY-β-AMINO ACIDS

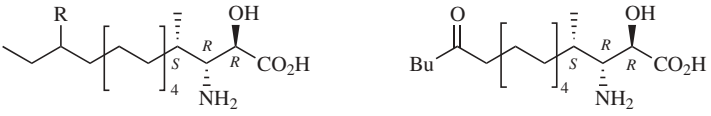
Aliphatic hydroxy-β-amino acids are not very widespread in nature except for isoserine (**137**), which is a constituent of several natural products, such as the edeines (see Section 2.2.6.5), the keramamides F–H, J (see Section 2.5.1), theonegramide (see Section 2.8.2.3), the theonellamides A–B (see Section 2.8.2.3), and theopalauamide (see Section 2.8.2.3) (Fig. 2.27). 2-Hydroxymethyl-



(*S*)-isoserine (**137**) **138** Ahmh (**139**)



Hamo (**140**) Ahda (**141**) Aound (**142**)



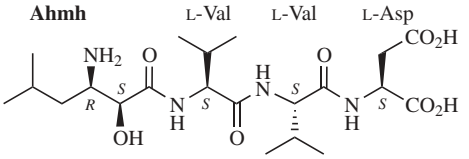
Hamp (**143**): R = H, Champ (**144**): R = Cl Ahmos (**145**)

Figure 2.27 Aliphatic hydroxy-β-amino acids.

β-alanine (**138**) is a constituent of DGTA [1,2-diacylglyceryl-*O*-2′-(hydroxymethyl)-(*N*,*N*,*N*-trimethyl)-β-alanine], a lipid that has been found in some marine algae species, such as Haptophyceae.[234] (2*S*,3*R*)-3-Amino-2-hydroxy-5-methylhexanoic acid (Ahmh, **139**) is a constituent of amastatin (**146**), 3-amino-2-hydroxy-6-methyloctanoic acid (Hamo, **140**) occurs in perthamide B (**148**), 3-amino-2-hydroxydecanoic acid (Ahda, **141**) in microginin (**147**), and 3-amino-2,5,7,8-tetrahydroxy-10-methylundecanoic acid (Aound, **142**) in schizotrin A (**149**). (2*R*,3*R*,4*S*)-3-Amino-2-hydroxy-4-methylpalmitic acid (Hamp, **143**) has been found as a constituent of calophycin (**150**) and puwainaphycin E (**155**), the chlorine containing (2*R*,3*R*,4*S*)-3-amino-14-chloro-2-hydroxy-4-methylpalmitic acid (Champ, **144**) is present in the puwainaphycins C–D (**153**–**154**), while (2*R*,3*R*,4*S*)-3-amino-14-oxo-2-hydroxy-4-methylstearic acid (Ahmos, **145**) occurs in the puwainaphycins A–B (**151**–**152**).

2.4.1 Amastatin and Microginins

Amastatin (**146**) isolated from *Streptomyces* sp. ME98-M3[235] is a tetrapeptide[236] with an N-terminal Ahmh (**139**) moiety. Amastatin inhibits aminopeptidase A and leucine aminopeptidase competitively (IC_{50} 0.5 μg/mL[235]) by binding at the active site of the enzyme. Similar to bestatin (see Section 2.8.2.1), **146** serves as a tool to study the reaction mechanism of peptidases. Therefore, a variety of analogs have been synthesized.[237] The microginins are natural products structurally related to amastatin (**146**) exhibiting similar activities (Fig. 2.28). Microginin (**147**) is an inhibitor of the angiotensin-converting enzyme (IC_{50} 7.0 μg/mL) that has been isolated from the cyanobacterium *Microcystis aeruginosa* NIES-100.[238] The absolute stereochemistry of the N-terminal (2*S*,3*R*)-Ahda (**141**) moiety has been revised after total syntheses of **141**[239] and **147**.[240,241] Meanwhile, several



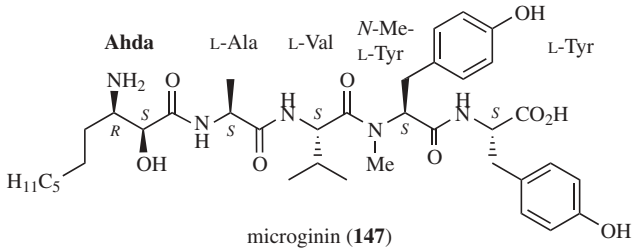
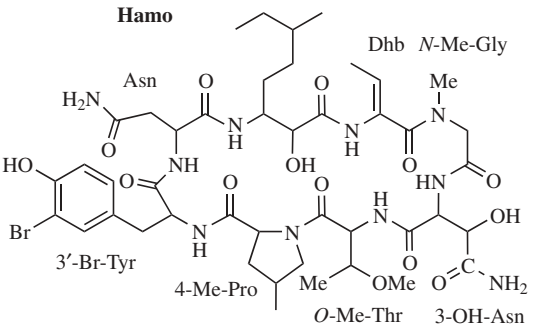


Figure 2.28 Amastatin and microginin.



148

Figure 2.29 Perthamide B.

congeners, such as microginins 299A–D with a (2*S*,3*S*)-Ahda, a (2*S*,3*S*)-10-chloro-Ahda, and a (2*S*,3*S*)-10,10-dichloro-Ahda moiety, respectively, have been isolated.[242,243] The microginins 299C–D inhibit leucine aminopeptidase (IC_{50} 2.0–6.5 μg/mL) and demonstrate the general importance of the 3-amino-2-hydroxy acid structure motif for the inhibition of peptidases.

2.4.2 Perthamide B

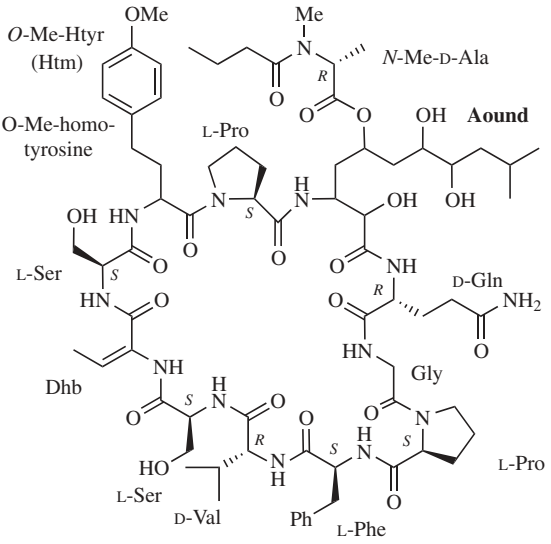
Perthamide B (**148**), a cyclic octapeptide, has been isolated from a marine sponge of the genus *Theonella*[50] (Fig. 2.29). It weakly inhibits the binding of [^{125}I]interleucin-1β to intact EL4.6.1 cells (IC_{50} 27.6 μM). However, the interleucin binding inhibition could not be separated from cytotoxic effects of **148**.

2.4.3 Schizotrin A

The cyclic undecapeptide schizotrin A (**149**), possessing a unique Aound (**142**) moiety, has been isolated from the terrestrial cyanobacterium *Schizotrix* sp. (TAU strain IL-89-2)[244] (Fig. 2.30). Schizothrin A shows moderate antibacterial (*B. subtilis*: 15 mm inhibition zone at 6.7 nM/6-mm disc) and antifungal activity.

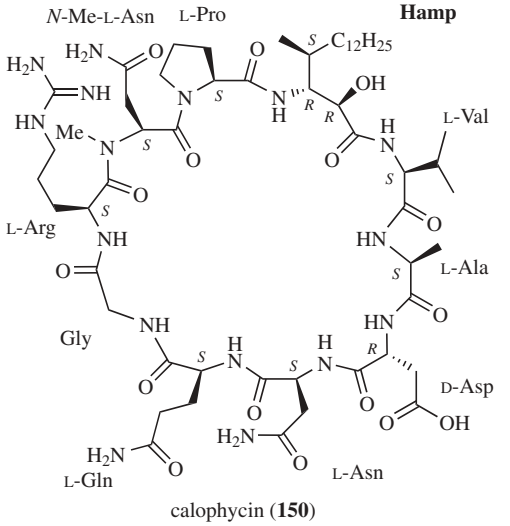
2.4.4 Calophycin and Puwainaphycins A–E

Calophycin (**150**), a cyclic decapeptide isolated from the terrestrial cyanobacterium *Calothrix fusca* EU-10-1,[245] exhibits a broad-spectrum activity against fungi. The structure and absolute configuration of the Hamp (**143**) moiety have been confirmed by stereoselective synthesis.[245] The puwainaphycins A–E (**151**–**155**),[246] decapeptides closely related to calophycin (Fig. 2.31), have been isolated from the



149

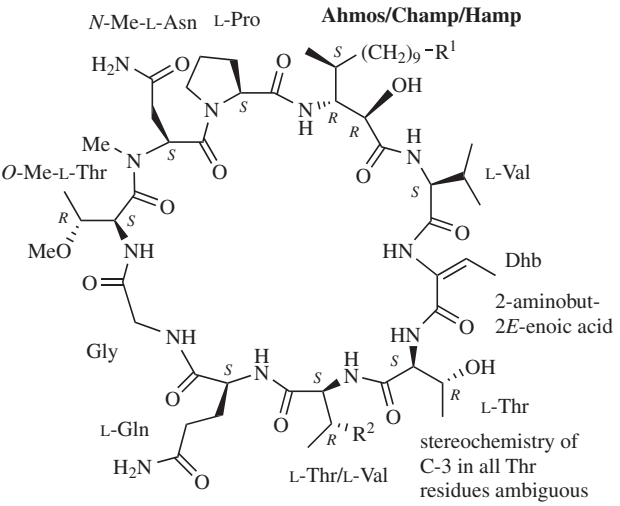
Figure 2.30 Schizotrin A.



calophycin (**150**)

Figure 2.31 Calophycin and puwainaphycins.

terrestrial cyanobacterium *Anabaena* sp. BQ-16-1.[247] Puwainaphycin C (**153**) shows cardioactivity, eliciting a strong, positive inotropic effect in isolated mouse atria (effective dose ED_{50} 0.2 ppm), while puwainaphycin D (**154**), in which only one amino acid is exchanged, is inactive.[247]



puwainaphycin A (**151**): R^1 = COBu, R^2 = OH
puwainaphycin B (**152**): R^1 = COBu, R^2 = H
puwainaphycin C (**153**): R^1 = CHClEt, R^2 = OH
puwainaphycin D (**154**): R^1 = CHClEt, R^2 = H
puwainaphycin E (**155**): R^1 = Pr, R^2 = OH

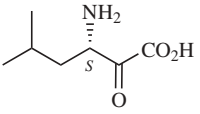
Figure 2.31 (*Continued*).

2.5 NATURAL PRODUCTS CONTAINING ALIPHATIC β-AMINO ACIDS WITH OXO GROUPS

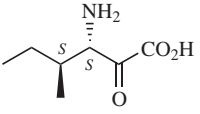
α-Keto-homoleucine (**156**) and α-keto-homoisoleucine (**157**), respectively, are constituents of some keramamides (**159–161**, **163–164**) and of orbicularamide A (**162**), while α-keto-homoarginine (**158**) is present in the cyclotheonamides (**165–166**) (Fig. 2.32).

2.5.1 Keramamides B–N and Orbiculamide A

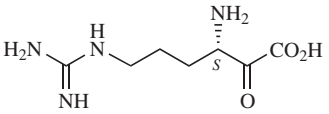
The keramamides B–D,[248] E,[249] F,[250] G–J,[249] K, and M–N[251] and orbiculamide A (**162**)[252] are cyclic peptides isolated from an Okinawan marine sponge of the genus *Theonella* (Fig. 2.33). The structure of keramamide J (**164**) has been confirmed by a total synthesis.[253] The keramamides B–D (**159–161**) inhibit the superoxide generation response of human neutrophils, elicited with a chemotactic peptide.[248] Keramamide F (**163**) shows moderate cytotoxicity against human epidermoid carcinoma KB cells (IC_{50} 1.4 μg/mL) and murine lymphoma L1210 cells (IC_{50} 2.0 μg/mL).[250] Orbiculamide A exhibits weak cytotoxicity against P-388 murine leukemia cells (IC_{50} 4.7 μg/mL).[252]



α-keto-homoleucine (k-Leu, **156**)



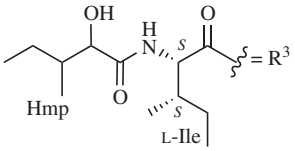
α-keto-homoisoleucine (k-Ile, **157**)



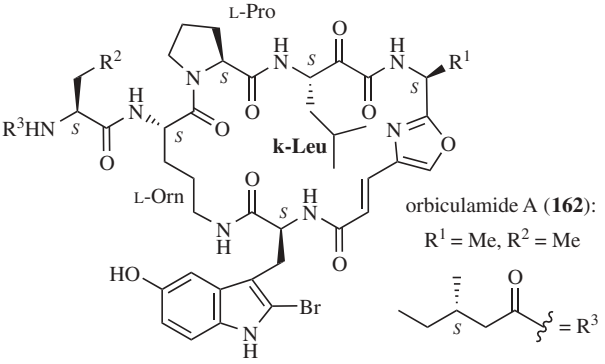
α-keto-homoarginine (k-Arg, **158**)

Figure 2.32 3-Amino-2-oxo acids.

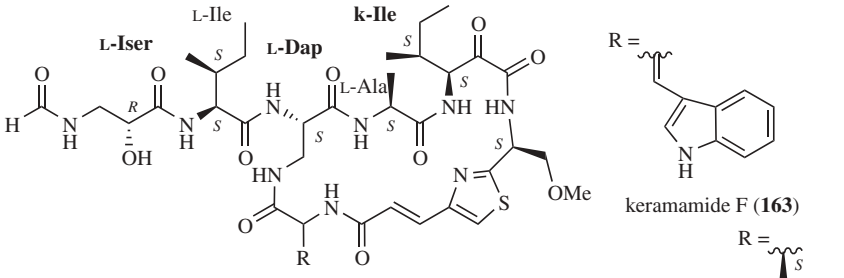
keramamides B-D:



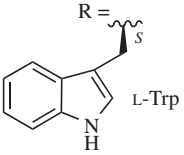
keramamide B (**159**): R^1 = Et, R^2 = Et
keramamide C (**160**): R^1 = Et, R^2 = Me
keramamide D (**161**): R^1 = Me, R^2 = Me



orbiculamide A (**162**):
R^1 = Me, R^2 = Me

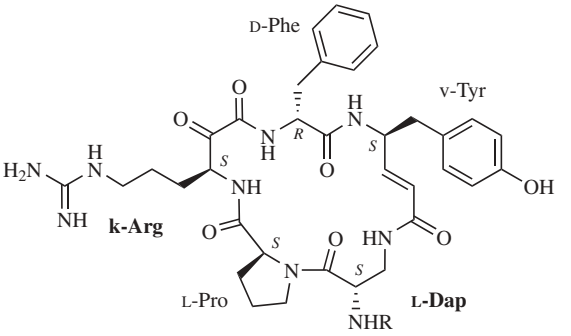


keramamide F (**163**)



keramamide J (**164**)

Figure 2.33 Selected keramamides and orbiculamide.



cyclotheonamide A (**165**): R = CHO cyclotheonamide B (**166**): R = Ac

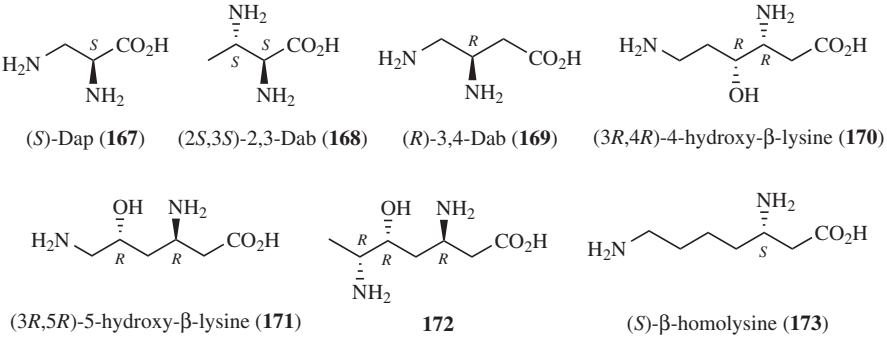
Figure 2.34 Selected cyclotheonamides.

2.5.2 Cyclotheonamides

The cyclotheonamides A (**165**) and B (**166**),[254,255] cyclic pentapeptides isolated from a marine sponge of the genus *Theonella*,[255] are potent inhibitors of serine proteases, including thrombin and trypsin, which play an important role in blood coagulation and fibrinogenolysis (Fig. 2.34). Because of their antithrombotic activity and unusual structure, including an α-keto-homoarginine (**158**) moiety, considerable attention has been given to the mode of action[256–258] of **165** and the total synthesis of cyclotheonamides A,[259] B,[254,260] and E2–E3[261] and of analogs.[262] Since the detection of the cyclotheonamides A and B in 1990,[255] several more representatives, for example, the cyclotheonamides C–E,[263] E2–E3,[264] and E4–E5,[265] have been isolated. Crystal structures of the complex between cyclotheonamide A and thrombin revealed that the α-keto group of **158** binds at the active site of the enzyme and forms a covalent C–O bond to the Ser 195 residue belonging to the catalytic triad. The resulting tetrahedral hemiacetal mimics the transition state of protein hydrolysis and inhibits the protease.[256]

2.6 NATURAL PRODUCTS CONTAINING AMINO-β-AMINO ACIDS (EXCEPT β-LYSINE)

Unusual aliphatic β-amino acids with more than one amino group are present in highly active natural products such as the bleomycins (Fig. 2.35). In several cases, they also serve as a branching point in peptides with lariat structures, for example, in the keramamides F (**163**) and J (**164**). Representatives of this class of β-amino acids can be divided in 2,3- and 3,4-diamino acids and in β-amino acids structurally related to β-lysine (**3**) and β-homolysine (**173**).



(*S*)-Dap (**167**) (2*S*,3*S*)-2,3-Dab (**168**) (*R*)-3,4-Dab (**169**) (3*R*,4*R*)-4-hydroxy-β-lysine (**170**)

(3*R*,5*R*)-5-hydroxy-β-lysine (**171**) **172** (*S*)-β-homolysine (**173**)

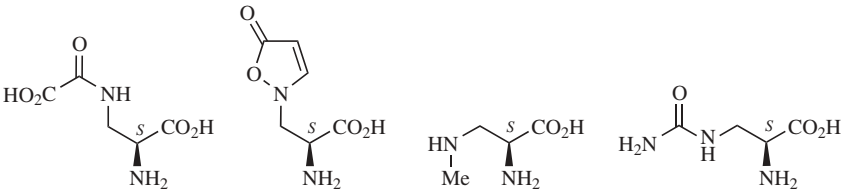
Figure 2.35 Unusual β-amino acids with two or more amino groups.

2.6.1 Diaminopropanoic Acid and Diaminobutanoic Acids

Diaminopropanoic acid (Dap, **167**)—reviewed in 1995 [266]—and 2,3-diaminobutanoic acid (2,3-Dab, **168**) have been found in free form and as derivatives such as β-ODAP (**174**) in several plants.[25,267] 2,3-Dab occurs in nature in the form of different isomers; for example, in the roots of *Lotus tenuis* both the (2*R*,3*S*) and the (2*S*,3*S*) isomer are present.[268] (*S*)-Dap (**167**) is a constituent of the bleomycins (**178–179**), capreomycins (see Section 2.7.2), cephalosporins (**182**), cyclotheonamides (see Section 2.5.2), edeines (see Section 2.2.6.5), some keramamides (see Section 2.5.1), penicillins (**181**), tuberactinomycins (see Section 2.7.2), and viomycin (see Section 2.7.2). 2,3-Dab (**168**) is present in the aciculitins A–C (**183–185**), papuamides A–B (**186–187**), and quinaldopeptin (**188**). Emeriamin (**190**) and emericedin (**189**) are derivatives of (*R*)-3,4-diaminobutanoic acid (**169**).

2.6.1.1 N^{β}-Oxalyl-L-diaminopropionic acid and Other L-Diaminopropionic Acid Derivatives

N^{β}-Oxalyl-L-diaminopropionic acid (β-ODAP, **174**) is present in the leaves and seeds of legumes, including *Lathyrus latifolius*, *L. sativus*, and several other *Lathyrus*, *Lens*, and *Pisum* species. β-ODAP shows neuroexcitotoxic properties in humans and is assumed to cause the disease neurolathyrism[9,269] (Fig. 2.36). Lathyrism is a neurone disease occurring in some



L-β-ODAP (**174**) L-BIA (**175**) L-BMAA (**176**) L-albizziine (**177**)

Figure 2.36 β-ODAP, its biosynthetic precursor, and some other Dap derivatives.

African and Asian countries that affects the lower limbs of the patients after prolonged consumption of *L. sativus* seeds. The ecological role of β-ODAP seems to be the protection of plants and seeds against predators, since it serves as feeding deterrent and phagostimulant in *Spodoptora littoralis* larvae.[270] In *L. sativus*, β-ODAP is biosynthetically derived from *O*-acetyl-L-serine and isoxazolin-5-one via β-(isoxazolin-5-on-2-yl)-L-alanine (BIA, **175**)[271] that is finally N-acylated with oxalyl-CoA. A variety of other heterocyclic β-substituted alanines such as (*S*)-mimosine and (*S*)-willardiine isolated from several plant sources originate from *O*-acetyl-L-serine.[272]

Free (*S*)-Dap (**167**) itself, present in plants, including *Acacia* species,[273] and the glutamate agonist N^{β}-methyl-L-diaminopropionic acid (BMAA, **176**), from *Cycas circinalis*, cause neurotoxic disorders.[274,275] The Dap derivative albizziine (**177**), however, which is present in *Acacia* species, has not been linked to neurotoxicity.[273]

2.6.1.2 Bleomycins The bleomycins are glycopeptide antibiotics isolated from *Streptomyces verticillus* in 1966[276] (Fig. 2.37). Their structures and absolute stereochemistry were determined in the following decade[277] and have been confirmed by total syntheses.[15,278–280] Besides closely related compounds such as phleomycin D_1 (**180**),[277,281] tallysomycin $S_{10}B$,[282] and bleomycin B_2 (**179**), especially bleomycin A_2 (**178**) has gained widespread interest, since it possesses outstanding antitumor activity.[283] It is already used as the main component of a drug for the treatment of Hodgkin lymphoma[284] and carcinomas of the skin, head, and neck.[15] The biological activity of **178** is based on a sequence-specific binding and subsequent fragmentation of DNA.[285] A variety of analogs have been synthesized and the mode of action of the different molecule parts has been rationalized.[15] The bleomycins possess a metal-binding domain that includes the Dap moiety.[15] Therefore, bleomycins are capable of forming a complex with Fe^{2+} ions that activates molecular oxygen and generates hydroperoxide radicals that initiate the cleavage of the DNA by abstraction of a hydrogen radical at C-4′ of the ribose.[285] Also the biosynthesis of bleomycin has been studied in detail. The cloning and characterization of the bleomycin gene cluster from *S. verticillus* ATCC15003 show that the (*S*)-Dap (**167**) moiety is derived from L-serine.[286]

2.6.1.3 Penicillins and Cephalosporins Since the detection of the outstanding antibiotic activity of the penicillins by Fleming in 1929,[287] their structure elucidation in the following 20 years,[288] and their first application for the treatment against a variety of infections in the 1940s, the β-lactams, also including the cephalosporins, have become the most important class of antibiotics[16] (Fig. 2.38). Nowadays they constitute approximately 60% of all clinically used antibiotics.[289] The cephalosporins and penicillins originally isolated from culture filtrates of fungi such as *Acremonium chrysogenum* and *Penicillium* species, respectively, were soon chemically modified and the natural penicillin G (**181**), the most important penicillin, is produced biotechnologically by feeding

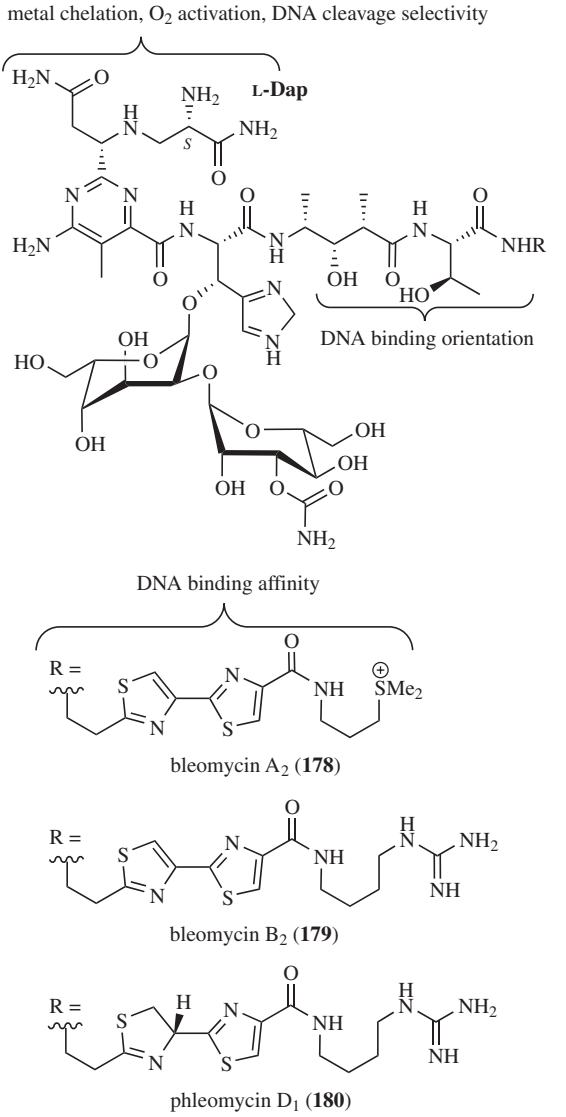
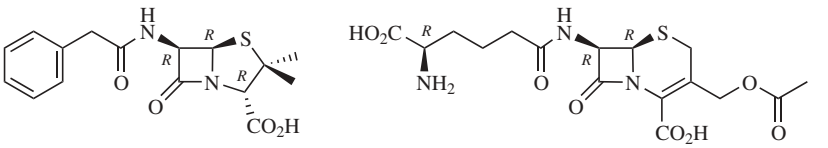


Figure 2.37 Bleomycins and analogs.



penicillin G (**181**) cephalosporin C (**182**)

Figure 2.38 Selected β-lactam antibiotics.

phenylacetic acid to the fermentation cultures to improve the yield.[290] The antibacterial activity of the β-lactam antibiotics is caused by an irreversible inhibition of a key enzyme of the bacterial cell wall synthesis.[291,292] The β-lactam antibiotics prevent the crosslinking of peptide residues on the bacterial peptidoglycan cell wall, since they inhibit the glycopeptide transpeptidase. They are reactive transition-state analogs that acylate a serine residue within the active site of the bacterial transpeptidase.[289] Due to the occurrence of resistant bacterial strains that possess β-lactamases[293] and are therefore able to inactivate β-lactam antibiotics[294] by hydrolytic ring opening, the development of new types of synthetic β-lactam antibiotics to overcome these problems remains a challange.[16] The biosynthesis of the penicillins involves the formation of the tripeptide δ-(D-α-aminoadipyl)-L-cysteinyl-D-valine from D-α-adipinic acid, L-Cys, and L-Val.[30] Therefore, (*S*)-Dap (**167**) does not occur directly as a building block in penicillin biosynthesis.

2.6.1.4 Aciculitins A–C The aciculitins A–C (**183**–**185**) are bicyclic glycopeptides isolated from the lithistid marine sponge *Aciculites orientalis*[295] (Fig. 2.39). The aciculitins A–C exhibit cytotoxicity against the human-colon tumor cell line HCT-116 (IC_{50} 0.5 mg/mL) and inhibit the growth of *C. albicans*.

2.6.1.5 Papuamides A–B The papuamides A (**186**) and B (**187**) are cyclic depsipeptides isolated from Papua New Guinea collections of the marine sponges *Theonella mirabilis* and *T. swinhoei*[296] (Fig. 2.40). The papuamides A and B inhibit the infection of human T-lymphoblastoid cells by HIV-1_{RF} in vitro (EC_{50} 3.6 ng/mL). Papuamide A also exhibits cytotoxicity against a variety of human cancer cell lines (mean IC_{50} 75 ng/mL).

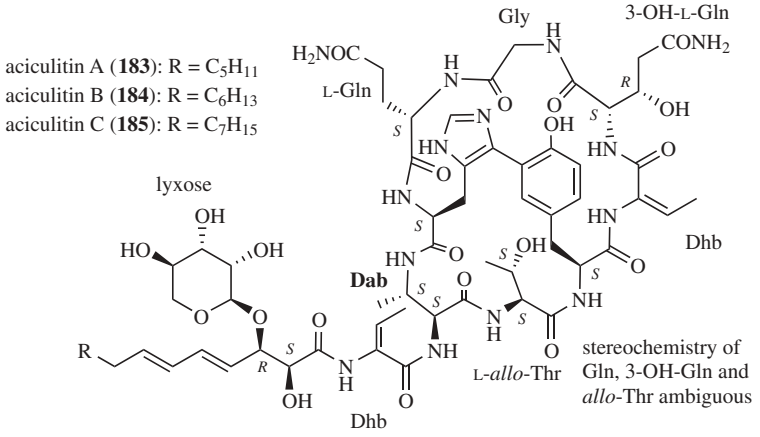


Figure 2.39 Aciculitins.

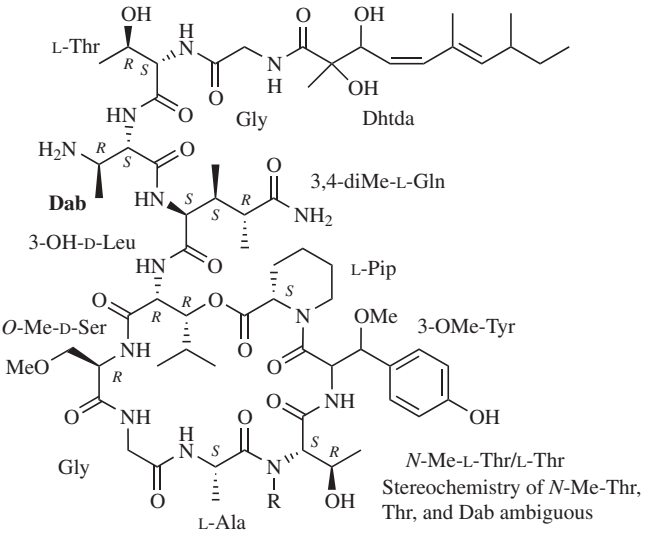


Figure 2.40 Papuamides.

2.6.1.6 Quinaldopeptin Quinaldopeptin (**188**),[297] a cyclopeptide closely related to the DNA-binding antitumor antibiotic sandramycin,[298,299] has been isolated from cultures of *Streptoverticillium album* Q132-6[297] and from an actinomycete strain A499[300] (Fig. 2.41). Quinaldopeptin exhibits strong antimicrobial activity against gram-positive bacteria and anaerobes and strong cytotoxicity against murine melanoma B16-F10 (IC_{50} 0.8 ng/mL). However, in an in vivo experiment with mice transplanted with P-388 leukemia, **188** showed only moderate activity.[297]

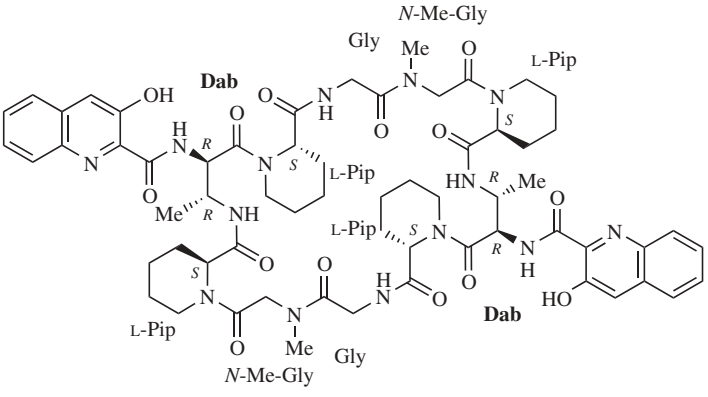


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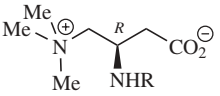
Figure 2.41 Quinaldopeptin.



emericedin (**189**): R = Ac
emeriamine (**190**): R = H

Figure 2.42 Emericedin and emeriamine.

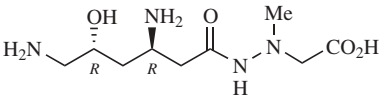
2.6.1.7 Emeriamine and Emericedin Emericedin (**189**) is a betaine that has been isolated from a culture filtrate of the fungus *Emericella quadrilineata* IFO 5859.[301] The desacetyl derivative of emericedin, emeriamine (**190**), is a strong and specific inhibitor of the carnitine-dependent oxidation of long-chain fatty acylcarnitines and triacylglycerols by inhibition of carnitine palmitoyltransferase-2 (IC_{50} 0.8 μM) in rat liver mitochondria (Fig. 2.42). In rats, intraperitoneal (i.p.) injected emeriamine causes severe metabolic disorders, for example, hypothermia ($33.9 \pm 0.5°C$), probably due to an inhibition of β-oxidation.[302]

2.6.2 β-Amino Acids Related to β-Lysine and β-Homolysine

(3*R*,4*R*)-4-Hydroxy-β-lysine (**170**) occurs in the tuberactinomycins A and N (see Section 2.7.2), (3*R*,5*R*)-5-hydroxy-β-lysine (**171**) in negamycin (**191**) and the sperabillins A (**192**) and C (**194**), (*S*)-β-homoarginine in TAN-1057 A–D (**196**–**197**), (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoic acid (**172**) in sperabillins B (**193**) and D (**195**), and (*S*)-β-homolysine (**173**) in resormycin.

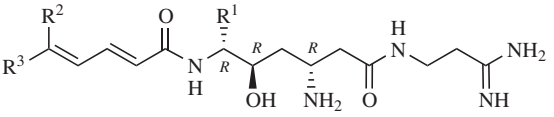
2.6.2.1 Negamycin Negamycin (**191**) is an unusual hydrazido dipeptide[303] that was first isolated in 1970 from bacteria closely related to *Streptomyces purpeofuscus*.[304] Its structure[303] has been confirmed by several total syntheses[305] (Fig. 2.43). Negamycin exhibits activity against multiple drug-resistant bacteria[304] by inhibition of the procaryotic protein biosynthesis with miscoding activity.[306]

2.6.2.2 Sperabillins A–D The sperabillins A–D (**192**–**195**) are antibiotics that have been isolated from cultures of the gram-negative bacterium *Pseudomonas fluorescens* YK-437.[307] Their structures[308] have been confirmed by total syntheses[309,310] (Fig. 2.44). They are effective against several gram-negative and gram-positive bacteria, including antibiotic-resistant strains of *S. aureus* and *Pseudomonas aeruginosa.* Pretreatment of mice with sperabillin A showed protective effects against *S. aureus* 308-A (ED_{50} 1.3 mg/kg) and *Serratia*



191

Figure 2.43 Negamycin.

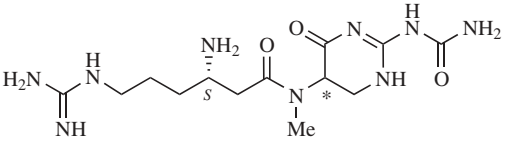


sperabillin A (**192**): R^1 = H, R^2 = Me, R^3 = H sperabillin B (**193**): R^1 = Me, R^2 = Me, R^3 = H
sperabillin C (**194**): R^1 = H, R^2 = H, R^3 = Me sperabillin D (**195**): R^1 = Me, R^2 = H, R^3 = Me

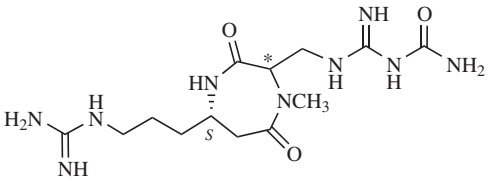
Figure 2.44 Sperabillins.

marcescens TN66 at a dose of 2 mg/kg. In *E. coli*, **192** did not show a selective target activity, since it inhibited DNA, RNA, protein, and cell wall biosynthesis.[307]

2.6.2.3 TAN-1057A–D TAN-1057 A/B (**196**) is a dihydropyridinone peptide that has been isolated from *Flexibacter* sp. PK-74.[311] The structure elucidation of the natural product that was termed TAN-1057 A/B revealed that it was a mixture of two epimers[312] (Fig. 2.45). The strain *Flexibacter* sp. PK-176 produces additionally to TAN-1057 A/B also TAN-1057 C/D (**197**).[312] TAN-1057A/B has attracted considerable interest as a new lead structure; several total syntheses of TAN-1057A/B[313,314] and analogs[315,316] have been published, since it shows strong antibacterial activity against methicillin-resistant strains of *S. aureus* in infected mice (*S. aureus* N133A: ED_{50} 0.026 mg/kg).[311] Vancomycin turned out to be less active in the same infection model (*S. aureus* N133A: ED_{50} 2.3 mg/kg). The activity of TAN-1057 has been linked to an inhibition of the protein biosynthesis after the formation of aminoacyl-tRNA.[311] The toxicological profile of TAN-1057 could be improved by exchange of guanidino-β-lysine with (*S*)-β-Lys or (*S*)-β-homolysine.[316]

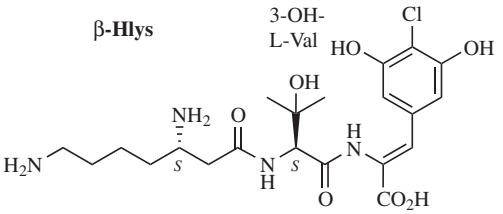


TAN-1057 A (**196a**): * = *S* TAN-1057 B (**196b**): * = *R*



TAN-1057 C (**197a**): * = *R* TAN-1057 D (**197b**): * = *S*

Figure 2.45 TAN-1057 A–D.



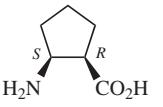
198

Figure 2.46 Resormycin.

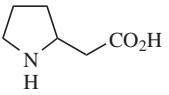
2.6.2.4 Resormycin Resormycin (**198**) is a tripeptide isolated from *Streptomyces platensis* MJ953-SF5.[317] Its structure and its absolute stereochemistry have been confirmed by X-ray analysis[318] (Fig. 2.46). It exhibits herbicidal and antifungal activity, especially against monocotyledoneous and dicotyledoneous weeds and phytopathogenic fungi; for example, the growth of lettuce (*Lactuca sativa*) seedlings treated with resormycin at concentrations of 6.25 ppm was completely inhibited.[317] Interestingly, the activity of **198** was much stronger against the unicellular green alga *Selenastrum capricornutum* ATCC22662 in the dark (IC_{50} 2 ng/mL) than in the light (IC_{50} 0.1–0.3 μg/mL), suggesting an inhibition of a biological process not involved in photosynthesis.[319]

2.7 ALICYCLIC AND HETEROCYCLIC β-AMINO ACIDS

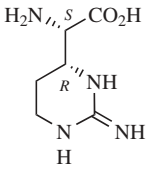
Cyclic β-amino acids are not very common in nature. However, some examples such as cispentacin (**199**) that occurs in amipurimycin (**204**) as well as in free form, 2-pyrrolidinylacetic acid (**200**), (2*S*,3*R*)-capreomycidine (**201**), and streptolidine (**202**) are known (Fig. 2.47). 2-Pyrrolidinylacetic acid (**200**) has been isolated from



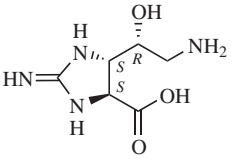
cispentacin (**199**)



2-pyrrolidinylacetic acid (**200**)



(2*S*,3*R*)-capreomycidine (**201**)



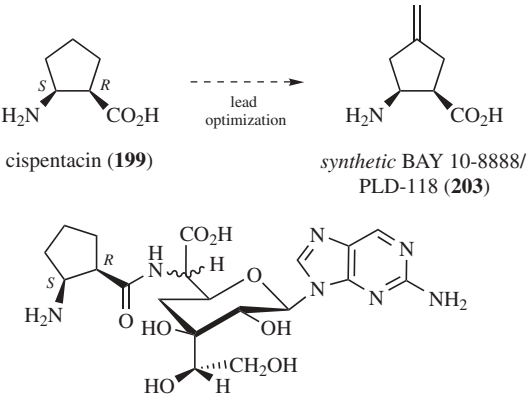
streptolidine (**202**)

Figure 2.47 Alicyclic and heterocyclic β-amino acids.

plants such as *Nicotiana tabacum*[320] and *Arnica* sp., *Tussilago farfara*, *Neurolaena lobata*, *Melampodium divaricatum*, and *Eupatorium semialatum*.[321] Capreomycidine (**201**)[322] is a cyclic guanidino amino acid occurring as a constituent of the capreomycins (**211**–**214**) and the closely related compounds LL-BM547α (**209**), LL-BM547β (**210**), the tuberactinomycins (**205**–**208**), and viomycin (**206**), while streptolidine (**202**) is present in the streptothricins (see Section 2.2.3.2).

2.7.1 (1*R*,2*S*)-2-Aminocyclopentanecarboxylic Acid (Cispentacin) and Amipurimycin

Cispentacin (**199**)[323] (FR109615[324]) has been found in its free form in *Bacillus cereus* L450-B2[323] and *Streptomyces setonii* 7562.[324] The structure of cispentacin was confirmed by X-ray analysis[325] and several total syntheses[326,327] (Fig. 2.48). Cispentacin shows antifungal activity in vitro and in vivo. It demonstrated good therapeutic efficacy against systemic *C. albicans* (i.v.: PD_{50} 10 mg/kg) and *C. neoformans* infections in mice pretreated with cispentacin 4 days before infection.[328] The mode of action is due to an active transport of cispentacin via proline and other amino acid permeases into the fungal cells.[329] After concentrative uptake in the fungal cells, it inhibits the prolyl-tRNA synthetase and, therefore, the protein biosynthesis.[330] The anti-*Candida* activity of cispentacin leads to a high interest in the structural optimization of this lead structure[326] that aimed at derivatives with superior (oral) efficacy and good tolerability for the treatment of yeast infections. This lead optimization yielded the synthetic methylene derivative BAY 10-8888 (**203**), which is currently being investigated in phase II clinical studies.[331] Interestingly, the additional methylene group of BAY 10-8888 caused a dual target shift. Here, the isoleucyl-tRNA is specifically inhibited, the active transport into the cells is carried out by permeases specific for branched-chain α-amino acids (e.g., L-Ile).[332]



cispentacin (**199**)

synthetic BAY 10-8888/ PLD-118 (**203**)

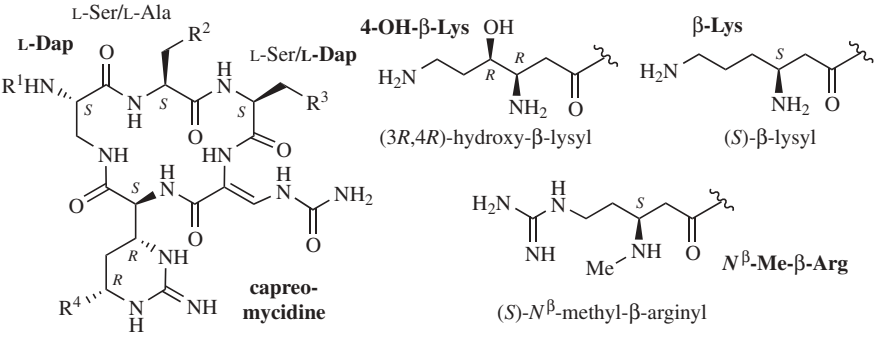
amipurimycin (**204**)

Figure 2.48 Cispentacin and amipurimycin.

Cispentacin is also a constituent of the nucleoside antibiotic amipurimycin (**204**)[333] that has been isolated from *Streptomyces novoguineensis* T-36496.[334,335] Partial structures of **204** have been synthesized.[336] Amipurimycin is strongly active both in vivo and in vitro against *P. oryzae*, the organism that causes rice blast disease. In field tests, it showed considerable curative effects on leaf blast at concentrations from 10 to 20 ppm.[334]

2.7.2 Capreomycins, LL-BM547α and LL-BM547β, Tuberactinomycins, and Viomycin

The capreomycins,[337] the tuberactinomycins,[338] and LL-BM547α and β[339] are tuberculostatic cyclic peptide antibiotics that are structurally closely related to each other (Fig. 2.49). However, the capreomycins IA (**211**), IB (**212**), IIA (**213**), and IIB (**214**) have been isolated from *Streptomyces capreolus*,[337] while the tuberactinomycins A (**205**),[338] B (viomcyin, **206**[340]), N (**207**),[341] and O (**208**)[342] have been isolated from *Streptomyces griseoverticillatus* var. *tuberacticus*,[338] and LL-BM547α (**209**) and β (**210**) from the *Nocardia* sp. Lederle culture BM547.[339] The structures of the tuberactinomycins[343] and viomycin[344] were established by X-ray analysis; however, first proposals for the structures of the capreomycins[345] were corrected in 1976, when the first total synthesis of capreomycins IA and IB



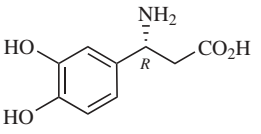
tuberactinomycin A (**205**): R^1 = (3*R*,4*R*)-hydroxy-β-lysyl, R^2 = OH, R^3 = OH, R^4 = OH
tuberactinomycin B (viomycin, **206**): R^1 = (*S*)-β-lysyl, R^2 = OH, R^3 = OH, R^4 = OH
tuberactinomycin N (**207**): R^1 = (3*R*,4*R*)-hydroxy-β-lysyl, R^2 = OH, R^3 = OH, R^4 = H
tuberactinomycin O (**208**): R^1 = (*S*)-β-lysyl, R^2 = OH, R^3 = OH, R^4 = H
LL-BM547α (**209**): R^1 = H, R^2 = OH, R^3 = OH, R^4 = OH
LL-BM547β (**210**): R^1 = (*S*)-N^{β}-methyl-β-arginyl, R^2 = OH, R^3 = OH, R^4 = OH
capreomycin IA (**211**): R^1 = H, R^2 = OH, R^3 = NH-[(*S*)-β-lysyl], R^4 = H
capreomycin IB (**212**): R^1 = H, R^2 = H, R^3 = NH-[(*S*)-β-lysyl], R^4 = H
capreomycin IIA (**213**): R^1 = H, R^2 = OH, R^3 = NH_2, R^4 = H
capreomycin IIB (**214**): R^1 = H, R^2 = H, R^3 = NH_2, R^4 = H

Figure 2.49 Capreomycins and related natural products.

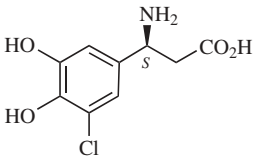
was completed.[346] Due to their strong antituberculostatic activity, several total syntheses of capreomycins[347] and tuberactinomycins[348] and syntheses of a variety of analogs[349] have been performed. Their activity is caused by an inhibition of the prokaryotic protein biosynthesis. Both the translocation of the peptidyl-tRNA and the dissociation of the ribosomal subunits are inhibited and misreading is induced.[350,351] Nowadays, the capreomycins and tuberactinomycins are used specifically for the treatment of multidrug-resistant tuberculosis infections in which therapy with other drugs has failed,[352] since they exhibit ototoxic[341] and nephrotoxic side effects. Recently, they have also become of interest as lead structures for the treatment of other bacterial infections caused by vancomycin- and methicillin-resistant strains of *S. aureus*.[349] Their biosynthesis is well investigated, and the gene cluster of viomycin from *Streptomyces* sp. ATCC11861 has been isolated, sequenced, and analyzed.[353,354] The (2*S*,3*R*)-capreomycidine (**201**) moiety is biosynthetically derived from arginine via an oxidative cyclization,[355] while (*S*)-Dap (**167**) is derived from L-serine [356], and (*S*)-β-Lys from L-lysine.[357]

2.8 NATURAL PRODUCTS CONTAINING UNUSUAL AROMATIC β-AMINO ACIDS

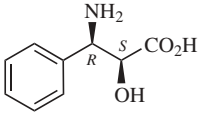
While aromatic β-amino acids such as β-Dopa (**215**) and 3-phenylisoserine (**217**) are in general biosynthetically derived from β-Tyr (**8**) or β-Phe (**7**), most of the aromatic β-amino acids with a longer side chain are probably of polyketidic origin with an aromatic carboxylic acid as starter unit (Fig. 2.50).



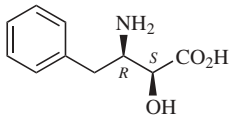
(*R*)-β-Dopa (**215**)



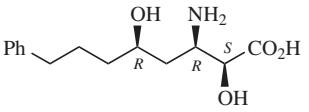
(*S*)-3-chloro-β-Dopa (**216**)



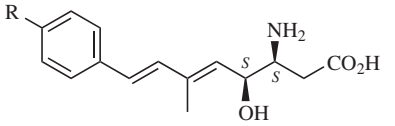
(2*S*,3*R*)-3-phenyl-isoserine (**217**)



(2*S*,3*R*)-Ahpa (**218**)

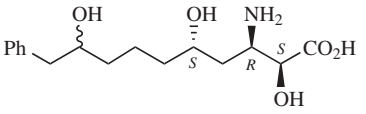


Ahoa (**219**)

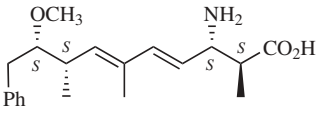


Apoa (Ahmp, **220**): R = H Aboa (**221**): R = Br

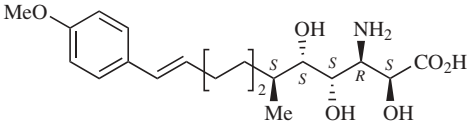
Figure 2.50 Unusual aromatic β-amino acids.



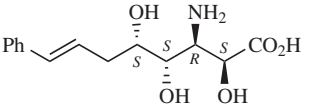
Ahda (**222**)



Adda (**223**)



Ammtd (**224**)



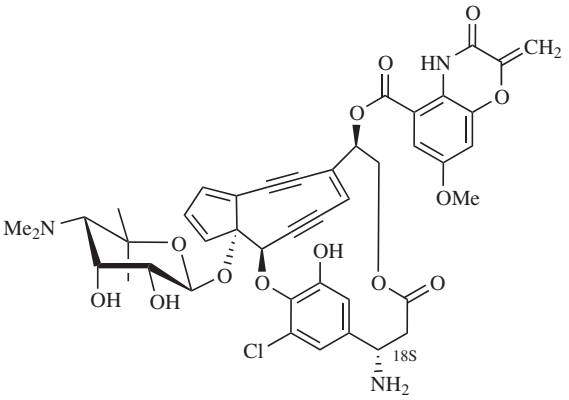
Apto (**225**)

Figure 2.50 (*Continued*).

2.8.1 Unusual Aromatic β-Amino Acids Biosynthetically Derived from Proteinogenic Amino Acids [β-Dopa, 3-Chloro-β-dopa, (2*S*,3*R*)-Phenylisoserine]

(*R*)-β-Dopa (**215**) has been found in free form in the basidiomycete *Cortinarius violaceus*.[29] It is also present in this mushroom in the form of an Fe(III) catechol complex (cortiferrin) that is responsible for its dark blue color. In *C. violaceus* (*R*)-β-Dopa is biosynthetically derived from (*R*)-β-Tyr that is generated from L-tyrosine via a tyrosine 2,3-aminomutase.[27] (*S*)-β-Dopa (**216**) is a constituent of the plant alkaloid chaenorhine (**52**) isolated from the Veronicaceae *Chaenorhinum minus* (see Section 2.2.6.2). (*S*)-3-Chloro-β-Dopa (**216**) is a constituent of C-1027 (**226**) and (2*S*,3*R*)-phenylisoserine (**217**) is present in taxol (**227**).

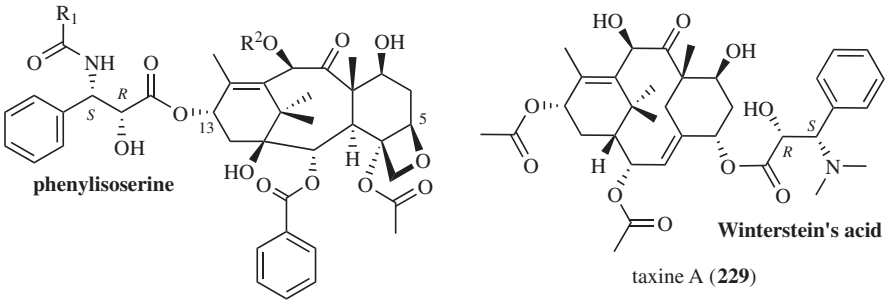
2.8.1.1 C-1027 The macromolecular antibiotic C-1027 has been isolated[358] from cultures[359] of the actinomycete *Streptomyces globisporus* C-1027. C-1027 consists of an acidic protein with a molecular weight of 15000 Da[358] and a labile chromophore **226** consisting of a highly strained nine-membered enediyne ring that is clamped by a (*S*)-3-chloro-β-Dopa (**216**) moiety[360] (Fig. 2.51). The antibiotic is highly active against a variety of human cancer cell lines such as A549 lung carcinoma (IC_{50} 1.5×10^{-17} M).[361] It also showed a strong activity against tumors such as L1210 and P-388 leukemia and hepatoma H22 transplanted in mice.[361] Unfortunately, however, its antitumor activity is correlated with a strong cytotoxicity that prevents the application of C-1027 in humans. The labile chromophore, essential for the activity of C-1027, acts as a DNA-cleaving toxophore via a Bergman-type reaction pathway.[362] Recent investigations of the C-1027 biosynthesis gene cluster[363] demonstrate that the (*S*)-3-chloro-β-Dopa (**216**) moiety is derived from L-tyrosine via (*S*)-β-Tyr (**8**).[364]



226

Figure 2.51 Chromophore of C-1027.

2.8.1.2 Taxol (Paclitaxel) Taxol (paclitaxel, **227**) was isolated from the stem bark of the western yew, *T. brevifolia*. Its structure was elucidated in 1971 to be a terpenoid with a phenylisoserine side chain[365] (Fig. 2.52). Interestingly, taxol is also produced in traces by *Taxomyces andreanae*, an the endophytic fungus isolated from the phloem of *T. brevifolia*.[366] Related compounds such as taxine A (**229**)[367] have been isolated from the European yew, *T. baccata*. Taxol showed promising antitumor activity against human cancer cell lines.[365] However, strong interest in this drug did not begin to develop until 1979, when it was recognized that taxol (**227**) promotes tubulin polymerization by binding and stabilization of assembled microtubuli.[368,369] This new mechanism of action stalls dividing cells in the G2-M phase.[369] By the early 1990s, it was detected that patients in phase II clinical trials with metastatic ovarian[370] and breast cancer showed significant responses to taxol.[371] Nowadays, taxol and its derivative taxotere (**228**)—both semisynthetically prepared from 10-deacetylbaccatin III[14,372]—belong to the most important anticancer drugs, while other congeners (e.g., BAY 59-8862/IDN 5109) are still in



taxol (paclitaxel, **227**): R^1 = Ph, R^2 = Ac
semisynthetic taxotere (docetaxel, **228**): R^1 = O*t*-Bu, R^2 = H

Figure 2.52 Taxol and related compounds.

the phase of clinical and preclinical trials.[373] The replacement of the benzoyl moiety at the phenylisoserine side chain by a Boc group improves the solubility. However, the presence of an α-hydroxy-β-amino acid side chain is essential for the microtubuli-stabilizing activity,[13,374] according to conformation studies with microtubuli-bound taxol.[375] Multistep total syntheses of taxol[376–379] as well as studies of its biosynthesis[380] by feeding experiments[381] and by isolation of taxol genes[382] have been published. In *T. brevifolia*, the phenylisoserine moiety is generated from L-phenylalanine via (*R*)-β-Phe by a 2,3-aminomutase.[383]

2.8.2 Polyketide-Type Aromatic β-Amino Acids

Most of the polyketide-type aromatic β-amino acids are not widespread in natural products. (2*S*,3*R*)-3-Amino-2-hydroxyphenylbutanoic acid (Ahpa, **218**) is a constituent of bestatin (**230**), phebestin (**231**), and probestin (**232**); (2*S*,3*R*,5*R*)-3-amino-2,5-dihydroxy-8-phenyloctanoic acid (Ahoa, **219**) is present in nostophycin (**233**); while (3*S*,4*S*,5*E*,7*E*)-3-amino-4-hydroxy-6-methyl-8-phenylocta-5,7-dienoic acid (Apoa/Ahmp, **220**) and its *p*-bromophenyl derivative (3*S*,4*S*,5*E*,7*E*)-3-amino-4-hydroxy-6-methyl-8-(4-bromophenyl)octa-5,7-dienoic acid (Aboa, **221**) occur in theonegramide, the theonellamides (**234–239**), and theonepalauamide. (2*S*,3*R*,5*S*)-3-Amino-2,5,9-trihydroxy-10-phenyldecanoic acid (Ahda, **222**) was found in scytonemin A (**240**), and (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,8-dimethyl-10-phenyldeca-4,6-dienoic acid (Adda, **223**) in the microcystins (**244–245**), motuporin (**241**), and the nodularins (**242–243**). A variety of aromatic 3-amino-2,4,5-trihydroxy acids—for example, (2*S*,3*R*,4*S*,5*S*,6*S*,11*E*)-3-amino-6-methyl-12-(*p*-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid (Ammtd, **224**) and (2*S*,3*R*,4*S*,5*S*, 7*E*)-3-amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid (Apto, **225**)—are known to be constituents of the microsclerodermins (**246–252**).

2.8.2.1 Bestatin, Phebestin, and Probestin Bestatin (ubenimex, **230**) is a dipeptide consisting of (2*S*,3*R*)-Ahpa and L-leucine which was first isolated from *Streptomyces olivoreticuli* in 1976.[384] Its structure has been confirmed by total syntheses[385] (Fig. 2.53), and numerous analogs have also been synthesized,[386] since bestatin acts as a potent inhibitor of several but not all aminopeptidases; for example, it inhibits competitively aminopeptidase B (IC_{50} 0.05 μg/mL) and leucine aminopeptidase.[387] Related compounds are probestin (**232**),[388] an inhibitor of aminopeptidase M[389] isolated from *Streptomyces azureus* MH-633-2F6,[389] and phebestin (**231**),[390] an inhibitor of aminopeptidase N isolated from *Streptomyces* sp. MJ716-m3.[390] The establishment of the X-ray structure of a complex of bestatin (**230**) with leucine aminopeptidase gave insights in the reaction mechanism of this important enzyme class. Bestatin binds at the active site of the enzyme with its β-amino group. The hydroxyl group is coordinated to a zinc ion similar to a tetrahedral intermediate that is formed during protein hydrolysis.[391] In accordance with that result, SAR studies on the inhibition effect of bestatin (**230**) and a variety of synthetic analogs to aminopeptidase B revealed that the β-amino acid only tolerates some modifications without a strong loss of activity.[386] The 2S

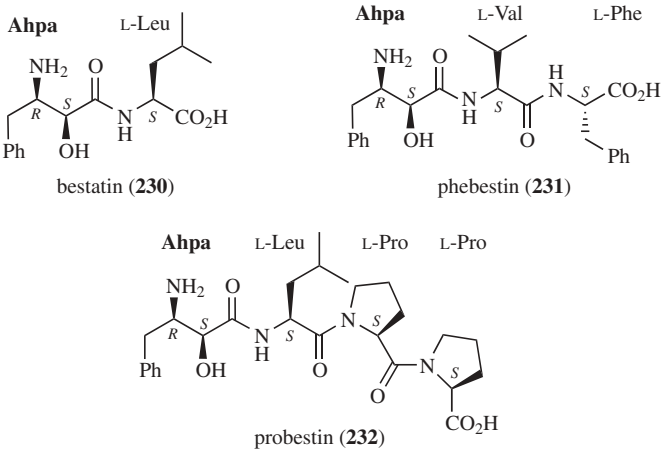


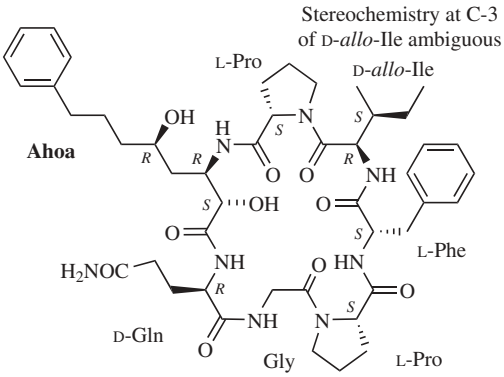
Figure 2.53 Bestatin and related natural products.

stereochemistry at the hydroxylated α-carbon and the presence of a benzyl residue is essential, while the stereochemistry of the β-amino group is not equally important.

Besides its role as a valuable tool to study the reaction mechanism of peptidases,[392,393] **230** serves as an important drug, since it retards the growth of tumors and has a low toxicity.[394] Therefore, bestatin is already used as a supplement to other drugs in the treatment of acute nonlymphocytic leukemia in adults.[395] The anticancer activity of bestatin is probably linked to its ability to inhibit leukotriene A_4 hydrolase, a potent inflammatory mediator. If this enzyme is overexpressed, inflammation-associated carcinogenesis is induced. In the case of esophageal adenocarcinoma, it has been demonstrated in a rat model that overexpression of leukotriene A_4 hydrolase and the tumor size can be reduced by treatment with bestatin.[396]

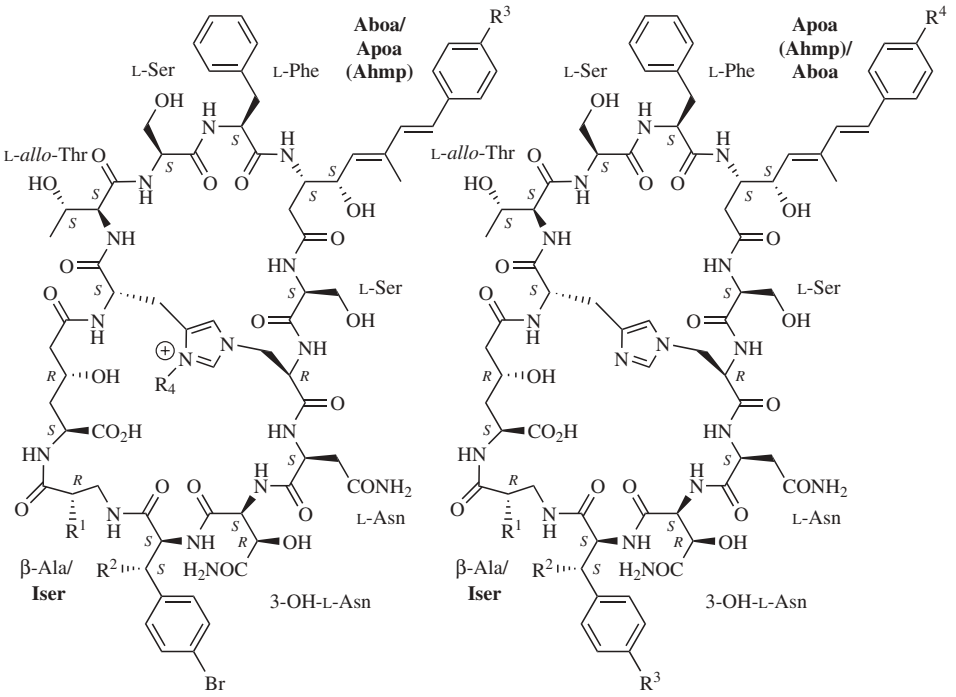
2.8.2.2 Nostophycin Nostophycin (**233**) is a cyclic heptapeptide isolated from the cyanobacterium *Nostoc* sp. strain 152[397] that also produces the toxic microcystins (**244**–**245**). However, nostophycin, although structurally related to the microcystins (Fig. 2.54), exhibited no activity against several bacteria and fungi and only weak cytotoxicity against lymphocytic mouse leukemia L1210 cells (40% growth inhibition at 10 μg/mL).[397]

2.8.2.3 Theonegramide, Theonellamides, and Theopalauamide The theonellamides A–E (**234**–**238**)[398] and F (**239**)[399] and theonegramide[400] are bicyclic dodecapeptides that have been isolated from a marine sponge *Theonella* species (Fig. 2.55). Theopalauamide was isolated from *T. swinhoei*.[401] Theonegramide only differs from theonellamide A with respect to its D-arabinose sugar moiety and its 2-aminoadipinic acid residue instead of 2-amino-4-hydroxyadipinic acid.[400] Theopalauamide is identical with theonegramide except



233

Figure 2.54 Nostophycin.



th. = theonellamide

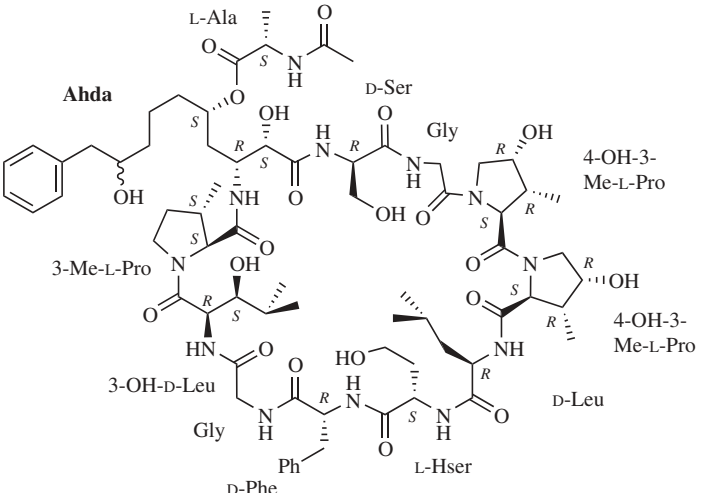
th. A (**234**): R^1 = OH, R^2 = Me, R^3 = H, R^4 = β-D-Gal
th. D (**235**): R^1 = H, R^2 = H, R^3 = Br, R^4 = β-D-Ara
th. E (**236**): R^1 = H, R^2 = H, R^3 = Br, R^4 = β-D-Gal
th. C (**237**): R^1 = OH, R^2 = Me, R^3 = Br, R^4 = H
th. C (**238**): R^1 = H, R^2 = H, R^3 = H, R^4 = Br
th. F (**239**): R^1 = H, R^2 = H, R^3 = Br, R^4 = Br

Figure 2.55 Theonellamides.

it possesses a β-D-galactose moiety.[401] The theonellamides A–F, theogramide, and theopalauamide exhibit moderate antifungal activity (IC_{50} 3–12 μg/mL), for example, against *Candida* ssp. and *Aspergillus* ssp. The theonellamides A–F are moderately active against P-388 murine leukemia cells (IC_{50} 0.9–5.0 μg/mL).[398,399] Theonellamide F (**239**) interacts with glutamate dehydrogenase and 17β-hydroxysteroid dehydrogenase IV from rabbit liver tissues.[402] It also induces the formation of large vacuoles in 3Y1 cells.[403]

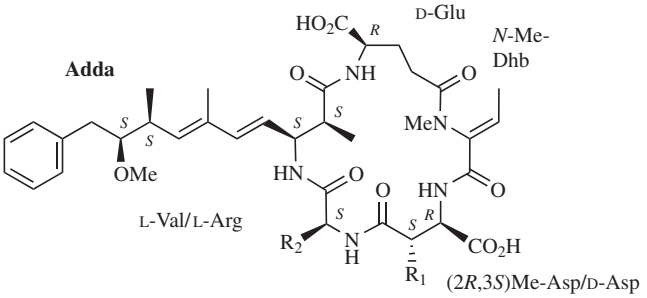
2.8.2.4 Scytonemin A Scytonemin A (**240**) isolated from the cultured terrestrial cyanobacterium *Scytonema* sp. U-3-3 is a cyclopeptide which possesses calcium antagonist properties[404] (Fig. 2.56). On atria, scytonemin A showed calcium antagonistic effects at 5 μg/mL, on rat portal vein at 20 μg/mL. It is also mildly cytotoxic against CCRF-CEM (IC_{50} 2.9 μg/mL) and weakly active against a broad spectrum of bacteria and fungi.[404]

2.8.2.5 Microcystins (Cyanoginosins) Nodularins and Motuporin The microcystins (**244**–**245**) are a class of cyclic heptapeptides all containing the β-amino acid Adda[7,405] (Fig. 2.57). They have been isolated from the freshwater cyanobacteria genera *Microcystis*, *Oscillatoria*, *Anabaena*, and *Nostoc*. The nodularins (**241**–**243**),[405,406] cyclic pentapeptides isolated from the cyanobacterium *Nodularia spumigena*, and motuporin (nodularin V, **241**),[407] isolated from the marine sponge *T. swinhoei*, are closely related to the microcystins. This observation suggests that cyanobacteria which are associated with *Theonella* are the real producers of motuporin. Moreover, it is therefore highly likely that marine sponges in general serve as hosts for the real (cyano)bacterial



240

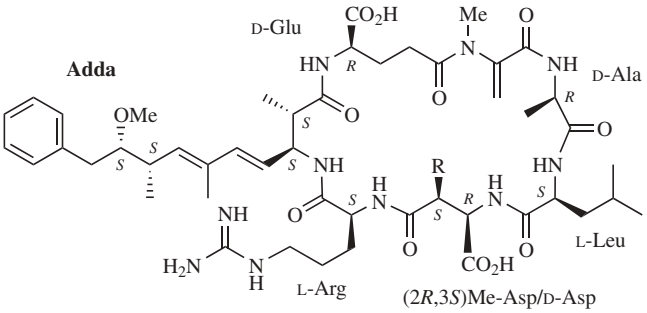
Figure 2.56 Scytonemin A.



motuporin (**241**): R^1 = Me, R^2 = *i*-Pr

nodularin (**242**): R^1 = Me, R^2 =

[D-Asp^1]nodularin (**243**): R^1 = H, R^2 =



microcystin-LR (**244**): R = Me

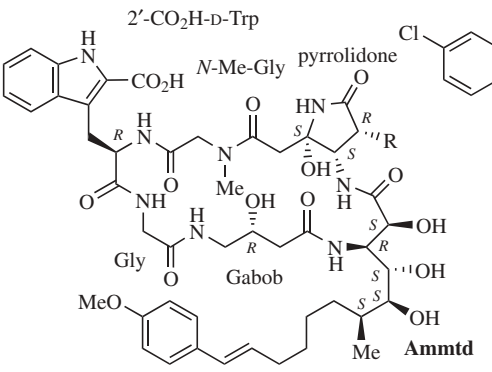
[D-Asp^3]microcystin-LR (**245**): R = H

Figure 2.57 Selected microcystins and nodularins.

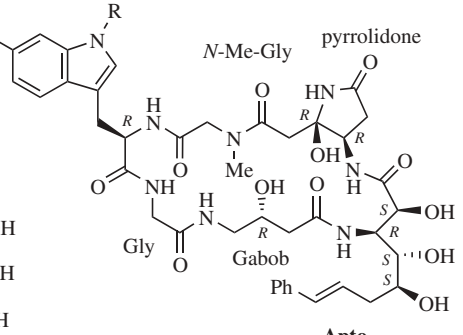
producers. Since sponges of the genus *Theonella* contain a variety of secondary metabolites, Faulkner called them "star performers or hosts to the stars."[21] Attempts to clarify the structure of the microcystins have been ongoing for decades[408] before the structure of cyanoginosin-LA (microcystin-LA) was elucidated, mainly by two-dimensional NMR and FABMS.[409] The absolute configuration of Adda (**223**)[410] and the structures of microcystin-LA[411] and motuporin[412] have been confirmed by total synthesis. The microcystins as well as the nodularins and motuporin exhibit strong hepatoxicity (mice i.p.: LD_{50} 50–100 μg/kg) inducing death in both animals and humans.[7,8] Their acute toxicity is caused by an active transport of the toxins into the hepatocytes and an inhibition of protein phosphatases 1 (PP-1) and 2A (IC_{50} 0.2 nM), first by initial binding of Adda, Glu, and Me-Asp to the enzyme and later by covalent bond formation between a cysteine residue of the phosphatase and the *N*-methyldehydroalanine moiety of microcystins,[7,413] as shown by X-ray analysis of a complex of the catalytic subunit of PP-1 with microcystin-LR (**244**).[414] Chronic ingestion of sublethal doses of microcystins and nodularins has been linked to the development of

primary liver cancer in mice.[7] Also, the biosynthesis of the microcystins has been investigated.[405] Recently, the biosynthetic gene cluster from *M. aeruginosa* PCC7806 has been isolated and characterized, suggesting a polyketide origin for Adda (**223**) and an assembly of the peptide via nonribosomal peptide synthases.[33]

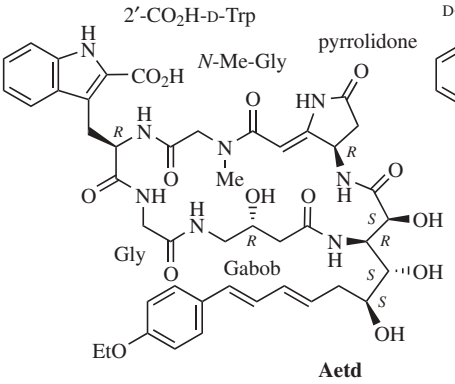
2.8.2.6 Microsclerodermins The microsclerodermins A–B (**246**–**247**),[415] C–E (**248**–**250**),[416] and F–I[417] are cyclic hexapeptides isolated from marine sponges of the order Lithistida (Porifera), a *Theonella* species, and a *Microscleroderma* species from the Philippines and Palau (Fig. 2.58). Recently, the structure of microsclerodermin E (**250**) was confirmed by a total synthesis.[418] A large variety of different ω-aryl-3-amino-2,4,5-trihydroxy acids, such as Ammtd (**224**) and Apto (**225**), have been found in the microsclerodermins. They show activity against *C. albicans* (**251**: 1.5 μg per disk) and exhibit cytotoxicity against HCT-116 cells (**251**: IC_{50} 1.8 μg/mL).[417]



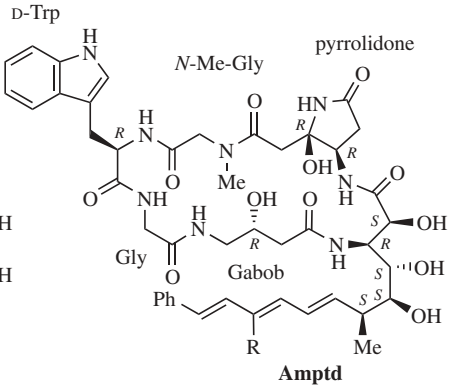
microsclerodermin A (**246**): R = OH
microsclerodermin B (**247**): R = H



microsclerodermin C (**248**): R = $CONH_2$
microsclerodermin D (**249**): R = H



microsclerodermin E (**250**)



microsclerodermin F (**251**): R = H
microsclerodermin H (**252**): R = Me

Figure 2.58 Microsclerodermins.

2.9 CONCLUSIONS AND FUTURE PROSPECTS

Several of the most prominent and most potent natural products known today, such as the bleomycins (**178–179**) or the penicillins (**181**), contain a β-amino acid moiety (see Table 2.1). Most of these bioactive natural products have been isolated from bacteria and cyanobacteria; however, the cephalosporins (**182**) and penicillins are produced by fungi and taxol (**227**) is of plant origin.

The majority of active natural products with a β-amino acid moiety are cyclopeptides, cyclodepsipeptides, glucopeptides, or peptides. However, bestatin (**230**) and TAN1057A/B (**196**) are dipeptides, while cispentacin (**199**) and β-ODAP (**174**) consist of a single amino acid only, indicating that selective bioactivity is not always restricted to complex structures. Investigation of SARs of several highly active compounds has revealed the crucial role of the β-amino acid moiety for their activity (Table 2.1), either as a direct part of the pharmacophore/toxophore or as a building block important for the distinctive activity-inducing structure of the natural product. Accordingly, in most cases, the presence of a free β-amino acid is not sufficient for activity.

Some general trends may be deduced from information presented in this review:

- β-Amino acids alone can generally interfere with natural α-amino acid processing systems (e.g., active transport, protein biosynthesis), as has been demonstrated for cispentacin and analogs (see Section 2.7.1).
- A β-amino-α-hydroxy acid residue or a β-amino-α-keto acid moiety can mimic a peptide bond in the transition state and thus acts as a peptidase inhibitor, as shown for amastatin, microginin, the cyclotheonamides, bestatin, and the microcystins (see Sections 2.4.1, 2.5.2, 2.8.2.1, and 2.8.2.5). It is probably no accident that many β-amino acids occurring in ancient organisms like cyanobacteria possess an α-hydroxy, γ-hydroxy, α-keto, or additional α-amino group, since these compounds might have evolved together with enzymes, for example, as ancient enzyme regulators. Since proteases are often highly conserved, there is a high probability that these natural products can interact with mammalian enzymes. Meanwhile, the activity of natural β-amino-α-hydroxy acids has stimulated the synthesis of artificial analogs to generate more effective synthetic protein inhibitors.[392,419]
- β-Amino acids with an additional amino group can serve several distinct purposes. Therefore, (*S*)-diaminopropanoic acid [(*S*)-Dap, **167**] occurs in many highly active compounds. In the penicillins and cephalosporins it is part of the pharmacophore, the β-lactam moiety (see Section 2.6.1.3); in the bleomycins it serves as metal chelator (see Section 2.6.1.2); in the capreomycidins (**211–214**) it is a branching point and (*S*)-Dap (**167**) itself and derivatives therof cause lathyrism (see Section 2.6.1.1).

In comparison with small molecules, complex structures tend to be more specific, since they often have the ability to bind and interact with the target molecule in a multivalent fashion and/or a multistep process, as shown for

TABLE 2.1 Properties of Selected Active Natural Products with β-Amino Acid Moiety

Compound	Natural Source	Activity	β-Amino Acid	Importance of β-Amino Acid for Activity
Taxol (terpenoid)	*Taxus brevifolia* (P)	Antitumor (cl. use)	Phenylisoserine	Very important
Penicillins/cephalosporins (β-lactam)	*Penicillium notatum* (F)	Antibacterial (cl. use)	Dap	Very important
Bleomycins (glycopeptide)	*Streptomyces verticillus* (B)	Antitumor (cl. use)	Dap	Important
Bestatin (peptide)	*Streptomyces olivoreticuli* (B)	Antitumor (cl. use)	Ahpa	Very important
Capreomycins/tuberactinomycins (CP)	*Streptomyces* sp. (B)	Antituberulostatic (cl. use)	Cap/Dap	Important (both)
Cryptophycins (CP)	*Nostoc* sp. (CB)	Antitumor (cl. phase II)	Aib	Important
Dolastatins (CP)	*Lyngbya majuscula* (CB)	Antitumor (cl. phase II)	Amba, Map, etc.	Unknown
TAN 1057 (peptide)	*Flexibacter* sp. (B)	Antibacterial against MDR	Guanidino-β-Lys	Important
Cispentacin (β-amino acid)	*Bacillus cereus* (B)	Antifungal	Cispentacin	Very important
Iturins (CP)	*Bacillus subtilis* (B)	Antifungal	Long-chain β-AA	Important
β-ODAP (β-amino acid)	*Lathyrus*, *Lens*, and *Pisum* sp. (P)	Highly toxic (lathyrism)	Dap	Very important
Microcystins/nodularins (CP)	*Microcystis*, *Nodularia* sp. (CB)	Highly toxic/cancerogenic	Adda	Very important

Abbreviations: CP, cyclopeptide; P, plants; F, fungi; B, bacteria; CB, cyanobacteria; cl, clinical; MDR, multidrug-resistant strains; Cap, capreomycidine.

bleomycin A_2 (see Section 2.6.1.2). Apart from high pharmacokinetic obstacles, this could be especially of importance for the development of antitumor active drugs, since the insufficient ability to target selectively only certain tumors but not healthy cells is one of the most serious problems that is still not well resolved. The reason for the lack of selective antitumor active natural compounds might be explained by considering that microorganisms have certainly not developed systematically specific antitumor agents, contrary to the development of fungicides, herbicides, insecticides, and bactericides for their defence, since procaryotes, as single-cell organisms, cannot develop cancer. Nevertheless, several lead structures from bacteria and cyanobacteria exhibit antitumor activity (Table 2.1).

At present, representatives of β-amino acid natural products such as taxol (**227**) play a crucial role in the treatment of human cancer and infectious diseases. Nevertheless, only a very limited number of drugs for effective anticancer cure are available. In addition, the rise of new diseases, such as acquired immunodeficiency syndrome (AIDS), and the growing number of antibiotic-resistant pathogens will increase the demand for new lead structures from nature.

Apart from the classical lead structure optimization by chemical synthesis, biochemical engineering might also be effective in the future, especially in the case of peptides and depsipeptides, since they are generated by nonribosomal peptide synthases, which are ideal targets for genetic engineering. Efforts to generate such ''nonnatural natural products'' have already led to the first encouraging results. By these means, it would be possible to generate biochemically new β-amino acids of polyketide origin.[32]

However, in comparison to artificially designed compound libraries, natural products have the inherent advantage that the optimization process has already been undergone during evolution.[3] Therefore, natural products often preserve ''privileged structures'' that fit to distinct protein-binding sites.[420] The example of the previously unknown variety of polyketidic β-amino acids from marine cyanobacteria teaches us that the most promising sources for new lead structures are still organisms obtained from natural habitats, such as protista or marine fungi, which have been poorly investigated.

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CHAPTER 3

Preparation of Enantiopure β-Amino Acids by Homologation of α-Amino Acids

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3.1 INTRODUCTION

α-Amino acids are ideal starting materials for the preparation of β-amino acids. This is due not only to the fact that a plethora of methods for their synthesis is available[1] but also to the stereogenic center present in these compounds that, on utilization of suitable methods, is retained without significant racemization in the homologated β-amino acids. Few methods are available for a homologation of α-amino acids, each having its special benefits. While hydrocyanation of α-amino aldehydes with subsequent hydrolysis of the cyano group leads to α-hydroxy-β-amino acids, α-nonsubstituted β-amino acids are available through an Arndt–Eistert homologation sequence.[2] Both methods are covered in this review, though the latter is discussed with much more detail since this approach is one of the most sucessful for the preparation of β-amino acids.

3.2 ARNDT–EISTERT HOMOLOGATION

3.2.1 Introduction

In the late 1920s Arndt, Eistert, and Partale developed a method for the homologation of carboxylic acids.[3] In this sequence an activated carboxylic acid (e.g., a carboxylic acid chloride) is reacted with diazomethane, forming a diazoketone.

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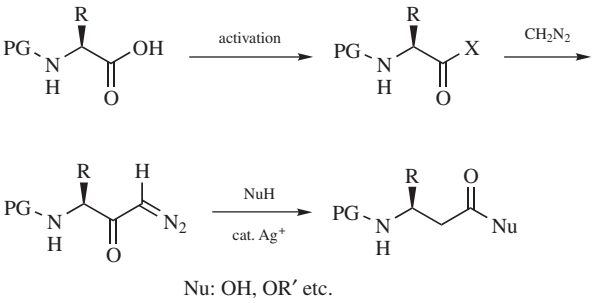
Upon photolysis, thermolysis, or treatment with catalytic amounts of silver cations in the presence of protic nucleophiles, a Wolff rearrangement[2b,4] with loss of nitrogen (N_2) leads to substrates elongated (homologated) by one CH_2 unit. Then in 1947 Balenović adapted this method for the formation of β-amino acids.[5a] Since no sophisticated activating methods for amino acids were available at that time, Balenović used activation with thionyl chloride, which increased the need for a robust protecting group with which a racemization of the substrates was avoided. Phthaloyl protection fulfilled these requirements, and between 1947 and 1959 Balenovic and co-workers tested virtually all proteinogenic amino acids with these reaction conditions.[5]

A breaktrough came with the development of milder activation methods and more suitable protecting groups for the amino function. Activation with dicyclohexyl carbodiimide or, better, via the mixed anhydride was compatible with the Arndt–Eistert sequence,[6] and amino acids protected as carbamates could be used as starting materials with good results (Scheme 3.1).



Scheme 3.1 Arndt–Eistert homologation sequence with amino acids.

3.2.2 Formation of Diazoketones

Though phthaloyl-protected amino acids can be subjected to the Arndt–Eistert protocol, carbamate-protected amino acids are used more conveniently, among them the most popular Boc-, Z-, or Fmoc-protected substrates. No interference of these protecting groups with the employed reaction conditions has been observed at any stage, and other carbamate-derived protecting groups should be similarly applicable. Activation via the acid chlorides is not recommended since this would lead to considerable racemization of most substrates (except proline). Most convenient is activation via the mixed anhydrides by reaction with triethylamine and ethyl chlorocarbonate (or *N*-methylmorpholine and isobutyl chlorocarbonate). Application of the dicyclohexylcarbodiimide (DCC) method is possible, though laborious separation of the side product dicyclohexylurea has been reported with this method.[6] Further activation methods have been reported and might be useful in special cases, for example, activation with *tert*-butyl pyrocarbonate (Boc_2O)[7] or toluenesulfonyl chloride[8] or utilization of the pentafluorophenylesters.[9]

The activated amino acid is used as acylating agent for diazomethane, which is conveniently prepared as an ethereal solution starting with, for example, *N*-methyl-*N*-nitrosotoluenesulfonamide. Nevertheless, with this method traces of water are present in the ethereal solution which lead to a partial hydrolysis of the activated amino acid.[10] Consequently varying amounts of the amino acid methyl ester are isolated as side products. Unfortunately, the corresponding trimethylsilyl-substituted diazomethane (TMS–CHN_2), which can be purchased as a water-free solution and is occasionally used as a stubstitute for diazomethane, is not sufficiently reactive for formation of the amino acid–derived diazoketone.[11] The only exception is proline, which due to its low tendency to racemize can be actived as the most reactive acid chloride, being reactive enough for acylation of trimethylsilyl diazomethane.[12] The methyl ester, which is the only side product in this reaction, is conveniently removed by chromatography on silicagel (the methyl ester is eluted first) or, if the substrate is solid, by recrystallization.

Most amino acids are more or less prone to racemization during activation, though this process is significantly supressed with the usually employed carbamate-protected amino acids. Nevertheless, this method finds its limitations when the extremely racemization-prone phenylglycine is used. Sophisticated investigations showed that with no activation method racemization could be significantly supressed, resulting in material with an enantiomeric excess of about 90%.[13]

Synthesis of α-Amino Acid–Derived Diazoketones: General Procedure.[4] A suitably N-protected amino acid (20 mmol) was dissolved in tetrahydrofuran (THF) under N_2 and cooled to 0°C. To this was added Et_3N (20 mmol) and $ClCO_2Et$ (20 mmol) with stirring, whereupon a white solid (Et_3NHCl) precipitated. Stirring was stopped and a ~0.5 M solution of CH_2N_2 in Et_2O was added (60 mL). (*Caution*: Carefully read safety instructions in Ref. 14). Further 40 mL of the solution was added after 30 min to achieve complete conversion (occasional short stirring might be useful). After 2 h excess CH_2N_2 was destroyed by addition of 0.5 N acetic acid and stirring for 20 min. The reaction mixture was extracted with $NaHCO_3$ solution (3×100 mL) and with brine (100 mL), dried ($MgSO_4$), and evaporated to dryness (40°C, 200 mbar). Purification was achieved with crystallization or chromatography (SiO_2).

3.2.3 Arndt–Eistert Homologation of Amino Acid Derivatives

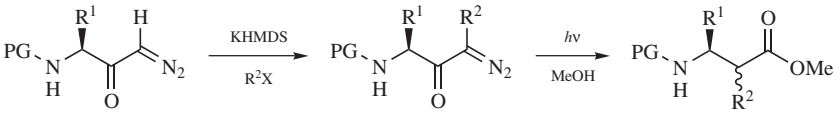
Rearrangement of diazoketones with loss of nitrogen (the Wolff rearrangement) is most conveniently achieved with catalytic amounts of silver cations, though photochemical or thermal conditions can be employed similarly.[4] The silver-catalyzed rearrangement—due to mechanistic studies an electron transfer process—is performed in an excess of the trapping nucleophil. About three equivalents of triethylamine are needed in this reaction, which might be a drawback in certain cases (c.f. p. 96). While silver benzoate or silver acetate[15] is preferred as a catalyst in the formation of esters (the catalyst can be removed during the subsequent

extraction process), silver trifluoroacetate turned out to be favorable in the formation of the homologated amino acids. Here the catalyst is removed simply by evaporation in vacuo. Though water and alcohols are most frequently used, the utilization of almost any protic nucleophile is possible with this protocol (c.f. p. 98). Steric hindrance in the nucleophile employed seems to be of minor significance; even *tert*-butanol has been used in the preparation of the respective esters with reasonable yields.[16]

While it is essential to use thoroughly purified diazoketone in the formation of amino esters (the amino methyl ester formed as side product with the diazoketone is hardly removable afterward), crude material can be employed during the formation of homologated amino acids. In the latter case, the methyl ester is simply removed during the washing procedure.

A slightly modified protocol has been developed for the homologation of Fmoc-protected amino acids in which the exposition time with basic conditions (Et_3N/silver salt) is significantly reduced by actively warming the solution to 0°C and quenching the solution with acid immediately after the rearrangement is complete.[17] Ultrasonication[18] and microwave[19] irradiation seem to be useful alternatives; the addition of triethyl amine proved to be redundant with this physical activation.

Rearrangement of C-1-alkylated diazoketones has been investigated repeatedly. It was found that silver catalysis at ambient temperatures does not give satisfying results, while either elevated temperatures or, better, photolytic reaction conditions lead to reasonable yields of the respective homologated α-substituted amino acid derivatives.[20] This gives further evidence for the proposed reaction mechanism of the silver-induced reaction in which deprotonation of the C-1 hydrogen is postulated what is obviously not possible for the C-1-alkylated species. A new stereogenic center is formed with this variation; selectivities ranged from 1 : 1 to >10 : 1 in favor of the anti product (Scheme 3.2).[20b] α-Alkyl-α′-diazoketones, precurors in this reaction, were readily prepared from the corresponding α-amino acids via anionic alkylation with potassium hexamethyldisilazide (KHMDS)/alkyl halide.[20b]



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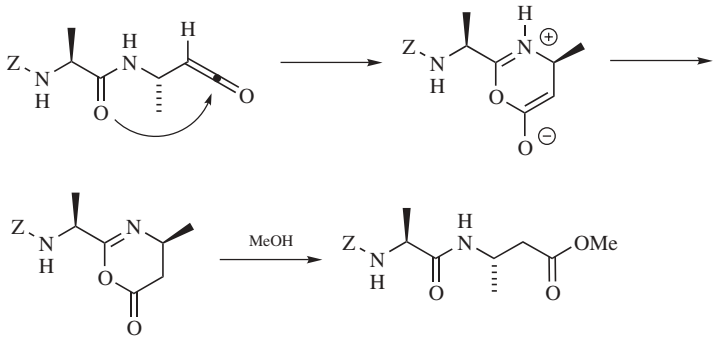
Scheme 3.2 Rearrangement of C-1-alkylated diazoketones.[20b]

It has been shown that ketenes formed intermediately from dipeptide-derived diazoketones stabilize in the absence of suitable nucleophiles by formation of stable cyclic intermediates. These 4,5-dihydro-1,3-oxazin-6-ones were identified by nuclear magnetic resonance (NMR) spectroscopy and are stable for several hours. Subsequent trapping with methanol leads to homologated substrates (Scheme 3.3).[13]



Scheme 3.3 Stabilization of acylaminoalkyl-substituted ketenes and subsequent trapping with nucleophiles.[13]

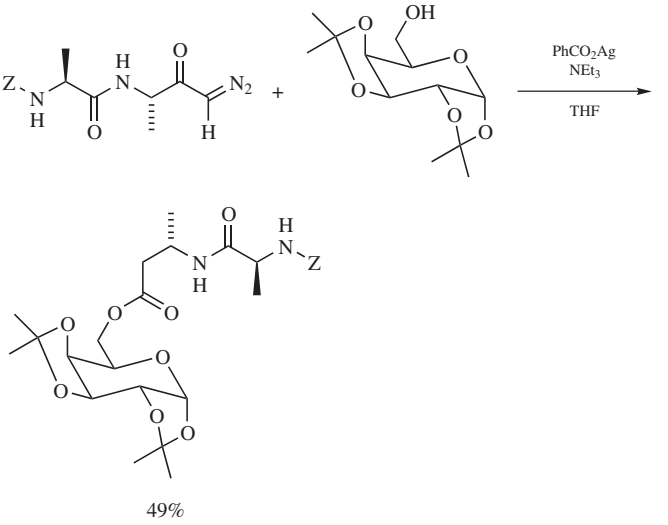
α-Alkylation of α-Amino Acid–Derived Diazoketones: General Procedure.[20b] A solution of KHMDS (2 eq.), hexamethyl phosphoric triamide (HMPA) (33% v/v), and alkyl halide (10 eq.) in THF was prepared and cooled to −78°C. A solution of the α-amino acid–derived diazoketone in THF at −78°C was then transferred dropwise to this solution. The reaction was stirred for 30 min and then a second portion of KHMDS (2 eq.) was added. The reaction proceeded for another 30 min and was then quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3 ×) and the combined organic layers were washed with water (2 ×) and brine (1 ×), dried ($MgSO_4$), and evaporated to dryness. The resulting mixture was purified using column chromatography (20% ethyl acetate, 80% heptane).

Synthesis of β-Amino Acids: General Procedure.[14] Under N_2 and with exclusion of light (e.g., by shielding with a towel), the diazoketone (20 mmol) was dissolved in THF (100 mL). Water (10 mL) was added and the flask was cooled to 25°C. Silver trifluoroacetate (4 mmol) dissolved in Et_3N (90 mmol) was added and the solution was allowed to warm to room temperature overnight. The solvents were removed with a rotary evaporator and the residue was stirred for 1 h with saturated aqueous $NaHCO_3$ solution (25 mL). The mixture was transferred into a 250-mL separatory funnel with H_2O (40 mL) and AcOEt (50 mL). The aqueous layer was separated and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (4 × 30 mL). The combined aqueous layers were washed with AcOEt (50 mL) and the organic layer was additionally reextracted with saturated aqueous $NaHCO_3$ solution (2 × 25 mL). The combined aqueous layers were washed with AcOEt (50 mL) and the organic layer was reextracted with saturated aqueous $NaHCO_3$ solution (2 × 20 mL). Congo red indicator and AcOEt (25 mL) were added to the cooled (0°C) combined aqueous layers. Then 6 N HCl was added dropwise with stirring until the color of the indicator changed from red to blue. The

organic layers were separated in a separatory funnel and the aqueous layer was additionally extracted with AcOEt (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness (finally high vacuum to remove F_3CCO_2H). Most protected β-amino acids solidify upon standing in the refrigerator and can be recrystallized (Et_2O/light petroleum).

Synthesis of β-Amino Carboxylic Esters: General Procedure.[21] The diazoketone was dissolved in MeOH (0.25 M) under N_2 at −25°C with exclusion of light (e.g., by shielding with a towel). After addition of silver benzoate (0.11 eq.) dissolved in Et_3N (2.9 eq.), the mixture was allowed to warm to room temperature within 3 h. The solvent was removed at reduced pressure and the residue was taken up in AcOEt. After workup by extraction with saturated solutions of $NaHCO_3$, NH_4Cl, and brine, the solution was dried ($MgSO_4$) and the solvents were removed in vacuo. Pure material was obtained after chromatography (SiO_2) or recrystallization.

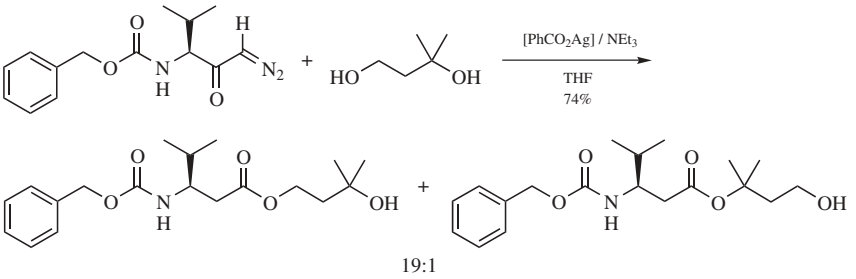
Not only water or alcohols have been used as nucleophiles in the formation of homologated amino acid derivatives but also amino esters,[13] peptides,[13] sugar,[21,22] nucleotide,[22] and nucleoside derivates (Scheme 3.4).[22] Rearrangement in the



Scheme 3.4 Sugar derivatives as nucleophiles in the Wolff rearrangement.[21]

presence of *N*,*O*-dimethylhydroxylamine proved to be a very convenient method for the preparation of the respective Weinreb hydroxamic acids, which can be further reduced to the corresponding β-amino aldehydes.[23]

Though ketenes are very reactive intermediates and thus might be expected to be nonselective acylating agents, selectivities are astonishingly high in competitive trapping experiments.[22,24] Using 2-methyl-butan-2,4-diol, a preferential

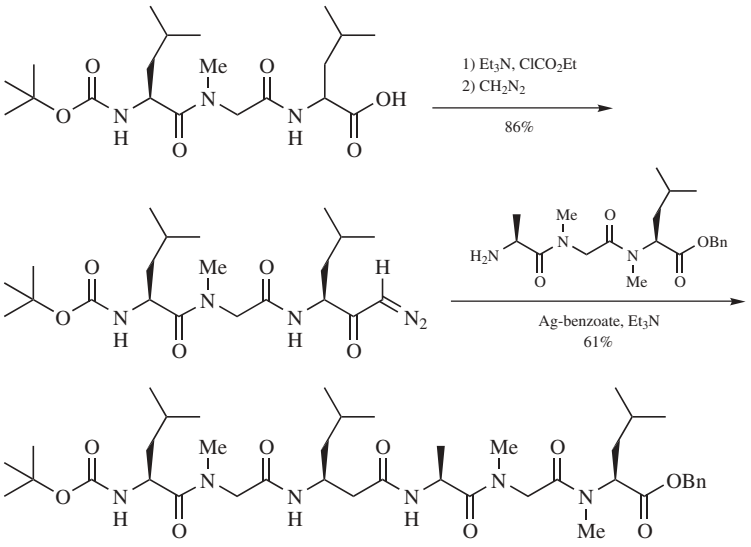


Scheme 3.5 Selective acylation of nucleophiles.[22]

acylation of the primary hydroxy function is observed with a selectivity of 19 : 1 (Scheme 3.5). With 2-aminoethanol an exclusive formation of the respective amide is achieved.[22]

3.2.4 Homologation of Substrates Other Than Parent Amino Acids

Though yields occasionally drop drastically when peptidic substrates are utilized, some examples have been published.[25] Z-protected alanyl-alanine, for example, is transferred into the corresponding diazoketone with a 33% yield. This is rearranged in the presence of methanol resulting the homologated methyl ester derivative. Performing the Wolff rearrangement of peptidic diazoketones in the presence of peptidic nucleophiles gives rise to oligopeptides bearing a β-amino acid in an inner position of the peptide strand (Scheme 3.6).[13]

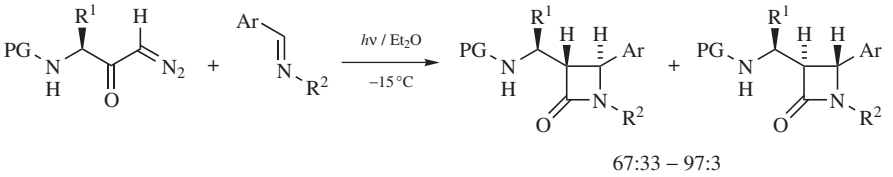


Scheme 3.6 Utilization of peptidic substrates in Arndt–Eistert homologation.[13]

The homologation of *N*-alkylated amino acids can be sucessfully applied not only to cyclic substrates like proline, homopipecolic acid, or serine-derived oxazolidine-4-carboxylic acids but also to *N*-methylated substrates, as has been shown by Seebach et al.[21,26]

3.3 HOMOLOGATION OF AMINO ACIDS WITH CONCOMITANT β-LACTAM FORMATION

The intermediacy of ketenes during the Wolff rearrangement has been utilized for a β-lactam synthesis by trapping these highly reactive carboxylic acid derivatives with imines. This reaction—named after its inventor Staudinger—is usually performed with ketenes generated from carboxylic acid chlorides but is here combined with homologation of amino acids. Imines complex silver salts and thus render them ineffective as catalysts in the Wolff rearrangement. Consequently the β-lactam formation has to be initialized with photochemical or thermal reaction conditions. Thus aminoalkyl-substituted β-lactams with a trans configuration are formed with yields usually exceeding 70% (Scheme 3.7).[27]

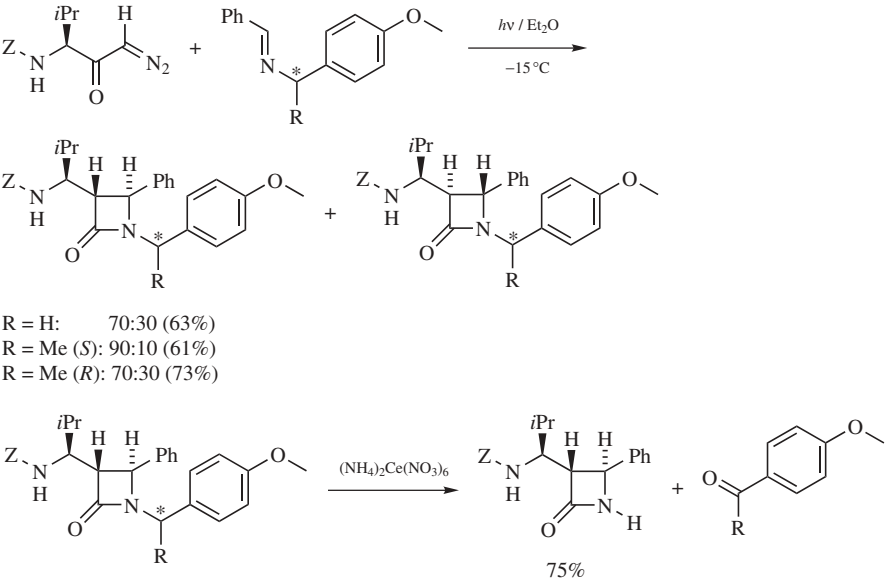


Scheme 3.7 β-Lactam formation starting with amino acid–derived diazoketones.

Selectivities in this reaction are exclusively ruled by the steric hindrance of the side chain introduced with the parent amino acid (R^1 in Scheme 3.7). Small primary residues (Me, sBu) give a poor 67 : 33 selectivity which is higher with secondary (*i*-Pr, *i*-Bu; 80 : 20) and tertiary residues (*t*-Bu; 97 : 3). Functionalized amino acids can be used when nucleophilic positions are suitably protected. A minor influence on the diastereoselectivities is observed when an additional stereogenic center is present in the imine. With S-configured *N*-phenethylimines selectivities are slightly higher while they drop with the respective R-configured imines.[27b]

Virtually any carbon substituent can be introduced with the imine at position N-1 (R^2 in Scheme 3.7), even a sterically hindered *tert*-butyl group or amino acid-derived substituents (vide infra). Nevertheless, it was not possible to react imines which bear a nitrogen heteroatom bond; that is a silyl, sulfonyl, or phosphoryl substituent cannot be introduced at position N-1. These drawbacks are overcome by cleavage of suitable substituents and further reaction of the thus liberated β-lactam nitrogen. The most favorably cleavable turned out to be the

p-methoxybenzyl group which is removed with oxidative reaction conditions, that is, with potassium peroxodisulfate.[27b] The simple cleavability of this electron-rich benzylic substituent can be combined with the slightly improved selectivities obtained with the phenethylimines bearing an additional stereogenic center. For this purpose a recently developed auxiliary is used, the 1-(*p*-methoxyphenyl)ethyl group (PMPE, Scheme 3.8). The PMPE-substituted imines lead to increased

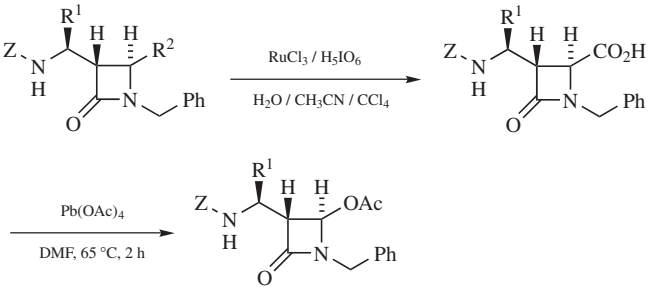


Scheme 3.8 Preparation of N-1-unprotected β-lactams by utilization of the PMPE group.[27c]

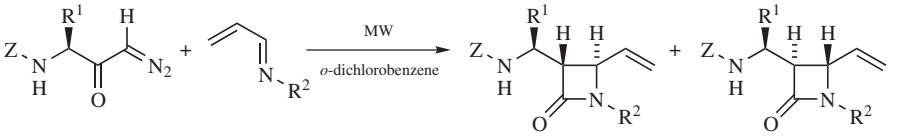
selectivities compared with the *p*-methoxybenzyl group and the PMPE group is again simply cleaved with oxidative reaction conditions (ammonium cerium nitrate, CAN).[27c]

A major drawback of this method is a restriction to imines derived from aromatic aldehydes. Surprisingly, neither aliphatic aldimines nor imines or iminoesters prepared from acrolein, glyoxalates, or formates lead to the formation of β-lactams. Nevertheless this can be circumvented by degradation of electron-rich aromatic substituents with in situ generated ruthenium tetroxide and subsequent Kolbe reaction of type II (leading to acetoxy-substitued β-lactams, Scheme 3.9).[27f]

Further flexibility arises with the utilization of thermic or, better, microwave conditions. By heating the reaction partners in *ortho*-dichlorobenzene at 180°C for 30 min, not only aromatic imines can be reacted but also imines derived from acrolein or crotonic aldehyde giving rise to C-3 vinyl- and crotyl-substituted β-lactams (Scheme 3.10).[28] These can be further transformed, for example, by ozonolysis.[27f]



Scheme 3.9 Preparation of acetoxy-substituted β-lactams.[27c]

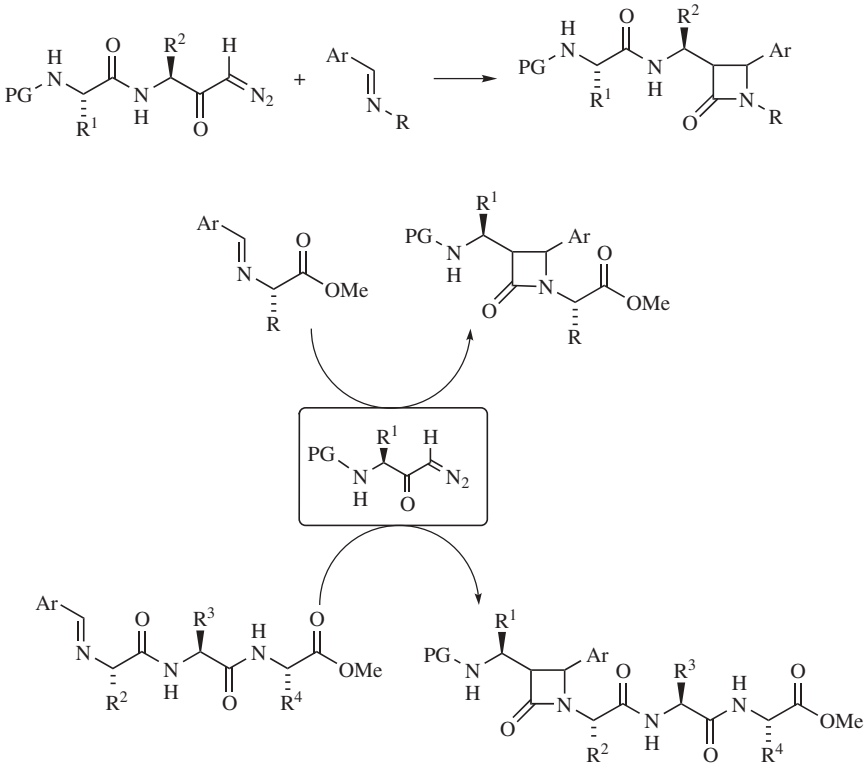


Scheme 3.10 Preparation of β-lactams with microwave (MW) conditions.[28]

Photochemically Induced Preparation of Azetidinones: General Procedure.[27f] In a quartz photoreactor diazoketone (up to 2–10 mmol) and imine (1.2–2 eq.) were dissolved in Et_2O (300 mL), and the mixture was cooled to −15°C and irradiated for 90 min. The mixture was stirred for another 30 min at this temperature and then warmed to room temperature. The solvent was removed and the diastereoisomers were separated by flash column chromatography or medium pressure liquid chromatography (MPLC).

Microwave-Induced Preparation of Azetidinones: General Procedure.[28] Diazoketone and imine (2 eq.) were dissolved in 1,2-dichlorobenzene or 1,2-dimethoxyethane. All reactions were performed under nitrogen atmosphere for 30 min, the reaction temperature being 180°C. When 1,2-dichlorobenzene was used as solvent, an oven-dried flask fitted with a nitrogen inlet was connected via a tube with an external (outside the microwave oven) reflux condenser. Reactions with 1,2-dimethoxyethane were performed in a Teflon autoclave (volume 100 mL) with mounted thermoelement. The solvent was removed and the diastereoisomers were separated by flash column chromatography or MPLC.

Peptidic substrates have been used in the formation of β-lactams as well.[29] While peptidic diazoketones give drastically reduced yields (diazoketones derived from tripeptides give rise to no product at all), the utilization of imines derived from amino acids or peptides leads to satifactory results. These variations have been used for the synthesis of β-lactam-containing peptidomimetics (Scheme 3.11).



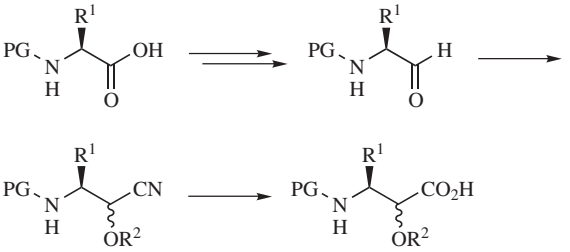
Scheme 3.11 Preparation β-lactam-containing peptides.[29]

It turned out that incorporation of β-lactams in peptide strands results in the stabilization of a reverse turn.[29b]

3.4 HOMOLOGATION OF AMINO ACIDS USING CYANO HYDRINS

Though the Wolff rearrangement is most frequently used for homologation of amino acids, another method might be useful in specific cases. Transformation of amino acids to suitably protected amino aldehydes,[30] formation of cyano hydrins, and hydrolysis of the cyano fuctions lead to α-hydroxy-β-amino acid derivatives. Nevertheless, selectivities in the cyanide addition are usually poor; the product is formed as a mixture of diastereoisomers (Scheme 3.12).[31,32] The hydroxy group formed during cyanide addition can be trapped with a variety of electrophiles, for example, silyl or stannyl moieties (which are hydrolyzed during work-up) and acyl or alkyl groups (R^2 in Scheme 3.12).

The substrates accessible with this method can be obtained alternatively by α-oxygenation of homologated amino acids using an oxodiperoxymolybdenum



Scheme 3.12 Formation of α-hydroxy-β-amino acid derivatives with cyano hydrin method.

(pyridine) (hexamethyl phosphoric triamide) complex (MoOPH). Nevertheless, almost no selectivity is observed in this reaction.[33]

Methyl 3-N-Benzyloxycarbonylamino-2-hydroxyalkanoates.[31c] A mixture of an optically pure 2-*N*-benzyloxycarbonylamino aldehyde (5 mmol) and tributyltin cyanide (1.90 g, 6 mmol) in dry CH_2Cl_2 (30 mL) was stirred at −40°C for 30 min. Then the mixture was evaporated and the crude mixture of *O*-tributylstannyl cyano hydrins was dissolved in dry and cooled Et_2O/MeOH (3 : 1) mixture, previously saturated with HCl (70 mL). This solution was stirred below 5°C for 24 h; then keeping the temperature below 10°C, ice water (15 mL) was added, and the stirring was kept at this temperature for 24–48°C [until the disappearance of the imidate intermediate detected by thin-layer chromatography ($CHCl_3$/MeOH, 5 : 1)]. The mixture was concentrated (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and evaporated to yield a crude mixture of the methyl esters which were separated by flash chromatography (hexane, EtOAc, 5 : 1).

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CHAPTER 4

Asymmetric Catalysis in Enantioselective Synthesis of β-Amino Acids

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4.1 INTRODUCTION

β-Amino acid derivatives have proven useful as building blocks for the preparation of pharmaceutical targets,[1] natural products,[2] and polypeptides with unique structural properties (for reviews see Ref. 3). In spite of the high demand for their availability, synthetic access to enantiopure β-amino acid derivatives has, until recently, relied predominantly on classical resolution,[3d,4] the use of chiral auxiliaries,[5] or the homologation of natural α-amino acids via the Arndt–Eistert reaction.[6] Current advances in catalytic enantioselective methods,[7] however, have significantly expanded the ease of their preparation and allowed general accessibility to both enantiomers. This chapter highlights catalytic asymmetric reaction methodologies developed within our own research group for the preparation of either β- or α-substituted β-amino acids with high yield and enantioselectivity.

4.2 CATALYTIC ASYMMETRIC CONJUGATE ADDITION FOR PREPARATION OF β-ALIPHATIC-β-AMINO ACIDS

4.2.1 Discussion and Results

The conjugate addition of amines or their synthetic equivalents to α,β-unsaturated carbonyl compounds represents a direct and attractive strategy for the preparation of β-amino acid derivatives. (For additional reports on Lewis acid–catalyzed

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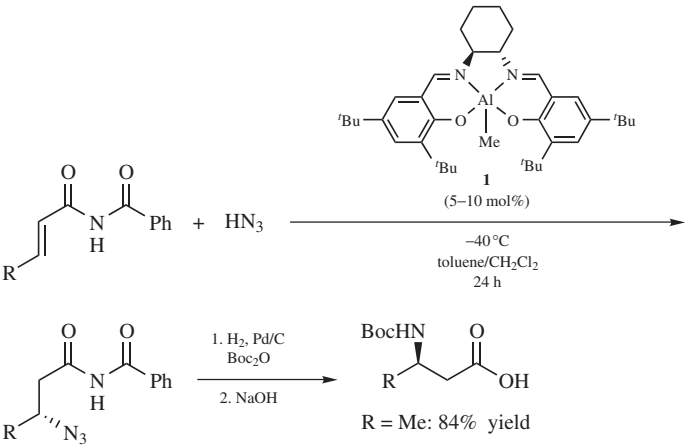


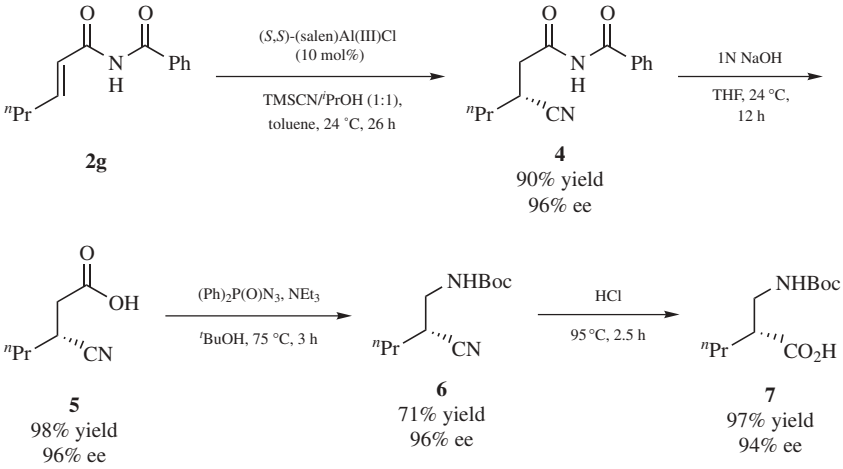
2a: R = Me **2d**: R = CH_2OBn
2b: R = Et **2e**: R = ^{i}Pr
2c: R = ^{t}Bu **2f**: R = Ph

3a–e: (93–99% yield, 95–97% ee)
3f: (60% yield, 58%ee)

Scheme 4.1 (salen)Al(III)-Catalyzed asymmetric conjugate addition.

asymmetric conjugate additions of amine equivalents to α,β-unsaturated compounds, see Ref. 8.) In 1999, we reported the catalytic enantioselective conjugate addition of hydrazoic acid (HN_3) to α,β-unsaturated imides utilizing chiral (salen)Al(III)Me complex **1** (Scheme 4.1).[9] Metal complexes incorporating the salen ligand had previously been shown to promote a wide variety of mechanistically distinct asymmetric nucleophile–electrophile reactions, including the opening of epoxides by azide,[10] water,[11] carboxylic acids,[12] and phenols,[13] the hydrocyanation of imines,[14] and hetero-Diels–Alder reactions between dienes and aldehydes.[15] Imides of general structure **2** readily underwent conjugate addition in the presence of catalyst **1** (5 mol %) to yield the corresponding azide adducts **3**. The enantioselectivity of the conjugate addition reaction proved largely insensitive to the steric properties of the β-substituent, with alkyl groups ranging from methyl to *tert*-butyl all providing products with similar enantioselectivity (95–97% ee). In the case of **2c** (R = *t*-Bu), a slightly higher reaction temperature (−30°C) was required to achieve full conversion. However, cinnamate derivatives such as **2f** (R = Ph) proved considerably less reactive, undergoing incomplete conversion in the presence of 10 mol % **1** after 24 h at 23°C with diminished enantioselectivity (58% yield, 60% ee). The resulting β-azido imide adducts can be converted to their β-amino acid derivatives via a one-pot hydrogenation/*N*-Boc protection sequence.[16] Regioselective cleavage of the imide group yielded the *N*-Boc-protected carboxylic acid.

Analogs of complex **1** bearing different counterions (Cl, μ-oxo) have been employed successfully in the asymmetric catalytic conjugate addition of cyanide[17]



Scheme 4.2 Preparation of an α-substituted β-amino acid via enantioselective conjugate addition of cyanide.

and electron-deficient nitrile derivatives[18] to **2**. The hydrocyanation adducts can be applied to the preparation of enantioenriched α-substituted β-amino acid derivatives (Scheme 4.2). (For additional asymmetric catalytic approaches, see Ref. 19.) Adduct **4** was generated in 90% yield and 96% ee via the catalytic asymmetric hydrocyanation of imide **2g** with (*S*,*S*)-(salen)Al(III)Cl (10 mol %). Conversion of **4** to the corresponding acid **5** followed by Curtius rearrangement afforded Boc-protected cyano amide **6**. Subsequent hydrolysis of the nitrile in hydrochloric acid afforded the amino acid product **7** in excellent yield with only a very small degree of racemization (97% yield, 94% ee).

4.2.2 General Experimental Procedures

4.2.2.1 Asymmetric Conjugate Addition of Hydrazoic Acid to Imide 2[9] A solution of hydrazoic acid (3.3 M in toluene; 1.0 mL, 3.3 mmol, 6.6 eq.) was added to a suspension of imide **2**[20] (0.50 mmol, 1.0 eq.) and catalyst **1** (14.5 mg, 0.025 mmol, 0.05 eq.) at −78°C in dichloromethane (1 mL). The reaction was warmed to −40°C (or −30°C for **2c**), and this temperature was maintained for 24 h. The reaction was subsequently allowed to warm to ambient temperature and flushed with nitrogen to remove residual hydrazoic acid. The reaction mixture was diluted with dichloromethane and purified via flash chromatography on silica gel (5% ethyl acetate in dichloromethane) to afford pure adduct **3**.

4.2.2.2 Asymmetric Hydrocyanation of Imide 2[17] (*S*,*S*)-(salen)Al(III)Cl complex (60.7 mg, 0.10 mmol, 0.10 eq.) and imide **2**[20] (1.0 mmol, 1.0 eq.) were

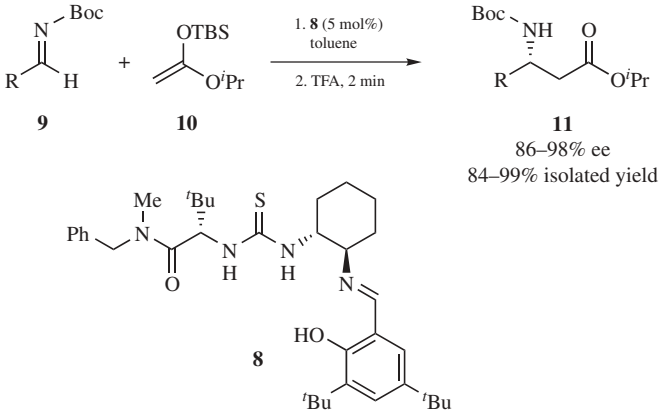
combined in a 25-mL Schlenk flask under an atmosphere of nitrogen (for a practical synthesis of these substrates, see Ref. 20). Toluene (0.4 mL) and TMSCN (333 μL, 2.5 mmol, 2.5 eq.) were then added via syringe, and the mixture was gently heated until the yellow solution became homogeneous. The reaction flask was then placed in a water bath at ambient temperature, and 2-propanol (193 μL, 2.5 mmol, 2.5 eq.) was added dropwise over a 2-min period. The system was sealed, and the mixture was allowed to stir for the specified length of time (26 or 48 h). Upon completion, the volatiles were removed in vacuo with a potassium carbonate (K_2CO_3) solution trap. The resulting residue was purified via flash chromatography on silica gel to afford pure adduct **4**.

4.3 ASYMMETRIC MANNICH REACTIONS CATALYZED BY THIOUREA DERIVATIVES FOR ENANTIOSELECTIVE PREPARATION OF β-ARYL-β-AMINO ACIDS

4.3.1 Discussion and Results

Of the methods available for the enantioselective preparation of β-amino acids, the addition of ester enolate equivalents to imines (the Mannich reaction)[21] is especially attractive as it involves the convergent assembly of two units of similar complexity with concomitant formation of a carbon–carbon bond. Various chiral auxiliary[22] and reagent-based[23] approaches to the Mannich reaction have been reported for the enantioselective preparation of β-amino acids. The development of a catalytic, enantioselective version of this reaction, however, has proven challenging: The catalyst must be capable of activating imines toward nucleophilic attack yet be resistant to inhibition by the strongly Lewis basic amine products. The discovery of chiral zirconium-based catalysts by Kobayashi in 1997[24] represented the first reported catalytic enantioselective Mannich reaction of imines with enolate equivalents and defined a benchmark for subsequent studies. [Replacement of BINOL with 2,2′-diphenyl-(3,3′-biphenanthrene)-4,4′-diol (VAPOL) in a related zirconium system was subsequently reported in Ref. 25.] These systems, however, are restricted to imine substrates bearing *N*-aryl substituents with a pendant chelating group for two-point binding to the catalyst. This requirement imposes several practical limitations, including the need for strong oxidative or reductive conditions for deprotection of the product amine.

In 2002, we reported a highly efficient route to *N-tert*-butoxycarbonyl- (*N*-Boc) protected β-amino acids via the enantioselective addition of silyl ketene acetals to *N*-Boc-aldimines catalyzed by thiourea catalyst **8** (Scheme 4.3).[26] (Thiourea catalyst **8** can be prepared in five steps in <24 h with 86% overall yield utilizing only a single chromatographic purification step. Refer to the Experimental Section of Ref. 26.) Urea derivatives of general structure **8** had previously been reported as useful catalysts for the asymmetric hydrocyanation of *N*-allyl or *N*-benzyl aldimines[27a,b,d] and ketoimines.[27c] Initial studies on the reaction of *N*-allyl or *N*-benzyl

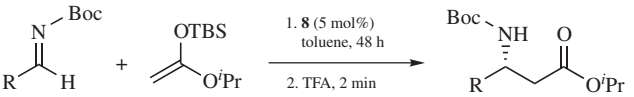


Scheme 4.3 Asymmetric catalytic Mannich reaction.

benzaldimines with trimethylsilyl ketene acetal derivatives proved unsuccessful, presumably as a result of the poor reactivity of the imine substrates. In contrast, the more electrophilic benzaldehyde *N*-Boc imines **9**[22a] underwent reaction with silyl ketene acetals in the presence of **8** (5 mol %) to afford the desired Mannich adducts in high yields and enantioselectivities. Reactions were run at reduced temperatures (−40 to 4°C) to suppress the presence of an uncatalyzed racemic reaction pathway. The steric bulk of the alkoxy substituent on the silyl ketene acetal coupled with optimization of the catalyst structure[28] proved crucial to achieving high asymmetric induction and the maintenance of useful reaction rates at these temperatures. (For full details regarding the catalyst structure/enantioselectivity profile for the asymmetric Mannich reaction, see Ref. 28.)

The scope of the optimized reaction system is summarized in Table 4.1. Ortho-, meta-, and para-substituted arylimines underwent addition with generally high enantioselectivity and in excellent yield. One of the attractive features of this methodology is the remarkable tolerance for Lewis basic substrates, enabling the highly enantioselective synthesis of thiophene-, furyl-, pyridine-, and quinoline-substituted, 3-amino propionic esters (entries 11–14). All *N*-Boc imines screened to date have proven to be excellent substrates with respect to both enantioselectivity and yield. (Other *N*-carbamate-protected imines examined under the same reaction conditions listed for imine **9a** in Table 4.1: *N*-Cbz benzaldimine, 75% ee; *N*-methoxycarbonyl benzaldimine, 85% ee. For both imines, the racemic background pathway remained accessible at −40°C.) Aliphatic *N*-Boc aldimines have as yet not been investigated in the Mannich reaction because no useful method has been identified for their synthesis. Reactions were carried out using two equivalents of silyl ketene acetal **10** relative to the imine, as this was found to have a beneficial

TABLE 4.1 Scope of Asymmetric Mannich Reaction Catalyzed by 8

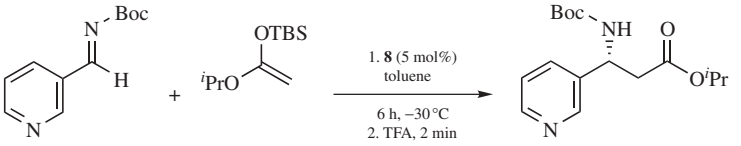


9a–n **10** 2.0 equiv **11a–n**

Entry	Imine	R	Temperature (°C)	Yield (%)[a]	ee (%)[b,c]
1	**9a**	Ph	−40	95	97
2	**9b**	*o*-$CH_3C_6H_4$	−30	88	91
3	**9c**	*m*-$CH_3C_6H_4$	−30	98	94
4	**9d**	*p*-$CH_3C_6H_4$	−30	87	96
5	**9e**	*p*-$OMeC_6H_4$	4	91	86
6	**9f**	*p*-FC_6H_4	−30	88	93
7	**9g**	*m*-BrC_6H_4	−30	96	92
8	**9h**	*p*-BrC_6H_4	−30	93	94
9	**9i**	1-Naphthyl	−30	93	87
10	**9j**	2-Naphthyl	−30	88	96
11	**9k**	2-Furyl	−40	84	91
12	**9l**	2-Thienyl	−30	95	92
13	**9m**	3-Quinolinyl	−30	99	96
14	**9n**	3-Pyridyl	−30	99	98

[a] Isolated yield after silica gel chromatography.
[b] Determined via chiral high-pressure liquid chromatography.
[c] Absolute stereochemistry assigned via correlation to authentic material (Ref. 6) and literature values (Ref. 30).

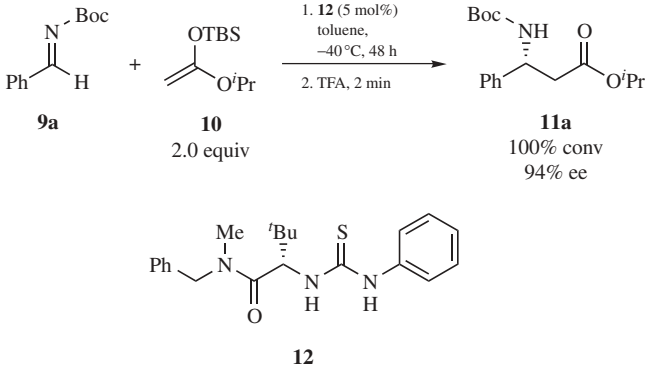
effect on rate, particularly with electron-rich substrates:



(4.1)

9n 5 mmol **10** 1.2 equiv **11n** 99% yield 98% ee

Electron-deficient imines proved more reactive, however, and their efficient conversion could be achieved with 1.2 eq. of nucleophile. For example, when 3-pyridinecarboxaldimine **9n** was combined with 1.2 eq. **10** in the presence of **8** (5 mol %), **11n** was obtained in 99% yield and 98% ee within 6 h (Equation 4.1). This and similar reactions have been carried out on scales as high as 10 mmol with no



Scheme 4.4 Asymmetric Mannich reaction catalyzed by aniline-derived catalyst **12**.

detrimental effect on yield or enantioselectivity. The resulting Boc-protected, β-amino acid derivatives are readily deprotected under mildly acidic conditions and are well suited for direct use in peptide synthesis.[6,29]

Mechanistic studies on the asymmetric Mannich reaction[28,31] have subsequently demonstrated that the entire diamine/Schiff base moiety can be excised from the catalyst structure with little detrimental effect on enantioselectivity. Reaction of imine **9a** with **10** in the presence of aniline-derived catalyst **12** afforded **11a** in 100% conversion and 94% ee (Scheme 4.4). Catalyst **12** represents a remarkable simplification in catalyst design, as it possesses less than half the molecular weight of parent catalyst **8** and two fewer stereocenters. It can be prepared readily from commercially available starting materials in three steps with 95% overall yield.

4.3.2 Representative Experimental Procedure: Catalytic Asymmetric Mannich Reaction for Preparation of 11a[26]

A 50-mL flask was charged sequentially with **8** (300 mg, 0.5 mmol, 0.05 eq.) and anhydrous toluene (5 mL). Then **9a** (2.0 g, 10 mmol, 1.0 eq.) was added in one portion with stirring. Once the solution was homogeneous, the flask was immersed in a dry ice/acetone bath and cooled to −40°C. Silyl ketene acetal **10** (4.3 g, 20 mmol, 2.0 eq.) was then slowly added along the flask wall over a 10-min period. The flask was placed under an atmosphere of nitrogen and stirred at −40°C. After 48 h, excess silyl ketene acetal was quenched at −40°C via the rapid addition of a 3 M solution of trifluoroacetic acid in toluene (10 mL; cooled to −20°C prior to addition). The reaction was stirred for 2 min at −40°C, allowed to warm to ∼5°C over a 3–5-min period, then partitioned between saturated aqueous sodium carbonate solution and dichloromethane (1 : 1, 30 mL). The aqueous layer was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified via flash chromatography on silica gel [5 × 16 cm

silica, 2.5–15% ethyl acetate in hexanes; $R_f = 0.27$ (15% ethyl acetate in hexanes); $KMnO_4$ thin-layer chromatography visualization] to yield **11a** as a white, crystalline solid (2.9 g, 95%) in 97% ee.

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CHAPTER 5

Enantioselective Synthesis of Conformationally Constrained β-Amino Acids

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5.1 GENERAL INTRODUCTION

Conformationally constrained β-amino acids (β-AAs) are of great interest in the preparation of oligomers with strong propensity to adopt specific, compact conformations giving rise to secondary structures, that is, helixes, turns, sheets.[1] These β-peptides, or foldamers, are relevant in biological studies to investigate the topology of receptors and also are prominent candidates in the development of new drugs. In most cases, constraint in these amino acids is induced by the presence of a small to midsized ring as a structural feature or by bulky substituents at the α- or β-position.

To classify β-AAs containing carbocyclic moieties it is useful to distinguish between those compounds in which the amino and carboxyl groups are directly linked to the ring, that is, cycloalkane β-AAs[2] and cycloalkyl β-AAs, which bear at least one of these groups on a side chain.

5.2 CYCLOALKANE β-AMINO ACIDS

Cycloalkane β-AAs are found in nature in free form or associated to other structural units in complex molecules. For instance, the antifungal antibiotic (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid [(1*R*,2*S*)-2-ACP; cispentacin] was isolated

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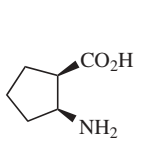
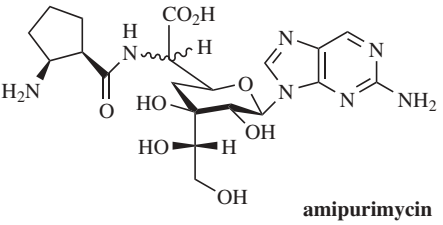
from *Bacillus cereus*[3] and *Streptomyces setonii*[4] and is also a component of the antibiotic amipurimycin:



cispentacin



amipurimycin

This product, produced by *Streptomyces novoguineensis*,[5] contains a nucleic base attached to the anomeric carbon of a branched-chain deoxy sugar, which is extended by a dipeptide containing *cis*-2-ACP.[6,7]

Small cycloalkane β-AAs are very restricted conformationally due to high steric congestion. Figure 5.1 shows conformations for *cis*-1-aminocyclopropanecarboxylate and *cis*-1-aminocyclobutanecarboxylate. For the former, both amino and carboxyl groups are eclipsed, the cyclopropane ring being rigid. This situation is reproduced in norbornane derivatives. For the cyclobutane derivatives, two conformations are possible, but in both cases the amino and the carboxyl groups are gauche. The severe constriction is expected to induce secondary structures in the peptidomimetics containing these residues and to influence their biological properties.

The most common methods to synthesize enantiopure cycloalkane β-AAs involve the desymmetrization of cyclic meso compounds, used as precursors, or a stereoselective cycloaddition reaction to create a carbocyclic system. The stereoselective 1,3-dipolar cycloaddition of diazoalkanes followed by denitrogenation of the resultant pyrazoline along with the cyclopropanation of chiral olefins by metal carbens and by the Corey–Chaykovsky method has been used for the synthesis of enantiomerically pure cyclopropane β-AAs. It is noteworthy that, although several synthetic methods have been described to prepare 2-aminocyclopropanecarboxylic acid derivatives,[8] only a few instances on the enantioselective synthesis of these β-AAs have been reported. Otherwise, data concerning the synthesis of cyclobutane β-AAs, both racemic[9] or optically active, are very scarce in the literature.

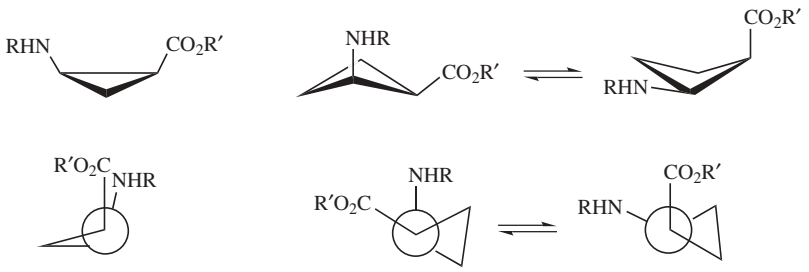
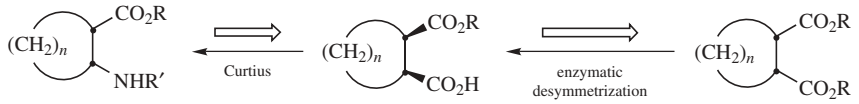


Figure 5.1 Conformations for cyclopropane and cyclobutane *cis*-β-AAs.

5.2.1 Desymmetrization of Cyclic meso Compounds

Two main procedures have been described for the desymmetrization of meso diesters or anhydrides involving the chemo- and enantioselective reaction with an enzyme or a conventional chiral reagent. The first method has been employed in the synthesis of cyclopropane and cyclobutane derivatives whereas the second one led to cyclopropane and norbornene amino acids.

5.2.1.1 Chemoenzymatic Hydrolysis of meso Diesters A useful strategy achieved in our laboratory is outlined in Scheme 5.1 and consists of enzymatic desymmetrization of a cyclic meso diester affording enantioselectively a half-ester. Introduction of the amino group was accomplished through the Curtius reaction.[10,11]

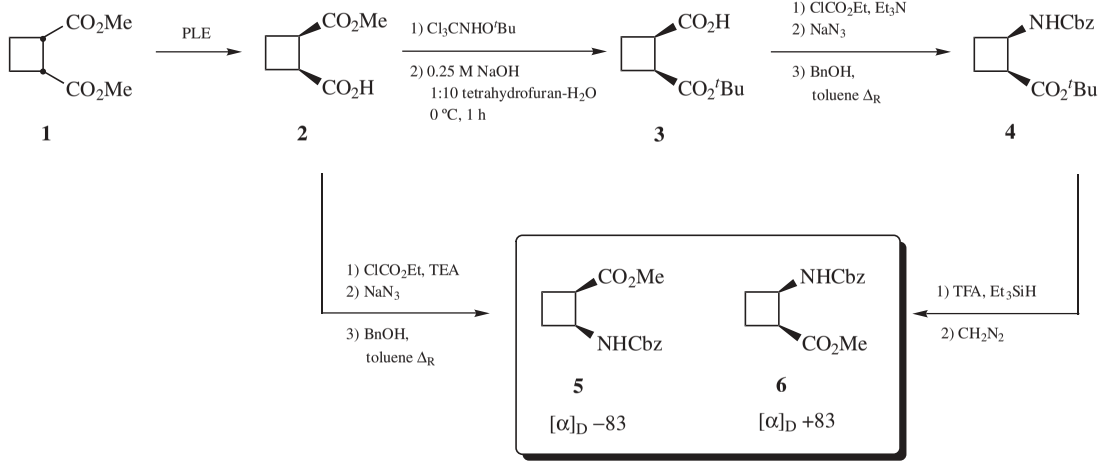


Scheme 5.1

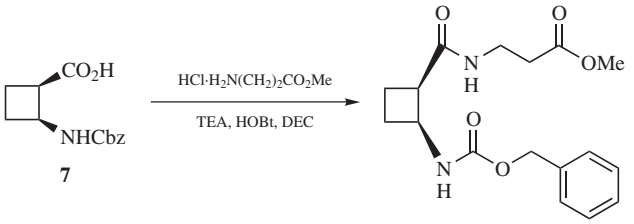
The protocol developed by Sabbioni and Jones[12] for the chemoselective hydrolysis of cycloalkane meso diesters has been applied successfully to the asymmetric synthesis of the enantiomeric cyclobutane β-AAs **5** and **6** (Scheme 5.2). Compound **1**, prepared by methylation of the commercial diacid, was hydrolyzed by pig leaver esterase (PLE) to afford half-ester **2**. The next synthetic step involves the degradative conversion of the carboxyl group into an amine via an intermediate acyl azide. Thus, treatment of **2** with ethyl chloroformate followed by reaction with sodium azide and subsequent heating in the presence of excess benzyl alcohol led to orthogonally protected amino acid **5** in 91% enantiomeric excess (ee) and 57% overall yield.[10]

The enantiomer, **6**, was also prepared from **2** through selective manipulation of the functional groups. Esterification of remaining free acid in **2** with *tert*-butyl trichloroacetamidine followed by careful saponification of the methyl ester (0.25 M NaOH, 0°C, 1 h) afforded half-ester **3** without epimerization. Under Curtius conditions, this compound led to fully protected amino acid **4**. Subsequent hydrolysis of the *tert*-butyl ester, by reaction of **4** with trifluoroacetic acid (TFA) and Et_3SiH, followed by methylation of the resultant acid with diazomethane afforded enantiomer **6** in 65% overall yield from **1**.[11]

β-Dipeptide **8** was synthesized in 86% yield by coupling of acid **7** with β-Ala-OMe in the presence of excess 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (DEC) as a dehydrating agent and one equivalent of 1-hydroxybenzotriazole (HOBt) as a catalyst (Scheme 5.3). The X-ray structural analysis of **8** revealed a hairpin-like conformation for this molecule in the solid state.[10a] A dimer of **8** adopts a 14-helical folding in solution.[10b]


CO2Me
CO2Me
1
PLE
CO2Me
CO2H
2
1) Cl3CNHO'Bu
2) 0.25 M NaOH
1:10 tetrahydrofuran-H2O
0 °C, 1 h
CO2H
CO2tBu
3
1) ClCO2Et, Et3N
2) NaN3
3) BnOH,
toluene ΔR
NHCbz
CO2tBu
4
1) ClCO2Et, TEA
2) NaN3
3) BnOH,
toluene ΔR
CO2Me
NHCbz
5
[α]D −83
NHCbz
CO2Me
6
[α]D +83
1) TFA, Et3SiH
2) CH2N2

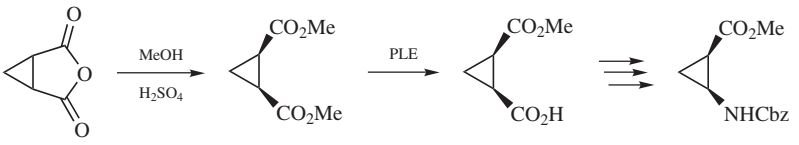
Scheme 5.2



7 8

Scheme 5.3

Similarly, the cyclopropane derivative **12** was prepared from the commercially available anhydride **9** through half-ester **11** (Scheme 5.4). Compound **12** was obtained in 89% total yield and 63% ee.[10] The low optical purity is due to partial racemization during the Curtius rearrangement and can be rationalized by the propensity of 1,2 capto-dative cyclopropane systems to open under a variety of conditions.[10,13,14]



9 10 11 12

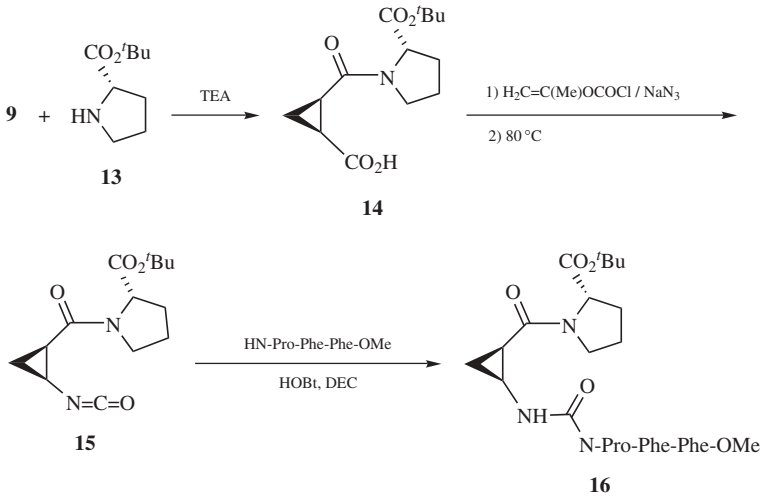
Scheme 5.4

Chemoenzymatic hydrolysis of meso diesters has also been applied to the synthesis of cyclohexane β-AAs[15] and 3(*S*)-aminopiperidine-5(*R*)-carboxylic acid.[16]

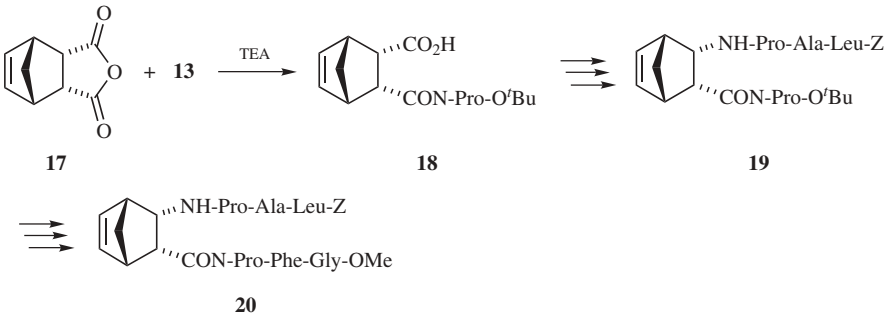
5.2.1.2 Reaction of meso Anhydrides with Chiral Amines North has published the desymmetrization of anhydride **9** and the norbornene anhydride **17** by reaction with (*S*)-prolinates affording chiral amides (Schemes 5.5 and 5.6). These products are useful synthetic intermediates for the incorporation of the norbornene moiety into pseudopeptides to induce β-sheet and β-turn structures.[17]

Product **14** (Scheme 5.5) resulted as the major diastereomer from the reaction between anhydride **9** and *tert*-butyl (*S*)-prolinate (57% yield, 50% de). Activation of the carboxyl group by reaction with isopropenyl chloroformate followed by treatment with sodium azide and subsequent heating at 80°C produced isocyanate **15**. This compound reacted with the amino group of amino esters or peptides, such as HN–Pro–Phe–Phe–OMe, to provide peptide analogs incorporating a urea bond.[18]

In a similar manner, *endo*-(2*S*,3*R*)-norbornen-5-ene-2,3-dicarboxylic acid anhydride **17** reacted with prolinates, giving half-amides. These compounds were



Scheme 5.5



Scheme 5.6

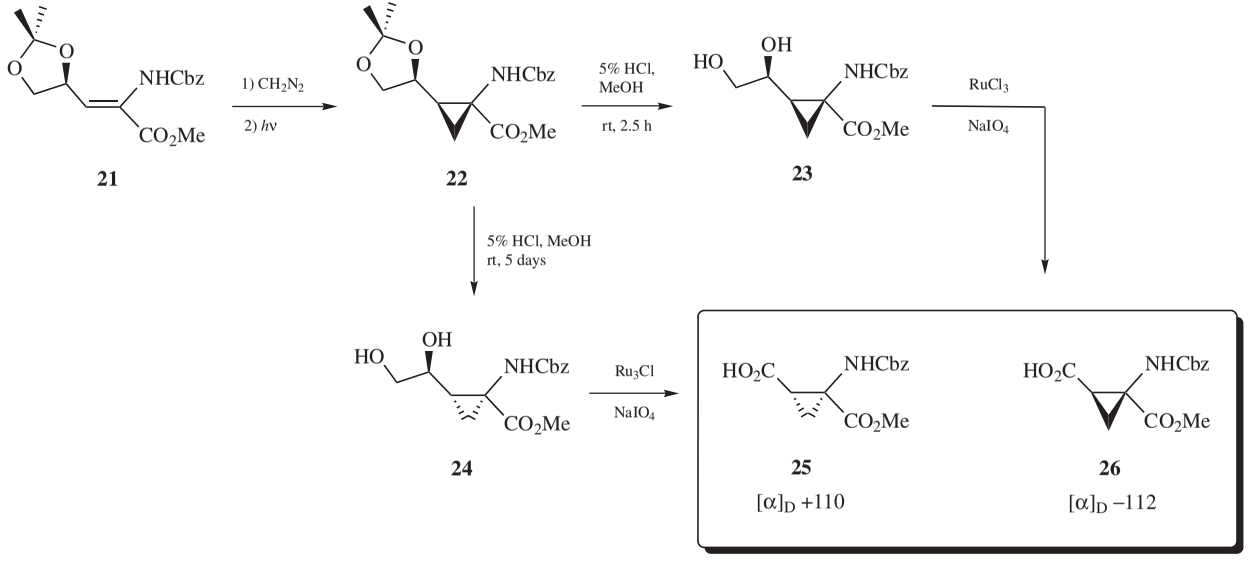
transformed into isocianates, which were incorporated into peptides and pseudo-peptides. An example is shown in Scheme 5.6 for the synthesis of **19** and **20**.[18]

Several cycloalkane β-AAs were synthesized through an alkaloid-mediated desymmetrization of meso anhydrides.[19]

Cyclopentane and cyclopentene β-AAs have been prepared in high enantiomeric excesses through the asymmetric alcoholisis of anydrides in the presence of an equimolecular amount of a chiral amine base.[20]

5.2.2 1,3-Dipolar Cycloadditions of Diazoalkanes

Cyclopropane β-AAs have been synthesized in our laboratory in high yields and excellent stereoselectivity through the cycloaddition of diazomethane to chiral enoates derived from (*S*)-glyceraldehyde. According to this strategy, the two enantiomers of cycloaspartic acid (cyclo-Asp) derivatives **25** and **26** were prepared


NHCbz
CO2Me
1) CH2N2
2) hν
5% HCl,
MeOH
rt, 2.5 h
OH
HO
RuCl3
NaIO4
21
22
23
5% HCl, MeOH
rt, 5 days
Ru3Cl
NaIO4
HO2C
24
25
[α]D +110
26
[α]D −112

Scheme 5.7

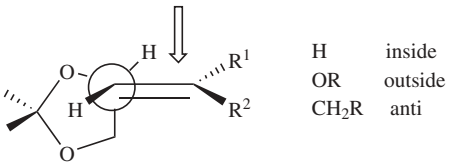


Figure 5.2 Preferential conformation to explain diastereoselectivity in addition of diazomethane to γ-alkoxy enoates (*outside alkoxy model*). The arrow shows the direction of the attack leading to major adducts.

as depicted in Scheme 5.7.[14] Cyclopropane precursor **22** was synthesized quantitatively as a single diastereomer by cycloaddition of diazomethane to the aminopentenoate **21** followed by photolysis of the produced pyrazoline. The total stereospecificity in both the cycloaddition[21] and the photolysis[22] steps is remarkable.

The diastereoselection in the cyclopropanation process has been rationalized according to the *outside alkoxy* model, as depicted in Figure 5.2, where the arrow shows the direction of the preferential attack of diazomethane to the double bond. Density functional theory (DFT) theoretical calculations pointed out that steric factors due to the dioxolane ring accounted for the observed π-facial diastereoselection whose origin lies on the chirality of the dioxolane stereogenic center as the most relevant feature determining the stereochemistry of the adducts produced.[21]

Otherwise, retention of the configuration during the photolysis has been explained by considering that cyclopropane ring closure of the trimethylene-type biradical (Fig. 5.3), resulting from extrusion of nitrogen, is faster than rotation about the tetrasubstituted C–C bond.[22]

Regarding the synthesis of the two cyclo-Asp enantiomers, methanolysis of the acetonide in **22** with 5% HCl in methanol at room temperature for 2.5 h afforded quantitatively diol **23**, which was oxidatively cleaved to partially protected (2*S*,3*R*)-cyclo-Asp, **26**. In turn, diol **24** was obtained in 45% yield when the reaction was carried out during a 5-day period. This diol is the precursor of acid **25**, enantiomer of **26**, and results from the cyclopropane ring opening and latter closure with the concomitant epimerization at C-1 and C-2. This process is favored by the electron donor neighboring effect of the secondary hydroxyl group that stabilizes the carbocation resulting from ester enolization in acid medium (Scheme 5.8).[14]

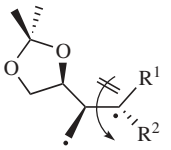
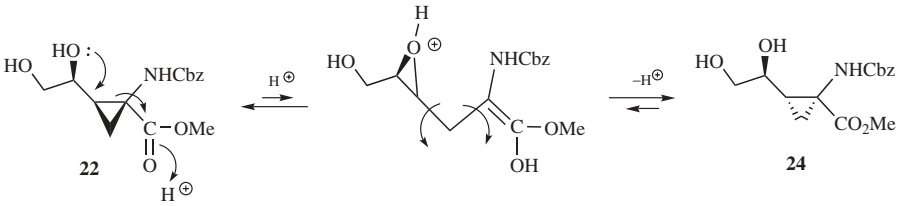


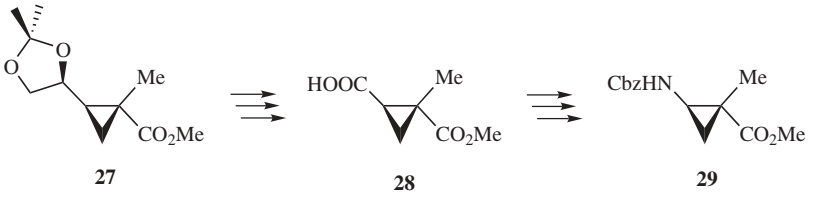
Figure 5.3 Trimethylene-type biradical resulting from extrusion of molecular nitrogen in precursor pyrazoline. Ring closure faster than rotation provides cyclopropanes with total configuration retention.



Scheme 5.8

Both amino acids **25** and **26** are conveniently protected for their incorporation into β-peptides, as described below.

Similarly, *cis*-β-AA **29** was synthesized as a single stereoisomer from cyclopropane **27** (Scheme 5.9). In turn, compound **27** resulted from the highly diastereoselective cyclopropanation [85% diastereomeric excess (de)] of a suitable chiral olefin.[10]

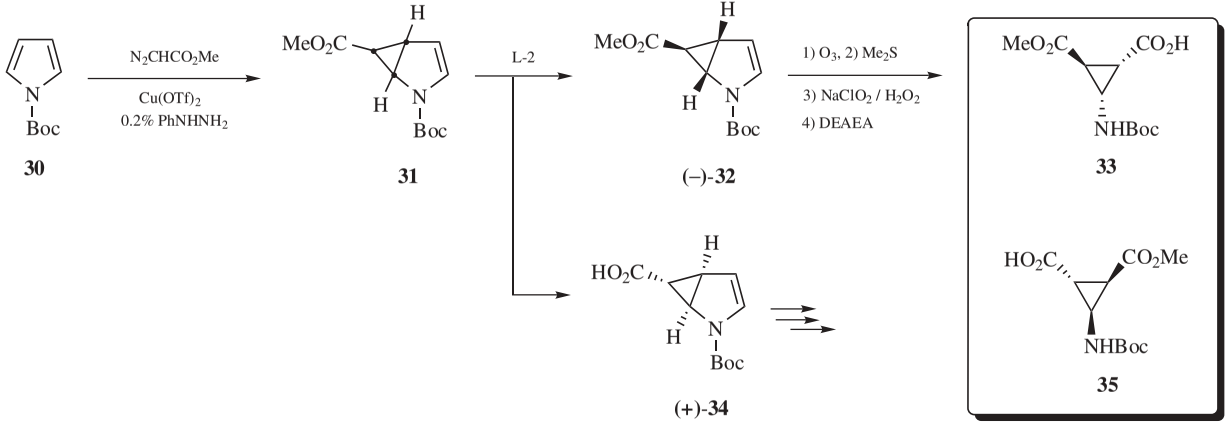


Scheme 5.9

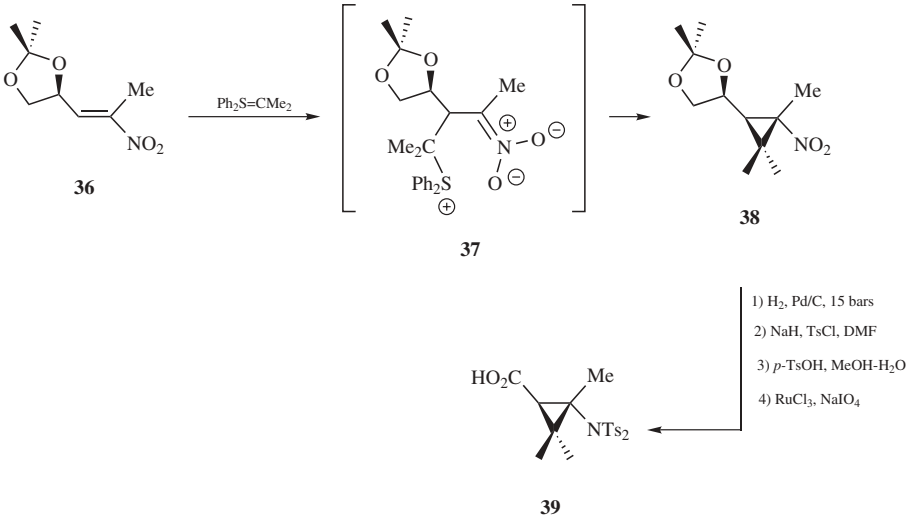
5.2.3 Reactions of Double Bonds with Carbenes and Sulfur Ylides

Beumer et al.[23] described the synthesis of diastereomeric cyclopropanes **33** and **35** (Scheme 5.10), which are useful for the preparation of peptide surrogates. Cyclopropanation of *N*-Boc- protected pyrrrole **30** by using methyl diazoacetate in the presence of Cu(II) triflate activated by phenylhydrazine afforded stereoselectively compound **31** in 39% yield along with 3% of its diastereomer and 36% recovered starting material. Kinetic enzymatic resolution of **31** with L-2 lipase and subsequent crystallization afforded methyl ester (−)-**32** and acid (+)-**34** in high enantiomeric purity. Ozonolysis of **32** followed by oxidation of the produced aldehyde and deformylation by treatment with 2-diethylaminoethylamine (DEAEA) led to trisubstituted cyclopropane **33**. Similarly, compound **35** was prepared from (+)-**34**.

Hübner et al. described the synthesis of the partially protected β-AA **39** from cyclopropanation of nitroolefin **36** with diphenylsulfoniumisopropylylide to afford **38** (94% de).[24] According to the authors, stereospecifity of the addition is due to the rapid ring closure of the intermediate species **37**. Subsequent manipulation of functional groups led to the production of **39** (Scheme 5.11).


N
Boc
30
N2CHCO2Me
Cu(OTf)2
0.2% PhNHNH2
MeO2C
H
H
N
Boc
31
L-2
MeO2C
H
H
N
Boc
(–)-32
1) O3, 2) Me2S
3) NaClO2 / H2O2
4) DEAEA
MeO2C
CO2H
NHBoc
33
HO2C
H
H
N
Boc
(+)-34
HO2C
CO2Me
NHBoc
35

Scheme 5.10



36 **37** **38** **39**

Scheme 5.11

5.3 ALKYL-SUBSTITUTED β-AMINO ACIDS

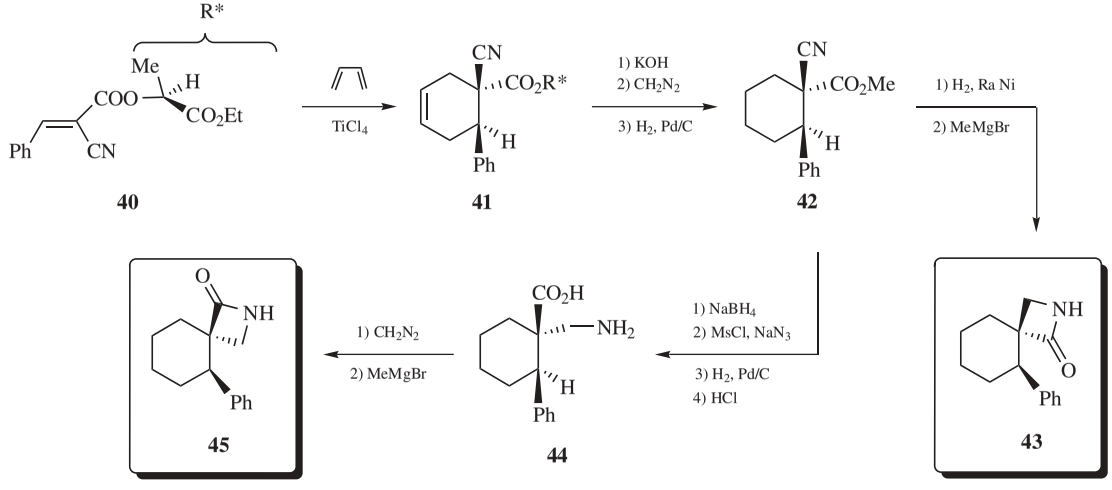
β-Amino acids substituted by bulky groups, frequently carbocyclic rings, are also conformationally constrained and convenient for their incorporation into rigid peptides, as shown below by some representative instances.

5.3.1 α,α-Disubstituted β-Amino Acids Through Diels–Alder Reactions

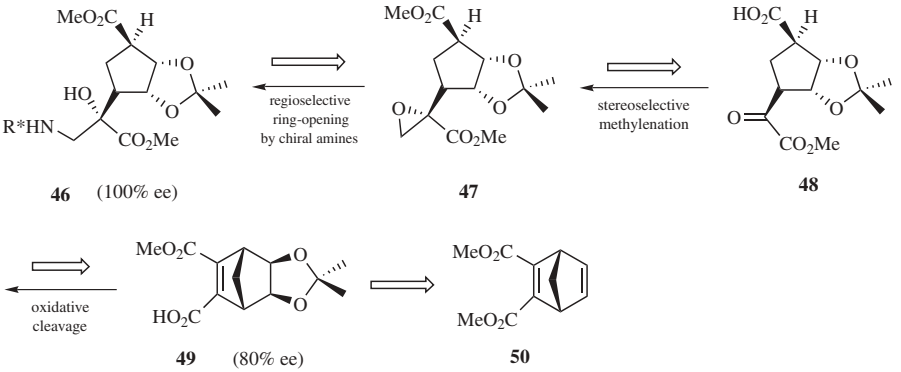
These cycloadditions have been used either to create the carbocyclic skeleton of the target molecule or to produce a carbocyclic scaffold to be elaborated into the final product.

In the former case, α,α-disubstitued (cyclohexyl) β-AAs were synthesized from the adducts of Diels–Alder reactions between butadiene and chiral (*E*)-2-cyanocinnamates. These amino acids easily cyclized to spiro β-lactams (Scheme 5.12).[25] Thus, chiral auxiliary ethyl (*S*)-lactate was removed and the double bond was hydrogenated in adduct **41** to afford the key cyano ester **42**. Reduction of the nitrile to amine followed by treatment with methylmagnesium bromide led to β-lactam **43**. Alternatively, **42** was easily transformed into amino acid **44** that cyclized to the diastereomer **45**. The enantiomers of **43** and **45** were obtained in a similar manner by employing (*R*)-pantolactone as a chiral auxiliary.

Highly constrained α-substituted isoserine derivatives containing a polyfunctionalized chiral cyclopentane moiety were synthesized from norbornene half-ester **49** (Scheme 5.13).[26] The synthesis of this compound from the Diels–Alder adduct **50** had been reported by Ohno in the context of the first asymmetric synthesis of


R*
Me
H
COO
CO2Et
Ph
CN
40
TiCl4
CN
CO2R*
H
Ph
41
1) KOH
2) CH2N2
3) H2, Pd/C
CN
CO2Me
H
Ph
42
1) H2, Ra Ni
2) MeMgBr
NH
O
Ph
43
1) NaBH4
2) MsCl, NaN3
3) H2, Pd/C
4) HCl
CO2H
NH2
H
Ph
44
1) CH2N2
2) MeMgBr
O
NH
Ph
45

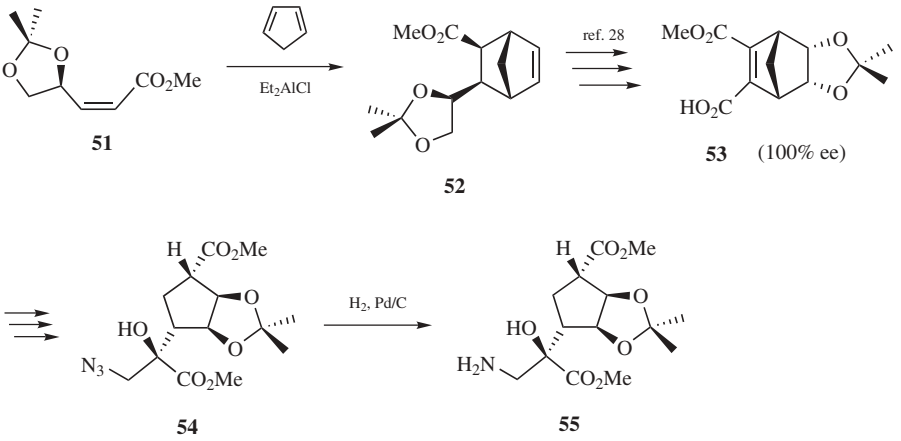
Scheme 5.12



Scheme 5.13

(−)-aristeromycin.[27] Regio- and stereoselective hydroxylation of the disubstituted double bond in **50**, protection of the resultant diol, and chemoselective hydrolysis of the meso- diester afforded compound **49** in 80% ee.

Compound **53**, enantiomer of half-ester **49**, was also available since it was prepared in our laboratory through the stereoselective Diels–Alder cycloaddition of chiral ester **51**, obtained from D-glyceraldehyde, followed by stereospecific dihydroxylation of the major adduct **52** (Scheme 5.14).[28]



Scheme 5.14

Scheme 5.13 shows the retrosynthetic pathway and the key steps for the preparation of β-AAs **46**. Ozonolysis of the double bond in **49** took place quantitatively with concomitant decarboxylation to afford the cyclopentane **48**. Subsequent reaction with diazomethane led to both methylation of the carboxyl group and diastereoselective methylenation of the ketone, providing **47** in 85% yield and 80% de.[26] Based on additional experiments and theoretical calculations, we

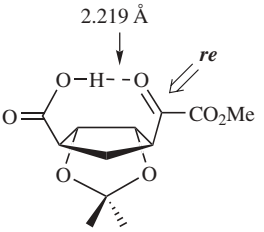
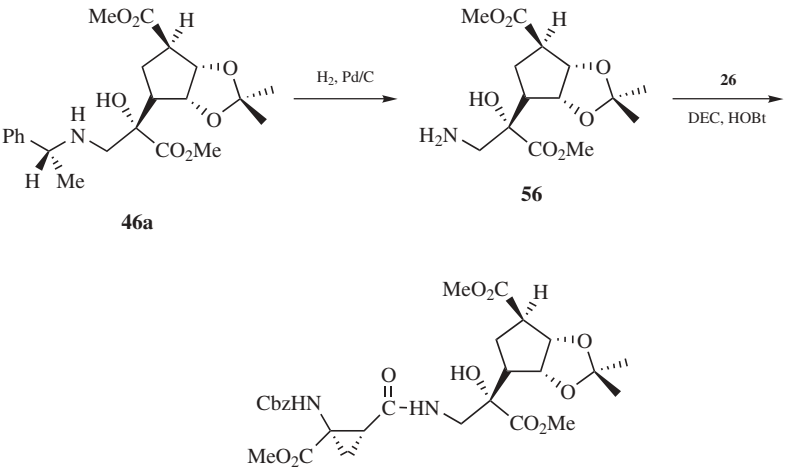


Figure 5.4 Intramolecular hydrogen bond in compound **48** accounting for π-facial discrimination.

suggested that methylenation must be prior to methylation of the carboxylic acid, diastereoselectivity being induced by the formation of an intramolecular hydrogen bond that severely hinders the *si* face of the carbonyl, as depicted in Figure 5.4. Moreover, this coordination enhances the reactivity of the ketone toward the nucleophilic attack of diazomethane.[29]

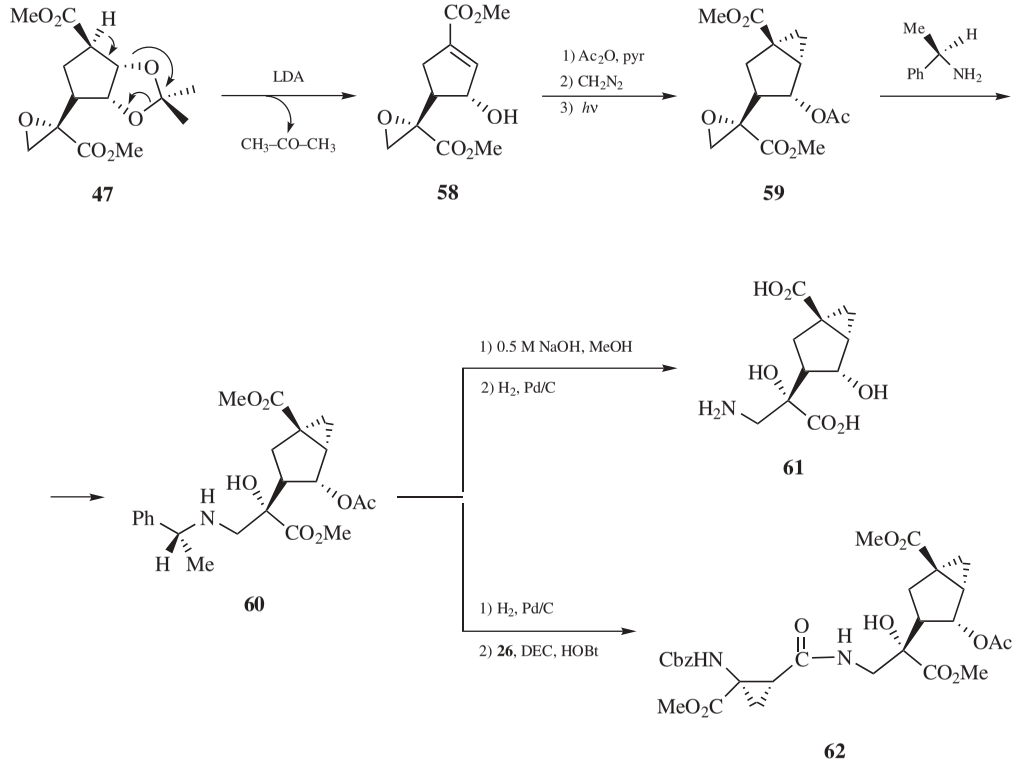
The synthesis of optically pure isoserine derivatives **46** was accomplished by regioselective oxirane ring opening by chiral amines such as (*R*)-α-methylbenzylamine, (*R*)-phenylglycine methyl ester, and (1*R*,2*S*)-norephedrine.[26] Benzyl amine **46a** was submitted to hydrogenolysis, affording amine **56**, which was coupled (HOBt, DEC) with (−)-cyclo-Asp-OMe (vide supra), giving the rigid polyfunctional β-dipeptide **57** in 72% yield (Scheme 5.15).[30] The enantiomer of **57** was prepared by condensation of (+)-cyclo-Asp-OMe with amine **55** (Scheme 5.14).

Locked-cyclopentane derivatives were synthesized as follows. Elimination of acetone was promoted by treatment of acetonide **47** with lithium diisopropylamide (LDA), giving unsaturated ester **58** (Scheme 5.16). Acetylation of the allylic



46a **56** **57**

Scheme 5.15

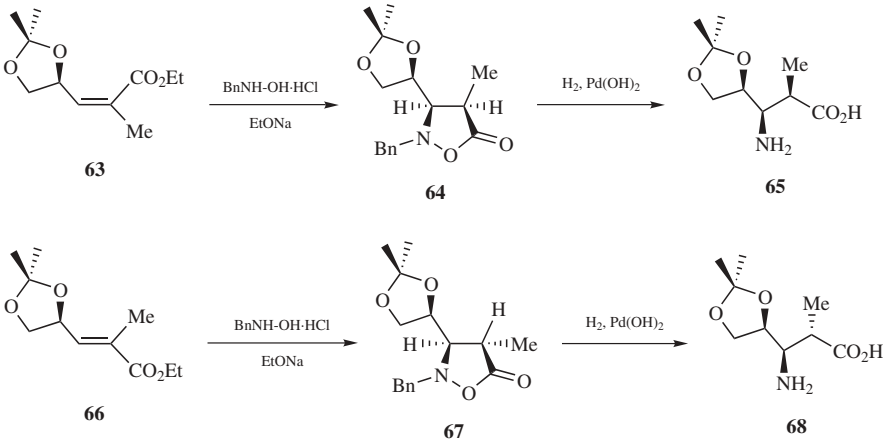

MeO2C
H
O
O
O
CO2Me
47
LDA
CH3–CO–CH3
CO2Me
OH
O
CO2Me
58
1) Ac2O, pyr
2) CH2N2
3) hν
MeO2C
OAc
O
CO2Me
59
Me
H
Ph
NH2
MeO2C
HO
OAc
H
N
Ph
CO2Me
H
Me
60
1) 0.5 M NaOH, MeOH
2) H2, Pd/C
HO2C
HO
OH
H2N
CO2H
61
1) H2, Pd/C
2) 26, DEC, HOBt
MeO2C
HO
OAc
O
H
C
N
CbzHN
CO2Me
MeO2C
62

Scheme 5.16

alcohol and reaction of the double bond with diazomethane afforded a 3 : 1 mixture of pyrazolines. Subsequent photochemical denitrogenation afforded compound **59** in 70% yield from **58**. Reaction of the epoxide in **59** with (*R*)-α-methylbenzylamine led to fully protected product **60**. Finally, saponification followed by hydrogenolysis of the benzylamine allowed us the obtention of the free amino acid **61**. Alternatively, deprotection of the amine in **60** and coupling with **26** produced the highly constrained dipeptide surrogate **62**.[31]

5.3.2 β-Substituted β-Amino Acids Through Addition of *N*-Alkyl Hydroxylamines to Conjugate Esters

The reaction of *N*-alkylhydroxylamines with unsaturated esters, lactones, and lactams has been successfully employed to synthesize β-AAs,[32] carbapenems,[33] heterocyclic nucleoside analogs,[34] and other products. Based on some experiments on achiral esters, Niu and Zhao suggested that the formation of hydroxamic acids leading to isoxazolidinones takes place through a concerted process instead of a conventional Michael addition.[35] The reaction carried out in our laboratory between the chiral (*Z*)-enoate **63** and *N*-benzylhydroxylamine was totally diastereospecific, affording isoxazolidinone **64** as a single stereoisomer in good yield (Scheme 5.17). In turn, reaction of the (*E*)-enoate **66** afforded optically pure compound **67**.[36]

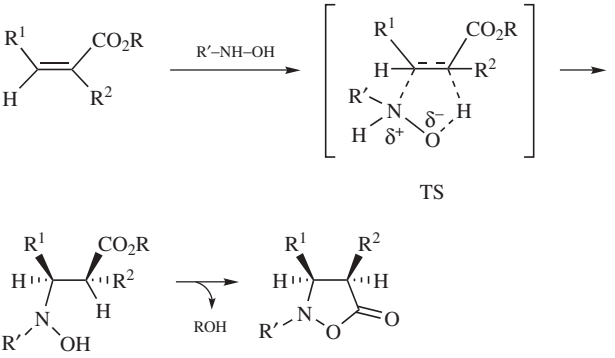


Scheme 5.17

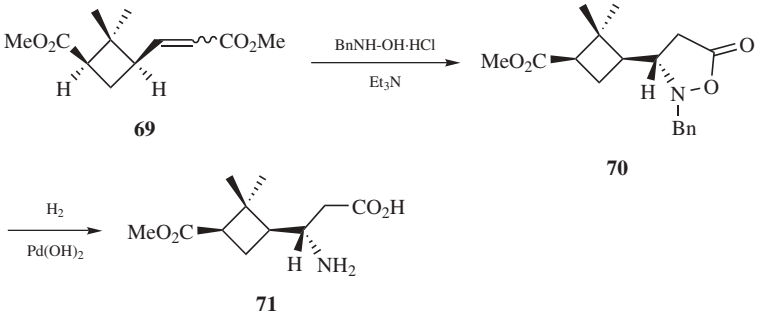
The DFT theoretical calculations considering several possible mechanistic pathways showed that the most favorable one is the concerted addition of the *N*-alkylhydroxylamine involving a cyclic transition state (Scheme 5.18).[36]

Facial diastereoselection was rationalized according to the model proposed for the 1,3-dipolar cycloadditions of diazomethane to similar substrates (vide supra).[31]

Other sterically hindered β-AAs have been prepared in our laboratory by addition of *N*-benzylhydroxylamine to cyclobutyl conjugate esters derived from



Scheme 5.18



Scheme 5.19

(−)-verbenone as chiral precursor.[37] One example is depicted in Scheme 5.19. Ester **69** in both (Z) or (E) isomeric form gave the same isoxazolidinone **70** as a single stereoisomer that led to β-AA **71** under catalytic hydrogenation.[36] Unsaturated esters of this series owing trisubstituted double bonds did not react, pointing out the high steric hindrance of the *gem*-dimethyl-substituted cyclobutane moiety. In fact, the *gem*-dimethyl group orients the preferential attack of the hydroxylamine considering the most stable conformation for these substrates (Fig. 5.5).[38]

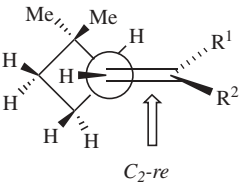
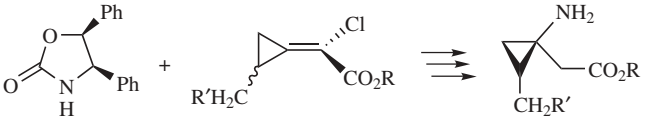


Figure 5.5 Preferred conformation for cyclobutyl verbenone derivatives orienting attack of reactants to the C_2 *re* face.

5.4 OTHER METHODOLOGIES

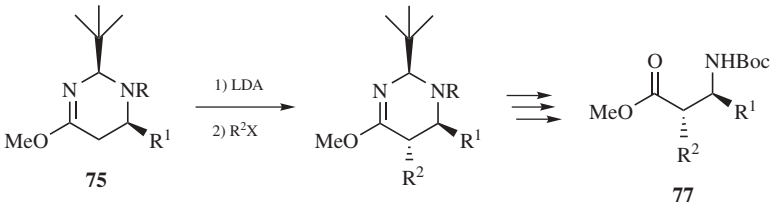
Cyclopropane derivatives **74** (Scheme 5.20) have been synthesized through the highly diastereoselective conjugate addition of optically active oxazolidinone **72** to cyclopropylidene acetates **73**.[39]



72 **73** **74**

Scheme 5.20

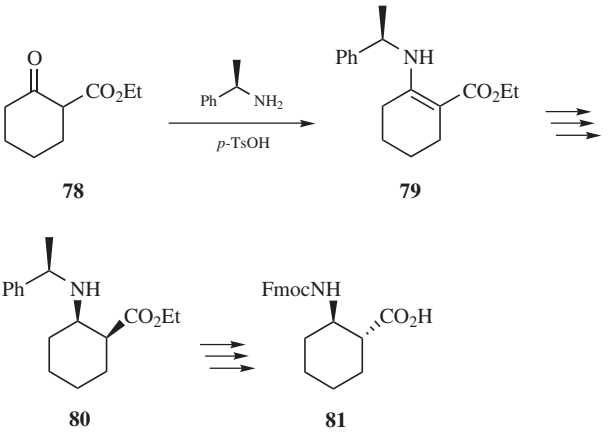
Seebach and co-workers have developed a methodology to prepare α-branched β-AA methyl esters **77** (Scheme 5.21) by alkylation of chiral lithium enaminates derived from tetrahydropyrimidines **75** followed by hydrolysis and protection of the amine.[40]



75 **76** **77**

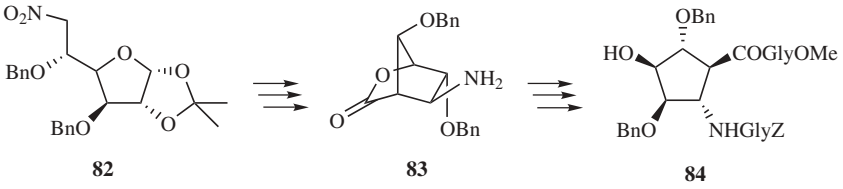
Scheme 5.21

Schinneri et al. have synthesized partially protected *trans*-2-aminocyclohexane carboxylic acid (ACHC) **81** (Scheme 5.22) from cyclohexanone **78** through the formation of the enamine derived from (*R*)-α-methylbenzylamine, subsequent reduction of the double bond in **79** to afford *cis*-amino ester **80**, and epimerization of the α-carbonyl stereogenic center.[41] Moreover, both enantiomers of *trans*-ACHC have been prepared by chiral resolution of racemic *trans*-1,2-cyclohexanedicarboxylic acid by using (*R*)- or (*S*)-1-phenylethylamine, cyclization to the anhydride, amide formation, and subsequent Hofmann-type degradation.[42] ACHCs are present in β-peptides adopting a helical conformation defined by 14 members (14-helix).[1]



Scheme 5.22

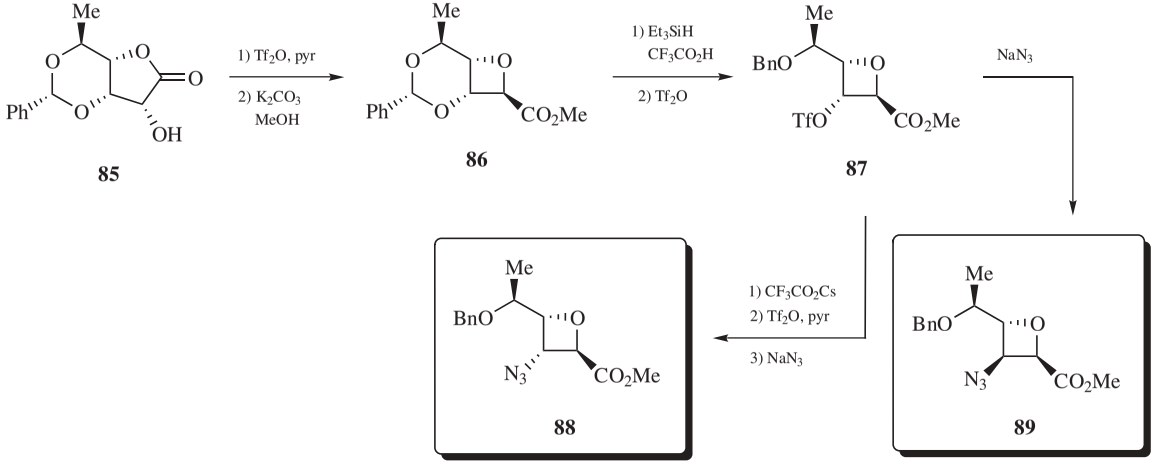
Polyhydroxylated cyclopentane β-AAs have been synthesized and incorporated into petides such as **84** (Scheme 5.23) by transformation of nitrohexofuranose **82** into cyclopentylamines, oxanorbornanone **83** being a key intermediate.[43]

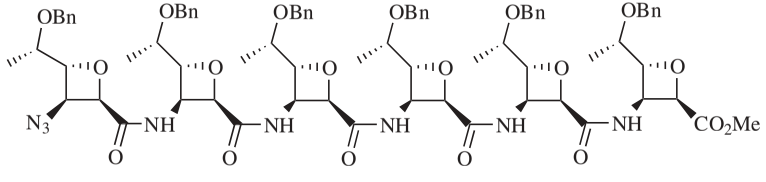


Scheme 5.23

Barker and co-workers have synthesized *cis*- and *trans*-3-azidooxetane-2-carboxylates as scaffolds for incorporation of oxetane β-AAs into oligomers.[44] The synthetic strategy is illustrated in Scheme 5.24. Compound **85**, derived from L-rhamnose, gave the oxetane **86** by treatment with triflic anhydride followed by saponification with potassium carbonate in methanol. Regioselective reduction of the benzyl ketal with triethylsylane and trifluoroacetic acid and subsequent esterification of the remaining free hydroxyl group produced compound **87**. Stereodivergent routes from triflate **87** led to diastereomeric azides **88** and **89**. After hydrolysis of the ester and reduction of the azide to amine, these compounds were converted into the corresponding hexamers by standard coupling techniques. As an instance, β-hexapeptide **90** forms a left-handed 10-helix. Other related hexapeptides showed a similar conformational preference.[45]

(−)-Cispentacin and analogs have been synthesized by means of stereoselective conjugate additions,[46] intramolecular nitrone cycloadditions,[47] and lipase-catalyzed hydrolysis of β-lactams,[48] respectively.





90

Scheme 5.24

ACKNOWLEDGMENTS

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CHAPTER 6

Catalytic Enantioselective Mannich Reactions

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6.1 INTRODUCTION

Asymmetric Mannich reactions provide useful routes for the synthesis of optically active β-amino ketones or esters, which are versatile chiral building blocks for the preparation of many nitrogen-containing, biologically important compounds. (General review articles on the Mannich reaction are given in Ref. 1.) While many approaches using chiral imines or chiral nucleophiles have been reported, these diastereoselective reactions have some disadvantages. First, the procedures to introduce chiral auxiliaries to substrates and to remove them after the diastereoselective reactions are often tedious. Second, more than stoichiometric amounts of chiral sources are needed to obtain chiral compounds according to these reactions. To address these issues, catalytic enantioselective reactions would be the most promising because large quantities of chiral compounds can be prepared using small amounts of chiral sources. However, examples of catalytic enantioselective Mannich reactions are much fewer than those of related aldol reactions (reactions of aldehydes). In 1991, Corey et al. reported the first example of the enantioselective synthesis of β-amino acid esters using chiral boron enolates which were prepared in situ from achiral reagents.[2] Ishihara et al. disclosed enantioselective reactions of achiral imines with an achiral ketene silyl acetal using a Brønsted acid-assisted chiral Lewis acid.[3] In both cases, however, stoichiometric amounts of chiral sources were needed. Enantioselective Mannich reactions using small amounts of chiral sources have not been reported before 1997. After that, several excellent examples

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of catalytic enantioselective reactions of imines have been reported, and these works have influenced synthetic organic chemistry as well as other fields of chemistry and chemistry-based science. (For more recent review articles on the catalytic asymmetric Mannich reactions, see Ref. 4.) This chapter presents an overview of catalytic enantioselective Mannich and related reactions to obtain optically active β-amino acid derivatives.

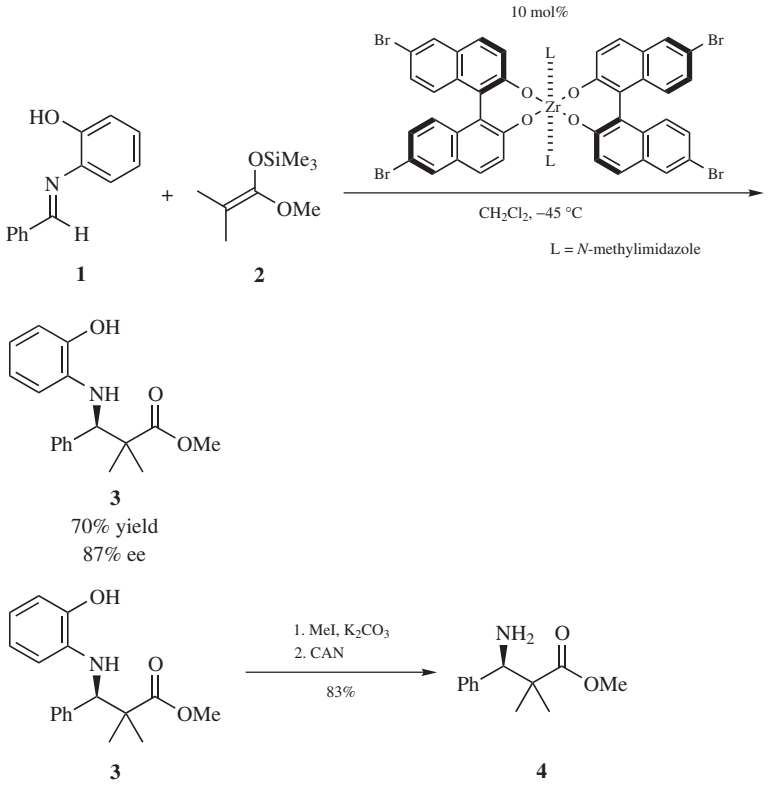
6.2 CATALYTIC ENANTIOSELECTIVE MANNICH REACTIONS USING CHIRAL LEWIS ACID CATALYSTS

6.2.1 Aryl or Alkyl Imines with Silicon Enolates

Although asymmetric reactions using chiral Lewis acids are of great current interest as one of the most efficient methods for the preparation of optically active compounds, examples using imines as electrophiles are much fewer than those using aldehydes. This is due to two main difficulties. First, many Lewis acids are deactivated or sometimes decomposed by the nitrogen atoms of starting materials or products, and even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are needed because the acids are trapped by the nitrogen atoms. Second, imine–chiral Lewis acid complexes are rather flexible and often have several stable conformers (including E/Z-isomers of imines), while aldehyde–chiral Lewis acid complexes are believed to be rigid. Therefore, in the reactions with imines activated by chiral Lewis acids, plural transition states would exist, decreasing the selectivities.

In 1997, the first truly catalytic enantioselective Mannich reaction of imines with silicon enolates using a novel zirconium catalyst was reported.[5] To solve the above problems, various metal salts were first screened in achiral reactions of imines with silylated nucleophiles, and finally, a chiral Lewis acid based on Zr(IV) was designed. On the other hand, regarding the problem of the conformation of the imine–Lewis acid complex, utilization of a bidentate chelation was planned; imines prepared from 2-aminophenol were used (Scheme 6.1). The *N*-substituent of the Mannich reaction product was easily removed according to Scheme 6.1. Thus, methylation of the phenolic OH of **3** using methyl iodide and potassium bicarbonate followed by deprotection using cerium ammonium nitrate (CAN) gave β-amino ester **4**. For the Zr(IV)-catalyzed Mannich reactions, not only imines derived from aromatic aldehydes but also imines from heterocyclic aldehydes worked well, and high levels of yields and enantioselectivity were attained. In the reactions with aliphatic aldehydes, high enantiomeric excesses were also obtained using the imines prepared from the aldehydes and 2-amino-3-methylphenol.

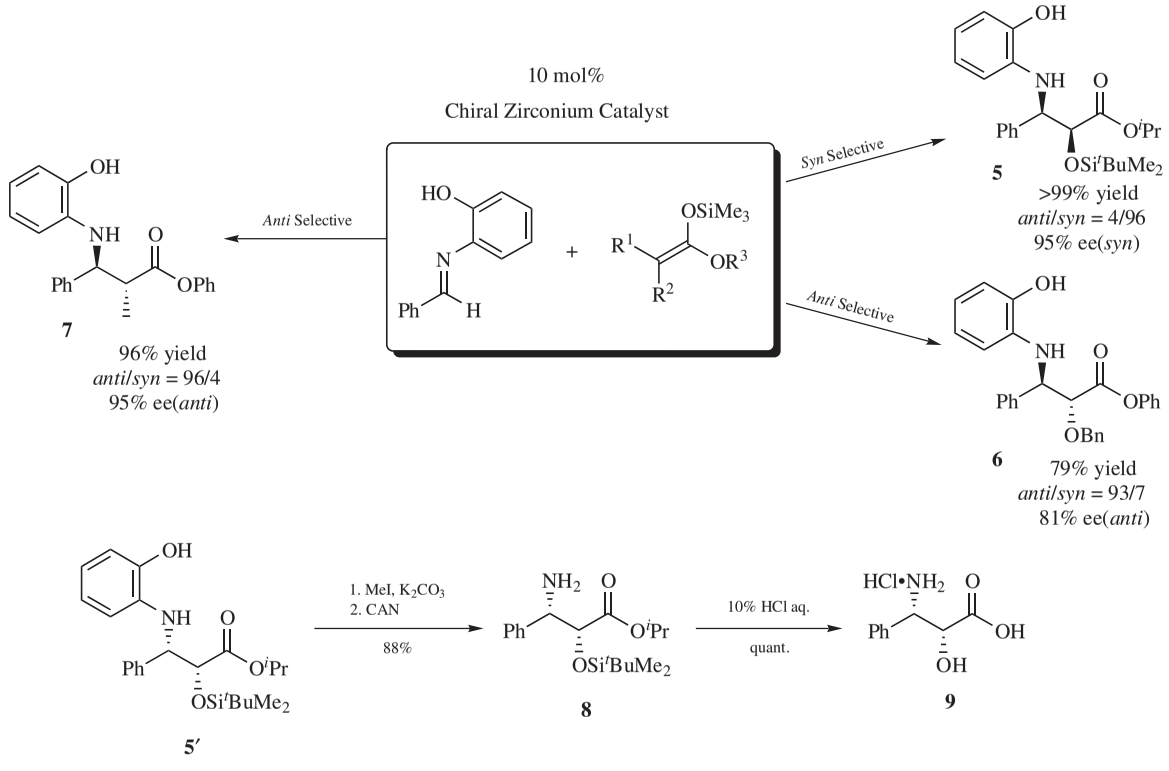
Introduction of electron-withdrawing groups at the 6,6′-positions of 1,1′-bi-2-naphthols (BINOLs) increased the Lewis acidity of Zr, improving the selectivity and the catalytic turnover number.[5c] Based on these Zr catalysts, an air-stable, storable, and highly selective chiral Lewis acid catalyst with powdered molecular sieves as a support material (ZrMS) has been developed, and ZrMS was successfully used in asymmetric Mannich reactions.[6] The catalyst was stable for more than 3 months in



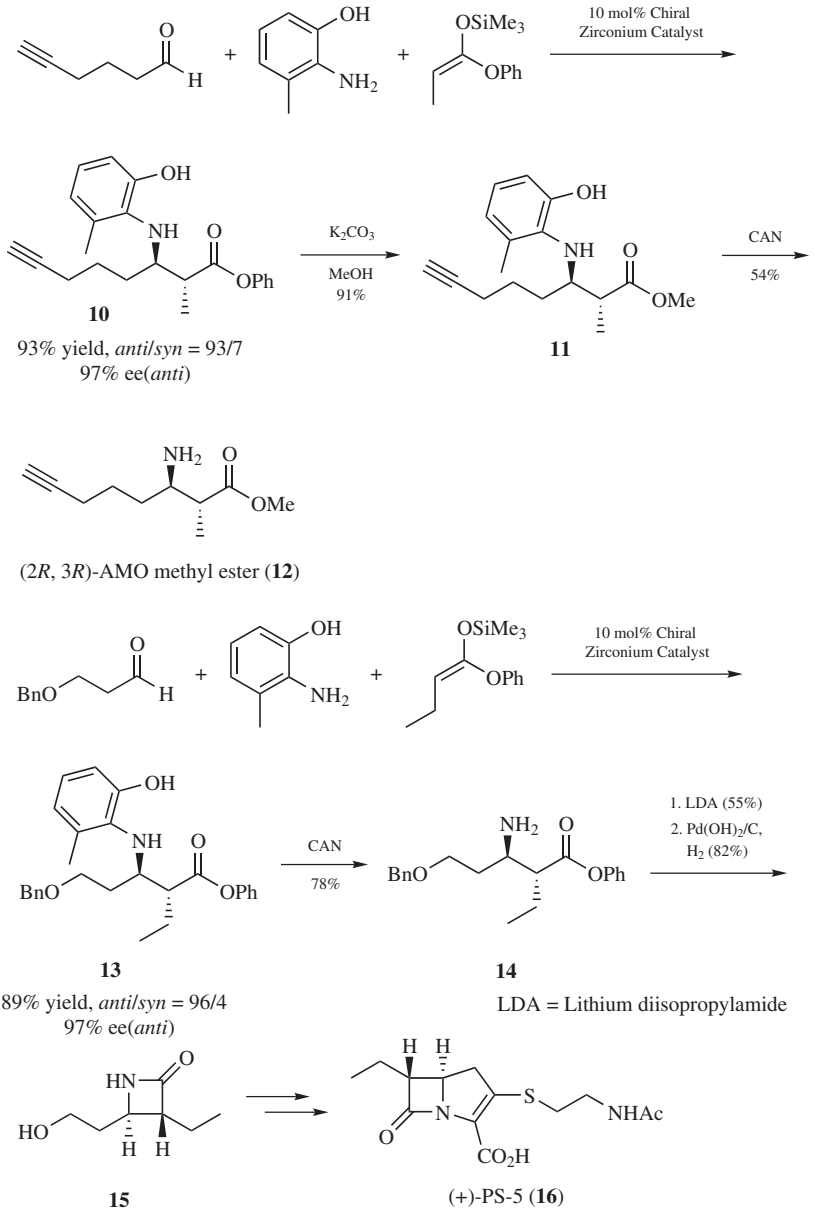
Scheme 6.1

air at room temperature without loss of activity. Moreover, the catalyst was recovered and reused.

The Zr-catalyzed Mannich reactions were applied to the synthesis of optically active β-amino alcohols; thus, catalytic diastereo- and enantioselective Mannich reactions of α-alkoxy enolates with imines (Scheme 6.2)[7] and of propionate enolates with imines (Scheme 6.3)[8] have been developed. The *O*-substituents of ketene silyl acetals and solvents also influenced the yield and selectivity. These reactions provide an efficient method for the synthesis of both *syn*- and *anti*-amino alcohol units in high yields with high selectivities. The protocol includes catalytic diastereo- and enantioselective carbon–carbon bond-forming processes, and the syn and anti selectivities were controlled by choosing the protective groups of the α-alkoxy parts and the ester parts of the silicon enolates. Since both enantiomers of the chiral source, (*R*)- and (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol, are commercially available, all four stereoisomers of β-amino alcohol units can be prepared according to this method. The utility of this protocol has been demonstrated by the concise synthesis of (*2R,3S*)-3-phenylisoserine hydrochloride (**9**), which is a precursor of the C-13 side chain of paclitaxel, known to be essential for its biological activity.


10 mol%
Chiral Zirconium Catalyst
Anti Selective
Syn Selective
Anti Selective
7
96% yield
anti/syn = 96/4
95% ee(anti)
5
>99% yield
anti/syn = 4/96
95% ee(syn)
6
79% yield
anti/syn = 93/7
81% ee(anti)
1. MeI, K2CO3
2. CAN
88%
10% HCl aq.
quant.
5′
8
9

Scheme 6.2

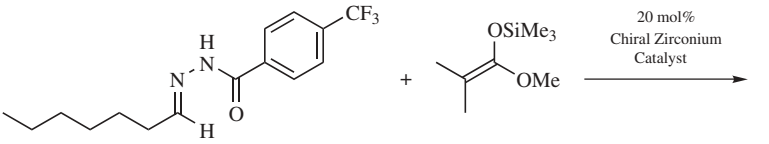


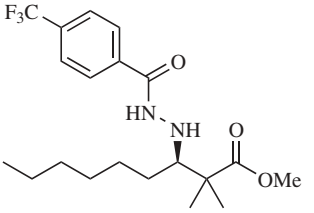
Scheme 6.3

On the other hand, an efficient method for the preparation of *anti*-α-alkyl-β-amino acid derivatives based on highly diastereo- and enantioselective Mannich reactions using a chiral zirconium catalyst has been developed. Synthetic utility of this reaction was demonstrated by the concise preparation of (*2R*, *3R*)-methyl

3-amino-2-methyl-7-octynoate (AMO methyl ester) (**12**), which is one of the units of a cytotoxic cyclic depsipeptide from marine mollusk onchidin, and an intermediate of carbapenem antibiotic (+)-PS-5 (**16**) (Scheme 6.3).

Moreover, this catalyst system can be utilized in Mannich reactions using hydrazone derivatives (Scheme 6.4)[9] as well as Aza Diels–Alder reactions,[10] Strecker reactions,[11] allylation of imines,[12] intramolecular [3 + 2]-cycloaddition reactions,[13] and so on (this catalyst system was also utilized for aldol and hetero Diels–Alder reactions[14]). Furthermore, a chiral iron catalyst,[15] which is one of the most abundant elements in nature, less harmful, and readily accessible, has been developed and successfully used in Mannich reactions of imines with silicon enolates.





60% yield, 96% ee

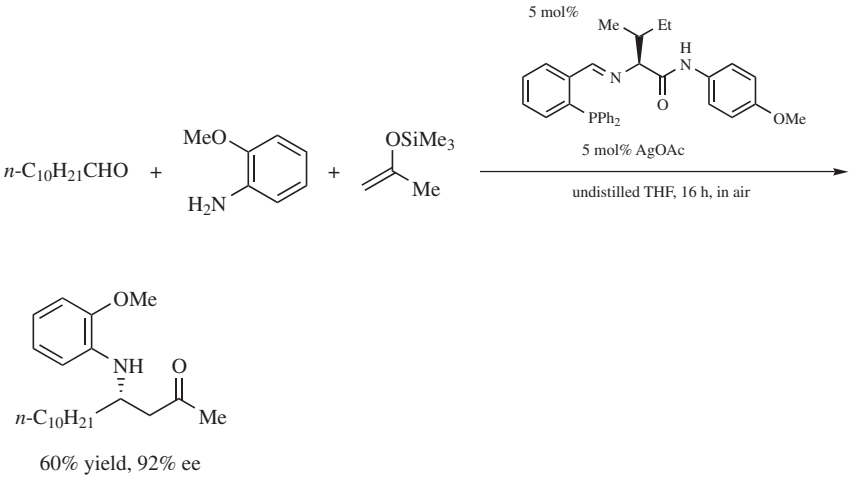
Scheme 6.4

Use of 2,2′-diphenyl-[3,3′-biphenanthrene]-4,4′-diol (VAPOL) instead of BINOL in a similar zirconium system was reported.[16] The rate of the reactions of imines with ketene silyl acetals using the VAPOL catalyst is slower with imines generated from substituted aminophenols; however, this effect can be offset by performing the reaction at higher temperature where greater turnover numbers are observed.

Vinylogous Mannich reactions of triisopyloxyfurans with aldimines prepared from aldehydes and 2-aminophenol proceeded with moderate selectivity in the presence of a catalytic amount of a Ti(IV)–BINOL complex.[17]

The catalytic asymmetric synthesis of optically active β-amino ester derivatives from benzyl nitrones and silicon enolates is reported.[18] This reaction is catalyzed by a chiral Ti(IV) complex, which is prepared from $Ti(O^iPr)_4$, (*S*)-BINOL, and achiral phenols, to afford the desired adducts in high yields and enantioselectivities. Interestingly, the absolute configuration of the products are changed by additional achiral phenols.

Silver-catalyzed asymmetric additions of silicon enolates to aryl, alkyl, alkenyl, and alkynyl imines were reported.[19] β-Amino ketones are obtained efficiently in the presence of 1–5 mol % of AgOAc and a readily available iso-Leu-derived phosphine ligand. In this reaction, all catalytic transformations are performed with undistilled solvents in air. In the reactions of imines derived from aliphatic aldehydes, a three-component process is effective (Scheme 6.5).



60% yield, 92% ee

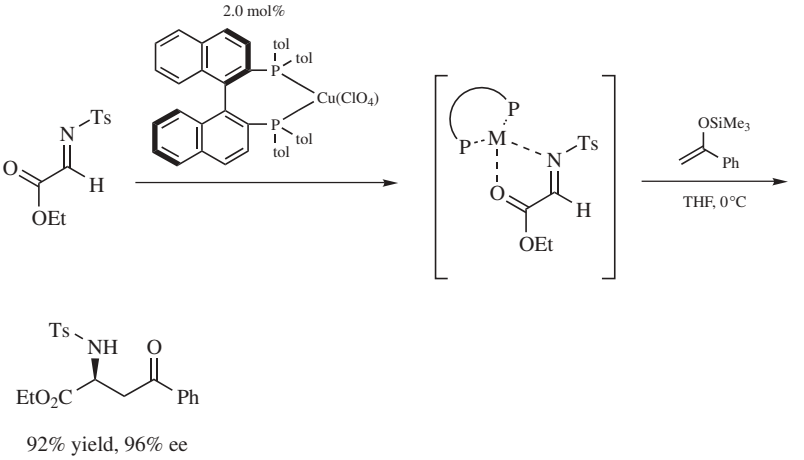
Scheme 6.5

6.2.2 α-Imino Esters with Silicon Enolates

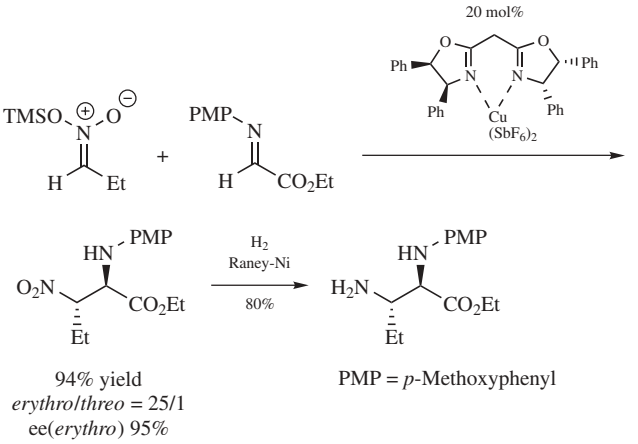
The catalytic asymmetric addition of organic nucleophiles to α-imino esters has emerged as one of the most promising and intensely investigated routes to optically enriched α- and β-amino acid derivatives. The importance of α-imino esters stems not only from the vast appeal of the potential product classes but also from their remarkable reactivity as highly electrophilic imines.

In the presence of water-free late transtition metal–phosphine cation complexes as Lewis acids, glyoxylate–tosylamine imine reacted with silicon enolate stereoselectivity.[20] It was proposed that the imine coodinated to the metal such as Ag(I), Pd(II), and Cu(I) in a bidentate manner.[20a] The copper-based catalyst was the most effective, and the desired product was obtained in high yields with high enantioselectivities (Scheme 6.6). α-Imino esters would make excellent electrophilic substrates for catalytic asymmetric reactions, where Lewis acids coordinate to both N and O atoms of the imines simultaneously in a chelate interaction that could enhance the selectivities.

Highly enantio- and diastereoselective copper–bisoxazoline-catalyzed aza-Henry reactions of silyl nitronates with an α-imino ester have been reported (Scheme 6.7).[21] Optically active α,β-diamino acid derivatives were prepared using these reactions.



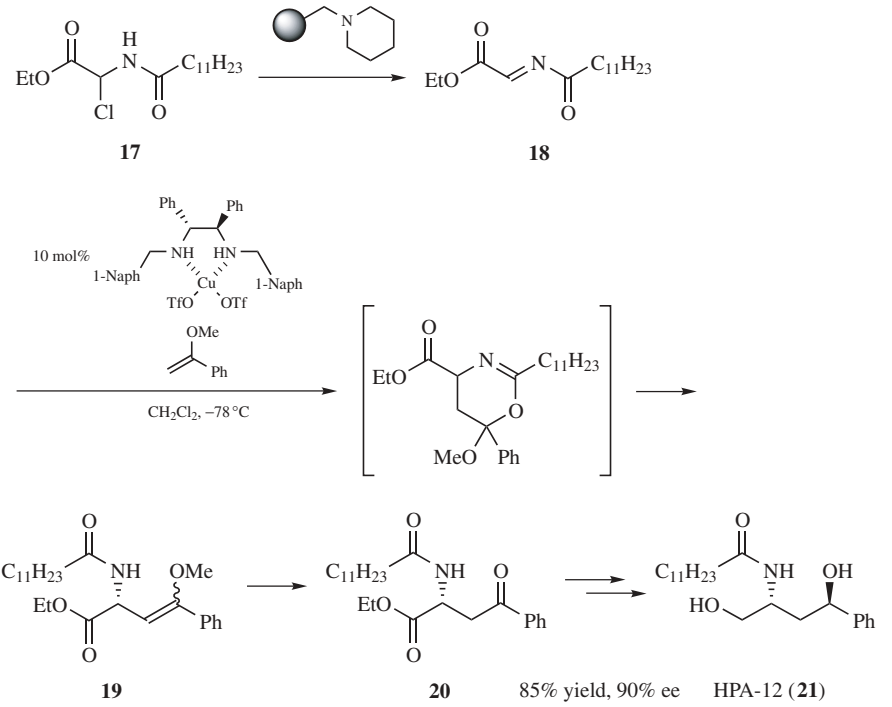
Scheme 6.6



Scheme 6.7

A convenient method for the preparation of *N*-acylimino esters using a polymer-supported amine has been developed. *N*-Acylimino esters were successfully prepared in catalytic asymmetric Mannich reactions with a chiral copper catalyst prepared from Cu(II) triflate and a chiral diamine ligand.[22] This reaction proceeded smoothly in high yields with excellent enantioselectivities, not only using silicon enolates derived from ketones, esters, and thioesters as for enolate components but also with alkyl vinyl ethers. In the reactions with alkyl vinyl ethers, the initial adducts are vinyl ethers, which are converted to the corresponding amino acid derivative under acidic conditions. A possible mechanism for the formation of vinyl

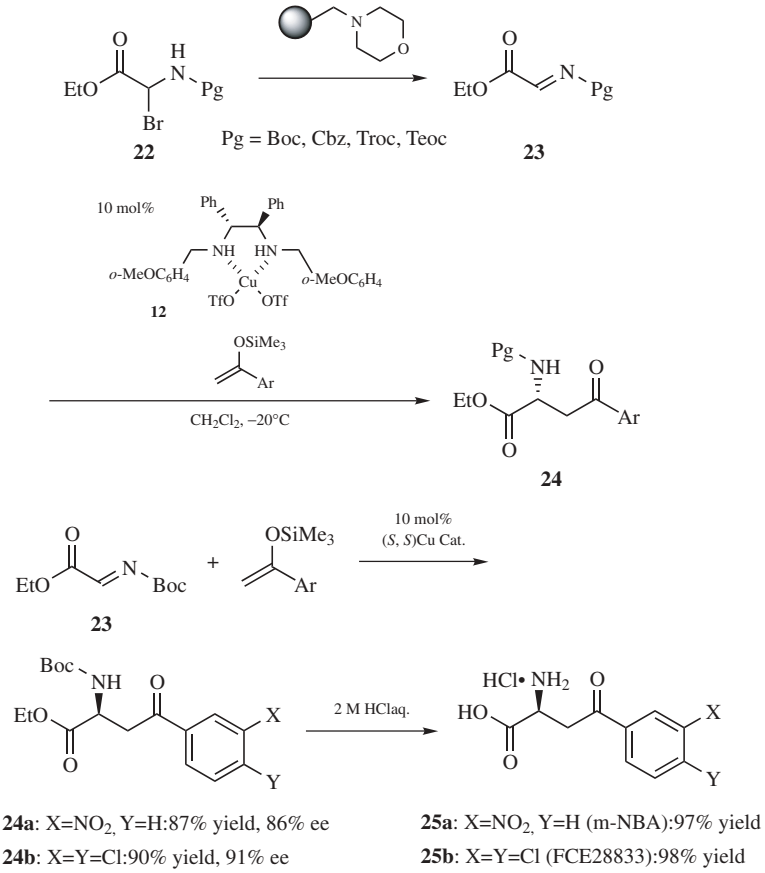
ethers is [4 + 2]-cycloaddition of *N*-acylimino esters to starting vinyl ethers followed by proton transfer. It was also reported that a new inhibitor of ceramide trafficking from endoplasmic reticulm to the site of sphingomyelin (SM) synthesis, HPA-12 (**21**), was efficiently synthesized using this catalytic asymmetric reaction (Scheme 6.8).[22a,c]



Scheme 6.8

To extend the applicability of the reaction, α-imino esters bearing other readily removable carbamates such as *N*-Boc-, *N*-Cbz-, *N*-Troc-, and *N*-Teoc-α-imino esters were investigated.[22b] α-Imino esters smoothly reacted with silicon enolates derived from ketones to afford the desired Mannich adducts in high yields with high enantioselectivity using a $Cu(OTf)_2$–diamine comlex. Mannich adducts **24a** and **24b** were successfully transformed to *m*-NBA (**25a**) and FCE28833 (**25b**), respectively, in excellent yields (Scheme 6.9). A single recrystallization of **25a** and **25b** increased the enantiomeric purity to 98 and 95% ee, respectively. These compounds are known to be selective kynurenine 3-hydroxylase inhibitors, which are promising drugs for neurological diseases.

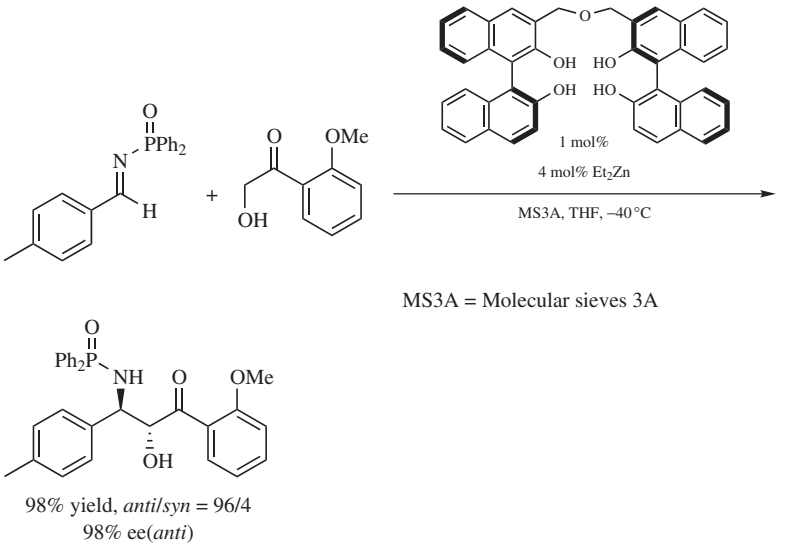
The use of samarium iodo bis-binaphthoxide as an enantioselective catalyst for the addition of ketene silyl acetals to α-imino esters was also reported. Under optimized conditions, the presence of aniline as an additive was found to be effective.[23]



Scheme 6.9

6.2.3 Direct Reactions

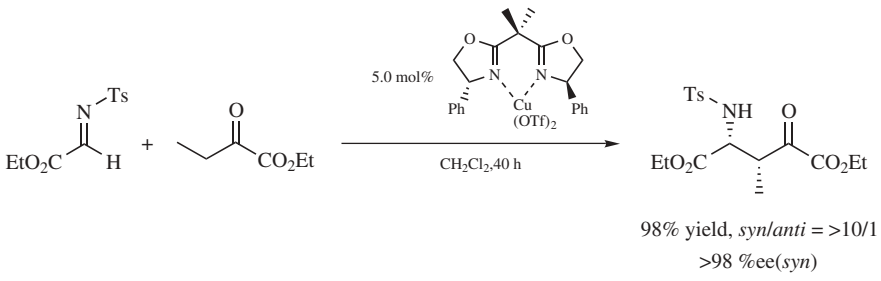
A direct catalytic asymmetric Mannich reaction is one of the most powerful methods for atom-economical synthesis.[24] The direct catalytic asymmetric Mannich reaction using unmodified ketones was reported using cooperactive catalysis of a AlLibis((*R*)-binaphtoxide) complex [(*R*)-ALB] and $La(OTf)_3 \cdot nH_2O$.[25] It was also reported that enantioselective and diastereoselective catalytic nitro-Mannich reactions of *N*-phosphinoylimines proceeded smoothly using a complex consisting of ALB and *tert*-BuOK.[26] More recently, anti-selective direct catalytic asymmetric Mannich reactions of 2-hydroxy-2′-methoxyacetophenone with *N*-diphenylphosphinoyl imines using a Et_2Zn/linked BINOL complex have been reported (Scheme 6.10).[27]



Scheme 6.10

On the other hand, syn-selective catalytic asymmetric direct Mannich reactions of 2-hydroxy-acetophenone derivatives with α-imino esters using a dinuclear zinc catalyst were reported.[28]

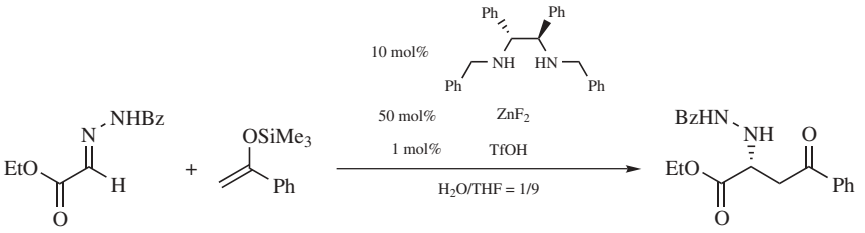
It was also disclosed that diastereo- and enantioselective Mannich reactions of activated carbonyl compounds with α-imino esters proceeded smoothly in the presence of a catalytic amount of a chiral Lewis acid derived from $Cu(OTf)_2$ and bisoxazoline (BOX) ligand (Scheme 6.11).[29] Catalytic enantioselective addition of nitro compounds to imines,[30] α-amination reactions of 2-keto esters,[31] Mannich reactions of malonates or β-keto esters with imines,[32] and Mannich reactions of glycine derivatives with imines[33] also proceeded under similar reaction conditions.



Scheme 6.11

6.2.4 Catalytic Asymmetric Mannich Reactions in Water

In recent years, organic reactions in aqueous media have attracted a great deal of attention, not only because these reactions eliminate the necessity of vigorous drying of solvents and substrates, but also because unique reactivity and selectivity are often observed in aqueous reactions.[34] The first examples of Mannich reactions in aqueous media proceeded smoothly using a combination of ZnF_2 and a chiral diamine (Scheme 6.12).[35] In this reaction, a catalytic amount of TfOH dramatically increased the yield. It was assumed that this reaction proceeded with double activation where Zn^{2+} acted as a Lewis acid to activate the hydrazono ester and the fluoride anion acted as a Lewis base to interact with the silicon atom of the enolate. The N–N bond of the hydrazine was easily cleaved by SmI_2.



89% yield, 92% ee

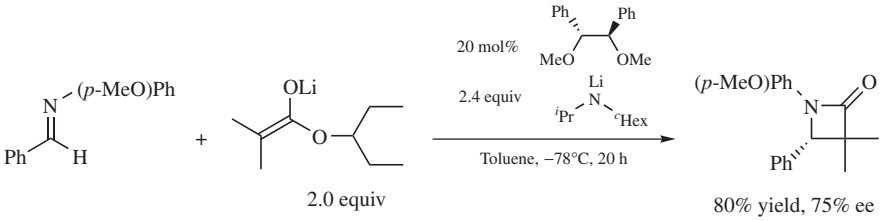
Scheme 6.12

6.3 CATALYTIC ASYMMETRIC MANNICH REACTIONS VIA METAL ENOLATES

Metal enolates are powerful nucleophils for the formation of carbon–carbon bonds.[36] Indeed, there have been significant achievements in the development of the chiral esters and their equivalents even though these require at least stoichiometric amounts of chiral auxiliaries.

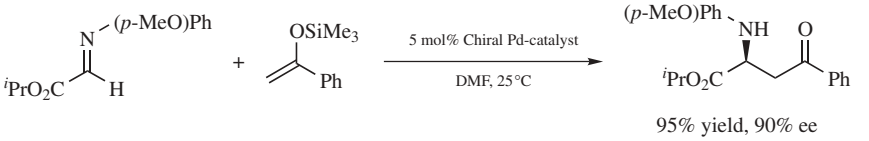
Catalytic asymmetric Mannich reactions of lithium enolates with imines were reported in 1997 using an external chiral ligand.[37] First, it was found that reactions of lithium enolates with imines were accelerated by addition of external chiral ligands. Then, it was also revealed that reactions were accelerated in the coexistence of excess amounts of lithium amides in most cases. A small amount of a chiral source was then used in the asymmetric version (Scheme 6.13), and chiral ligands were optimized to succeed in the catalytic turnover improvement.[37b]

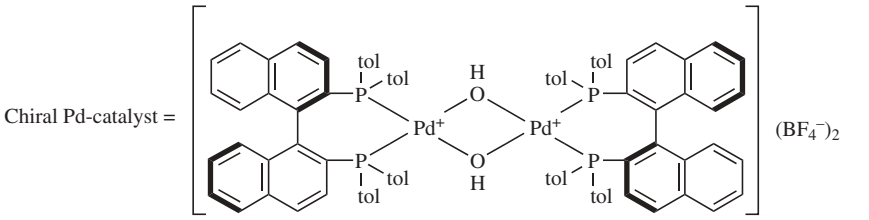
In 1998, it was found that a new type of Pd(II) binuclear complex was effective for Mannich reactions of an imine derived from glyoxylate and anisidine with silicon enolates.[38] In these reactions, use of solvents including a small amount of water was essential. Indeed, water was revealed to play an important role in this system; namely, water not only activated the Pd(II) complex to generate a cation



Scheme 6.13

complex but also cleaved the N–Pd bond of the intermediate to regenerate the chiral catalyst. Nuclear magnetic resonance (NMR) and electrospray ionization (ESI)-mass spectrometry (MS) analysis revealed that this reaction proceeded via an optically active palladium enolate. A unique binuclear palladium-sandwiched enolate was obtained in the reaction of a μ-hydroxo palladium complex with a silyl enol ether (Scheme 6.14).





Scheme 6.14

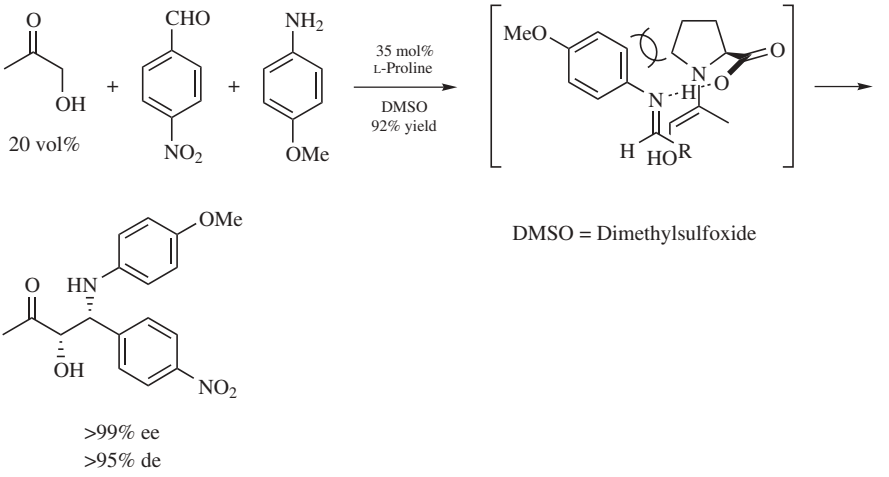
It was also reported that azaferrocene catalyzed enantioselective [2 + 2]-cycloaddition of a ketene with an imine to provide a β-lactam.[39]

6.4 CATALYTIC ASYMMETRIC REACTION USING AN ORGANOCATALYST

Many enzymes are remarkable asymmetric catalysts performing reactions effectively and selectively. Use of a short peptide as a catalyst would allow an expansion beyond the repertoire amino acids while conserving the advantages of a small-molecule catalyst. The ability of an enzyme's primary structure to mediate catalysis suggests that short peptides could also be successful catalysts. More

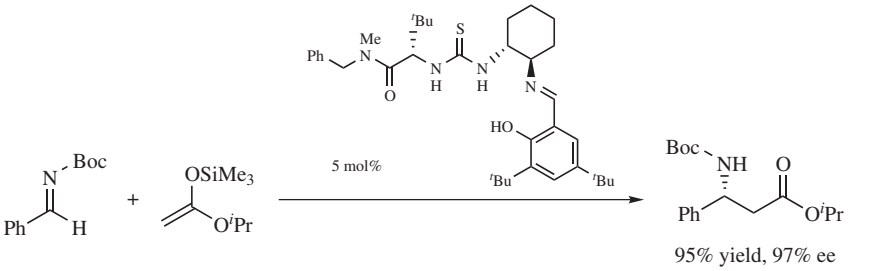
recently, examination of short peptide catalysts has resulted in the discovery of very selective catalysts.[40]

It was reported that proline catalyzed direct catalytic asymmetric Mannich reactions of hydroxyacetone, aldehydes, and aniline derivatives (Scheme 6.15).[41] (Recently, Hayashi et al. reported one-pot cross Mannich reaction and application of high pressure induced by water-freezing reaction.[42]) Not only aromatic aldehydes but also aliphatic aldehydes worked well in this reaction, and good to excellent enantioselectivity and modest to excellent yields were observed. Mannich reactions of glyoxylate imines with aldehydes or ketones were also successfully performed.[43]



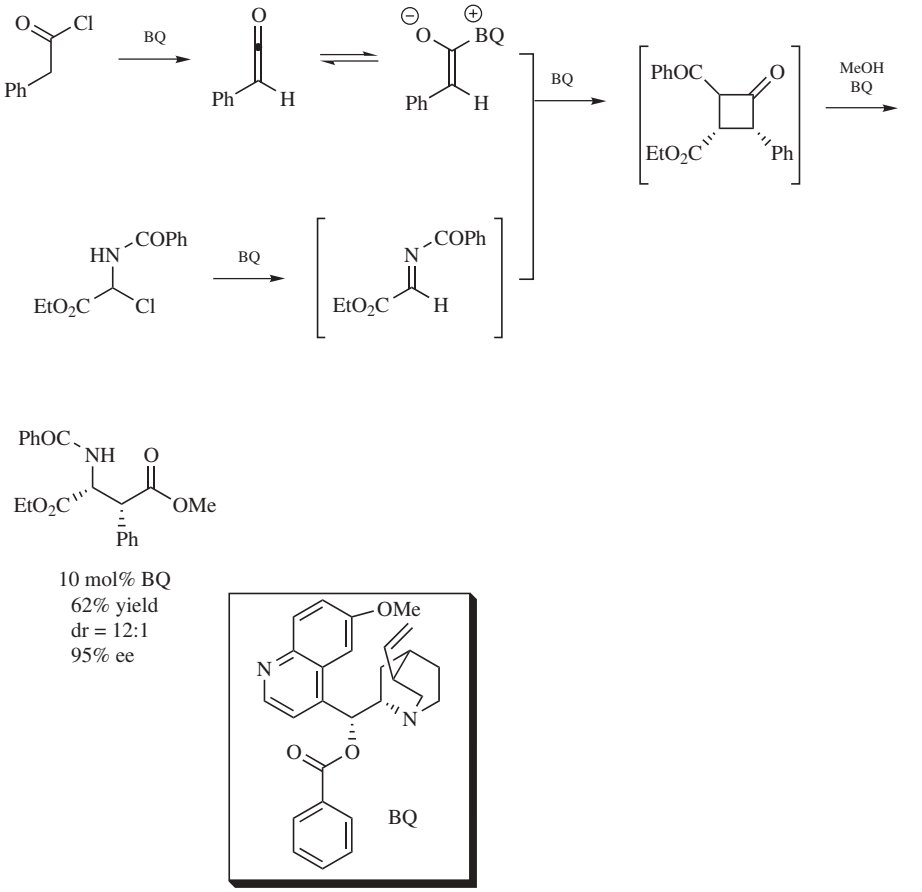
Scheme 6.15

Urea derivatives emerged as useful catalysts for the asymmetric hydrocyanation of *N*-allyl or *N*-benzyl aldimines and were reported to provide a highly efficient route to *N*-Boc-protected β-amino acids via the enantioselective addition of silyl ketene acetals to *N*-Boc-aldimines (Scheme 6.16).[44]

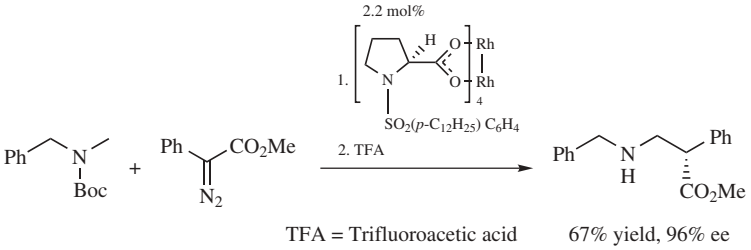


Scheme 6.16

It was reported that benzoquinine derivatives catalyzed reactions of ketenes with imines to afford β-lactams stereoselectively.[45] Moreover, a new method for catalytic asymmetric synthesis of β-substituted aspartic acid derivatives was disclosed. The nucleophilic catalyst serves up to four discrete roles in a one-pot procedure: catalytic dehydrogenation of acid chlorides to form ketenes; catalytic dehydrohalogenation of α-chloroamines to form the corresponding imines; catalyzed [2 + 2]-cycloaddition to produce intermediate acyl β-lactams; and nucleophilic ring opening to afford optically enriched β-substituted aspartic acids in high enantio- and diastereoselectivities (Scheme 6.17).



Scheme 6.17



Scheme 6.18

6.5 MISCELLANEOUS

Metal-stabilized carbenoid intermediates have been impressively used for intramolecular asymmetric C–H activation.[46] Enantioselective intermolecular C–H insertion using metal carbenoid intermediates provided a β-amino ester in high enantioselectivity (Scheme 6.18).[47]

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CHAPTER 7

Enantioselective Synthesis of β-Amino Acids via Stereoselective Hydrogenation of β-Aminoacrylic Acid Derivatives

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7.1 INTRODUCTION

An early review article on the subject of enantioselective synthesis of β-amino acids[1] pointed out the scarcity of reports on catalytic asymmetric hydrogenation of prochiral β-(acylamino)acrylic acid derivatives to provide enantioenriched β-amino acids[2–5] (Scheme 7.1*a*). This situation seemed unjustified in view of the enormous success achieved in the rhodium-catalyzed enantioselective hydrogenation of α-(acylamino)acrylic acids and their esters, which has become a standard procedure for the synthesis of optically active α-amino acids[6–10] (Scheme 7.1*b*).

The pioneering study of Achiwa and Soga[3] consisted of the catalytic asymmetric hydrogenation of prochiral 3-aminoacrylic acid derivatives **1** in the presence of chiral catalyst **2** to give the optically active *N*-acyl β-amino esters **3** in modest enantiomeric purities (ee 2–56%) (Scheme 7.2).

Based on previously successful employment of BINAP–transition metal complexes [BINAP = 2,2′-bis(diarylphosphino)-1,1′-binaphthyl] as catalysts for the enantioselective hydrogenation of α-(acylamino)acrylic acids,[11] Lubell and coworkers examined the enantioselective reduction of β-enamido esters (*Z*)-**4** and

Enantioselective Synthesis of β-Amino Acids, Second Edition
Edited by Eusebio Juaristi and Vadim A. Soloshonok
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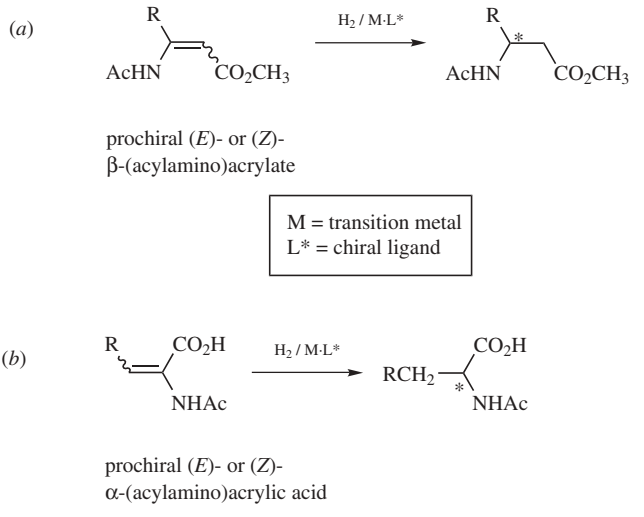
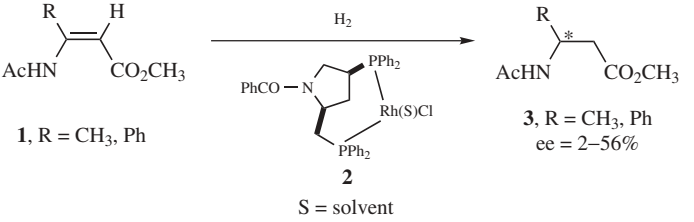


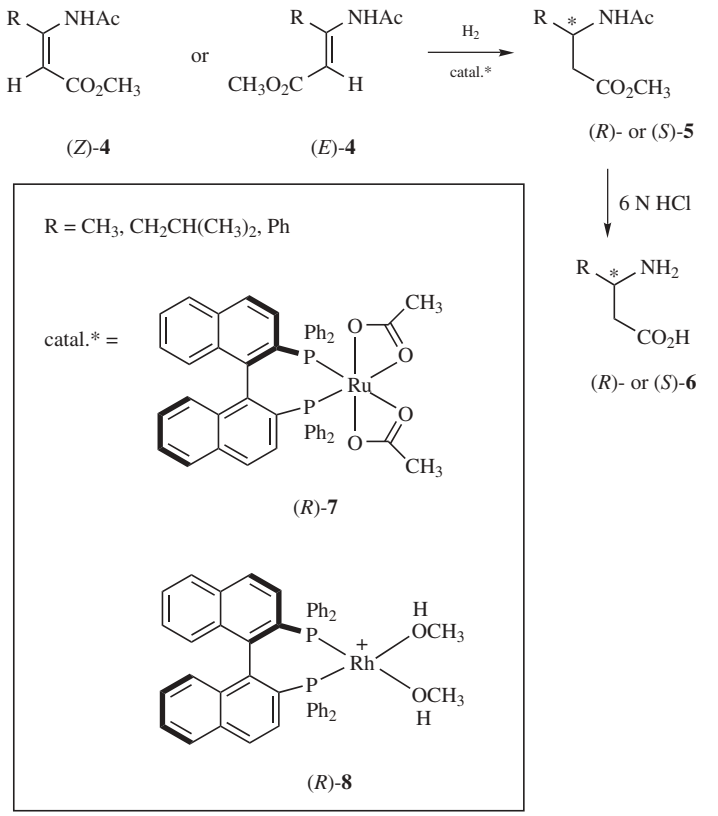
Scheme 7.1



Scheme 7.2

(*E*)-**4** to prepare β-amino acid derivatives **5**, which were converted to β-amino acids (*R*)-**6** and (*S*)-**6** on treatment with 6 N HCl[5] (Scheme 7.3).

Lubell et al.[5] examined first the hydrogenation of (*Z*)-**4** and (*E*)-**4** using (*R*)-BINAP•$Ru(OAc)_2$ complex (*R*)-**7**. The results are summarized in Table 7.1 and exhibit a dramatic effect of the substrate's double-bond configuration on the stereoselectivity of the process. Thus, hydrogenation of (*Z*)-**4** ($R = CH_3$) with 0.5 mol % of (*R*)-**7** in solvent methanol, at room temperature and under 4 atm of hydrogen, provided β-amino ester (*R*)-**5** in only 5% ee. By contrast, hydrogenation of stereoisomer (*E*)-**4** with the same catalyst and under the same reaction conditions afforded (*S*)-**5** ($R = CH_3$) in 92% ee and in quantitative yield. (Compare entries 2 and 4 in Table 7.1.) The enantioselectivity of the reduction reaction could be improved to 96% ee by conducting the reaction at atmospheric pressure (entry 1 in Table 7.1), whereas increasing the hydrogen pressure to 100 atm resulted in a decrease of the enantiomeric excess to 88% (entry 3).



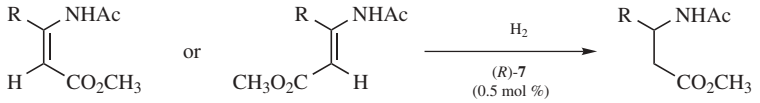
Scheme 7.3

Interestingly, the (Z) double-bond isomers, which possess an intramolecular hydrogen bond between amide and ester groups, are more reactive but are hydrogenated with poor enantioselectivity.

When the cationic $[Rh(I)\cdot(R)\text{-BINAP}\cdot(CH_3OH)_2]^+ClO_4^-$, (*R*)-**8**, catalyst was employed in the hydrogenation of either (*E*)-**4** or (*Z*)-**4** ($R = CH_3$) enamido ester, product (*R*)-**5** was obtained in modest enantiomeric purity[5] (Scheme 7.4). Therefore, the sense of asymmetric induction by the Ru•BINAP and Rh•BINAP complexes was opposite (Scheme 7.4).

In the previously cited review, one of us stated that "because the enantioselective hydrogenation of prochiral 3-aminoacrylic acid derivatives under the influence of a chiral catalyst may offer the most efficient route for large scale preparation of enantiopure β-amino acids, it is not dangerous to predict that many more developments will appear in time" (Ref, 1, p. 6). The following account discusses some of the impressive developments that, indeed, have taken place in the last 5 years.

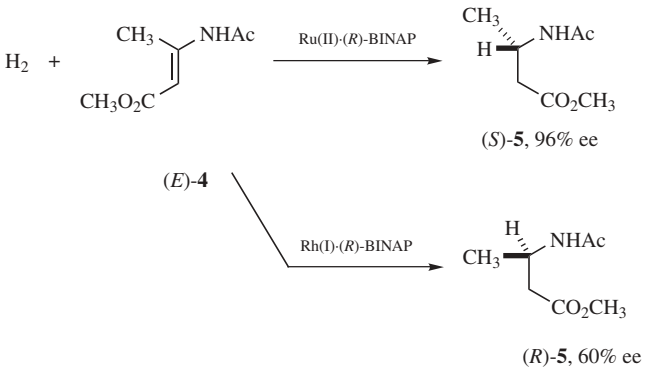
TABLE 7.1 Asymmetric Hydrogenation of Enamido Esters (*Z*)-4 and (*E*)-4 Catalyzed by (*R*)-BINAP·Ru(OAc)$_2$, (*R*)-7[a]



(*Z*)-**4** (*E*)-**4** (*R*)- or (*S*)-**5**

Entry	Substrate Configuration	R	H_2 (atm)	Time (h)	Product % ee	Product Configuration
1	E	CH_3	1	19	96	S
2	E	CH_3	4	20	92	S
3	E	CH_3	100	19	88	S
4	Z	CH_3	4	20	5	R
5	E	Ph	4	100	90	R
6	Z	Ph	4	16	9	R

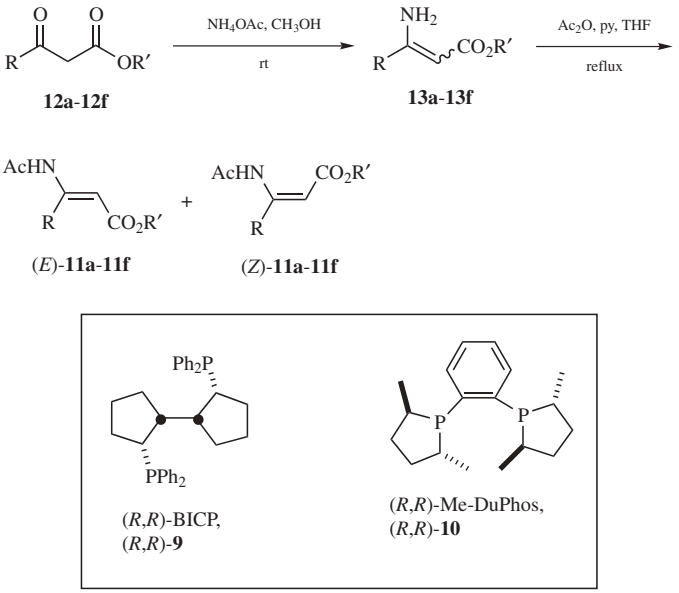
[a]From Ref. 5.



Scheme 7.4

7.2 RECENT DEVELOPMENTS: RHODIUM COMPLEXES WITH CHIRAL PHOSPHORUS BIDENTATE LIGANDS

In 1999, Zhu and co-workers[12] reported the highly enantioselective hydrogenation of β-(acylamino)acrylates for the synthesis of β-amino acid derivatives using Rh•(*R*,*R*)-BICP, (*R*,*R*)-**9**,[13] and Rh•(*R*,*R*)-Me-DuPhos, (*R*,*R*)-**10**,[14] catalysts (Scheme 7.5). The E/Z-mixture of enamides **11a–11f** were easily prepared from the corresponding β-keto esters **12**, as shown in Scheme 7.5, and the individual E/Z-isomers could be separated by column chromatography.[12]



Scheme 7.5

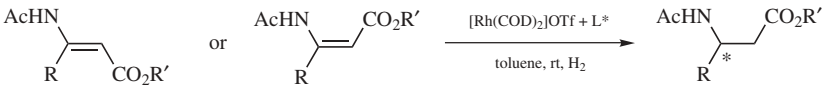
Optimal conditions for the hydrogenation reaction were established from a systematic study with prototypical substrate **11a**. Thus, under 40 psi of H_2 at ambient temperature and in toluene solvent, (*E*)-**11a** was completely reduced to (*R*)-**14a** in 24 h (entry 1 in Table 7.2). By constrast and unlike the results obtained by Lubell et al.[5] with a Ru•BINAP catalyst in which (*Z*)-**11a** was hydrogenated more rapidly than (*E*)-**11a**, higher H_2 pressure (294 psi) was required for the complete reduction of (*Z*)-**11a** (Entry 2 in Table 7.2).

As can be appreciated from the data collected in Table 7.2, hydrogenation of the E-isomer of enamides **11a–g** gave in general higher enantioselectivity than the corresponding Z-isomer, and hydrogenation of the E-isomer is faster than with the corresponding Z-isomer. Catalyst Rh•Me-DuPhos (*R*,*R*)-**10** is slightly more enantioselective than is the Rh•BICP (*R*,*R*)-**9** catalyst.

A limitation of the reaction is that only moderate enantioselectivities were obtained with aryl-substituted acrylates **11f** using either (*R*,*R*)-**9** or (*R*,*R*)-**10** catalyst (entries 21 and 22 in Table 7.2). Very recently, You and co-workers[15] discovered that 1,1′-bis(2,4-diethylphosphetanyl)ferrocene [Et-Ferrotane,[16] (*R*,*R*)-**15**] is a highly effective ligand for the Rh-catalyzed enantioselective hydrogenation of (*E*)-β-aryl-substituted β-(acylamino)acrylates (Scheme 7.6 and Table 7.3).

You et al.[15] suggested that the high selectivity observed with the use of Et-Ferrotane as chiral ligand may arise from the large P–Rh–P bite angle[17] of 98.3° for the complex [Rh•(*R*,*R*)-Et-Ferrotane]. By comparison, an average bite angle of $84.8 \pm 0.5°$ has been found for the P–Rh–P segment in seven DuPhos derivatives.[18–20]

TABLE 7.2 Rh-Catalyzed Asymmetric Hydrogenation of Enamides 11a–11g in Presence of Chiral Ligands (*R*,*R*)-BICP and (*R*,*R*)-Me-DuPhos[a]



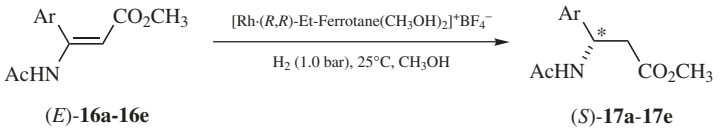
(*E*)-**11a-11g** (*Z*)-**11a-11g** (*R*)- or (*S*)-**14**

Entry	Ligand (L*)	Substrate	R	R′	H_2 (psi)	% ee	Configuration
1	(*R*,*R*)-BICP	(*E*)-**11a**	Me	Me	40	96.1	R
2	(*R*,*R*)-BICP	(*Z*)-**11a**	Me	Me	294	88.6	R
3	(*R*,*R*)-Me-DuPhos	(*E*)-**11a**	Me	Me	40	99.3	R
4	(*R*,*R*)-Me-DuPhos	(*Z*)-**11a**	Me	Me	294	63.7	R
5	(*R*,*R*)-BICP	(*E*)-**11b**	Et	Me	40	96.8	R
6	(*R*,*R*)-BICP	(*Z*)-**11b**	Et	Me	294	86.9	R
7	(*R*,*R*)-Me-DuPhos	(*E*)-**11b**	Et	Me	40	99.6	R
8	(*R*,*R*)-Me-DuPhos	(*Z*)-**11b**	Et	Me	294	21.2	R
9	(*R*,*R*)-BICP	(*E*)-**11c**	*i*-Bu	Me	40	90.9	R
10	(*R*,*R*)-BICP	(Z)-**11c**	*i*-Bu	Me	294	92.9	R
11	(*R*,*R*)-Me-DuPhos	(*E*)-**11c**	*i*-Bu	Me	40	98.5	R
12	(*R*,*R*)-Me-DuPhos	(*Z*)-**11c**	*i*-Bu	Me	294	62.4	R
13	(*R*,*R*)-BICP	(*E*)-**11d**	Me	Et	40	96.0	R
14	(*R*,*R*)-BICP	(*Z*)-**11d**	Me	Et	294	88.0	R
15	(*R*,*R*)-Me-DuPhos	(*E*)-**11d**	Me	Et	40	98.7	R
16	(*R*,*R*)-Me-DuPhos	(*Z*)-**11d**	Me	Et	294	62.3	R
17	(*R*,*R*)-BICP	(*E*)-**11e**	Pr	Et	40	96.6	R
18	(*R*,*R*)-BICP	(*Z*)-**11e**	Pr	Et	294	90.7	R
19	(*R*,*R*)-Me-DuPhos	(*E*)-**11e**	Pr	Et	40	99.6	R
20	(*R*,*R*)-Me-DuPhos	(*Z*)-**11e**	Pr	Et	294	34.4	R
21	(*R*,*R*)-BICP	(*E*/*Z*)-**11f**	Ph	Me	294	66.0	S
22	(*R*,*R*)-Me-DuPhos	(*E*/*Z*)-**11f**	Ph	Me	294	65.1	S

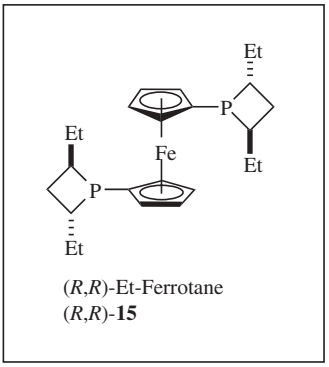
[a]From Ref. 12.

While You and co-workers[15] succeeded in the highly enantioselective hydrogenation of (*E*)-β-aryl-β-(acylamino)acrylic acid derivatives (vide supra), Tang, et al.[21] described very recently a new chiral catalyst for the asymmetric hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylates. Indeed, the Rh complex of the chiral bisphosphepine ligand (*S*,*S*,*S*)-**18**, which incorporates two stereogenic phosphorus centers, promoted excellent enantioselectivities in the asymmetric hydrogenation of acrylates (*Z*)-**19a–19i** (Scheme 7.7 and Table 7.4).

In contrast with other Rh catalysts (vide supra), the use of Rh•(*S*,*S*,*S*)-**18** catalyst led to superior enantioselectivity for the hydrogenation of the (Z)-substrates. As shown in Table 7.4, a wide array of chiral β-aryl-β-amino acid derivatives was obtained with enantioselectivity values greater than 99%, regardless of the electronic properties of the aryl group on the substrate (*Z*)-**19**. The hydrogenation of



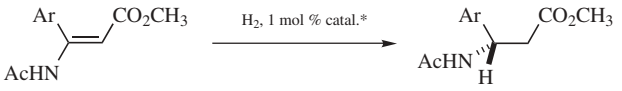
(*E*)-**16a-16e** (*S*)-**17a-17e**



(*R*,*R*)-Et-Ferrotane
(*R*,*R*)-**15**

Scheme 7.6

TABLE 7.3 Enantioselectivity of Hydrogenation of β-Aryl-Substituted (*E*)-β-(Acetylamino)acrylates 16a–16e with [Rh·(*R*,*R*)-Et-Ferrotane($CH_3OH)_2$]$^+BF_4^-$ Catalyst[a]



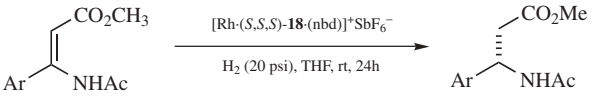
(*E*)-**16a-16e** (*S*)-**17a-17e**

Substrate	Ar	Enantiomeric Excess (% ee)
16a	Phenyl	>99
16b	*p*-Methylphenyl	>99
16c	*p*-Methoxyphenyl	98
16d	*p*-Chlorophenyl	98
16e	*p*-Fluorophenyl	>99

[a]From Ref. 15.

methyl (*Z*)-β-(3-pyridyl)-β-(acetylamino)acrylate **19h** afforded the β-amino acid derivative **20h** with 96% ee. Derivative **20h** is a key component for the synthesis of the GP IIb/IIIa antagonist RWJ-53308.[22]

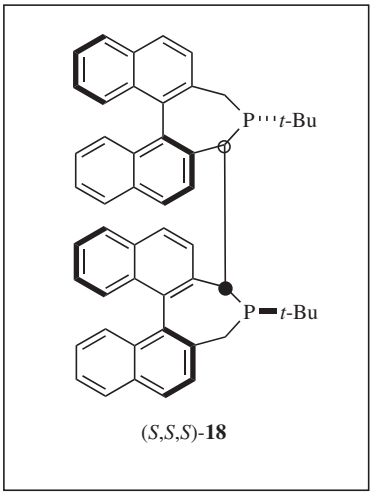
A potential limitation in Zhu et al.'s key studies on the asymmetric hydrogenation of both (*E*)- and (*Z*)-β-(acylamino)acrylates with Rh catalysts[12] is the use of toluene as solvent. In particular, Heller and co-workers[20] reported the formation



(*Z*) (*S*)-**20a**-**20h**

nbd = 3,5-norbornadiene

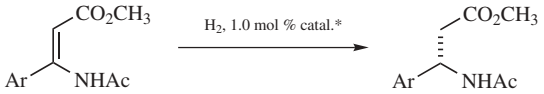
19a, Ar = phenyl
19b, Ar = *p*-fluorophenyl
19c, Ar = *p*-chlorophenyl
19d, Ar = *p*-methylphenyl
19e, Ar = *p*-methoxyphenyl
19f, Ar = *o*-methylphenyl
19g, Ar = *o*-methoxyphenyl
19h, Ar = 3-pyridyl



(*S*,*S*,*S*)-**18**

Scheme 7.7

TABLE 7.4 Rh-Catalyzed Asymmetric Hydrogenation of Methyl (*Z*)-β-Aryl-β-(acetamido)acrylates with [Rh· (*S*,*S*,*S*)-bis-binaphthophosphepine·(nbd)]$^{+}$SbF$_6^-$ Catalyst[a]

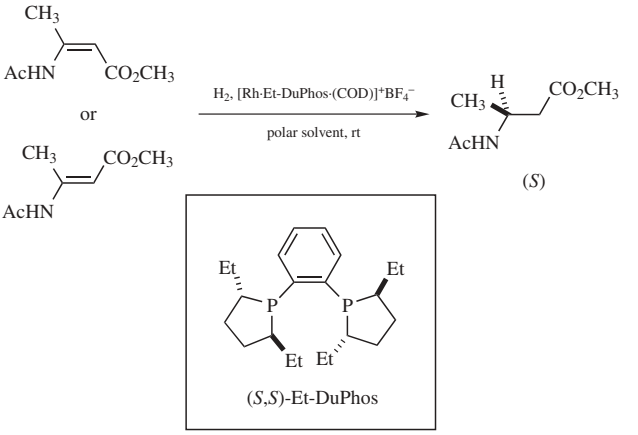


(*Z*)-**19a**-**19h** (*S*)-**20a**-**20h**

Entry	Substrate	Ar	ee (%)
1	**19a**	Phenyl	>99
2	**19b**	*p*-Fluorophenyl	>99
3	**19c**	*p*-Chlorophenyl	>99
4	**19d**	*p*-Methylphenyl	>99
5	**19e**	*p*-Methoxyphenyl	>99
6	**19f**	*o*-Methylphenyl	>99
7	**19g**	*o*-Methoxyphenyl	99
8	**19h**	3-Pyridyl	96

[a]From Ref. 21.

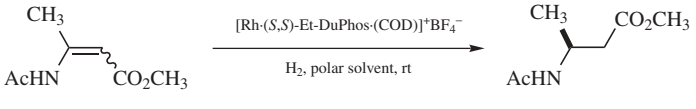
of catalytically inactive Rh•η^6-toluene complexes and suggested that the use of aromatic solvents for the hydrogenation reactions of interest is not to be recommended. In this regard, Heller et al.[23,24] discovered that by application of polar solvents the rate of the hydrogenation of either (E)- or (Z)-enamides is greatly accelerated (Scheme 7.8).



Scheme 7.8

Typical results obtained by application of different H_2 pressures and solvents are collected in Table 7.5. It can be appreciated that higher enantioselectivities were observed at unenhanced H_2 pressure, especially with (Z)-enamides as substrates. Quite good enantioselectivity was found with the (E)-enamide as substrate (entry 4 in Table 7.5).

TABLE 7.5 H_2 Pressure and Solvent Effect on the Enantioselective Hydrogenation of Isomeric Methyl β-(acetylamino)acrylates[a]

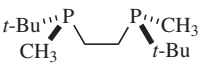


(*E*) or (*Z*) (*S*)

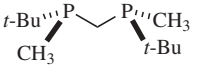
Entry	Solvent	Substrate Configuration	H_2 Pressure (bar)	ee (%)
1	CH_3OH	Z	45	35.0
2	CH_3OH	Z	30	47.0
3	CH_3OH	Z	1	86.7
4	CH_3OH	E	1	97.0
5	*i*-PrOH	Z	1	82.4
6	CH_2Cl_2	Z	1	87.2
7	THF	Z	1	85.0

[a]From Ref. 23.

Recently, Imamoto and co-workers[25,26] demonstrated that (*S*,*S*)-1,2-bis(*tert*-butylmethylphosphino)ethane, (*S*,*S*)-**21** (abbreviated as *t*-Bu-BisP*), and (*R*,*R*)-1,1′-bis(*tert*-butylmethylphosphino)methane, (*R*,*R*)-**22** (abbreviated as MiniPhos), afforded excellent enantioselectivities in the rhodium-catalyzed hydrogenation of dehydro-α-amino acid derivatives. It is argued that the electron-rich character of diphosphines (*S*,*S*)-**21** and (*R*,*R*)-**22** results in significant affinity of their rhodium complexes to dihydrogen, which leads to more efficient catalytic systems (Scheme 7.9).



(*S*,*S*)-*t*-Bu-BisP*,
(*S*,*S*)-**21**

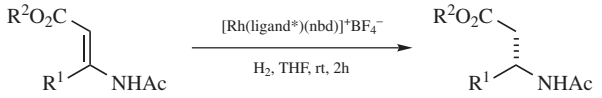


(*R*,*R*)-*t*-Bu-MiniPhos
(*R*,*R*)-**22**

Scheme 7.9

Based on these observations, Yasutake et al.[27] examined the asymmetric hydrogenation of methyl (*E*)-3-acetamido-2-butenoate (**23a**) in several solvents, at ambient temperature and under 3 atm of H_2 pressure for 2 h. Quantitative conversion was obtained and the enantioselectivity was mostly independent on the solvent, except for toluene: CH_3OH (92.7% ee), CH_2Cl_2 (98.2% ee), tetrahydrofuran (THF) (98.7% ee), and $C_6H_5CH_3$ (51.0% ee). The best results in the hydrogenation of **23a** were achieved by the use of $[Rh\cdot(t\text{-Bu-BisP}^*(nbd)]^+BF_4^-$ in THF at ambient temperature and under 3 atm of H_2, leading to **24a** in 100% conversion and 98.7% ee. (Table 7.6).

TABLE 7.6 Asymmetric Hydrogenation of (*E*)-β-(Acylamino)acrylates 23a–23d with Rh·(*t*-Bu-BisP*) and Rh·(*t*-Bu-MiniPhos) Catalysts[a]

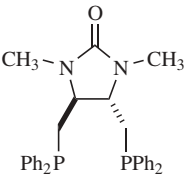


(*E*)-**23a**-**23d** (*R*)-**24a**-**24d**

Entry	Ligand*	Substrate	R^1	R^2	ee (%)
1	(*S*,*S*)-**21**	**23a**	Me	Me	98.7
2	(*R*,*R*)-**22**	**23a**	Me	Me	96.4
3	(*S*,*S*)-**21**	**23b**	Me	Et	99.7
4	(*R*,*R*)-**22**	**23b**	Me	Et	99.3
5	(*S*,*S*)-**21**	**23c**	Et	Me	97.2
6	(*R*,*R*)-**22**	**23c**	Et	Me	95.6
7	(*S*,*S*)-**21**	**23d**	Pr	Et	98.5
8	(*R*,*R*)-**22**	**23d**	Pr	Et	98.7

[a]From Ref. 27.

A novel Rh-catalytic system that is particularly effective in the enantioselective hydrogenation of (Z)-enamides was recently described by Lee and Zhang.[28] The catalyst incorporates the imidazolidin-2-one-based ligand (*S*,*S*)-BDPMI, (*S*,*S*)-**25**[29] (Scheme 7.10), and provided the results collected in Table 7.7.

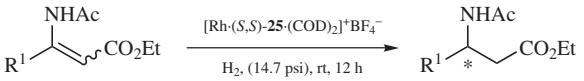


(*S*,*S*)-BDPMI,
(*S*,*S*)-**25**

Scheme 7.10

Komarov et al.[30] employed the new hydroxydiphosphine ligand **28**, synthesized from natural camphor, in the preparation of the complex [Rh·**28**·(COD)]$^{+}$BF$_4^-$ that was used as precatalyst in the asymmetric hydrogenation of prochiral substrates **29** and **30** (Scheme 7.11). The results are collected in Table 7.8 and show that the enantioselectivity induced by the catalyst is highly dependent on the nature of the substrate. In particular, (E)-enamides lead to higher enantioselectivity values

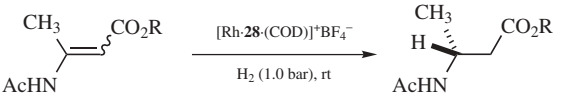
TABLE 7.7 Rh·BDPMI-Catalyzed Asymmetric Hydrogenation of (*E*)- and/or (*Z*)-26[a]



(*E*)- or (*Z*)-**26** → (*R*)- or (*S*)-**27**

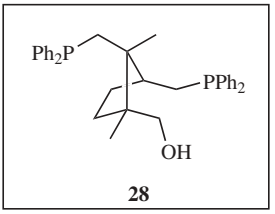
Entry	Substrate	R^1	Solvent	Conversion (%)	% ee	Configuration
1	(*E*)-**26a**	CH_3	CH_2Cl_2	100	94.6	R
2	(*Z*)-**26a**	CH_3	CH_2Cl_2	66.1	94.6	R
3	(*E*)-**26a**	CH_3	THF	11.1	94.1	R
4	(*Z*)-**26a**	CH_3	THF	21.0	97.4	R
5	(*E*)-**26a**	CH_3	acetone	94.6	91.0	R
6	(*Z*)-**26a**	CH_3	acetone	57.3	93.4	R
7	(*E*)-**26a**	CH_3	CH_3OH	100	92.3	R
8	(*Z*)-**26a**	CH_3	CH_3OH	100	94.6	R
9	(*E*)-**26b**	Et	CH_2Cl_2	100	94.0	R
10	(*Z*)-**26b**	Et	CH_3OH	100	94.0	R
11	(*E*)-**26c**	*i*-Pr	CH_2Cl_2	100	92.0	S
12	(*Z*)-**26c**	*i*-Pr	CH_3OH	100	91.9	S
13	(*E*)-**26d**	*i*-Bu	CH_2Cl_2	100	90.3	R
14	(*Z*)-**26d**	*i*-Bu	CH_3OH	100	90.1	R

[a]From Ref. 28.



(*E*)- or (*Z*)-**29**, R = H
(*E*)- or (*Z*)-**30**, R = CH_3

(*R*)-**31**, R = H
(*R*)-**32**, R = CH_3



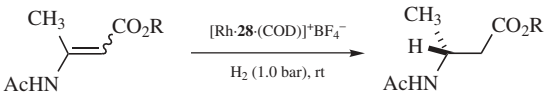
28

Scheme 7.11

relative to the (Z)-isomers, and methyl esters **30** are better substrates than carboxylic acids **29** (Table 7.8).

Interestingly, nuclear magnetic resonance (NMR) examination of rhodium complex $[Rh\cdot\mathbf{28}\cdot(COD)]^+BF_4^-$ excluded structures with the OH group coordinated to the metal. This observation may be relevant in the design and understanding of monodentate phosphine ligands. (See next section.)

TABLE 7.8 Hydrogenation of Prochiral Substrates 29 and 30 with $[Rh\cdot\mathbf{28}\cdot(COD)]^+BF_4^-$[a]



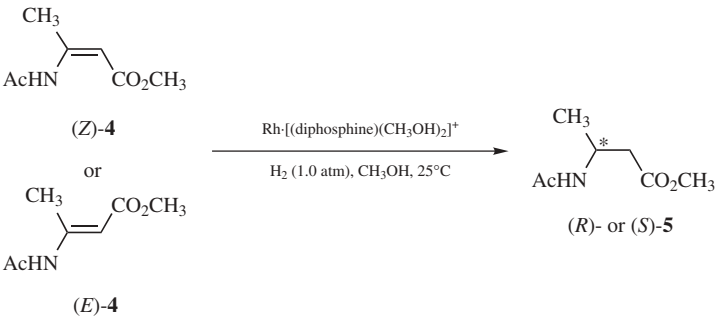
(*E*)- or (*Z*)-**29** or -**30**

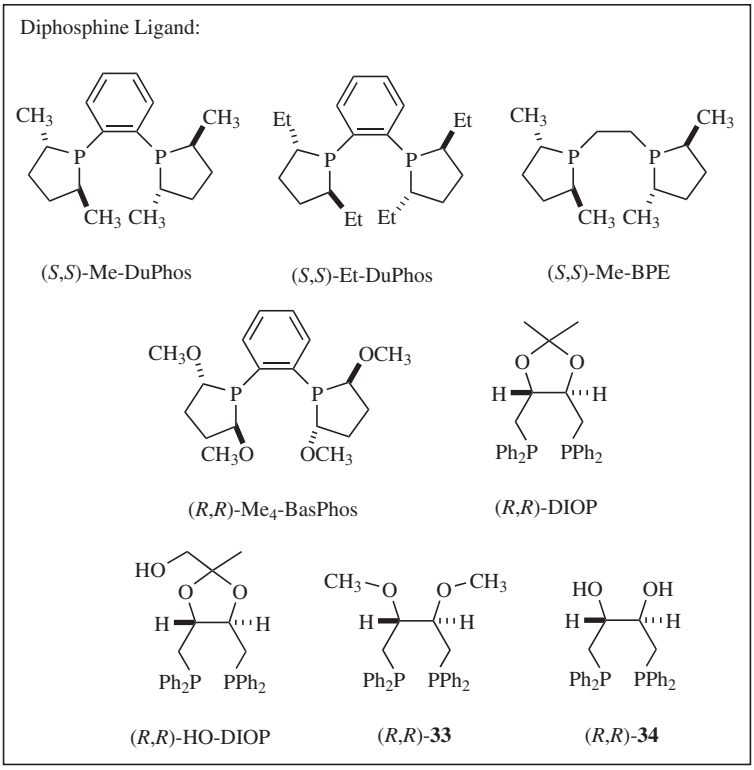
(*R*)-**31** or -**32**

Entry	Substrate	R	Solvent	Time	Conversion	ee (%)
1	(*E*)-**30**	CH_3	CH_3OH	40 min	100	93
2	(*E*)-**30**	CH_3	CH_2Cl_2	12 min	100	95
3	(*E*)-**30**	CH_3	Toluene	300 min	98	97
4	(*Z*)-**30**	CH_3	CH_3OH	20 min	100	46
5	(*Z*)-**30**	CH_3	CH_2Cl_2	45 min	72	58
6	(*Z*)-**30**	CH_3	Toluene	700 min	7	50
7	(*E*)-**29**	H	CH_3OH	120 min	82	81
8	(*E*)-**29**	H	CH_2Cl_2	>24 h	54	82
9	(*Z*)-**29**	H	CH_3OH	13 h	53	54
10	(*Z*)-**29**	H	CH_2Cl_2	>24 h	8	12

[a]From Ref. 30.

A recent kinetic study reported by Heller and co-workers[31] compared the first-order rate constants and enantioselectivities observed in the hydrogenation of (*E*)- and (*Z*)-methyl β-*N*-acetylamido butenoate, (*E*)- and (*Z*)-**4**, with chiral ligands (*S*,*S*)-Me-DuPhos, (*S*,*S*)-Et-DuPhos, (*S*,*S*)-Me-BPE, (*R*,*R*)-Me_4-BasPhos, (*R*,*R*)-DIOP, (*R*,*R*)-HO-DIOP, (*R*,*R*)-**33**, and (*R*,*R*)-**34** (Scheme 7.12).





Scheme 7.12

TABLE 7.9 First-order Rate Constants (k) and Enantioselectivities Observed in Asymmetric Hydrogenation of (*Z*)-4 and (*E*)-4 with [Rh·(ligand) $(CH_3OH)_2]^+$ in Methanol Solvent and at Atmospheric Pressure[a] (Scheme 7.12)

	(*Z*)-**4**		(*E*)-**4**	
Ligand*	k (L/min)	% ee	k (L/min)	% ee
(*S*,*S*)-Me-DuPhos	1.3	88	ND	99
(*S*,*S*)-Et-DuPhos	0.3	87	0.1	98
(*S*,*S*)-Me-BPE	1.0	68	ND	98
(*R*,*R*)-Me_4-DuPhos	0.02	67	0.09	98
(*R*,*R*)-DIOP	0.25	17	0.1	71
(*R*,*R*)-HO-DIOP	0.1	36	0.04	71
(*R*,*R*)-**33**	[b]	0	[c]	0
(*R*,*R*)-**34**	[d]	37	[e]	57

[a]From Ref. 31. ND = not determinated.
[b]100% conversion after 3 h.
[c]86% conversion after 3.8 h.
[d]72% conversion after 80 h.
[e]55% conversion after 40 h.

The kinetic results are summarized in Table 7.9 and generally confirm the trends established previously:

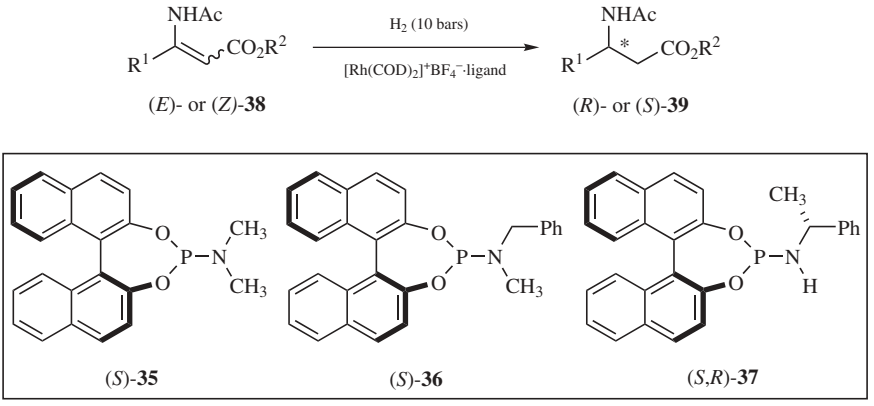
1. Highest enantioselectivities with either isomeric enamide are achieved at room temperature and below, whereas highest reactivity is observed at 30–40°C.
2. The enantioselectivity of the hydrogenation of (*Z*)-**4** is strongly dependent on the H_2 pressure—high pressure dramatically diminishes the enantiomeric excess in product **5**.
3. The Et-DuPhos catalyst reduces (*Z*)-**4** at room temperature (rt) about three times faster than the corresponding (*E*)-**4**; however, substitution of the four ethyl groups in Et-DuPhos by four methoxy groups (to give Me_4-BasPhos) reverses this order: now, the (E)-substrate is reduced faster than the (Z)-substrate.
4. Replacement of the methyl groups in Me-DuPhos by ethyl groups (to give Et-DuPhos) slightly diminishes the rate of hydrogenation.
5. Generally, Me-DuPhos and Et-DuPhos catalysts induce significantly higher enantioselectivities than complexes containing BPE or Me_4-BasPhos ligands. Nevertheless, these four diphosphines are much more efficient than DIOP, HO-DIOP, **33**, and **34**.
6. The hydrogenation of the (*Z*)-**4** enamide takes place faster with catalysts involving five-membered chelates (DuPhos, BasPhos, and BPE ligands) relative to catalysts involving seven-membered chelates [DIOP, HO-DIOP, **33**, **34** ligands].

7. The catalyst containing hydroxylated ligand (*R*,*R*)-**34** is less reactive than the catalyst containing methoxylated (*R*,*R*)-**33**; nevertheless, the former gives racemic product (±)-**5** whereas the latter induces significant enantioselectivity.

7.3 RECENT DEVELOPMENTS: RHODIUM COMPLEXES WITH CHIRAL PHOSPHORUS MONODENTATE LIGANDS

As can be appreciated in the previous section, the field of asymmetric hydrogenation of prochiral enamides has been dominated by the use of *bidentate* chiral phosphorus-containing ligands, assumed to be essential to achieve high enantioselectivities in these hydrogenations. However, recent reexamination of chiral *monodentate* phosphorus ligands has demonstrated that high enantioselectivities can also be found with hydrogenation catalysts containing such monodentate ligands.[32]

Very recently, Peña et al.[33] reported the use of new monodentate phosphoramidites (*S*)-**35**, (*S*)-**36**, and (*S*,*R*)-**37** in the rhodium-catalyzed asymmetric hydrogenation of (*E*)- or (*Z*)-β-(acetylamino)acrylates **38a**–**38f** (Scheme 7.13), achieving enantioselectivities in the 92–99% ee range (Table 7.10).



Scheme 7.13

While phosphorus ligand (*S*,*R*)-**37** proved the most efficient for the catalytic hydrogenation of (Z)-enamides, (*S*)-**36** turned out to be the best ligand for the asymmetric hydrogenation of the (E)-substrates. In this case, better conversion and enantioselectivity were obtained by using a nonprotic solvent, CH_2Cl_2.

Because of the coordination environment of the metal, the catalytically active species in the rhodium catalysts can accommodate either a single bidentate or two monodentate ligands. Very recently, Peña and co-workers[34] considered that the use of mixtures of monodentate phosphorus ligands should give rise to the formation of a heterocomplex $Rh(L_1)(L_2)$, which could be more effective than the homocomplexes $Rh(L_1)_2$ or $Rh(L_2)_2$. To test this hypothesis, ligand (*S*,*R*)-**37** was mixed with

TABLE 7.10 Asymmetric Hydrogenation of (*E*)- or (*Z*)-38 with Rhodium Complexes Containing Monodentate Ligands 35–37[a] (Scheme 7.13)

Substrate	R^1	R^2	Ligand	Solvent	Time (h)	% ee	Configuration
(*Z*)-**38a**	Me	Me	(*S*,*R*)-**37**	*i*-PrOH	1	94	R
(*Z*)-**38b**	Et	Me	(*S*,*R*)-**37**	*i*-PrOH	0.3	94	R
(*Z*)-**38c**	Me	Et	(*S*,*R*)-**37**	*i*-PrOH	0.3	94	R
(*Z*)-**38d**	*i*-Pr	Et	(*S*,*R*)-**37**	*i*-PrOH	0.3	92	R
(*Z*)-**38e**	Ph	Et	(*S*,*R*)-**37**	*i*-PrOH	0.3	92	S
(*Z*)-**38f**	*p*-F-Ph	Me	(*S*,*R*)-**37**	*i*-PrOH	0.3	94	S
(*E*)-**38a**	Me	Me	(*S*)-**35**	CH_2Cl_2	18	95	R
(*E*)-**38b**	Et	Me	(*S*)-**36**	CH_2Cl_2	4	99	R
(*E*)-**38c**	Me	Et	(*S*)-**36**	CH_2Cl_2	4	98	R
(*E*)-**38d**	*i*-Pr	Et	(*S*)-**36**	CH_2Cl_2	4	99	R

[a]From Ref. 33.

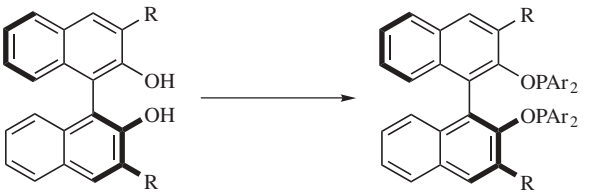
other monophosphoramidites, and the catalytic activity of the resulting rhodium heterocomplexes was compared with the corresponding homocomplexes. Indeed, all enantioselectivities obtained using only one particular ligand were lower than those obtained from the combination of ligands. Interestingly, similar observations were very recently disclosed by Reetz and co-workers,[35] in the asymmetric hydrogenation of α-dehydroamino acids.

7.4 RECENT DEVELOPMENTS: RUTHENIUM COMPLEXES WITH CHIRAL PHOSPHORUS BIDENTATE LIGANDS

In their pioneering studies, Noyori and co-workers demonstrated that BINAP, **40a**, is an effective ligand for many catalytic reactions.[11,36] By contrast, BINAPO ligand **40b** is less effective as a consequence of the increased distance between the chiral binaphthyl moiety and the phosphino groups. Furthermore, the presence of the C–O–P bond in BINAPO increases the flexibility of the ligand's backbone. To develop more effective, tunable BINAPO ligands, Zhou and co-workers[37] have synthesized diols **40c–40f** (Scheme 7.14).

To test the synthetic utility of bisphosphinite ligands **40b–40f**, Zhou et al.[37] explored the Ru-catalyzed asymmetric hydrogenation of β-aryl-substituted β-(acylamino)acrylates **41** (Table 7.11). Substrates **41a–41f** were made from the corresponding β-keto esters and were obtained as 5 : 95 to 40 : 60 isomeric (E)/(Z)-mixtures that could not be separated by silica gel column chromatography. The Ru catalyst was prepared by mixing $[Ru(p\text{-cymene})Cl_2]_2$ and the ligand in hot dimethylformamide (DMF).

As can be appreciated in Table 7.11, the enantioselectivity varied dramatically. For example, substrate **41a** was reduced with only 2% ee using a Ru•BINAPO



40a, BINAP, R = H

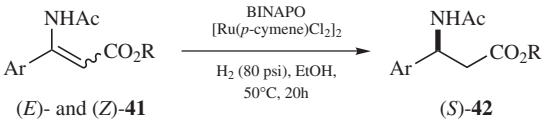
40b, BINAPO, R = H; Ar = Ph
40c, R = Me; Ar = Ph
40d, R = Ph; Ar = Ph
40e, R = 3,5-$Me_2C_6H_3$; Ar = Ph
40f, R = Ph; Ar = 3,5-$Me_2C_6H_3$

Scheme 7.14

(Ru•**40b**) complex as the catalyst. The enantioselectivity increased to 22% with Ru•**40c**, but enantioselectivity values increased dramatically (to 97–99% ee) when an aryl substituent was introduced in the ortho position (**40d**–**40f** ligands).

Very recently, Tang and co-workers[38] succeeded in the development of the first catalytic synthesis of chiral *cyclic* β-amino acids, which are essential building blocks for the synthesis of β-peptides[39] or may present relevant biological properties

TABLE 7.11 Asymmetric Hydrogenation of β-Aryl-Substituted β-(Acylamino)acrylates 41a–41f with BINAP-(40a) and BINAPO- (40b–40f) Containing Ru Catalysts[a]

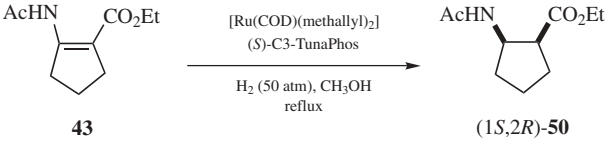


(*E*)- and (*Z*)-**41** (*S*)-**42**

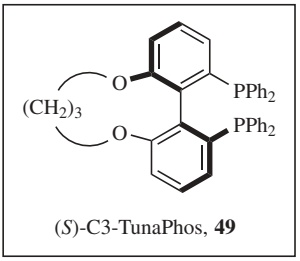
Substrate	Ar	R	Ligand	ee (%)
41a	Ph	Me	**40b**	2
41a	Ph	Me	**40c**	22
41a	Ph	Me	**40d**	98
41a	Ph	Me	**40e**	99
41a	Ph	Me	**40f**	97
41a	Ph	Me	**40a**	31
41b	*p*-F-C_6H_4	Me	**40e**	99
41c	*p*-Cl-C_6H_4	Me	**40e**	97
41d	*p*-Me-C_6H_4	Me	**40e**	99
41e	*p*-MeO-C_6H_4	Me	**40e**	99
41f	Ph	Et	**40e**	98

[a]From Ref. 37.

(compare Ref. 40). The method involves asymmetric hydrogenation of tetrasubstituted cyclic β-(acylamino)acrylates **43**–**48** with Ru catalysts containing (*S*)-C3-TunaPhos ligand **49** (Scheme 7.15).



43 (1*S*,2*R*)-**50**

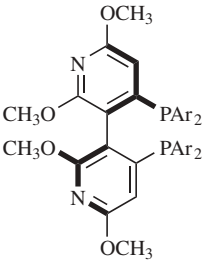


(*S*)-C3-TunaPhos, **49**

Scheme 7.15

As shown in Table 7.12, excellent enantioselectivities were achieved with five- and six-membered cyclic enamides **43**–**46**; however, lower enantioselectivities were observed in the hydrogenation of seven- and eight-membered substrates **47** and **48**.[38]

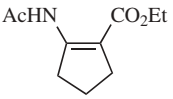
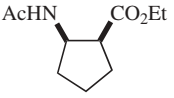
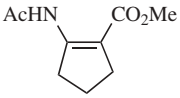
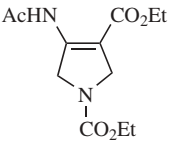
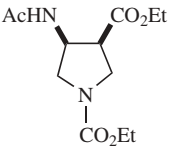
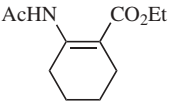
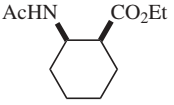
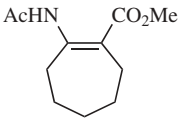
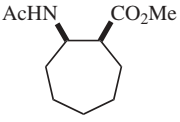
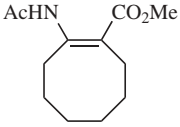
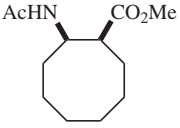
Very recently, Wu and co-workers[41] reported the use of ruthenium complex [Ru•(*R*)-Xyl-P-Phos•(C_6H_6)Cl_2] in the highly enantioselective hydrogenation of β-alkyl-substituted (*E*)-β-(acylamino)acrylates. The effectiveness of chiral dipyridylphosphine ligand (*R*)-Xyl-P-Phos, (*R*)-**56** (Scheme 7.16) in the enantioselective Ru-catalyzed hydrogenation of β-ketoesters had been previously shown by Wu et al.[42]



Ar = 3,5-$(CH_3)_2C_6H_3$

Scheme 7.16

TABLE 7.12 Asymmetric Hydrogenation of Cyclic β-(Acylamino)acrylates 43–48 with a Ru·(*S*)-C3 TunaPhos Catalyst[a]

Entry	Substrate	Product	% ee
1	 **43**	 (1*S*,2*R*)-**50**	99
2	 **44**	 (1*S*,2*R*)-**51**	>99
3	 **45**	 (1*S*,2*R*)-**52**	95
4	 **46**	 (1*S*,2*R*)-**53**	92
5	 **47**	 (1*S*,2*R*)-**54**	80
6	 **48**	 (1*S*,2*R*)-**55**	44

[a]From Ref. 38.

Note added in proof: Chemists at the pharmaceutical company Merck have recently shown that enamine substrates for the enantioselective synthesis of β-amino acids need not be protected at the amino group during asymmetric hydrogenation.[43]

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CHAPTER 8

Asymmetric Synthesis of β-Amino Acids by Enolate Additions to *tert*-Butanesulfinyl Imines

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8.1 INTRODUCTION

Addition of Ti(O*i*-Pr)$_3$ ester enolates to *tert*-butanesulfinyl imines provides β-substituted, α,β- and β,β-disubstituted, α,β,β- and α,α,β-trisubstituted, and α,α,β,β,-tetrasubstituted β-amino acid derivatives in high yields and with high diastereoselectivities. This chapter describes the synthesis of each of these classes of β-amino acids. Applications to the synthesis of a variety of biologically relevant compounds are also reported.

8.2 SYNTHESIS OF *N-tert*-BUTANESULFINYL IMINES

Enantiopure *tert*-butanesulfinamide **3** is synthesized in two steps in 65% overall yield on a large scale (> kg)[1] and is also commercially available from Aldrich and Advanced Asymmetrics. The most expedient method for the preparation of *tert*-butanesulfinamide is via asymmetric oxidation of *tert*-butyl disulfide (**1**) (Fig. 8.1). Displacement of *tert*-butanethiol with lithium amide affords enantiopure *tert*-butanesulfinamide after one recrystallization. Importantly, both enantiomers of *tert*-butanesulfinamide are easily accessible from this route. Additionally, the asymmetric oxidation is run at very low catalyst and ligand loading using H_2O_2 as an inexpensive stoichiometric oxidant. The ligand (**4**) used in this oxidation can be

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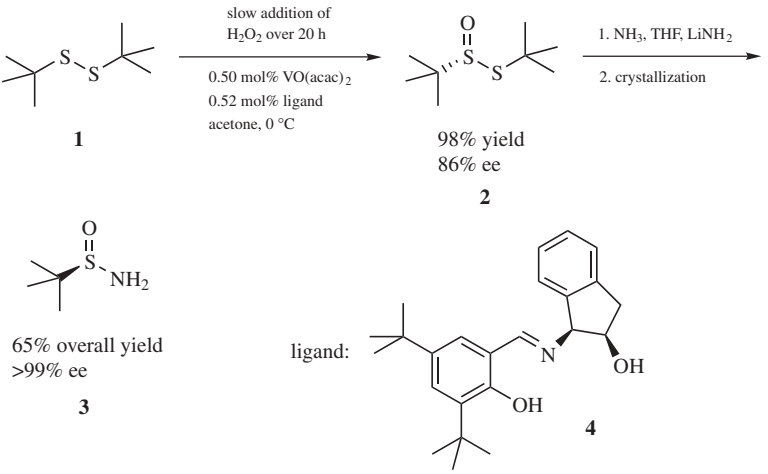
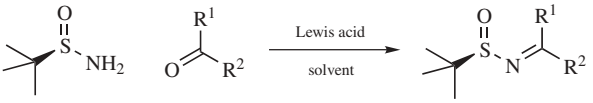


Figure 8.1 Synthesis of *tert*-butanesulfinamide on large scale.

prepared in one step from commercially available enantiopure *cis*-aminoindan-2-ol and 3,5-di-*tert*-butylsalicylaldehyde.

A number of syntheses of racemic and enantiopure *N*-sulfinyl imines have previously been reported (see Ref. 2 for reactions of sulfinate esters with imine anions and Ref. 3 for stoichiometric oxidation of sulfenimines). *N-tert*-Butanesulfinyl imines are synthesized via Lewis acid–mediated condensation of *tert*-butanesulfinamide with aldehydes and ketones.[4] These reactions proceed in high yield for a wide variety of aldehydes and ketones. Many *N*-sulfinyl aldimines can be synthesized using $CuSO_4$ (entries 1–4, Table 8.1). For more sterically or electronically

TABLE 8.1 Synthesis of *N-tert*-Butanesulfinyl Imines



Entry	R^1	R^2	Lewis Acid	Solvent	T (°C)[a]	Yield (%)
1	H	*i*-Pr	$CuSO_4$	CH_2Cl_2	rt	90
2	H	Et	$CuSO_4$	CH_2Cl_2	rt	96
3	H	Ph	$CuSO_4$	CH_2Cl_2	rt	91
4	H	2-Pyridyl	$CuSO_4$	CH_2Cl_2	rt	95
5	H	*t*-Bu	$Ti(OEt)_4$	THF	rt	82
6	H	3-Pyridyl	$Ti(OEt)_4$	THF	rt	Quant.
7	Me	Ph	$Ti(OEt)_4$	THF	75	89
8	Bu	*i*-Pr	$Ti(OEt)_4$	THF	75	77
9	Me	*t*-Bu	$Ti(OEt)_4$	THF	75	82

[a]rt = room temperature.

demanding aldehydes (entries 5 and 6) and for ketones (entries 7–9), the *N*-sulfinyl imines are synthesized in good yields using $Ti(OEt)_4$.

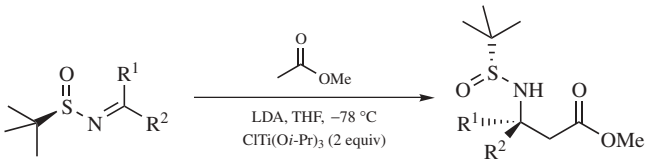
8.3 SYNTHESIS OF *N*-SULFINYL-PROTECTED β-AMINO ACIDS

Many synthetic routes to β-amino acids employ addition of ester enolate nucleophiles into ketimine or aldimine electrophiles[5] (for leading reviews see Ref. 6). However, these routes can suffer from modest stereoselectivities or lack substrate generality. In addition, *N*-substituents necessary for stereoselectivities are often inconvenient to remove.[7] Prompted by Davis's success in the addition of the enolates of acetate esters to a limited set of *N*-*p*-toluenesulfinyl imines[8], this methodology was extended to the *N*-*tert*-butanesulfinyl imines.[9] The additions of the titanium enolate of methyl acetate to aryl-, branched alkyl-, and unbranched alkyl-*N*-*tert*-butanesulfinyl aldimines were shown to proceed in high yields and diastereoselectivities (entries 1–4, Table 8.2). Very high selectivities and yields are also observed for the additions of acetate enolates to ketimines (entries 5 and 6).

By extension, *N*-*tert*-butanesulfinyl-protected α,β-disubstituted and α,β,β-trisubstituted β-amino esters are synthesized in good yields and diastereoselectivities through addition of a variety of ester enolates to *N*-*tert*-butanesulfinyl aldimines and ketimines (Table 8.3). Significantly, α,α,β-trisubstituted and α,α,β,β-tetrasubstituted β-amino esters can be obtained in good to high yields with greater than 99 : 1 diastereoselectivity in all cases (Table 8.4).

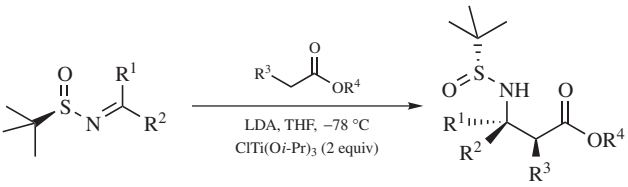
The observed diastereoselectivity in the syntheses of the β-amino esters, regardless of substitution pattern, can be explained through a six-membered transition state (Fig. 8.2). Enolate addition occurs from the least hindered face of the imine.

TABLE 8.2 Synthesis of *N*-*tert*-Butanesulfinyl-Protected β-Monosubstituted and β,β-Disubstituted β-Amino Esters[a]



Entry	R^1	R^2	Yield (%)	dr
1	H	Me	94	99 : 1
2	H	*i*-Pr	85	98 : 2
3	H	Ph	90	98 : 2
4	H	3-Pyridine	70	95 : 5
5	Me	*i*-Pr	85	99 : 1
6	Me	Ph	89	98 : 2

TABLE 8.3 Synthesis of *N-tert*-Butanesulfinyl-Protected α,β-Disubstituted and α,β,β-Trisubstituted β-Amino Esters

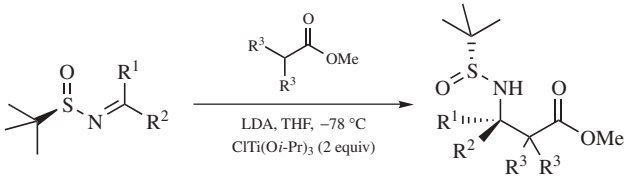


Entry	R^1	R^2	R^3	R^4	Yield (%)	dr
1	H	Me	Me	Me	96	92 : 7 : 1 : 0
2	H	*i*-Bu	Me	Me	81	95 : 3 : 2 : 0
3	H	*i*-Bu	Me	CMe_3	87	59 : 19 : 17 : 5
4	H	*i*-Bu	Me	4-MeOBn	85	88 : 12 : 0 : 0
5	H	Ph	Me	Me	85	96 : 4 : 0 : 0
6	H	Et	Bn	Me	67	90 : 10 : 0 : 0
7	H	Et	Bn	4-MeOBn	70	93 : 7 : 0 : 0
8	H	Me	4-MeOBn	Me	65	83 : 17 : 0 : 0
9	H	Me	4-MeOBn	4-MeOBn	70	89 : 11 : 0 : 0
10	Me	Ph	Me	Me	81	91 : 9 : 0 : 0

[a]LDA = lithium diisopropylamide; THF = tetrahydrofuran.

N-tert-Butanesulfinyl aldimines were key to a synthetic route to α,α-difluoro β-amino acid derivatives reported by Merck.[10] This class of compounds has been the subject of great interest in medicinal chemistry and was recently used in a CH_2-to-CF_2 transposition in the naturally occurring antifungal Rhodopeptin.[11] This change resulted in a compound with an improved toxicity profile. There had only been one previous report of a stereoselective preparation of β-branched α,α-difluoro

TABLE 8.4 Synthesis of *N-tert*-Butanesulfinyl-Protected α,α,β-Trisubstituted and α,α,β,β-Tetrasubstituted β-Amino Esters



Entry	R^1	R^2	R^3	Yield (%)	dr
1	H	*i*-Bu	Me	83	99 : 1
2	H	Ph	Me	86	99 : 1
3	Me	Ph	Me	86	99 : 1
4	Me	Ph	$-(CH_2)_5-$	65	99 : 1

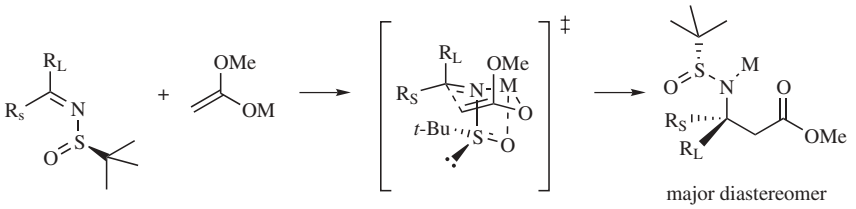


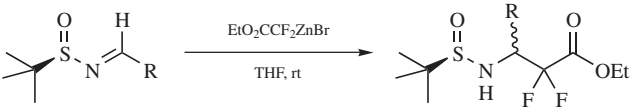
Figure 8.2 Proposed transition state to explain observed diastereoselectivity of addition of ester enolates to *N*-sulfinyl imines.

β-amino acids, but it suffered from a series of deprotections required to reveal the desired amino acid.[12] Aliphatic and aromatic *N-tert*-butanesulfinyl aldimines were synthesized and treated with an excess of the Reformatsky reagent at room temperature to afford sulfinamide adducts in moderate to good yields and diastereoselectivities (Table 8.5).

8.4 *N-tert*-BUTANESULFINYL PROTECTING GROUP

In addition to serving as a powerful directing group in the asymmetric synthesis of a wide variety of β-amino esters, the *N-tert*-butanesulfinyl group serves as a versatile protecting group that parallels the reactivity of the Boc protecting group. It is stable to base, easily cleaved with one equivalent of HCl, and attenuates the nucleophilicity of the protected amine. The *N-tert*-butanesulfinyl protecting group is cleaved using HCl in MeOH to afford β-amino esters. For β-substituted amino esters, the methyl ester is saponified using LiOH in MeOH and H_2O without any deprotection of the *N*-sulfinyl-protected amine (Fig. 8.3).

TABLE 8.5 Synthesis of *N*-Sulfinyl-Protected α,α-Difluoro β-Amino Acids



Entry	R	Yield (%)	dr
1	*i*-C_4H_9	51	81 : 19
2	*n*-C_3H_7	55	80 : 20
3	Ph	82	90 : 10
4	*c*-C_6H_{11}	81	87 : 13
5	2-Thiazolyl	58	95 : 5

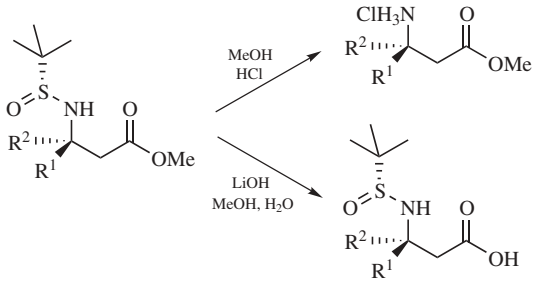


Figure 8.3 Chemoselective cleavage of protecting groups of *N*-sulfinyl-protected β-amino esters.

For α-substituted β-amino esters, a different synthetic scheme is required due to the facile epimerization of the α-stereocenter under basic conditions. The methyl ester can be transformed under neutral conditions to the free acid using $(Bu_3Sn)_2O$-mediated cleavage. This method suffers from the requirement of a series of filtrations and the generation of a toxic tin by-product that is expensive in terms of disposal costs. To circumvent these problems, an alternative ester protecting group was explored. The enolate of para-methoxybenzyl (PMB) propionate adds to *N-tert*-butanesulfinyl imines with high stereoselectivity (entries 4, 7, and 9, Table 8.3). Deprotection of the *N-tert*-butanesulfinyl amine requires both a strong acid and an external nucleophile, for example, Cl^- or methanol. The PMB protecting group can thus be cleaved in neat trifluoroacetic acid (TFA) in the presence of 1.2 eq. of anisole without cleavage of the *N-tert*-butanesulfinyl protecting group (Fig. 8.4).

8.5 SYNTHETIC UTILITY

The chemistry described in this chapter has been exploited in the synthesis of a variety of biologically important compounds. Our group first applied the β-amino acid methodology to the synthesis of a GPIIbIIIa antagonist investigated by Monsanto Co. that contains a β-3-pyridyl β-amino acid.[13] *N*-Sulfinyl β-amino ester **6** was

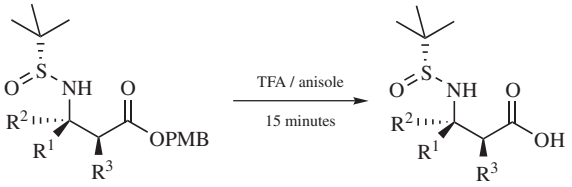


Figure 8.4 TFA-mediated cleavage of PMB ester protecting group in presence of *N*-sulfinyl-protected β-amino esters.

hydrolyzed to the free acid with LiOH in good yield, and the acid was then coupled with β-Ala-OEt to afford **7**. Deprotection of the *N*-sulfinyl group was followed by reaction with 4-cyanophenylisocyanate to afford urea **8**. The nitrile was transformed to amidine **9** to complete the formal synthesis of the agonist (Fig. 8.5).

The same β-amino acid methodology was again used in the Ellman group to synthesize a β-peptide known to adopt a helical conformation in solution (Fig. 8.6).[14] Three *N*-sulfinyl-protected β-amino acids (**10**–**12**) were synthesized as described in this review. These were used in the solid-phase synthesis of two β-peptides. The first β-amino acid was loaded onto sulfonamide resin **13**, the *N*-sulfinyl group of the coupling product **14** was then deprotected using HCl, and the liberated amine was coupled with a second β-amino acid to afford **15**. This process was repeated until hexa-β-peptide **16** was complete. The *N*-sulfinyl-protected β-peptide was activated for cleavage from support by alkylating the sulfonamide resin with bromoacetonitrile to give **17**, which was then treated with NaOH or ammonia to afford the acid or primary amide, respectively. Lastly, the sulfinyl protecting groups were cleaved to afford the free foldamers **18** and **19** in excellent overall yields.

A traceless solid-phase synthesis of chiral 3-aryl β-amino acid–containing peptides was reported by the Silverman group at Northwestern.[15] Their method used a *N-tert*-butanesulfinyl-protected β-amino ester functionalized with a silicon-based tether **22**, which could be loaded onto support through a Suzuki coupling reaction. The silyl tether then enables solid-phase synthesis products to be cleaved from support with acid. The requisite *p*-silylbenzaldehyde **20** can be efficiently synthesized in three steps from *p*-bromobenzaldehyde. Aldehyde **20** was then condensed with *tert*-butanesulfinamide, and the resultant *N*-sulfinyl imine **21** was reacted with the titanium enolate of methyl acetate to afford product **22** in 79% yield and with greater than 99 : 1 diastereoselectivity (Fig. 8.7). The protected β-amino ester was loaded onto support through a Suzuki coupling reaction. Following acidic deprotection of *N-tert*-butanesulfinamide **23**, the free amine was then coupled with *N*-Fmoc-alanine (Fig. 8.8). The Fmoc group was cleaved, and the free amine was coupled with benzoic acid to afford **24**. Saponification of the methyl ester was followed by coupling with glycine ethyl ester. The peptide was then cleaved from support with TFA, HBr, or HI to afford **25**, **26**, and **27**, respectively.

A β-amino phosphotyrosyl mimetic suitably protected for peptide synthesis was developed by scientists at the National Institutes of Health and the University of Michigan.[16] Previous efforts toward this goal using a conjugate addition onto *N*-acylimides derived from Evans's auxiliary or Mannich-type reactions of chiral enolates with imines failed to produce the desired product. Aldehyde **28** was synthesized in two steps from commercially available 4-vinylbenzyl chloride. This was condensed with *tert*-butanesulfinamide to afford the corresponding *N*-sulfinyl imine in 79% yield (Fig. 8.9). The titanium enolate of methyl acetate was added into the imine to give an 83% yield of the *N-tert*-butanesulfinyl-protected β-amino ester **29** in >90% de. To further demonstrate the suitability of these compounds in the synthesis of β-amino pTyr mimetic-containing peptides, the methodology was successfully used to synthesize a Grb2 SH2 domain-binding ligand. *N*-Sulfinyl β-amino acid **31** was coupled with amine **30** (Fig. 8.10). Cleavage of the *N*-sulfinyl

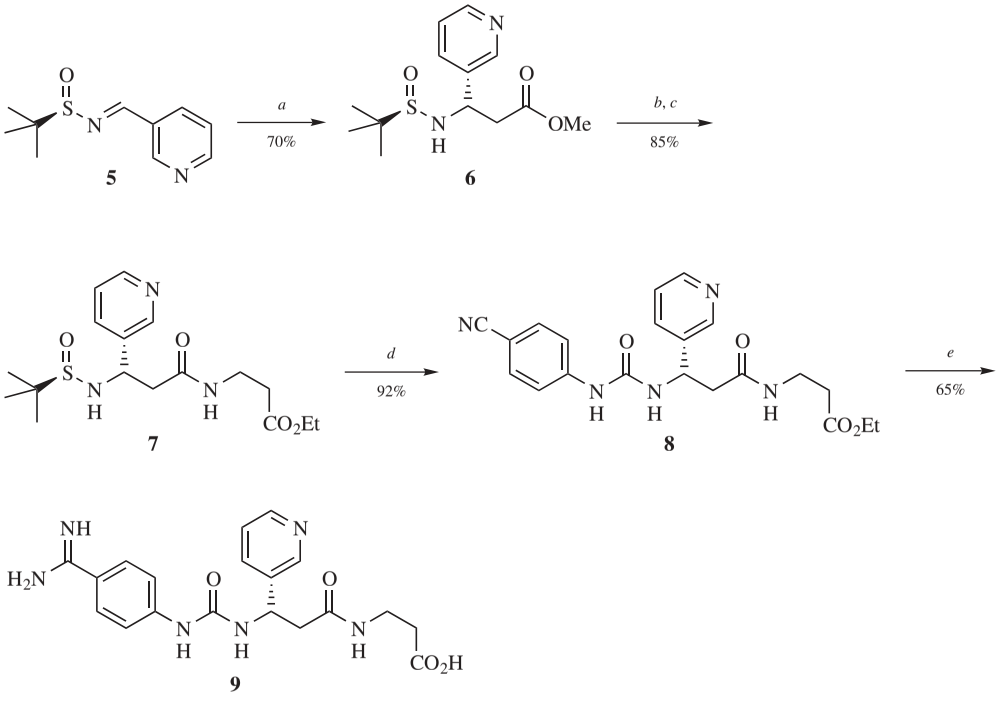


Figure 8.5 Formal synthesis of Monsanto Co. GPIIbIIIa antagonist via sulfinamide β-amino acid methodology: (*a*) methyl acetate, LDA, then ClTi (O*i*-$Pr)_3$; (*b*) LiOH, MeOH, H_2O; (*c*) β-Ala-OEt • HCl, DCC, HOBt, CH_2Cl_2; (*d*) HCl, EtOH, then 4-cyanophenylsocyanate, *i*-Pr_2NEt, DMF; (*e*) HCl, EtOH, then NH_4OH, NH_4Cl.

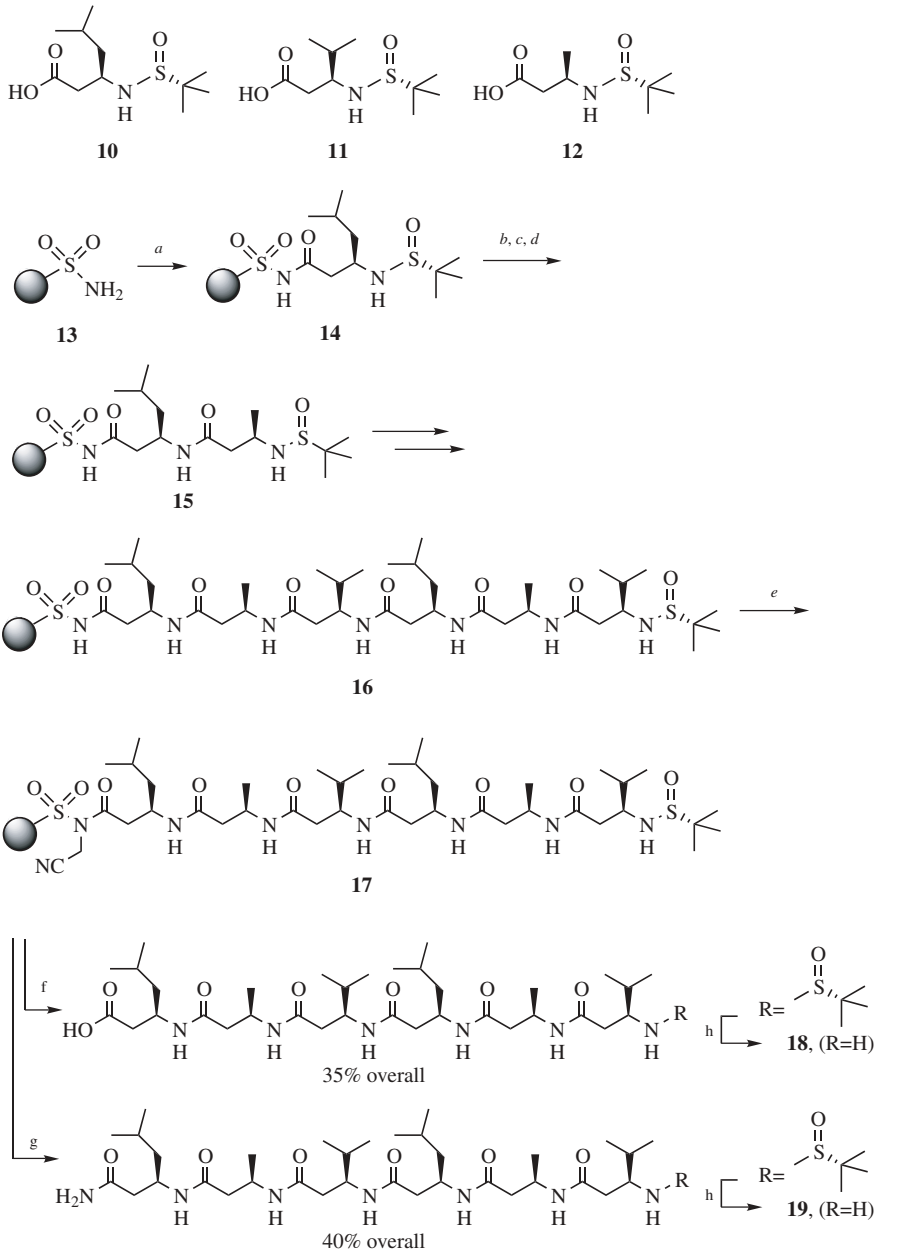


Figure 8.6 Synthesis of helical β-peptides via sulfinamide β-amino ester methodology: (*a*) **10** (3 eq), PyBOP, *i*-Pr_2NEt, $CHCl_3$, −40°C; (*b*) HCl, BuOH, CH_2Cl_2, (*c*) *i*-Pr_2NEt (*d*) **12** (3 eq), PyAOP, HOAt, DMF, CH_2Cl_2; (*e*) $BrCH_2CN$, *i*-Pr_2NEt, NMP; (*f*) NaOH, H_2O, THF; (*g*) NH_3, DMF; (*h*) HCl, MeOH.

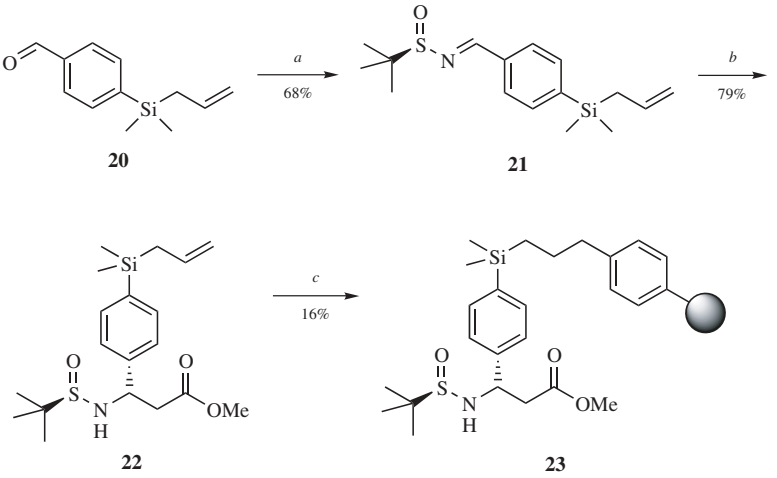


Figure 8.7 Synthesis and loading of *N*-sulfinyl-protected β-amino ester onto polystyrene solid support: (*a*) *tert*-butanesulfinamide, $Ti(O\textit{i}\text{-}Pr)_4$, THF, reflux, 1 h; (*b*) methyl acetate, LDA, THF, −78°C, then $ClTi(O\textit{i}\text{-}Pr)_3$; (*c*) 9-BBN, THF, 5 h, then bromopolystyrene, DMF, $Pd(PPh_3)_4$, Na_2CO_3, 75°C 48 h.

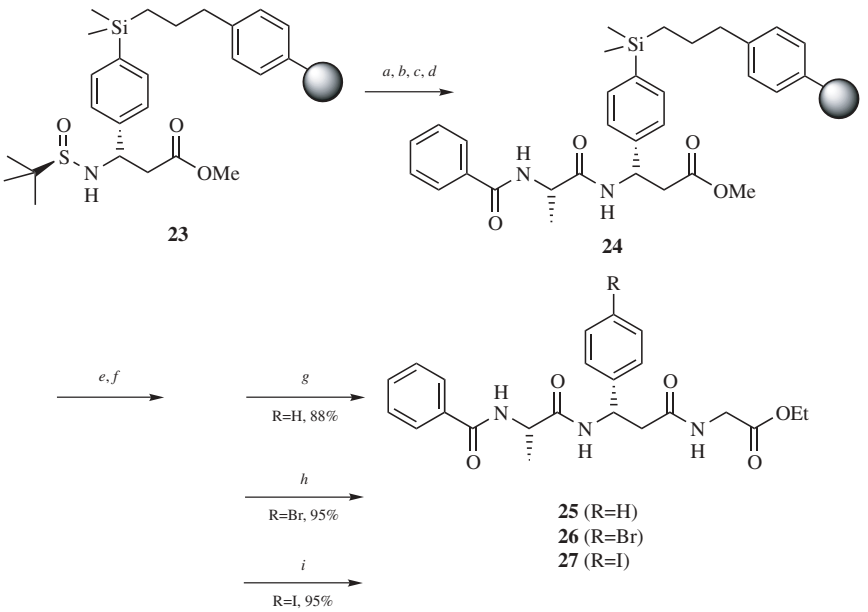


Figure 8.8 Synthesis of chiral 3-aryl β-amino acid–containing peptides: (*a*) 1 : 1 $TFA:CH_2Cl_2$, 5 min; (*b*) Fmoc-Ala-OH, EDC, HOBt, Et_3N, DMF; (*c*) 20% piperidine in DMF; (*d*) benzoic acid, EDC, HOBt, Et_3N, DMF; (*e*) LiOH (5 eq) THF/H_2O (8 : 1), heat; (*f*) H_2N-Gly-OEt, EDC, HOBt, Et_3N, DMF; (*g*) 1 : 1 $TFA:CH_2Cl_2$, 24 h; (*h*) Br_2/CH_2Cl_2, 20 min; (*i*) ICl/CH_2Cl_2, 20 min.

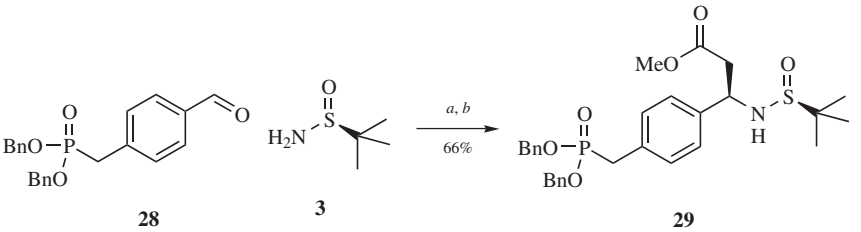
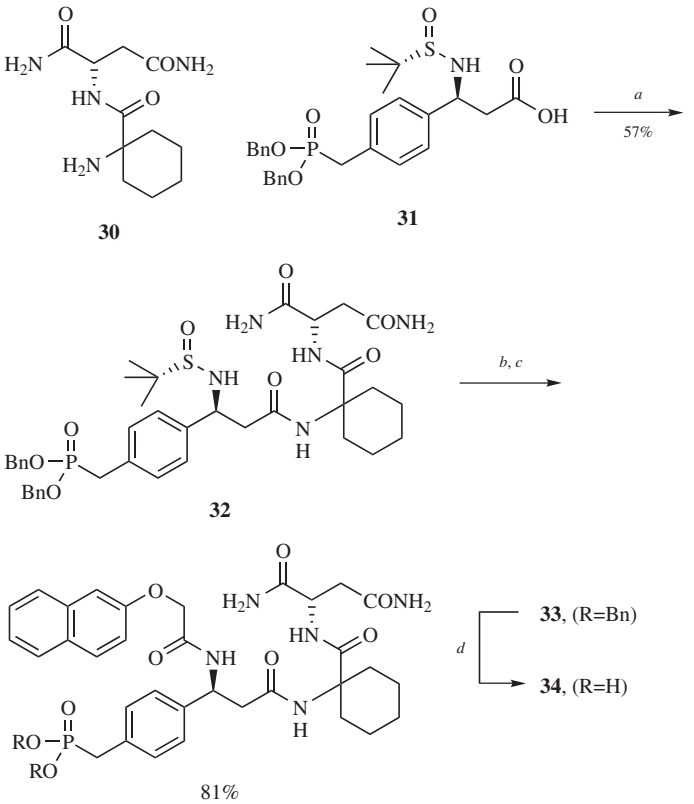


Figure 8.9 Synthesis of *N*-sulfinyl-protected β-amino ester precursor of phosphotyrosyl mimetic; (*a*) Ti(O*i*-Pr)$_4$, reflux; (*b*) methyl acetate, *n*-BuLi, THF, then ClTi (O*i*-Pr)$_3$.



(a) HOBt, DIC, DMF; (b) 4N HCl /dioxane; (c) 2-naphthyloxyacetic acid, HOBt, DIC, DMF; (d) H_2, 40 psi, 10% Pd/C, MeOH

Figure 8.10 Synthesis of Grb2 SH2 domain-binding ligand: (*a*) HOBt, DIC, DMF; (*b*) 4 N HCl/dioxane; (*c*) 2-naphthyloxyacetic acid, HOBt, DIC, DMF; (*d*) H_2, 40 psi, 10% Pd/C, MeOH.

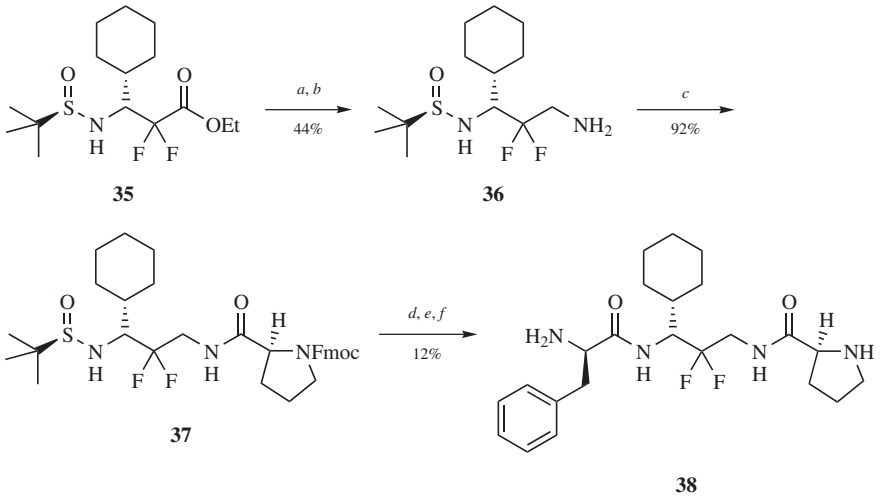


Figure 8.11 Extension of α,α-difluoro β-amino ester methodology to synthesis of pseudotripeptides: (*a*) NH_3, Et_2O; (*b*) BH_3-DMS, THF; (*c*) Fmoc-L-Pro, EDC, HOAt, DMF; (*d*) HCl, Et_2O; (*e*) Fmoc-D-Phe, EDC, HOAt, DMF; (*f*) piperidine, DMF.

protecting group from **32** was followed by coupling of the liberated amine with 2-naphthyloxyacetic acid. Lastly, the phosphate benzyl protecting groups were removed by hydrogenation to afford the final functionalized pTyr mimetic **34**.

The methodology developed by Merck toward the synthesis of α,α-difluoro β-amino acids was further shown to be adaptable and compatible with standard peptide synthesis. Additionally, this chemistry exploited the *N-tert*-butanesulfinyl group as an ideal Boc surrogate. *N*-Sulfinyl α,α-difluoro β-amino ester **35** was treated with ammonia to afford the corresponding primary amide, which was reduced to the amine with BH_3-DMS to afford amine **36** (Fig. 8.11). This was then acylated with Fmoc-L-Pro to give **37**. The *N*-sulfinyl protecting group was then cleaved with HCl, and the resultant amine acylated with Fmoc-D-Phe. The compound was finally deprotected with piperidine to afford pseudotripeptide **38**. Additionally, ester **35** was hydrolyzed to the free acid with NaOH and the acid coupled with L-Phe-OMe using standard peptide coupling conditions to afford **39** (Fig. 8.12). The *N*-sulfinyl protecting group was then removed with HCl to give **40** and the resultant amine acylated with Boc-L-Pro. Removal of the Boc group with HCl afforded the alternative pseudotripeptide **41**. This sequence elegantly demonstrates the *N-tert*-butanesulfinyl group as a versatile protecting group.

8.6 SUMMARY

Ester enolates add cleanly and in excellent diastereoselectivities to *N-tert*-butanesulfinyl imines. β-Substituted, α,β- and β,β-disubstituted, α,β,β- and α,α,β-trisubstituted, and α,α,β,β,-tetrasubstituted β-amino acids are all readily accessible

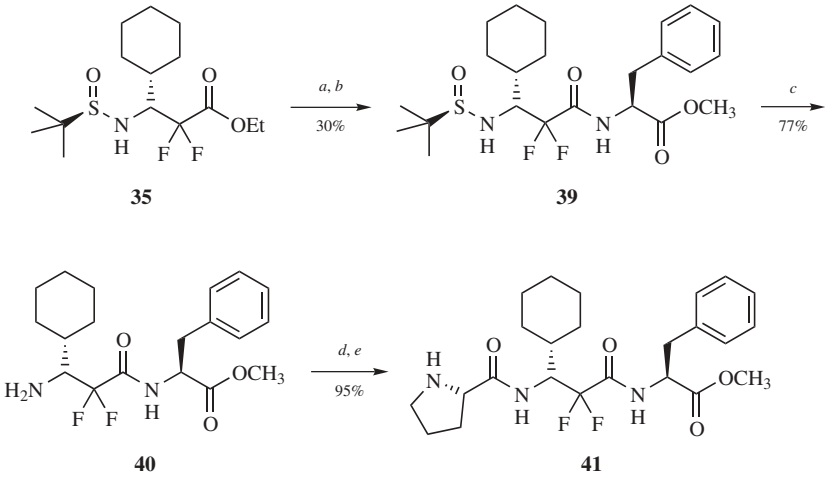


Figure 8.12 Extension of α,α-difluoro β-amino ester methodology to synthesis of pseudotripeptides: (*a*) NaOH, EtOH; (*b*) L-Phe-OMe HCl, EDC, HOAt, DMF; (*c*) HCl, MeOH; (*d*) Boc-L-Pro, EDC, HOAt, DMF; (*e*) HCl, Et_2O/MeOH.

through this route. Additionally, the *N-tert*-butanesulfinyl group serves as an ideal Boc surrogate, allowing for orthogonal deprotection of the ester and further synthetic manipulation of the molecule before *N-tert*-butanesulfinamide deprotection. This approach has been demonstrated in the synthesis of a variety of biologically active compounds and has been further extended to chemistry on solid support as well as for the synthesis of α,α-difluoro β-amino acids. Finally, *tert*-butanesulfinamide, the essential building block for this chemistry, is commercially available and is easily synthesized in enantiopurity on a large scale in 65% yield.

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CHAPTER 9

Organocatalytic Approaches to Enantioenriched β-Amino Acids

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9.1 INTRODUCTION

Mannich-type reactions provide a direct entry into β-amino carbonyl products. Two key features that render the Mannich reaction and its products very attractive are (a) the reaction tolerates a large diversity of reactants and (b) the β-amino carbonyl products are valuable synthons for natural product synthesis and can be readily transformed to create ever larger families of derivatives, including α- and β-amino acids. Of particular significance to the synthesis of α- and β-amino acids, the use of aldehyde enolates or their equivalents as nucleophiles in Mannich-type reactions provides β-amino aldehydes that can be readily transformed into β-amino acids and derivatives (Scheme 9.1). The first part of this chapter focuses on the recent development of proline- and organoamine-catalyzed direct asymmetric Mannich-type reactions using aldehydes as nucleophiles. Recently, we described the first organocatalytic asymmetric aldol,[1] Michael,[2] and Mannich reactions[3,4] involving unmodified, or "naked," aldehydes as nucleophiles. These studies have since been further elaborated by my former postdoctoral fellows and other laboratories allowing for the use of aldehydes[5–7] in a range of significant organocatalytic transformations including α-amination,[8] α-oxidation,[9] α-alkylation,[10] α-halogenation,[11] and Diels–Alder[12] reactions. Common to all of these reactions is the reaction of the catalyst, L-proline, and other small organoamines, with the aldehydes forming enamines in situ that then act as nucleophiles. The transient chiral enamines that result then react in a stereocontrolled fashion with electrophiles.

Enantioselective Synthesis of β-Amino Acids, Second Edition
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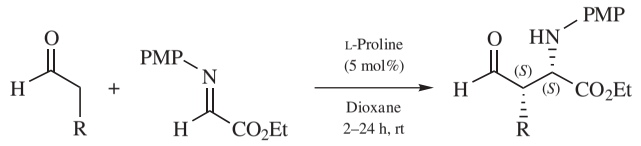
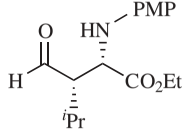
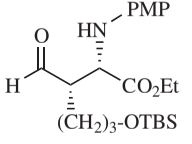
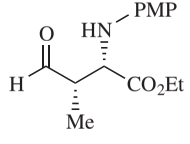
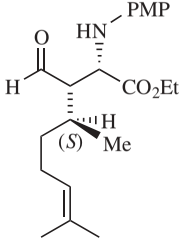
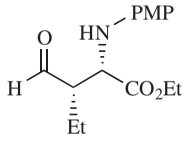
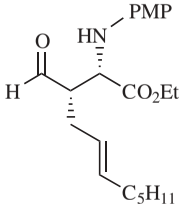
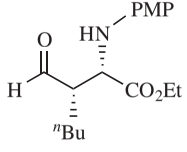
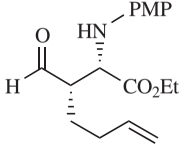
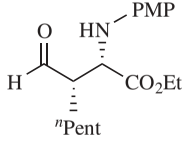
TABLE 9.1 L-Proline-Catalyzed Mannich-Type Reactions Using Unmodified Aldehydes and α-Imino Ethyl Glyoxylate[a]

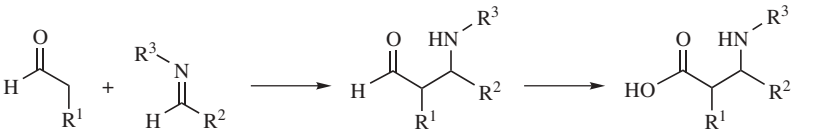


(1.5 equiv.)

Entry	Product	Yield (%)	syn:anti[b]	ee (%)	Entry	Product	Yield (%)	syn:anti[b]	ee (%)
1	 **1**	81	10 : 1 (19 : 1)	93	6	 **6**	81	1.5 : 1	91
2	 **2**	72	1.1 : 1 (3 : 1)	99	7	 **7**	42	>19 : 1	—

3	 **3**	57	1.5 : 1 (7 : 1)	99	8	 **8**	89	>19 : 1 (>19 : 1)	99
4	 **4**	81	3 : 1 (>19 : 1)	99	9	 **9**	71	>19 : 1 (>19 : 1)	>99
5	 **5**	81	>19 : 1 (>19 : 1)	>99					

[a]The yield is the combined yield of the syn and anti products. The ee is for the syn product.
[b]Ratio after purification. Ratio of the crude product is indicated in parentheses.



Scheme 9.1 Synthesis of β-amino acids based on Mannich reactions of aldehydes with imines.

Preformation of enamines or preactivation of aldehydes, for example as silyl enol ethers, is not necessary in this methodology. Furthermore, these reactions exhibit characteristics of ''green'' reactions since they do not use toxic metals or unstable or moisture-sensitive reagents for the preparation of highly enantioenriched products. In the latter part of this chapter, other types of organocatalytic asymmetric reactions are considered based on their relevance to the preparation of β-amino acid derivatives.

9.2 MANNICH-TYPE REACTIONS USING ALDEHYDES AND α-ETHYL GLYOXYLATE

Our laboratory demonstrated the first examples of direct asymmetric Mannich-type reactions using unmodified aldehydes as nucleophiles.[3,4] Reactions of unmodified aldehyde and *N-p*-methoxyphenyl (PMP)–protected glyoxylate imine in the presence of catalytic amounts of L-proline in dioxane at room temperature afforded enantiomerically enriched β-aminoaldehydes **1**–**9**, as shown in Table 9.1.[3] Only 5 mol % of L-proline and 1.5 eq. of the aldehyde donor as compared to the imine reactant were sufficient to afford the desired products in good yields. The reactions afforded the syn product as the major diastereomer and the diastereoselectivities were excellent when aldehydes with a longer alkyl chain were used ($\geq$10 : 1, Table 9.1, entries 1, 4, 5, and 7–9). The enantioselectivities (ee) of the syn products were also excellent (91 to >99% ee). Significantly, the reactions proceeded efficiently using a wide range of solvents; dimethyl sulfoxide (DMSO), Et_2O, EtOAc, and tetrahydrofuran (THF), also afforded **1** in good yields (>70%) with high diastereoselectivities (syn : anti >10 : 1) and enantioselectivities (>80% ee for syn products).[3a,b] These reactions were readily scaled to the multigram scale without reduction in reaction efficiency. Addition of water up to 20% v/v into the reactions did not affect the enantioselectivity, although the yield was moderate in the reaction with 20% v/v water.[3b,c] Lower amounts of water facilitated the reaction and increased products yields. It should be noted that D-proline is also readily available, making the synthesis of each syn enantiomer accessible.

In recent years, ionic liquids have attracted a great attention from synthetic chemists as a novel green reaction media. This is mainly due to their nonvolatile nature, tunable polarity, and high thermal stability. The insolubility of ionic liquids

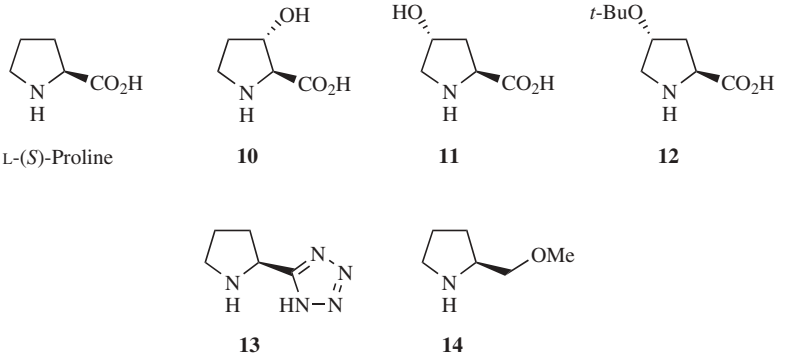


Figure 9.1 Catalysts useful for Mannich reactions.

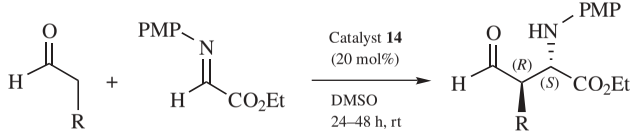
in some solvents and their ability to dissolve catalysts have made them attractive with respect to both solvent and catalyst recycling. Significantly, the use of ionic liquids [bmim]BF_4 and [bmim]PF_6 (bmim = 1-butyl-3-methylimidazolium) as solvents in the proline-catalyzed direct asymmetric Mannich reactions of *N*-PMP-protected α-imino ethyl glyoxylate with various aldehydes and ketones in ionic liquids afforded both α- and β-amino acid derivatives with excellent yields and enantioselectivities of the syn products (93 to >99% ee).[3d] The use of ionic liquids in these reactions provided facile product isolation, catalyst recycling, and significantly improved the reaction rates, about 4- to 50-fold. Reactions using ionic liquid solvents were complete within 30 min when the standard reaction conditions were maintained. The increased catalytic efficiency of proline in the Mannich reaction afforded by the use of ionic liquids allowed catalyst loading to be reduced to 1 mol %. For reactions using α,α-disubstituted aldehydes or α-imidoaldehyde, see Section 9.8.

Proline derivatives **10**–**12**[3b] and tetrazole-containing pyrrolidine **13**[7a] (Fig. 9.1) also catalyzed Mannich-type reactions using aldehydes as nucleophiles via enamine intermediates and afforded the syn isomer as the major diastereomer with high enantioselectivity. On the other hand, use of (*S*)-2-(methoxymethyl)pyrrolidine (**14**) rather than L-proline in the same reactions afforded the anti isomer (**15**–**21**) as the major diastereomer (Table 9.2).[3e]

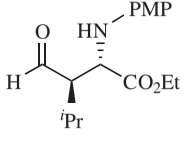
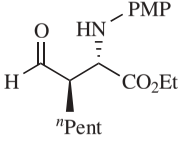
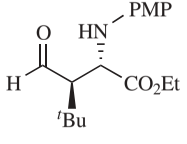
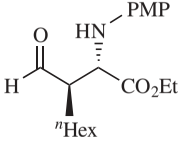
9.3 MANNICH-TYPE REACTIONS USING ALDEHYDES AND PREFORMED ALDIMINES

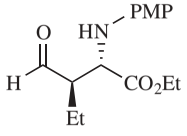
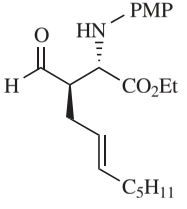
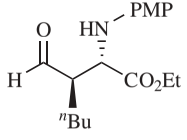
Mannich-type reactions of unmodified aldehydes and *N*-PMP-protected aldimines in the presence of catalytic amounts of L-proline also afforded corresponding

TABLE 9.2 (*S*)-2-(Methoxymethyl)pyrroridine (14)–Catalyzed Mannich-Type Reactions Using Unmodified Aldehydes and α-Imino Ethyl Glyoxylate[a]



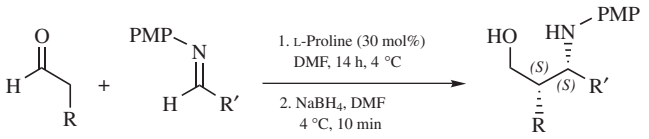
(2 equiv.)

Entry	Product	Yield (%)	anti:syn[b]	ee (%)	Entry	Product	Yield (%)	anti:syn[b]	ee (%)
1	 **15**	52	10 : 1 (19 : 1)	82	5	 **19**	78	>10 : 1 (>19 : 1)	76
2	 **16**	57	>10 : 1 (>19 : 1)	92	6	 **20**	68	19 : 1 (>19 : 1)	76

3	 **17**	44	1 : 1 (5 : 1)	75	7	 **21**	67	>19 : 1 (>19 : 1)	78
4	 **18**	54	10 : 1 (>10 : 1)	74					

[a]The yield is the combined yield of the syn and anti products. The ee is for the syn product.
[b]Ratio after purification. Ratio of the crude product is indicated in parentheses.

TABLE 9.3 L-Proline-Catalyzed Mannich-Type Reactions Using Unmodified Aldehydes and Preformed Aromatic Aldimines[a]



Entry	R	R′	Product	Yield (%)	syn:anti	ee (%)
1	Me	*p*-$NO_2C_6H_4$	**22**	81	>10 : 1	99
2	Me	*p*-CNC_6H_4	**23**	72	7 : 1	98
3	Me	*p*-BrC_6H_4	**24**	57	6 : 1	95
4	Me	*p*-ClC_6H_4	**25**	81	>10 : 1	93
5	Me	Ph	**27**	65	4 : 1	93
6	Me	*m*-BrC_6H_4	**27**	89	3 : 1	96
7	Pent	*p*-$NO_2C_6H_4$	**28**	60	>19 : 1	90

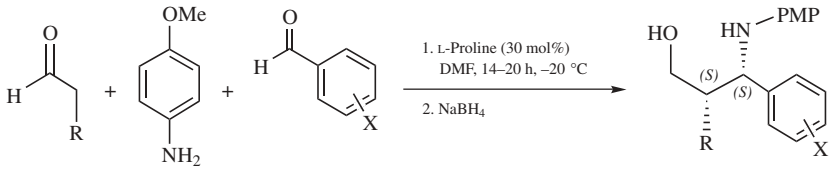
[a]The yield is the combined yield of the syn and anti products. The ee is for the syn product.

enantiomerically enriched β-aminoaldehydes (Table 9.3).[3b] The products were isolated after reduction with $NaBH_4$, though oxidation to the β-amino acid is also possible. These reactions also provided the syn isomer as the major diastereomer with high enantioselectivities (90–99% ee). These reactions also proceeded well in other solvents, for example, dioxane, THF, and Et_2O. In the reaction of propionaldehyde and *N*-(*p*-nitrobenzylidene)-*p*-anisidine in dimethylformamide (DMF) that afforded **22**, addition of water up to 20% v/v did not affect the enantioselectivity; similar results were obtained for the L-proline-catalyzed Mannich-type reactions with the glyoxylate imine where water did not reduce enantioselectivity.[3b] However, the enantioselectivity of the reaction that afforded **27** in DMF was decreased by the addition of water or MeOH.[3b] These results suggest that proton transfer from the L-proline's carboxylic acid proton to the imine nitrogen in the transition state is key for the high enantioselectivity (see Section 9.5).

9.4 THREE-COMPONENT MANNICH REACTIONS USING ALDEHYDE DONORS

The Mannich reactions also proceeded in a three-component (donor aldehyde, *p*-anisidine, aryaldehyde) protocol in the presence of the L-proline, that is, without preformation of the aldimine.[3b,7b] Our results are shown in Table 9.4.[3b] This

TABLE 9.4 L-Proline-Catalyzed One-Pot Three-Component Mannich Reactions Using Unmodified Aldehydes[a]

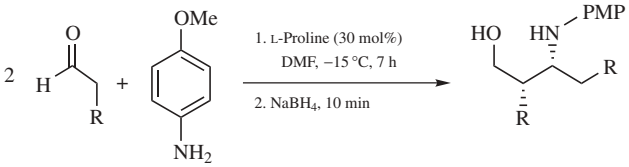


Entry	R	X	Product	Yield (%)	syn:anti	ee (%)
1	Me	*p*-NO_2	**22**	87	65 : 1	98
2	Me	*p*-CN	**23**	83	65 : 1	99
3	Me	*p*-Br	**24**	77	16 : 1	89
4	Me	*p*-Cl	**25**	92	12 : 1	84
5	Me	H	**26**	82	4 : 1	94
6	Me	*m*-Br	**27**	86	11 : 1	90
7	*n*-Pent	*p*-NO_2	**28**	87	138 : 1	>99

[a]The yield is the combined yield of the syn and anti products. The ee is for the syn product.

three-component format also afforded the Mannich products in good yields with high diastereoselectivity and enantioselectivities. The Hayashi group also reported the same reactions in *N*-methyl-2-pyrrolidinone.[7b] In the absence of arylaldehyde, self-Mannich products were obtained (Table 9.5).[3b]

TABLE 9.5 L-Proline-Catalyzed One-Pot Self-Mannich Reactions Using Unmodified Aldehydes[a]



Entry	R	Product	Yield (%)	syn:anti	ee (%)
1	Me	**29**	85	4 : 1	82
2	*n*-Bu	**30**	51	5 : 1	85
3	*n*-Octyl	**31**	90	4 : 1	81
4	allyl	**32**	92	5 : 1	87
5	*i*-Pr	**33**	64	2 : 1	18

[a]The yield is the combined yield of the syn and anti products. The ee is for the syn product.

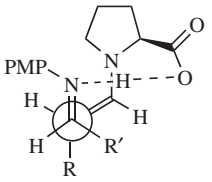


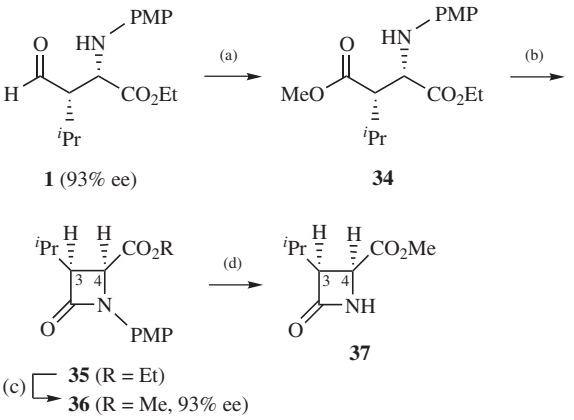
Figure 9.2 Transition state for L-proline-catalyzed direct asymmetric Mannich reactions.

9.5 PROPOSED MECHANISM FOR L-PROLINE-CATALYZED MANNICH REACTIONS

The Houk group has reported computational studies on L-proline-catalyzed direct asymmetric Mannich reactions.[13] The transition state of the reaction using an aldehyde enamine is shown in Figure 9.2. The proposed transition state explains the preferential formation of (*S,S*)-isomer. L-Proline directs the reaction between the *si* face of an (*E*)-enamine of aldehyde and the *si* face of the (*E*)-PMP-imine. The carboxylic acid proton is completely transferred to the imine. It is hypothesized that the interaction between the protonated imine and carboxylate anion is retained even when water is present, and therefore the addition of water does not significantly affect the enantioselectivity of the reactions of glyoxylate imine or aldimine bearing electron-withdrawing groups. The substituent of the aldimine used for the L-proline-catalyzed Mannich-type reactions may effect on the nature of the hydrogen bond N···H···O and as a result, the ee is influenced by the addition of water. For the L-proline-catalyzed aldol reactions, the addition of water reduced the ee, because less basic aldehydes involve less proton-transfer in the transition state.[1d] In the case of amine **14**–catalyzed Mannich reactions, the lack of a stereodirecting carboxylate in **14** altered the transition state and provided a (2*S*,3*R*)-isomer as the major product for **15**–**21**.

9.6 TRANSFORMATION OF PRODUCT OF L-PROLINE-CATALYZED MANNICH REACTION INTO β-AMINO ACID AND β-LACTAMS

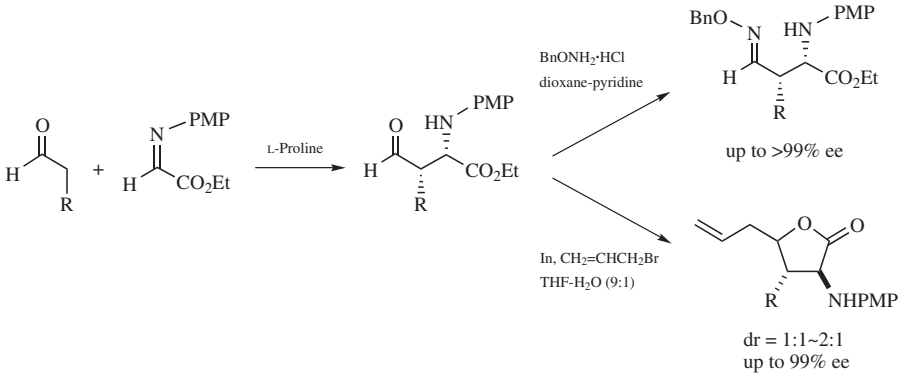
The amine-catalyzed direct asymmetric Mannich reactions using unmodified aldehydes as nucleophiles are efficient routes to access enantiomerically enriched β-amino acid derivatives. A transformation of the Mannich product into β-amino acid and its acid is shown in Scheme 9.2.[3a,b] Oxidation with $NaClO_2$ afforded the β-amino acid and this acid was esterified with CH_2N_2 to afford methyl ester **34**. Base-promoted cyclization of **34** afforded β-lactam **35** and it was further transformed into **36** without loss of the enantioselectivity or the diastereomeric ratio. The *N*-PMP group in **36** was oxidatively removed by ceric ammonium nitrate (CAN).



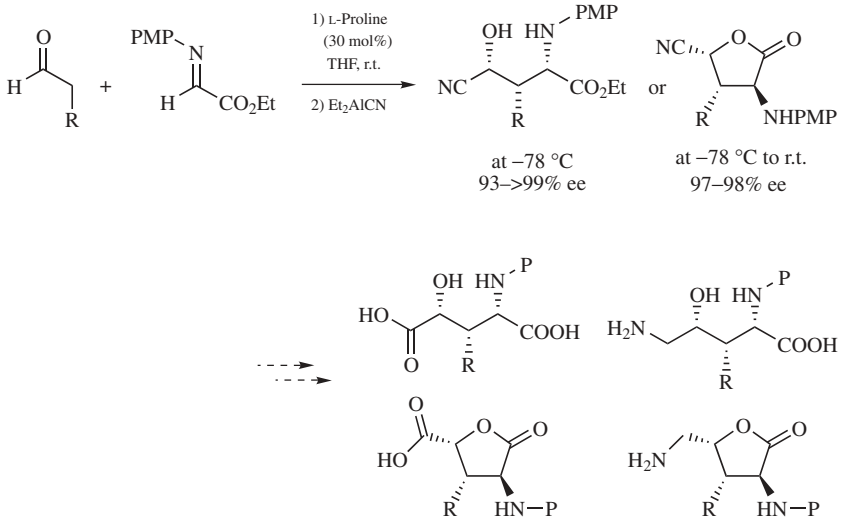
Scheme 9.2 Synthesis of β-amino acid ester and β-lactams from a product of L-proline-catalyzed Mannich-type reactions. Reagents and conditions: (a) (i) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O; (ii) CH_2N_2, Et_2O, 89% (2 steps); (b) LHMDS, THF, –20 °C, 96%; (c) (i) LiOH, dioxane/H_2O; (ii) CH_2N_2 Et_2O, 92% (2 steps); (d) $(NH_4)_2Cl(NO_3)_6$, CH_3CN/H_2O, 0 °C, 87%.

9.7 ONE-POT TRANSFORMATIONS VIA L-PROLINE-CATALYZED MANNICH REACTIONS USING ALDEHYDES AS NUCLEOPHILES

The Mannich products obtained from the reactions using unmodified aldehydes as nucleophiles retain the aldehyde group that can be used for further transformations without purification. One-pot Mannich-oxime formation,[3b] Mannich-allylation,[3c] and Mannich cyanation[14] reactions have been demonstrated (Schemes 9.3 and 9.4). These one-pot reactions are useful for the preparations of functionalized derivatives.



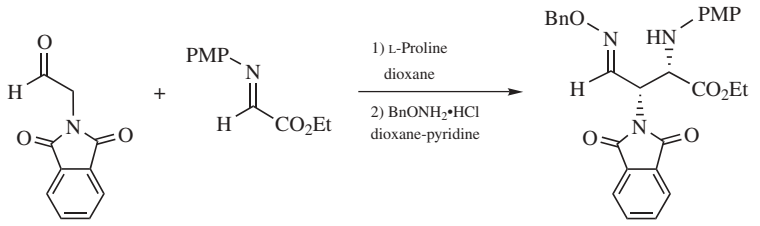
Scheme 9.3 One-pot Mannich-oxime formation and Mannich allylation reactions.



Scheme 9.4 One-pot Mannich cyanation reactions.

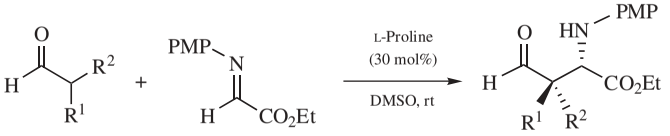
9.8 MANNICH REACTIONS USING α,α-DISUBSTITUTED ALDEHYDES OR α-IMIDOALDEHYDE FOR PREPARATION OF HIGHLY FUNCTIONALIZED β-AMINO ACID DERIVATIVES

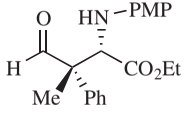
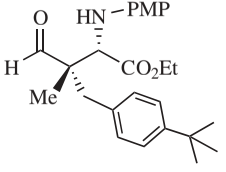
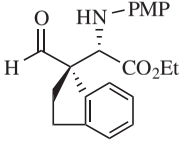
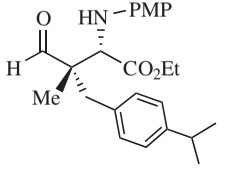
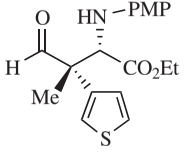
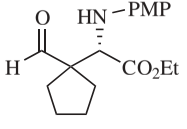
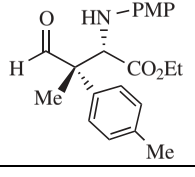
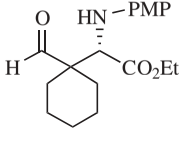
Use of α,α-disubstituted or other functional group–substituted aldehydes in the organoamine-catalyzed direct asymmetric Mannich reactions can be useful methods for the preparation of highly functionalyzed β-amino acid derivatives. α,α-Disubstituted aldehydes have been used in L-proline-catalyzed Mannich reactions to provide β-amino aldehydes with a stereogenic quaternary carbon center (Table 9.6).[15] The syn isomer was the major product and the enantioselectivities of the syn products were typically excellent. α,β-Diamino acid derivatives were also readily prepared by the L-proline-catalyzed Mannich-type reaction using α-imidoaldehyde (Scheme 9.5).[16]



Scheme 9.5 L-Proline-catalyzed Mannich reaction with α-imidoaldehyde to afford α,β-diamino acid derivative.

TABLE 9.6 L-Proline-Catalyzed Mannich-type Reactions Using α,α-Disubstituted Aldehydes and α-Imino Ethyl Glyoxylate[a]

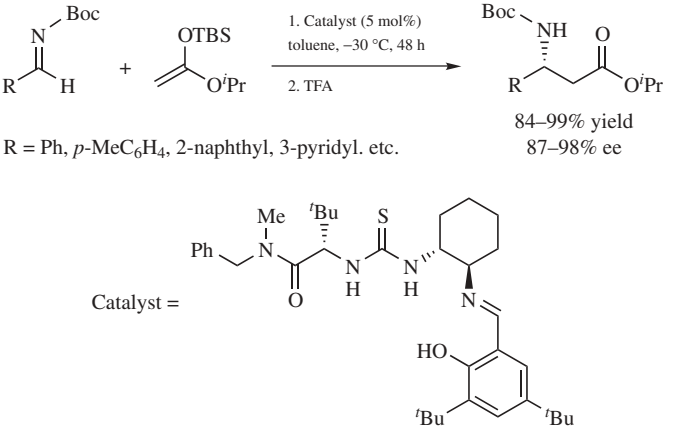


Entry	Product	Yield (%)	syn:anti	ee (%) (syn/anti)	Entry	Product	Yield (%)	syn:anti	ee (%) (syn/anti)
1		66	85 : 15	86/25	5		80	60 : 40	>99/10
2		99	96 : 4	93/5	6		80	61 : 39	96/64
3		80	83 : 17	92/40	7		94	—	98
4		82	75 : 25	99/47	8		85	—	55

[a]The yield is the combined yield of the syn and anti products.

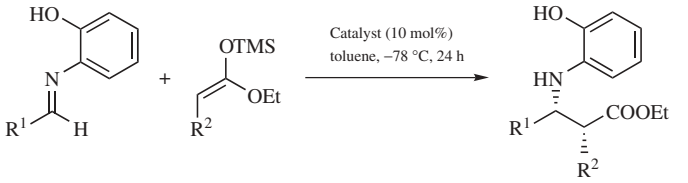
9.9 OTHER ORGANOCATALYTIC REACTIONS FOR PREPARATION OF ENANTIOENRICHED β-AMINO ACIDS

A number of significant organocatalytic syntheses of β-amino acid derivatives have been developed that do not exploit an enamine pathway. For example, Mannich-type reactions with ester enolate equivalents also provide β-amino acid derivatives. The Jacobsen group used thiourea derivatives to catalyze direct asymmetric Mannich-type reactions that provide β-amino acid derivatives via this route[17] (Scheme 9.6, see also Jacobsen's chapter). Chiral phosphates were also effective catalysts for other related asymmetric Mannich-type reactions (Scheme 9.7).[18] Furthermore, the Miller group developed the small peptide-catalyzed asymmetric Michael addition of azide to afford β-amino acid derivatives[19] (Scheme 9.8, see also Chapter 15).



Scheme 9.6 Thiourea-catalyzed asymmetric Mannich-type reaction to afford β-amino acid derivatives (TFA = trifluoroacetic acid; TBS = *tert*-butyldimethylsilyl).

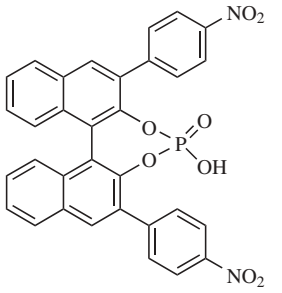
The Lectka group reported asymmetric synthesis of β-lactams by the reaction of ketenes and imines using chiral nucleophilic amines (Scheme 9.9)[20]. The catalyst benzoylquinine nucleophilically reacted with acid chloride to generate a ketene intermediate. The catalyst benzoylquinine then nucleophilically reacted with the in situ–generated ketene and the ketene–catalyst adduct reacted as the nucleophile to form the imine. Use of a proton sponge allowed for turnover of the benzoylquinine catalyst. The Lectka group also developed a one-pot procedure starting from acid chloride and *N*-acyl-α-chloramine to afford β-amino acid derivatives.[21] In this one-pot format, imine formation from *N*-acyl-α-chloramine, ketene formation, β-lactam formation, and β-lactam ring-opening steps were all catalyzed by benzoylquinine.



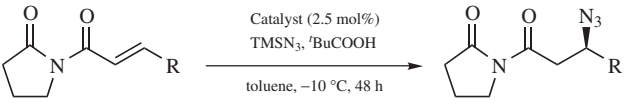
R^1 = Ph, *p*-$MeOC_6H_4$, *p*-FC_6H_4, 2-thienyl, etc.
R^2 = Me, $PhCH_2$, Ph_3SiO

65–100% yield
syn:*anti* = 86:14–100:0
81–96% ee for *syn* isomer

Catalyst =



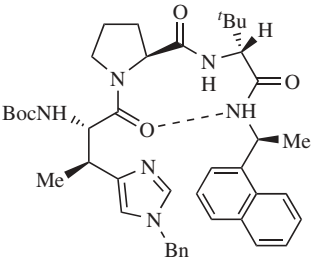
Scheme 9.7 Phosphate-catalyzed asymmetric Mannich-type reaction to afford β-amino acid derivatives (TMS = trimethylsilyl).



R = Me, Et, cyclohexyl, etc.

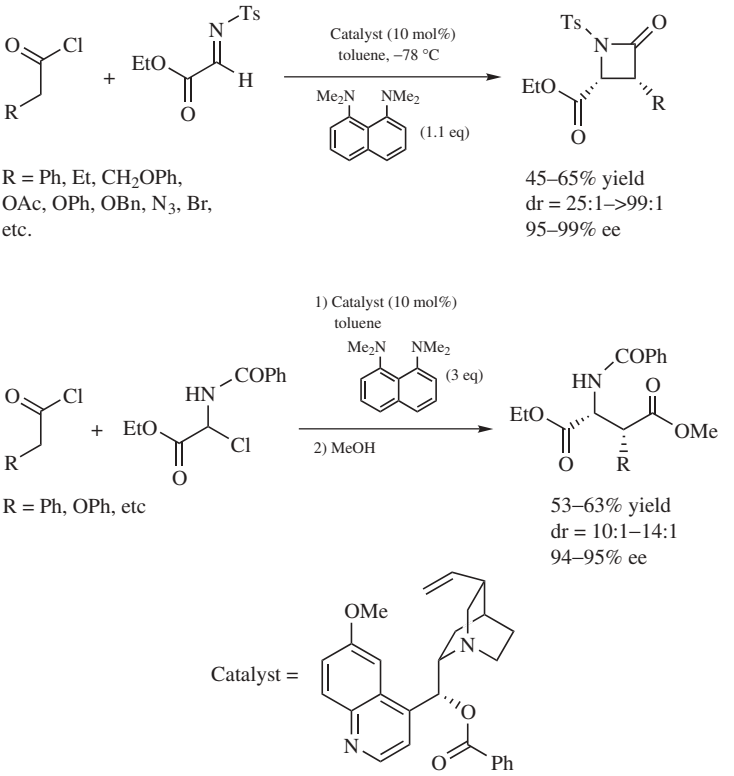
65–90% yield
86–92% ee

Catalyst =

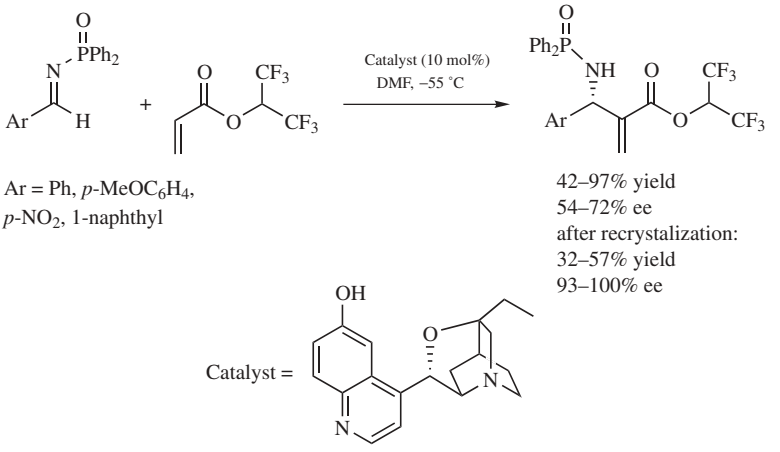


Scheme 9.8 Peptide-catalyzed asymmetric azidation that affords β-amino acid derivatives.

Another strategy to access β-amino acid derivatives is through exploitation of the Baylis–Hillman reaction. Here, too, organocatalysis has made significant in-roads. Chiral amine–catalyzed asymmetric Baylis–Hillman reactions with imines provide for a direct synthesis of β-amino acid ester derivatives (Scheme 9.10).[22]



Scheme 9.9 Catalytic asymmetric synthesis of β-lactam and β-amino acid derivatives via reaction of imines and ketenes (dr = diastereomeric ratio).



Scheme 9.10 Catalytic asymmetric Baylis–Hillman reactions that afford β-amino acid ester derivatives.

9.10 SUMMARY

In recent years, asymmetric organocatalysis has contributed significantly to the development of new routes to both α-amino acid and β-amino acid derivatives. Of these routes, proline-catalyzed Mannich-type reactions involving aldehyde donors are, at present, the most developed. This methodology is atom economic, starts with achiral readily available and inexpensive materials, and provides a facile route to either enantiomer of both α-amino acid and β-amino acid derivatives with high stereocontrol. Further research addressing the scope and applicability of this methodology is currently under investigation. These reactions do not require inert conditions or heavy metals and can often be performed at room temperature. Significantly preactivation of the donor substrates is not required allowing for the facile use of aldehyde nucleophiles for the first time. Given that we have shown that a variety of optically active amino acids can be synthesized with proline catalysis, where an L-amino acid begets other L-amino acids, our results may stimulate thoughts concerning prebiotic syntheses of optically active amino acids based on this route. Future studies will undoubtedly expand the types of chemistry that can be addressed with organocatalysis and further expand the variety of β-amino acids that can be synthesized using this approach.

Procedure for L-Proline-Catalyzed Asymmetric Mannich-Type Reactions of Aldehydes and N-PMP-Protected α-Imino Ethyl Glyoxylate (Table 9.1)[3] *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol) was dissolved in 1,4-dioxane (5 mL), aldehyde (0.75 mmol) was added, followed by L-proline (0.025 mmol) at room temperature. After stirring for 2–24 h at room temperature, the mixture was diluted with EtOAc and was added to half-saturated NH_4Cl. The mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel flash column chromatography (EtOAc/hexanes) to afford the Mannich product. This reaction is readily scaled to the multigram level without loss of reaction efficiency.

Transformation of Mannich Product to β-Amino Acid and Its Ester (Scheme 9.2)[3] The crude Mannich product **1** (1 mmol) was oxidized with $NaClO_2$ (6 mmol) in the mixture of 2-methyl-2-butane (2 M in THF, 0.5 mmol) and KH_2PO_4 (2.9 mmol) in *t*-BuOH-H_2O (5 : 1 v/v) according to the reported procedure.[23] The acid was purified by silica gel flash column chromatography (EtOAc/hexanes). The acid was then treated with CH_2N_2 (3 mmol) in Et_2O to afford **34**.

Three-Component, One-Pot Procedure for L-Proline-Catalyzed Asymmetric Mannich-Type Reactions of Aldehydes and p-Anisidine (Table 9.4)[3b] The donor aldehyde (5.0 mmol) in anhydrous DMF (2 mL) was added with a syringe pump over 12–14 h to a vial containing the acceptor aldehyde (0.5 mmol), *p*-anisidine (0.5 mmol), L-proline (0.15 mmol), and anhydrous DMF (3 mL) at −20°C. After

14–16 h of total reaction time, the reaction mixture was diluted with anhydrous Et_2O (2 mL) and $NaBH_4$ (400 mg) was added at 0°C. After 10 min, the mixture was poured into a vigorously stirred biphasic solution of Et_2O and saturated aqueous NH_4Cl (or alternatively sodium phosphate buffer pH 7.2). The organic layer was separated and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by silica gel flash column chromatography (EtOAc/hexanes) to afford the β-amino alcohols.

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CHAPTER 10

Asymmetric Synthesis of Cyclic β-Amino Acids via Cycloaddition Reactions

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10.1 INTRODUCTION

Over the last decade there has been a rapid development in the asymmetric synthesis of β-amino acids. Since the appearance of the first 2 reviews in 1994,[1] almost 15 other revisions have been published,[2] as well as one monograph,[3] in less than 10 years. On the other hand, some of the first catalytic enantioselective versions of very useful classic and modern reactions emerged from or were developped in the field of the enantiomerically pure compounds (EPC) synthesis of β-amino acid derivatives within this period: The asymmetric aminohydroxylation reaction,[4] the Mannich-type reaction,[5] and the Michael-type amination reaction[6] constitute good examples. This gives an idea about the important role played by the chemistry of β-amino acids in asymmetric synthesis duting the last years. It is also well known[7–9] that β-amino acids either in free form or combined in natural products or β-peptides exhibit interesting biological and pharmaceutical activity.

Cyclic β-amino acids are mentioned only specifically in general revisions on β-amino acids. The only reviews so far in the area are dedicated to the synthesis[2b,10] and applications[2b,10a] of 2-aminocycloalkanecarboxylic acids. Some representative compounds of this family have biological properties and/or are useful intermediates in organic synthesis. In this context, cispentacin **1**[11] (Fig. 10.1) isolated from natural sources is an antifungal antibiotic and is also a component of the antibiotic amipurimycin **2**,[12] active against the causative agent for rice blast disease; the synthetic (±)-tilidine **3**[13] is an opioid analgesic

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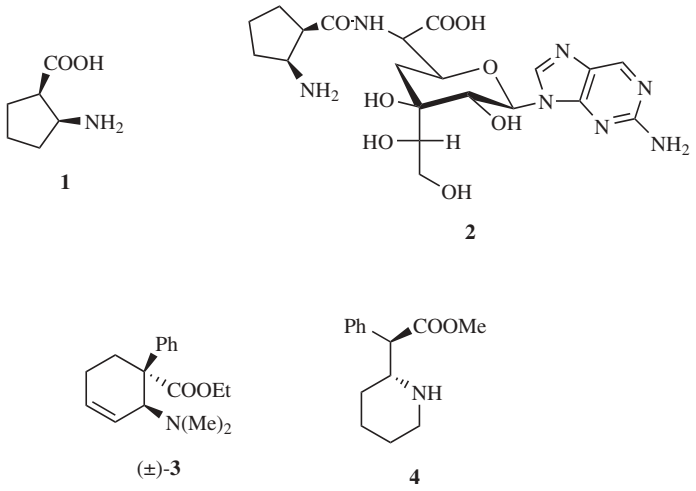


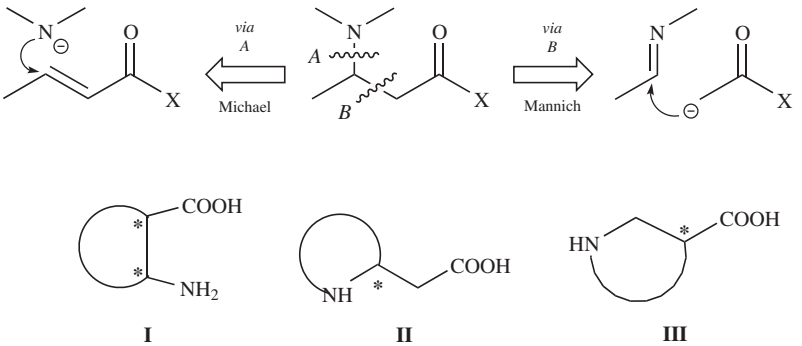
Figure 10.1

used in therapy to control moderate to severe pain, and methylphenidate **4**[14] is the common medication for the treatment of hyperactive children with attention-deficit disorder.

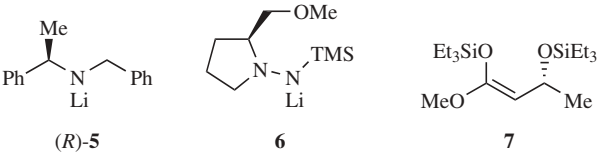
In addition, cyclic β-amino acids can be used as building blocks for the synthesis of different heterocycles and alkaloids, in drug research, and in peptide mimetics; enantiomerically pure forms can also serve as chiral auxiliaries or additives.[10a]

10.2 GENERAL STRATEGIES IN ASYMMETRIC SYNTHESIS OF CYCLIC β-AMINO ACIDS

Conceptually, there are two main synthetic pathways to achieve the skeleton of a β-amino acid in an asymmetric manner which are mostly found in the bibliography: the Michael-type amination, which basically creates C_β–N bond (via *A*, Scheme 10.1), and



Scheme 10.1 Cyclic β-amino acids.



(*R*)-**5** **6** **7**

Figure 10.2

the Mannich-type reaction, which forms C_α–C_β bond (via *B*, Scheme 10.1). These are also the main strategies for the construction of cyclic β-amino acid skeletons, either as carbocyclic β-amino acids **I** or as heterocyclic β-amino acids **II** or **III**.

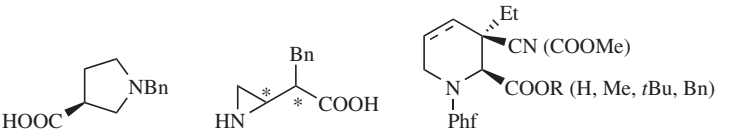
Diastereoselective conjugate addition of "chiral NH_3" equivalents to α,β-unsaturated esters, followed by removal of the chiral unit at nitrogen, has been demonstrated to be the method of choice via *A*. Davies et al.[15] have repeatedly carried out the reaction of (*R*)-**5** (Fig. 10.2) with conjugated cycloalkenecarboxylates to prepare five- and six-membered 2-aminocycloalkanecarboxylic acids, some of them with known pharmacological applications. Enders et al.[16] used lithiated TMS-SAMP **6** to perform Michael additions followed by cyclization on open-chain ω-halo-α,β-alkenoates to obtain five-, six-, and seven-ring carbocyclic and heterocyclic β-amino esters. Other groups[17] have demonstrated the usefulness of these methodologies in the asymmetric synthesis of several sizes and substitution patterns of cyclic β-amino acid derivatives.

The reliability of the strategies mentioned above as well as the accessibility of both enantiomers of **5** and **6** makes Michael-type amination a versatile synthetic tool in the preparation of enantiopure cyclic β-amino acids. Other reaction pathways that employed achiral amides and chiral α,β-unsaturated carboxylic acid derivatives have also been reported.[18]

The reaction of a cyclic imine or nitrone with an ester enolate or equivalent, a chiral controller being attached either to the imine nitrogen, the enolate, or an external compound, has been so far the most employed Mannich-type approach (via *B*) to cyclic β-amino acids. Murahashi et al.[19a,b] have made important contributions to this area by using chiral ketene silyl acetal **7** (Fig. 10.2) and cyclic nitrones to prepare several heterocyclic β-amino-β′-hydroxy esters which are highly useful for the synthesis of a wide range of alkaloids. A catalytic enantioselective version of this protocol was very recently developed by the same group by utilizing a (*S*)-1,1′-bi-2-naphthol derived titanium catalyst.

Allef and Kunz[20] reported a good sample of an asymmetric Mannich-type reaction with a chiral *N*-D-galactopyranosylaldimine in the preparation of an isoquinoline-derived β-amino ester. On the other hand, enantiopure piperidine and pyrrolidine β-amino acids have recently been obtained through processes which can be considered as surrogates for asymmetric Mannich reactions.[21]

Among other strategies, a convenient route to enantiomerically enriched cyclic β-amino acids is the selective reduction of the corresponding enantiopure β-enamino esters. Leading work in this field has been made by Palmieri et al.[22] by employing chiral α-methylbenzylamine-derived cyclic β-enamino esters in the



8 **9** **10**

Figure 10.3

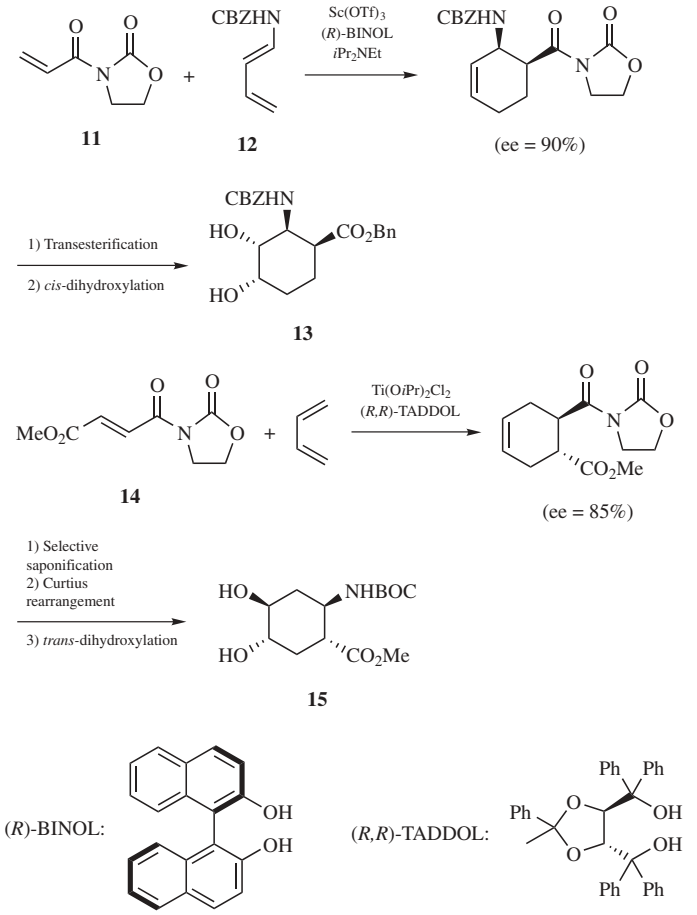
synthesis of five- and six-membered alicyclic and heterocyclic β-amino esters. Others[23] have also used the same protocol in the preparation of related compounds. (Very recently, the first asymmetric synthesis of cyclic β-amino acids via enantioselective catalytic hydrogenation has been reported.[23c]) Curtius rearrangements performed with enantiomerically enriched functionalized cyclic succinates[24] and the Arndt–Eistert homologation reaction with chiral α-amino acids[25] have been utilized as key steps in the obtention of three, four, five, six, and seven-membered ring cyclic β-amino esters.

Aspartic acid as well as asparagine can be regarded as a natural β-amino acid derivatives due to its β-amino carboxylic moiety. During the last decade, aspartic acid and to a lesser extent asparagine have been largely employed as chiral building blocks in the asymmetric synthesis of β-amino acids.[26] In this regard, β-proline **8**[27] (Fig. 10.3) and all four stereoisomers of 2-benzyl-3,4-iminobutanoic acid **9**[28] were synthesized in an optically pure form through C_β and C_γ homologations from L- and D-aspartic acids. Several *N*-phenylfluorenyl-protected piperidine-2,3-dicarboxylic acid derivatives **10**, intermediates in alkaloid synthesis, have been prepared from L-aspartic acid by intra- and intermolecular alkylations.[29]

10.3 CYCLIC β-AMINO ACIDS VIA CYCLOADDITION REACTIONS

Cycloaddition reactions are very useful synthetic tools to achieve cyclic molecules. The Diels–Alder reaction is of special usefulness to construct six-membered carbocycles, and it has been employed as key step in the asymmetric synthesis of 2-aminocyclohexanecarboxylic acid derivatives as racemates. In this context, cycloaddition of 1-(dimethylamino)-1,3-dienes[30] as well as 1-*N*-acylamino-1,3-dienes[31] with acrylate derivatives became a generally used reaction to prepare a wide variety of 2-amino-3-cycloalkenecarboxylates [e. g., (±)-tilidine **3**, see Fig. 10.1]. Further Diels–Alder approaches to a number of six-membered β-amino acid derivatives as well as cyclopropanation reactions and [2 + 2]-cycloadditions to obtain 2-aminocyclopropane- and 2-aminocyclobutanecarboxylic acid derivatives, all of them in racemic form, have also been reported. (Most of them use subsequent racemic resolutions to achieve enantiomerically pure cyclic β-amino acids (see Ref. 10a) for a recent list of publications.)

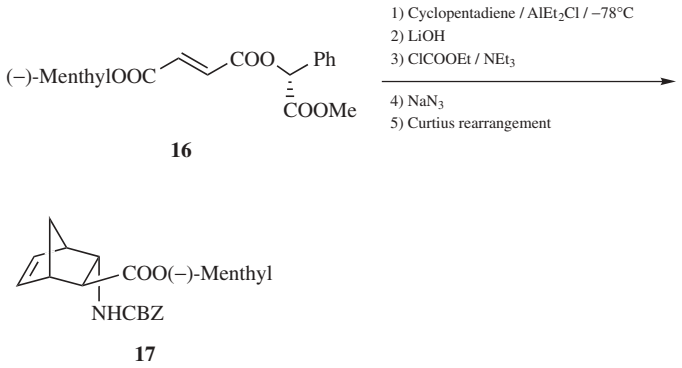
By contrast, very few examples have been published on the use of asymmetric cycloaddition reactions in the synthesis of enantiopure cyclic β-amino acids. In this sense, Wipf et al.[32] recently reported the preparation of the dihydroxylated aminocyclohexane β-amino acid derivatives **13** and **15** (Scheme 10.2). The key steps



Scheme 10.2

of both synthesis are catalytic asymmetric Diels–Alder reactions. The synthesis of *cis*-β-amino ester **13** starts with the cycloaddition reaction of acyl oxazolidinone **11** with 1-aminodiene **12** in the presence of scandium triflate and (*R*)-BINOL as chiral ligand, which proceeds with 90% ee. Further elaboration of the cycloadduct gives rise to dihydroxylated amino ester **13**. On the other hand, the synthesis of dihydroxylated *trans*-β-amino ester **15** was achieved through a titanium-catalyzed Diels–Alder reaction of desymmetrized fumarate **14** with butadiene, this time with (*R*,*R*)-TADDOL as chiral ligand. After the dihydroxylation, the *t*-butyloxycarbonyl (BOC) protected amino function in **15** was created by a Curtius rearrangement with diphenylphosphoryl azide (DPPA)/*t*-BuOH.

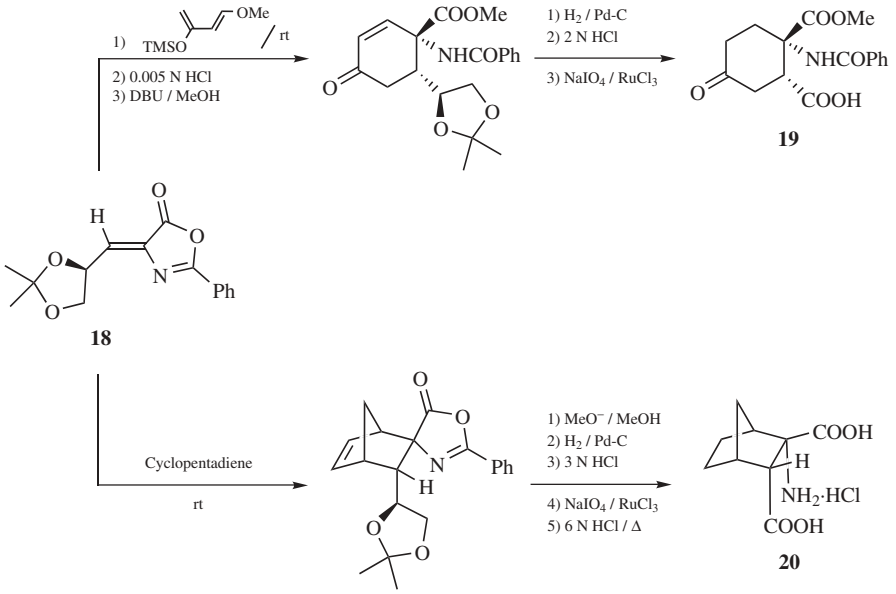
Yamamoto et al.[33] reported the reaction of the unsymmetrically modified chiral fumarate **16** with cyclopentadiene in the presence of an excess of diethyl aluminum chloride as a key step in the preparation of the bicyclic β-amino ester **17**, intermediate in the synthesis of a thromboxane receptor antagonist (Scheme 10.3). The



Scheme 10.3

initial [4 + 2]-cycloaddition was performed with high diastereoselectivity (>99%), and subsequent selective hydrolysis followed by a Curtius protocol led to the carbamate function in **17**.

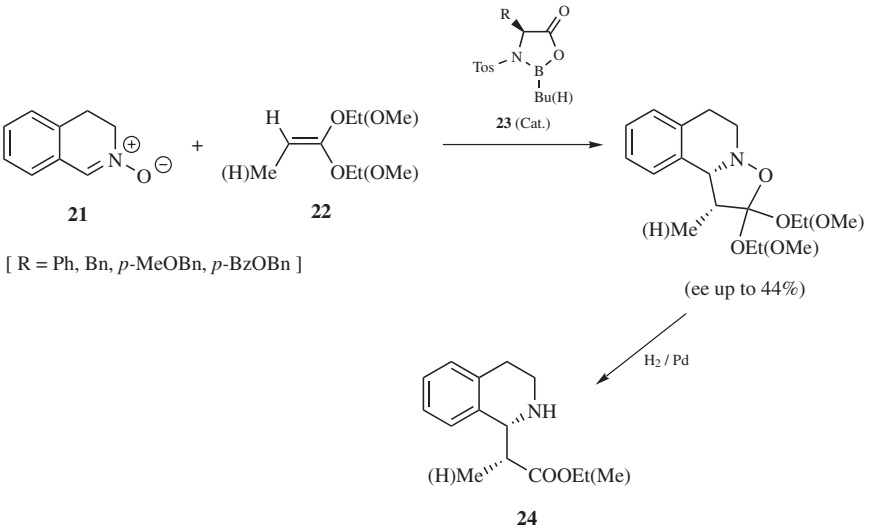
Cativiela et al.[34] employed the cycloaddition of the chiral methylenazalactone **18**, derived from (*R*)-glyceraldehyde, with Danishefsky's diene and cyclopentadiene, respectively, in the preparation of cyclic β-aminodicarboxylic acids **19** and **20** (Scheme 10.4). The [4 + 2]-cycloaddition of **18** with Danishefsky's diene gave a 1/1 mixture of cycloadducts,[34a] which after mild hydrolysis and treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in MeOH both afforded the same cyclohexenone intermediate which was transformed into **19** by oxidative degradation as



Scheme 10.4

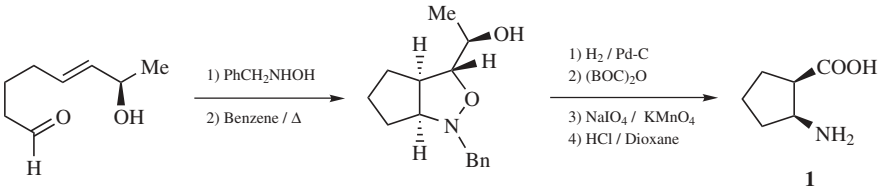
the key step. On the other hand, the cyclopentadiene-derived cycloadduct[34b] was obtained with moderate diastereoselectivity (40%); its transformation into the final amino acid **20** followed a similar protocol to that described above. Moreover, the authors reported the synthesis of a diastereoisomer of **20** in this paper[34b] following the same procedure.

Asymmetric [3 + 2]-cycloadditions have scarcely been used in the synthesis of enantiopure cyclic β-amino acids with simple structures. Scheeren et al.[35] carried out the asymmetric 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline *N*-oxides **21** with ketene acetals **22**, catalyzed by *N*-tosyl-L-α-amino acid–derived chiral oxazaborolidines **23** (Scheme 10.5). The intermediate isoxazolidines were obtained with complete regio- and diastereoselectivity in high yield but with only moderate enantioselectivity. Mild hydrogenolysis of the N–O bond led to the corresponding β-amino esters **24**.

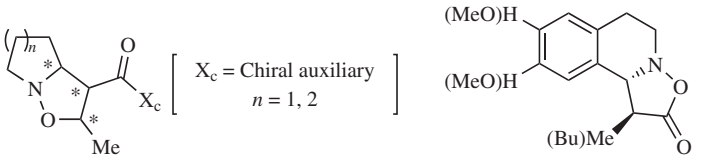


Scheme 10.5

Konoshu and Oida reported an interesting protocol to achieve cispentacin **1** (see Fig. 10.1) by starting from chiral aldehyde **25** and *N*-benzylhydroxylamine (Scheme 10.6)[36]. (A similar intramolecular [3 + 2]-cycloaddition protocol has



Scheme 10.6



26 (±) **–27**

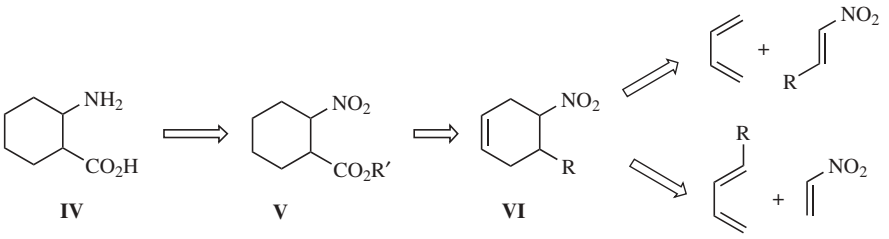
Figure 10.4

been very recently applied for the preparation of cispentacin and several heterocyclic analogs.[36b]) In a first stage, the starting materials were converted to the corresponding nitrone which underwent an intramolecular [3 + 2]-cycloaddition to yield an intermediate isoxazolidine (de 88%); the latter was transformed into cispentacin by sequential ring opening, protection, oxidation, and removal of the protecting group.

Enantiopure isoxazolidines **26**[37] and isoquinoline-derived isoxazolidinones (±)–**27**[38] (Fig. 10.4), precursors of cyclic β-amino acids, were also obtained through [3 + 2]-cycloadditions of nitrones with several dipolarophiles, but the authors did not complete the conversion into the final β-amino acid derivatives. Later in this chapter, reference will be made to more complex molecules containing the cyclic β-amino acid unit obtained through asymmetric [3 + 2]-cycloaddition reactions.

10.4 SYNTHESIS OF *cis*- AND *trans*-2-AMINOCYCLOHEXANE-CARBOXYLIC ACID DERIVATIVES VIA [4 + 2]-CYCLOADDITION REACTIONS

Enantiomerically pure 2-aminocyclohexanecarboxylic acid derivatives **IV** have also been approached by asymmetric cycloaddition reactions involving nitroolefins as dienophiles. The retrosynthetic analysis is depicted in Figure 10.5. The key compound in this strategy is cycloadduct **VI**, readily available from the cycloaddition of a nitroolefin with a properly substituted diene. Reduction of the nitro group into an amino group and transformation of R into a carboxylate would furnish the



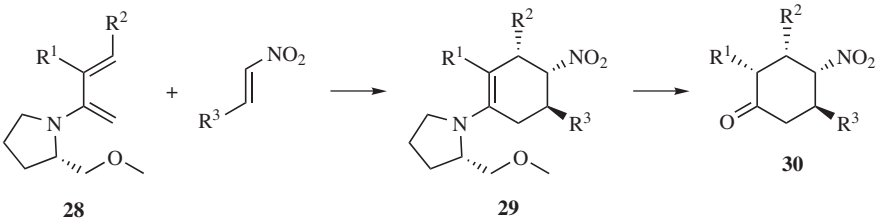
IV **V** **VI**

R = CO_2R, CH_2OR', Furyl

Figure 10.5

desired cyclic β-amino acid **IV**. Therefore, the R group has to be a carboxylic ester itself or a synthetic equivalent, which could be placed either in the diene or the dienophile.

The ability of nitroolefins to participate in cycloaddition reactions with 2-aminodienes had been first reported by Pitacco et al.[39] More detailed work of Barluenga et al. showed that the cycloadditions can be carried out with very high diastereoselectivities to provide, after the enamine hydrolysis, the corresponding 4-nitrocyclohexanones as pure diastereoisomers.[40] The asymmetric version of this cycloaddition was reported independently by Barluenga et al.[41] and Enders et al.[42] by using 2-aminodienes **28** bearing a chiral amine as auxiliary. When metoxymethylpyrrolidine is used as chiral auxiliary, the cycloaddition proceeds with very high facial diastereoselectivity to afford cyclic nitroenamines **29** (Scheme 10.7). Interestingly, after release of the chiral amine by mild aqueous hydrolysis, the 4-nitrocyclohexanones **30** are obtained with very high enantioselectivity and, noteworthy, with creation of up to four new stereogenic centers.



Scheme 10.7

A detailed study on the scope of this cycloaddition demonstrated that it allows for the preparation of structurally diverse nitrocyclohexanones **30** by using different dienes and nitroolefins.[43] Interestingly, the stereochemical outcome of the cycloaddition places the nitro group in a cis relationship with R^2 and in a trans relationship with R^3 (Fig. 10.6). Therefore, it was possible to devise synthetic strategies to prepare both *cis*- and *trans*-2-aminocyclohexanecarboxilyc acid derivatives by following the strategy depicted in Figure 10.5, simply choosing appropriate R^2 or R^3 carboxylate synthetic equivalents.[44]

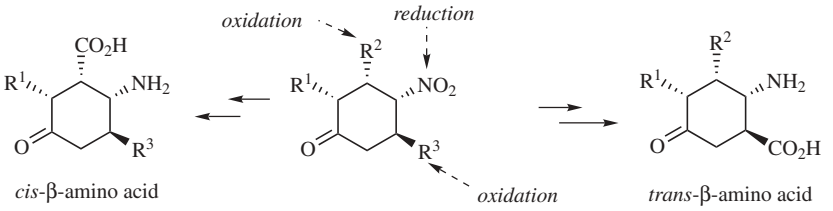
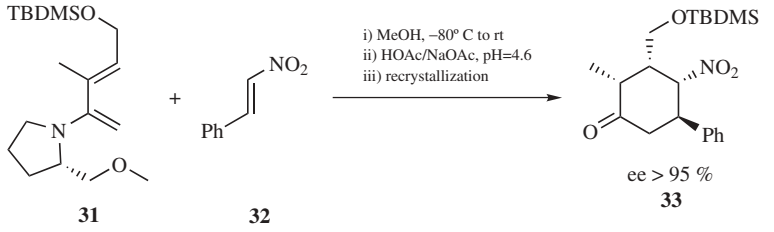


Figure 10.6

10.4.1 Synthesis of cis Isomer

The preparation of derivatives of *cis*-2-aminocyclohexanecarboxylic acid requires a R^2 that could be easily transformed into a carboxylate. Thus, diene **31** ($R^2 = CH_2OTBDMS$), featuring a protected hydroxymethyl substituent as carboxylate precursor, was selected for the cycloaddition. The cycloadditon reaction of **31** proceeds with high enantioselectivity with several nitroolefins. For instance, the reaction with β-nitrostyrene **32** gives rise to the nitrocyclohexanone **33** with 94% ee, and furthermore, enantiomerically pure material can be obtained after recrystallization (Scheme 10.8).



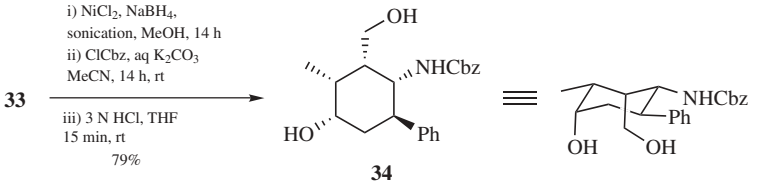
31 **32** **33**

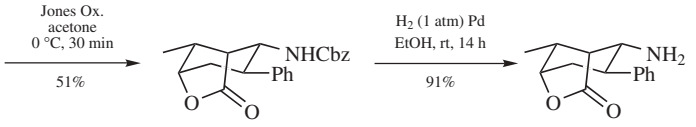
Scheme 10.8

The transformation of **33** into a β-amino acid requires two main synthetic operations: (1) reduction of the nitro group to the amino functionality and (2) conversion of the protected alcohol into the carboxylate by a deprotection–oxidation protocol. It turned out that, given the high functional group density of **33**, the sequence in which these steps are carried out is decisive, and in fact, different amino acid derivatives are obtained depending on the synthetic route.

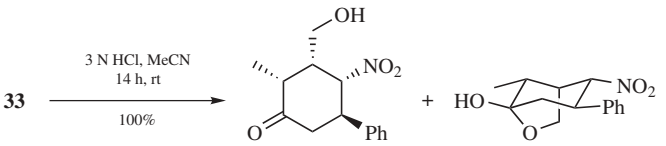
For instance, bicyclic lactone **36**, the first class of *cis*-β-amino acid derivative, can be synthesized from nitroketone **33** if the sequence starts by the reduction of the nitro group (Scheme 10.9). Thus, treatment of **33** with the $NiCl_2/NaBH_4$-reducing system[45] followed by protection of the amino group and deprotection of the hydroxy functionality affords diol **34**. Interestingly, under the reaction conditions required for the reduction of the nitro group, the ketone functionality is also reduced with complete stereoselectivity. Surprisingly, Jones oxidation of diol **34** did not furnish the expected ketoacid coming form the oxidation of both hydroxy groups, but lactone **35** was obtained instead. Clearly, upon oxidation of the primary alcohol, lactonization takes place at a faster rate than the oxidation of the secondary hydroxy group. Finally, cleavage of the Cbz group under standard conditions yields aminolactone **36** (Scheme 10.9).

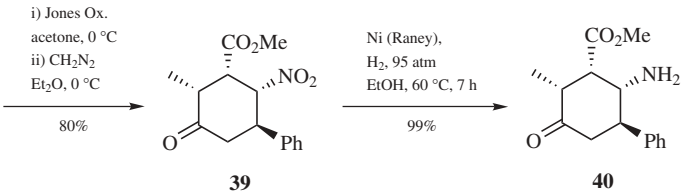
A more straightforward approach into the *cis*-β-amino acid moiety results by reversing the reaction sequence (Scheme 10.10). Deprotection of the hydroxy group of **33** gives rise to alcohol **37** in equilibrium with hemiketal **38**, and oxidation of the mixture followed by diazotation provides nitroester **39**. Finally, chemoselective reduction of the nitro group with Raney Ni gives rise to amino ester **40** in nearly 80% overall yield from the starting ketone **33**.





Scheme 10.9



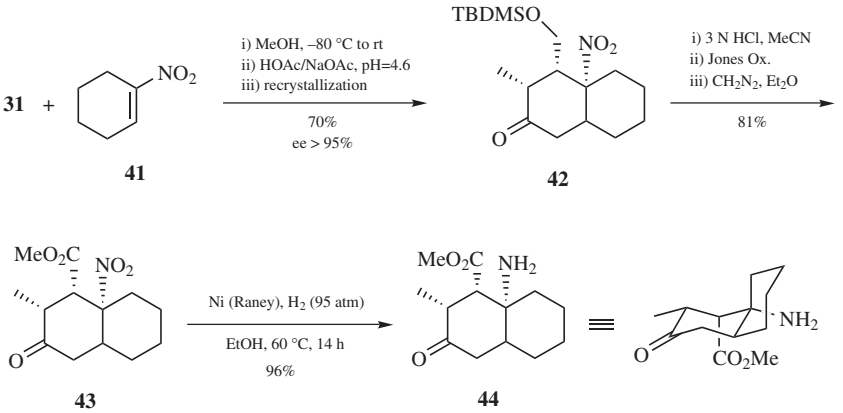


Scheme 10.10

The same methodology was applied to sterically encumbered nitrocyclohexanone **42**, available in enantiomerically pure form by cycloaddition of **31** with nitrocyclohexene **41**. Aminoester **44** was obtained with excellent overall yield following the same synthetic pathway (Scheme 10.11). It is noteworthy the particular structure of **44** which features the β-amino acid moiety in a hindered and completely rigid structure can be of great interest in the design of β-peptides.

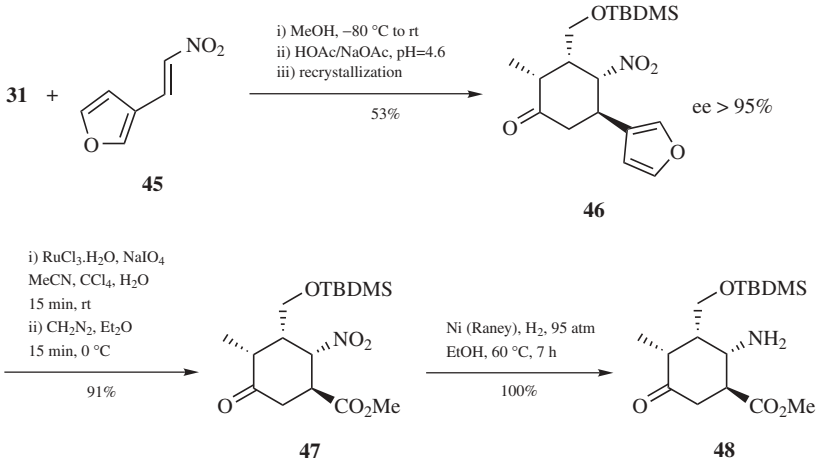
10.4.2 Synthesis of trans Isomer

The synthesis of *trans*-β-aminoesters requires a R^3-substituent that can be easily converted into a carboxylate. The 3-furyl ring proved to be a good choice for this



Scheme 10.11

particular synthetic sequence. The cycloadditon reaction of diene **31** with 2-(3-furyl)-1-nitroethylene **45** afforded the required nitroketone **46** with very high enantioselectivity, although with moderate yield. Nevertheless, the transformation of the nitroketone into the aminoester was carried out in a very straightforward and high-yielding manner (Scheme 10.12). First, the furyl group was quantitatively transformed into the carboxylate by oxidation using Sharpless's protocol,[46] giving rise to the corresponding acid, which upon treatment with diazomethane provided nitroester **47**. Subsequent reduction of the nitro group by hydrogenation in the presence of Raney Ni led to the highly functionalized derivative of *trans*-β-



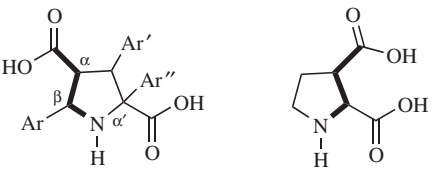
Scheme 10.12

aminocyclohexanecarboxylic acid **48** in enantiomerically pure form and with an excellent 91% overall yield from nitroketone **46**.

General Experimental Procedure for Key Asymmetric Cycloaddition: Synthesis of Enantiomerically Pure 4-Nitrocyclohexanones To a solution of the corresponding nitroalkene in dry MeOH cooled at −80°C was added dropwise the chiral diene dissolved in 5 mL of dry MeOH. (For an optimized experimental procedure for the synthesis of chiral 2-aminodienes, see Ref. 47.) The reaction mixture was stirred overnight at −80°C and then slowly allowed (10 h) to reach room temperature. The MeOH was removed under reduced pressure and the residue was redissolved in tetrahydrofuran (THF). The solution was then treated with a HOAc/NaOAc aqueous buffer solution (pH 4.6) and stirred for 10 min. The organics were extracted with EtOAc (3 × 25 mL) and the organic layer washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting 4-nitrocyclohexanone was purified by column chromatography and crystallized from CH_2Cl_2/MeOH (**33**) or EtOH (**42** and **46**).

10.5 SYNTHESIS OF β-PROLINE DERIVATIVES VIA [3 + 2]-CYCLOADDITION REACTIONS

Five-membered ring heterocyclic β-amino acids **A** and **B** (general structure, Fig. 10.7) of type **III** (Scheme 10.1) have been prepared, as highly enantiomerically enriched compounds, through different synthetic sequences that involve as key step an asymmetric [3 + 2]-cycloaddition reaction in which the chiral control element is incorporated to either the electron-deficient olefinic substrate (dipolarophile) or to the azomethine ylide (1,3-dipole). These cyclic β-amino acids **A**, **B** that are simultaneously α′-amino acid derivatives, can be considered as β-proline-α′-proline chimeras in addition to constrained analogs of β,γ-disubstituted glutamic acids in the case of compounds **A** and conformationally restricted analogs of aspartic acid in the case of **B**. The asymmetric synthesis of proline derivatives that selectively incorporate the side-chain functionality of other amino acid is currently attracting much attention due to the interest to study conformational constraints into peptides that influence their biological properties.[9,48]



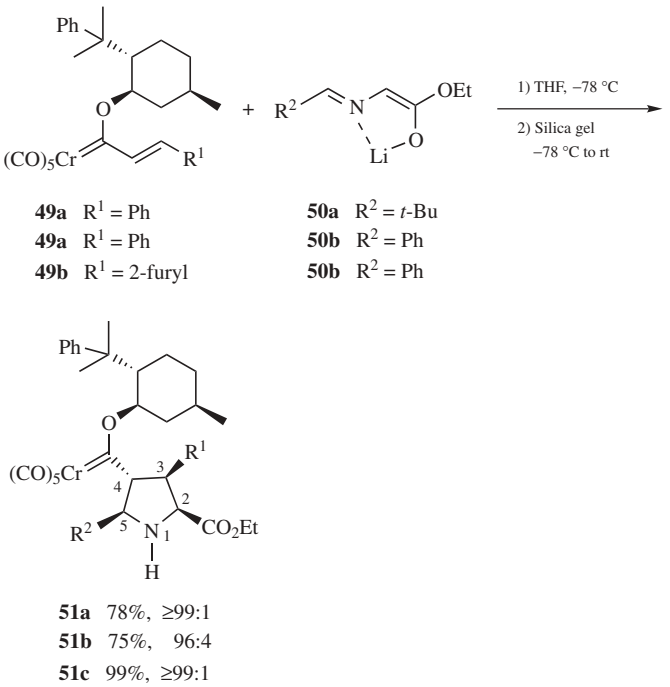
A **B**

Figure 10.7

10.5.1 Chiral Fischer Alkenylcarbene Complex Route

Chiral alkoxy alkenylcarbene complexes of chromium bearing (−)-8-phenylmenthol as chiral auxiliary have been successfully applied to the asymmetric synthesis of cyclic β-amino acids **A** ($Ar'' = H$). The methodology involves a formal [3 + 2]-cycloaddition reaction with an aldimine-protected glycine ester enolate, oxidation of the metal–carbene moiety, and hydrolysis of the carboxylic ester functional groups.[49]

10.5.1.1 Preparation of [3 + 2]-Cycloadducts The reaction of (−)-8-phenylmenthyloxy alkenylcarbene complexes **49a**,**b** with lithium glycine ester enolates **50a**,**b** occurred rapidly at −78°C and after quenching with silica gel at this low temperature and purification by column chromatography afforded selectively *syn*,*exo*-3-pyrrolidinylcarbene complexes **51a-c** (Scheme 10.13). (For the preparation of carbene complexes **49a**,**b**, see Ref. 50.) These [3 + 2]-cycloadducts **51** were formed with total regioselectivity, very high stereoselectivity (syn = cis relative configuration at C2,C3 and anti = trans relative configuration at C2,C3[51] and exo denotes the relative stereochemistry at C4,C5*) and very high

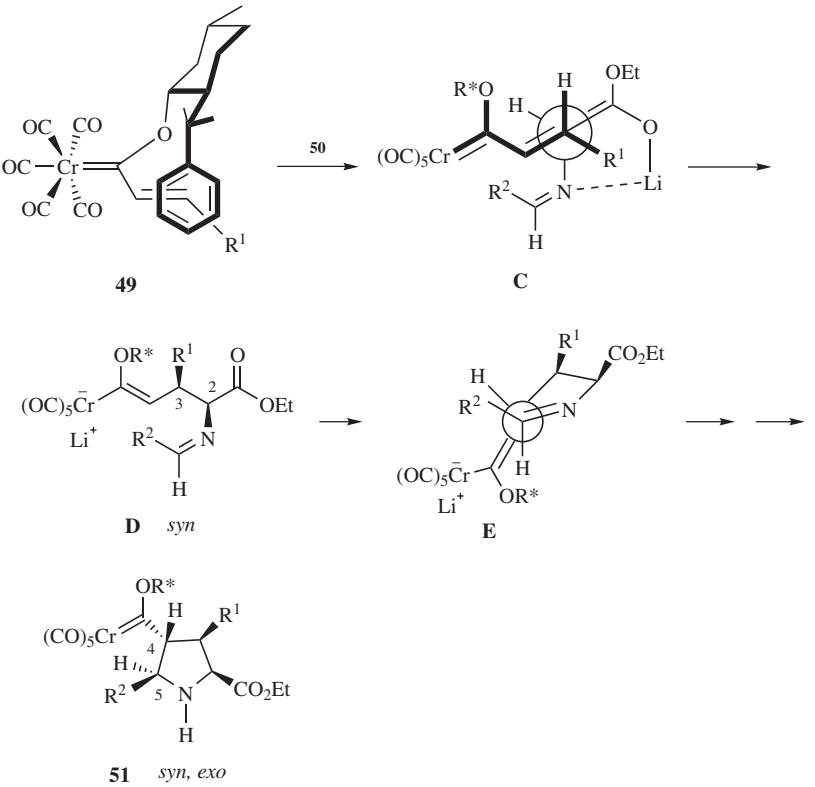


Scheme 10.13

*In the [3 + 2]-cycloaddition between *N*-metalated azomethine ylides and electron-deficient alkenes the exo,endo nomenclature has been employed to denote respectively a trans and cis relationship between the electron-withdrawing group at C4 coming from the alkene and the substituent at the C5 position coming from the azomethine ylide. See Ref. 52.

facial diastereoselectivity. The minor isomer formed in the case of compound **51b** corresponds to the epimeric isomer at the C2 carbon (anti,exo cycloadduct). Lithium enolates **50a**,**b** were prepared by deprotonation of ethyl *N*-(2,2-dimethylpropylidene)glycinate[53] or ethyl *N*-(phenylmethylidene)glycinate[54] with lithium diisopropylamide (LDA) in THF at −60°C.

The selective formation of syn, exo cycloadducts **51** with four stereogenic centers created simultaneously and with very high facial selectivity has been rationalized through the stepwise mechanism depicted in Scheme 10.14. This proposal involves conjugate addition of enolate **50** to alkenylcarbene complex **49** to give the corresponding syn Michael adduct **D** which subsequently undergoes a 5-endo-trig cyclization[55] in a nucleophilic addition/ring closure (NARC) sequence.[56] The sense of asymmetric induction follows from the known model **49** (Scheme 10.14) of the most stable conformation of (−)-8-phenylmenthyloxy alkenylcarbene complexes,[57] which is favored by the alkene–arene π-stacking effect.[58] The phenyl ring on the chiral auxiliary group shields the double bond (*re,re*) face of the alkene



49 **C** **D** *syn* **E** **51** *syn, exo*

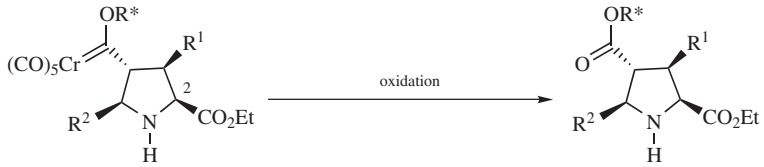
Scheme 10.14

inducing nucleophilic attack selectively from the back (*si,si*) face. The syn diastereoselectivity observed in the first Michael addition step has been explained in terms of approach topology **C**, which assumes a *s*-trans conformation for the vinylcarbene complex and the Michael addition occurs with an anti relationship of the donor and acceptor π-systems, placing the bulky substituent of the enolate away from the $(CO)_5Cr{=}C(OR^*)$ group to avoid steric interactions. Finally, the exo diastereoselectivity achieved in the subsequent intramolecular addition of the carbene complex enolate-type anion to the imine unit can be interpreted in terms of arrangement **E** in which H as the smallest substituent on the imine is placed in a syn disposition with the bulky metal fragment to minimize steric strain.

General Experimental Procedure for Formal [3 + 2]-Cycloaddition Reactions: Synthesis of 3-Pyrrolidinylcarbene Complexes All the operations were carried out under a nitrogen atmosphere. The LDA (1.6 eq.) was prepared by adding BuLi (1.6 eq.) to a solution of *i*-Pr_2NH (1.6 eq.) in THF at −60°C. After being stirred for 15 min at −60°C, this LDA solution was cooled to −78°C, and a solution of the corresponding ethyl *N*-alkylidene glycinate (1.6 eq.) was added via an addition funnel. The resulting yellow-orange solution was stirred for 30 min at −78°C, and then a THF solution of the corresponding alkenylcarbene complex **49** (1 eq.) was added dropwise from the addition funnel at −78°C. By the end of the addition step, the dark red starting carbene complex solution had turned into a bright yellow one which was stirred for 1 h at −78°C and then quenched with silica gel at −78°C for the adducts derived from phenylalkenylcarbene complex **49a** or with a saturated NH_4Cl aqueous solution and silica gel at −78°C for the adduct derived from furylalkenylcarbene complex **49b** and allowed to quickly rise to room temperature. Tetrahydrofuran was evaporated under reduced pressure, and the silica-adsorbed product was placed on top of a column and purified by flash chromatography. Elution with hexane/CH_2Cl_2, 9 : 1 removed some starting carbene complex left and no polar materials. Sequential elution with hexane/CH_2Cl_2, 4 : 1, 1 : 1 and hexane/CH_2Cl_2/EtOAc, 1 : 1 : 0.1 gave pure carbene complexes **51**.

10.5.1.2 Conversion of Cycloadducts to Free β-Amino Acids

Elimination of the pentacarbonylchromium fragment of cycloadducts **51** was effected by oxidation of these carbene complexes with an excess of ceric ammonium nitrate (CAN) or pyridine *N*-oxide to give the corresponding carboxylic diesters **52** (Scheme 10.15). Reactions with the milder reagent pyridine *N*-oxide were slower processes than when the stronger oxidation reagent CAN was employed. Under both reaction conditions only moderate chemical yields and a small loss of diastereoselectivity were observed (the ratio of diastereoisomers in the starting carbene complex was not maintained after the oxidation step). Some decomposition of the carbene complex and part of epimerization of the labile α-amino ester C2 carbon under the oxidation reaction conditions would account, respectively, for those results. In the oxidation of carbene complex **51a** with CAN to give diester **52a**, a small amount of a third diastereoisomer was formed. Oxidation of substrate



51a R^1 = Ph R^2 = *t*-Bu — CAN, Me_2CO/H_2O, 0 °C to rt — **52a** 62%, 85:11:4

51b R^1 = Ph R^2 = Ph — CAN, Me_2CO/H_2O, 0 °C to rt — **52b** 53%, 89:11

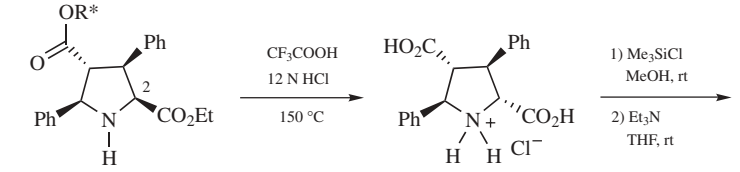
51c R^1 = 2-furyl R^2 = Ph — $C_5H_5N^+–O^-$, Et_2O, rt — **52c** 65%, 92:8

Scheme 10.15

51c containing a furyl group was most efficiently carried out with pyridine *N*-oxide, since oxidation with CAN yielded only 21% of product **52c**.

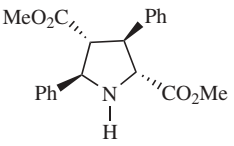
To remove the chiral auxiliary and form the corresponding amino acids, pyrrolidine-2,4-dicarboxylates **52b**,**c**, each one as a pure diastereoisomer, were subjected to hydrolysis of the carboxylic ester functional groups. Acidic hydrolysis of pyrrolidine **52b** [trifluoroacetic acid (TFA), 12 N HCl, 150°C, 36 h, sealed tube] took place with total epimerization of the labile C2 carbon to provide selectively *anti*,*exo*-proline hydrochloride **53b** (Scheme 10.16). The enantiomeric purity of this β- and α′-amino acid hydrochloride **53b** was established after transformation to the corresponding dimethyl diester derivative **54b**, as shown in Scheme 10.16, which was subsequently analyzed by high-performance liquid chromatography (HPLC) on a chiral support and in comparison with the corresponding racemic compound.

In contrast, basic hydrolysis of pyrrolidine **52c** carried out by treatment with LiOH in a 3 : 1 mixture of 1,4-dioxane/H_2O at 100°C for 16 h occurred, maintaining the configuration at the C2 carbon and affording *syn*,*exo*-proline hydrochloride **53c** (Scheme 10.17) The enantiomeric excess of this amino acid derivative **53c** was



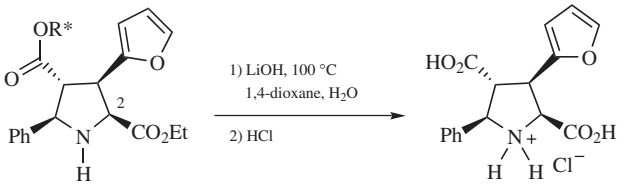
52b

53b 77%



54b 69%, 90% ee

Scheme 10.16



52c **53c** 37%, 96% ee

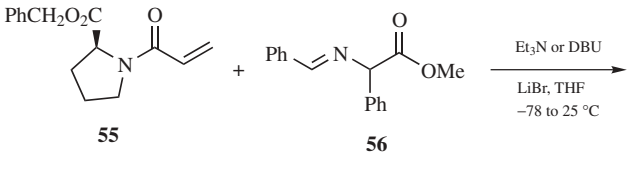
Scheme 10.17

determined by a chiral electrophoresis analysis in comparison with the corresponding racemic product.

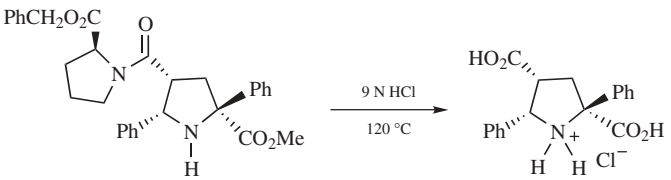
10.5.2 Other Chiral Substrate Routes

A cyclic β-amino acid of general structure **A** (Ar′ = H, Fig. 10.7) has been prepared by the asymmetric 1,3-dipolar cycloaddition reaction summarized in Scheme 10.18.[59] *N*-Acryloyl-(*S*)-proline benzyl ester **55** reacted with the *N*-metalated azomethine ylide generated in situ by deprotonation of **56** with a nitrogen base in the presence of anhydrous LiBr to give [3 + 2]-cycloadduct **57** with complete regiocontrol and very high endo and facial diastereoselectivity. The chiral auxiliary group was removed by acid hydrolysis (9 N HCl, 120°C, 24 h). This treatment resulted in the simultaneous hydrolysis of the amide and the two ester groups fo furnish enantiomerically pure amino acid hydrochloride **58**, although the enantiomeric excess of this product was not measured.

A similar methodology but using a chiral azomethine ylide instead of a chiral dipolarophile has been applied to the preparation of β-proline **61** (**B** in Fig. 10.7)



55 **56**

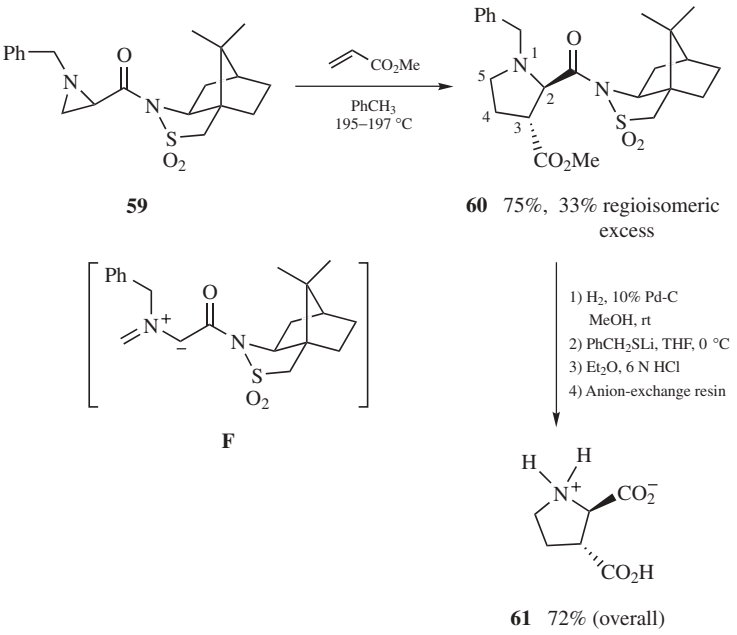


57 67%, *endo*/*exo*, ≥99:1
≥98% de

58 70%

Scheme 10.18

that contains an embedded aspartic acid moiety.[60] Thermolysis of aziridine carboxylate sultam (Oppolzer's camphor sultam) **59** generated chiral azomethine ylide **F** which was in situ trapped with methyl acrylate leading to the formation of a 2 : 1 mixture of [3 + 2]-cycloadduct **60** and its corresponding regioisomer (CO_2Me group at the C4 position) (Scheme 10.19). The major regioisomer **60** was converted by the reaction sequence shown in Scheme 10.19 to the known optically active β- and α-amino acid **61** which allowed to establish its stereochemistry.



Scheme 10.19

A stereoselective 1,3-dipolar cycloaddition of a photochemically generated azomethine ylide to Oppolzer's (+)-acryloyl sultam has been used to assemble the 3,8-diazabicyclo[3.2.1]octane moiety in the first asymmetric synthesis of the antibiotic (−)-quinocarcin (Fig. 10.8) that contains in its structure a β-proline unit.[61]

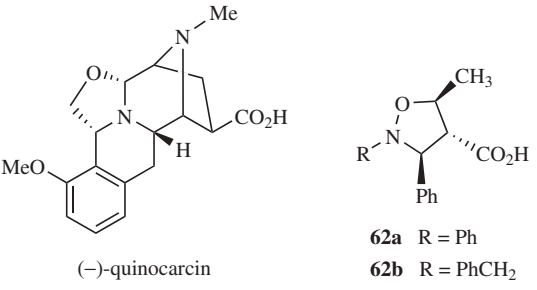
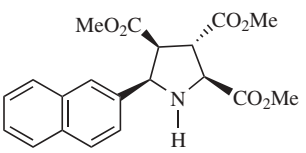
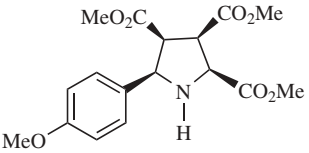


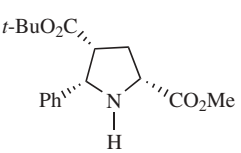
Figure 10.8



63 90% ee



64 92% ee



65 91% ee

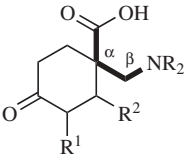
Figure 10.9

Cyclic β-amino acid derivatives **62** (Fig. 10.8) have been prepared as intermediates by hydrolysis of the corresponding thioester derivatives and then converted to optically active isoxazolidines of known structure. The corresponding thioesters were formed with high selectivity by nitrone [3 + 2]-cycloaddition to a chiral diiron crotonyl complex followed by oxidative removal (CAN) of the metal.[62]

Additionally, several enantiomerically enriched five-membered ring heterocyclic compounds with different substitution patterns and different relative and absolute configuration and which are potential precursors of cyclic β-amino acids of type **III** have been obtained through different [3 + 2]-cycloaddition processes[63] that involve a chiral Michael acceptor/dipolarophile,[64] a chiral metal enolate/azomethine ylide,[65] or a chiral ligand as catalyst.[66] But the potential conversion of these adducts to the corresponding free cyclic β-amino acid has not been reported. Products **63**,[66b] **64**,[66c] and **65**[66d] (Fig. 10.9) represent recent examples of this type of derivatives.

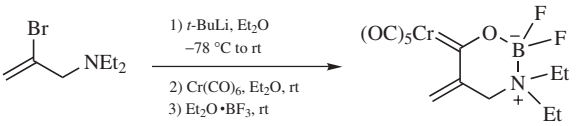
10.6 SYNTHESIS OF CONSTRAINED SIX-MEMBERED RING α,α-DISUBSTITUTED β-AMINO ACID DERIVATIVES VIA [4 + 2]-CYCLOADDITION REACTIONS

In a more broad context, β-amino acids of general structure **G** (Fig. 10.10) containing a cyclic gem disubstitution at the α-carbon can be included in this chapter. The fact that the C_α of this type of β-amino acids is inserted in a cyclohexane ring imposes some conformational restriction on the molecule which could be used for structure–activity studies. The asymmetric synthesis of this kind of β-amino acid has been achieved through a [4 + 2]-cycloaddition reaction between Fischer boroxy alkenylcarbene complexes and chiral 2-amino-1,3-dienes followed by elimination of the $Cr(CO)_5$ fragment and the BF_2 group.[67]



G

Figure 10.10



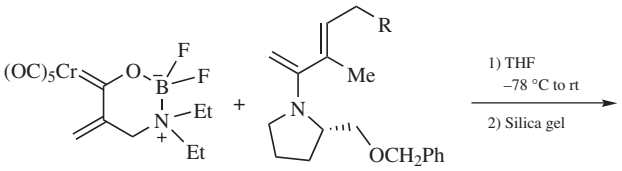
66 39%

Scheme 10.20

10.6.1 Synthesis of Spiro [4 + 2]-Cycloadducts

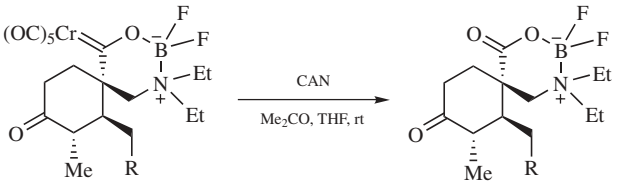
The starting amino-functionalized boroxy vinylcarbene complex of chromium **66** was prepared from 2-bromo-*N*,*N*-diethylallylamine, as shown in Scheme 10.20. Treatment of this amine with *tert*-butyllithium led to the corresponding β-amino-functionalized vinylic organolithium compound which subsequently was added to an ethereal solution of hexacarbonylchromium. The lithium acylmetalate anion thus generated was then treated with an excess of boron trifluoride etherate affording cyclic carbene complex **66** that was purified by silica gel column chromatography. This compound **66** contains a six-membered ring oxazaboracycle structure that locks the vinylcarbene complex into an *s*-cis conformation by means of an eventually removable BF_2 group.

The reactions of chromium carbene complex **66** with enantiomerically pure 2-amino-1,3-dienes[68] **67** derived from (*S*)-benzyloxymethylpyrrolidine were conducted under the conditions indicated in Scheme 10.21 and provided directly



66

67a R = MeO
67b R = $PhCH_2O$
67c R = CH_2=$CHCH_2O$



68a 39%, 92% ee
68b 50%, 93% ee
68c 26%, 76% ee

69a 80%
69b 73%
69c 88%

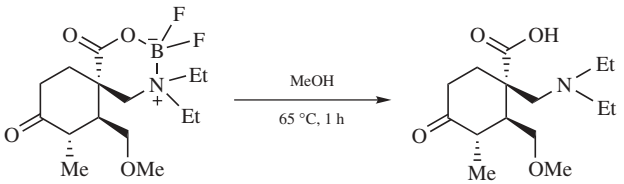
Scheme 10.21

spiranic keto carbene complexes **68** as single Diels–Alder adducts and with a high level of enantioselectivity in the case of products **68a**,**b**. Chelate boroxycarbene complexes **68** contain three contiguous stereogenic centers, one of which is a quaternary carbon atom. The regioselectivity of this [4 + 2]-cycloaddition reaction is in agreement with the polarization of diene and dienophile whereas the stereochemistry of compounds **68** corresponds to a formal exo topology of diene and dienophile.

10.6.2 Conversion of Spiro Carbene Complexes to the Free β-Amino Acids

The transformation of cycloadducts **68** to metal-free organic products was accomplished by selective oxidative cleavage of the pentacarbonylchromium fragment with CAN (Scheme 10.21). This oxidation process afforded the corresponding BF_2-protected β-amino acids **69** bearing an additional carbonyl group.

The free β-amino acids can be readily obtained by methanolysis of the chelate BF_2 complexes (Scheme 10.22). Thus, heating boron complex **69a** in refluxing



69a **70a** 50%

Scheme 10.22

methanol for 1 h led to free β-amino acid **70a** as a single diastereoisomer. A longer reaction time (3 h, reflux) induced partial epimerization of the stereogenic center α to the ketone carbonyl group.

10.7 SUMMARY

This chapter deals with the construction of enantiomerically enriched cyclic β-amino acid derivatives by means of an asymmetric cycloaddition reaction as the key step. Most of the published strategies in this area refer to [4 + 2]- and [3 + 2]-cycloaddition reactions, which have been mentioned or discussed here. (Very recently, the synthesis of two examples of enantioenriched ethyl *trans*-2-aminocyclopropanecarboxylate derivatives has been reported, an enantioselective catalytic cyclopropanation being the key step; see Ref. 69.) In this context, asymmetric [4 + 2]-cycloaddition of aminodienes with different dienophiles can be considered

a remarkable procedure to achieve chiral nonracemic 2-aminocyclohexanecarboxylic acid and derivatives; cis derivatives **13**, **40**, and **44** as well as the trans isomer **48** constitute good examples of them. On the other hand, asymmetric 1,3-dipolar cycloaddition has been so far the most employed strategy to get heterocyclic β-amino acid derivatives of different sizes. In this regard, most of the known examples in this field are β-proline derivatives of general structures **A** and **B** containing other α-amino acidic structural units. The preparation of the constrained six-membered β-amino acid **70** via a [4 + 2]-cycloaddition of a Fischer vinylcarbene complex with an enantiomerically pure aminodiene has also been included.

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CHAPTER 11

Enantioselective Synthesis of Novel β-Amino Acids

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As compared to their α-analogs, β-amino acids are not as abundant in nature; however, they are present[1] in a wide variety of natural products. They are biosynthesized in humans, animals, plants, and marine organisms and are present either in free form or as part of small peptides which exhibit antibiotic, antifungal, cytotoxic, and other pharmacological properties. β-Amino acids are also structural components of important medicinal compounds such as anticancer compound[2] taxol, where the β-amino acid side chain is essential for its biological activity. Other important β-amino acid derivatives are the β-lactams,[3] which are present in antibiotics, human leukocyte elastase inhibitors,[4] and cholesterol uptake inhibitors.[5] The pioneering work by Seebach et al.,[6a,b] Abele et al.,[6c] and Appella et al.[6d] have shown that oligomeric structures of β-amino acids could fold into defined secondary structures which are analogous to the ones observed in regular proteins. It is also known that β-amino acids exhibit reduced normal metabolism of those foldmers, which suggests that peptides with β-amino acids might also be, in vivo, metabolically more stable than their regular α-amino acid analogs. The synthesis of β-amino acids have been reviewed recently by several groups.[7] This chapter is intended to give a brief summary of the more recent developments in the enantioselective synthesis of β-amino acids. In the following section we present a practical approach to the enantioselective synthesis of β-amino acids. The section is divided in to two broad categories:

1. Acyclic β-amino acids
2. Cyclic and conformationally constrained β-amino acids

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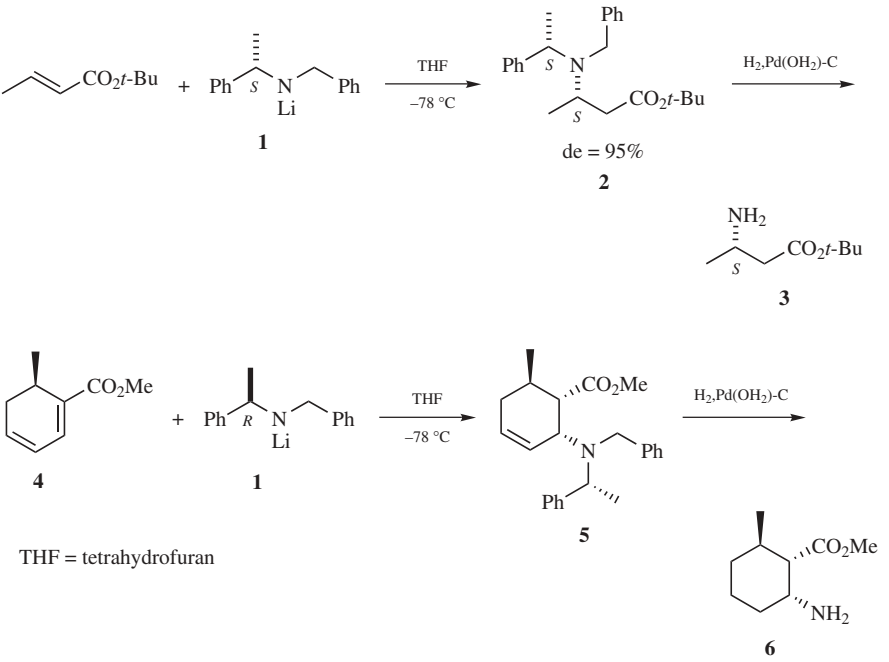
11.1 ACYCLIC AMINO ACIDS

A variety of α,α- and α,β-disubstituted β-amino acids are present as key structural elements in several natural products, for example, astins,[8] xemilofiban,[9] dolastatin,[10] and bestatin,[11] whose biological activity is to a large extent due to the presence of these amino acid residues. A variety of diastereoselective methods have been reported for the synthesis of acyclic β-amino acids and they are covered in the following sections.

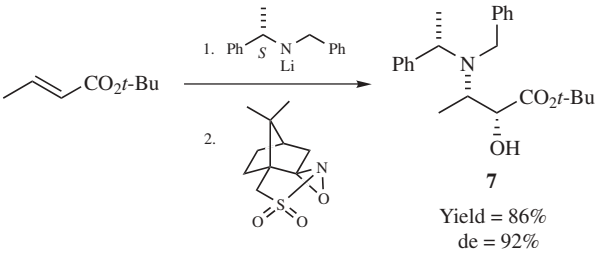
11.1.1 Diastereoselective Addition of Chiral Amines to α,β-Unsaturated Esters

One of the approaches to the asymmetric synthesis of β-amino acid esters involves the addition of chiral nonracemic metal amides to α,β-unsaturated esters. Davies and co-workers[12] reported the synthesis of enantiomerically pure β-amino esters via the stereoselective addition of chiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to α,β-unsaturated esters (Scheme 11.1). The subsequent debenzylation of **2** was carried out using catalytic hydrogenation to afford the desired β-amino ester **3** in high enantiopurity. The usefulness of the reaction was demonstrated by Davies and co-workers, who have applied this methodology for the enantioselective synthesis of (*S*)-β-tyrosine and cispentacin.



Scheme 11.1

Later they also described the asymmetric synthesis of cyclohexyl β-amino ester **6**, a key intermediate for the synthesis of pumilotoxin C, using as the key step a highly diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **1** to enantiopure diene **4**. The enolate formed by 1,4-addition was trapped with various electrophiles under diastereomeric control of both chiral centers. Thus the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to *tert*-butyl esters followed by in situ hydroxylation with (+)-(camphorsulfonyl)oxaziridine provides the corresponding *anti*-β-amino-α-hydroxy amino acid derivative **7** with excellent diastereoselectivity (Scheme 11.2). Following the same



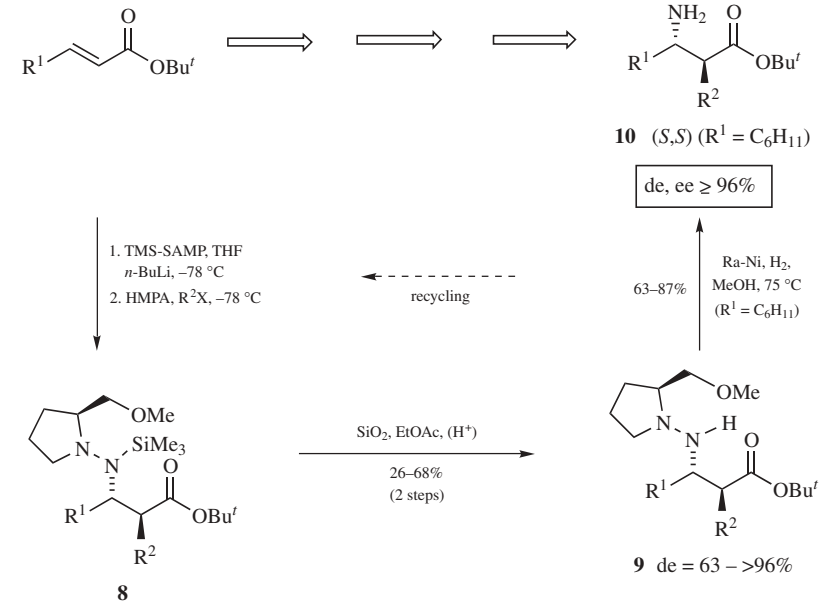
Scheme 11.2

protocol, 3-amino-2-hydroxydecanoic acid (AHDA) was obtained as both the (2S,3S)-anti and (2S,3S)-syn diastereomer. Similarly, for the synthesis of *anti*-α-alkyl β-amino acids, alkyl halides were utilized to trap the enolate obtained by Michael addition. The diastereomeric excesses were less satisfactory, and thus a modified procedure using toluene as reaction medium and modified reaction workup afforded high diastereoselectivity. This modified procedure was used to synthesize (2*S*,3*R*)-2-methyl-3-aminopentanoic acid in good yield with 99 : 1 syn/anti selectivity after reduction of the amine moiety and acid hydrolysis of the ester.

In an elegant approach, Enders and co-workers[13] employed the hetero Michael addition of (*S*)-(−)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP) to α,β-unsaturated esters followed by alkylation of the intermediate ester enolate with various electrophiles leading to the diastereoselective synthesis of *anti*-β-hydrazino esters **8** in high diastereomeric excess. Subsequent reductive N–N bond cleavage of **9** led to β-amino acid esters **10** in good yields and high diastereomeric excess (Scheme 11.3).

11.1.2 Chiral Lewis Acid–Catalyzed Addition of Nonchiral Amines to α,β-Unsaturated Amides

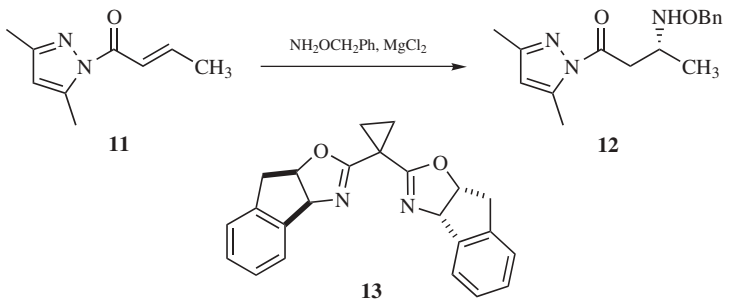
Only a few reports of chiral Lewis acid–catalyzed conjugate addition of amines to enoates have appeared. The first report was the work of Falborg and Jørgensen[14] in which a chiral titanium Lewis acid was employed. In a subsequent report they



HMPA = hexamethylphosphoramide

Scheme 11.3

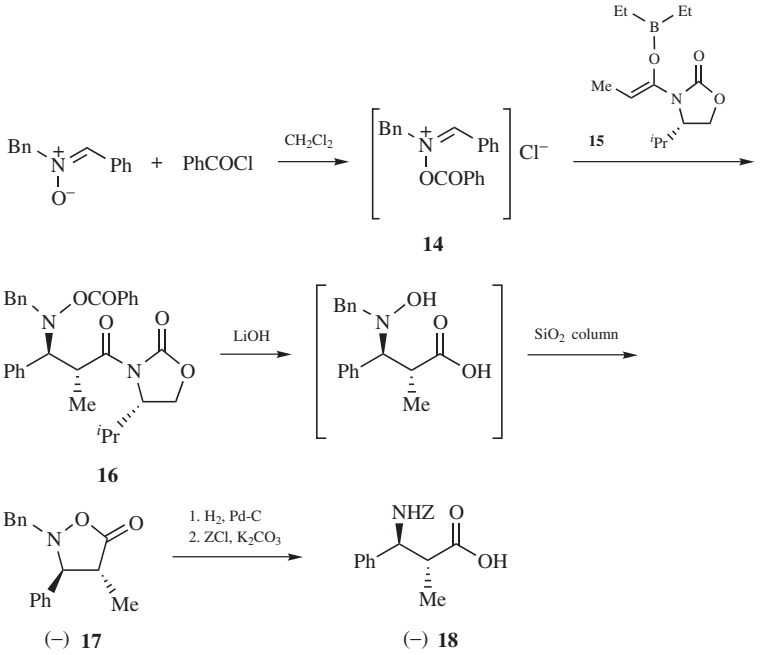
demonstrated the enantioselective addition of aromatic amines to α,β-unsaturated oxazolidinones in the presence of catalytic chiral nickel complex. The most successful chiral catalyst–promoted synthesis of enantiopure β-amino acid derivative **12** was reported by Sibi and co-workers,[15] who demonstrated high levels of enantioselectivity in the conjugate addition of *O*-benzyl hydroxylamine to α,β-unsaturated pyrazole amide **11** in the presence of chiral Lewis acid **13** (Scheme 11.4).



Scheme 11.4

11.1.3 Addition of Chiral Enolates to Nitrones and *N*-Alkoxycarbonyl-1-methoxyamines

Optically active β-amino acids can be prepared[16] by the reaction of *N*-acyloxyiminium ions **14**, generated by the reaction of nitrones with acyl halides, with both boron and Ti(IV) enoates **15** bearing chiral auxiliaries (Scheme 11.5). Hydrolysis



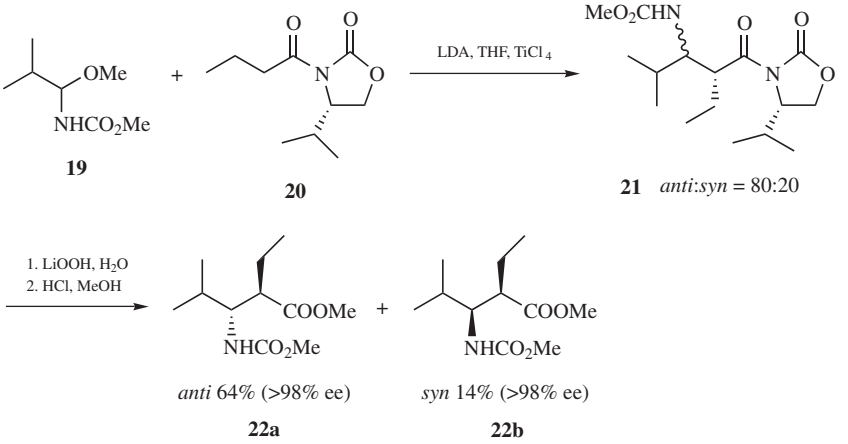
Scheme 11.5

of the intermediate adduct **16** followed by the hydrogenolysis of cyclic oxime ester **17** afforded β-amino acid derivative **18** in high diastereoselectivity.

Kise and Ueda[17] have developed an efficient procedure for the synthesis of *anti*-α,β-disubstituted β-amino acid derivatives by reaction of *N*-alkoxycarbonyl-1-methoxyamines **19** with optically active 2-oxazolidinones (Scheme 11.6). Thus the reaction of **19** and **20** with lithium diisopropylamide (LDA) in the presence of $TiCl_4$ gave the adduct **21** as an 80 : 20 diastereomeric mixture in 86% yield. The diastereochemistry of each isomer of **21** was assigned by its transformation to known β-amino acid methyl ester **22**. The major isomer **22a** was proved to be the anti isomer and its enantioselectivity value was found to be 98% by proton nuclear magnetic resonance (^{1}H NMR) analysis.

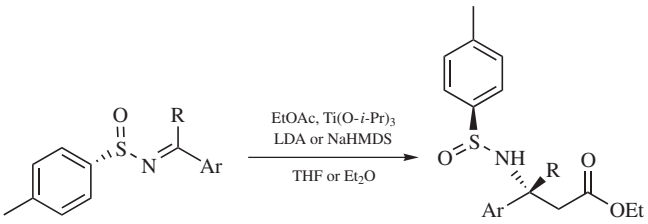
11.1.4 Addition of Enoates to Chiral Sulfinimine

Chiral sulfinimines can be reacted with enoates to give β-amino acids, and this procedure has been exploited for the synthesis of L-azatyrosine analogs in high



Scheme 11.6

enantioselectivity. Tang and Ellman[18] have developed an efficient protocol for the enantioselective synthesis of β-amino acid derivatives **24** by reacting chiral *tert*-butanesulfinyl imines **23** with Ti(O-*i*-Pr)$_3$ ester enoates (Scheme 11.7). The *N*-sulfinyl-β-amino ester products **24** were amenable to orthogonal deprotection, which was efficiently utilized for the synthesis of β-amino acid–derived peptides using standard solution-phase or solid-phase techniques.

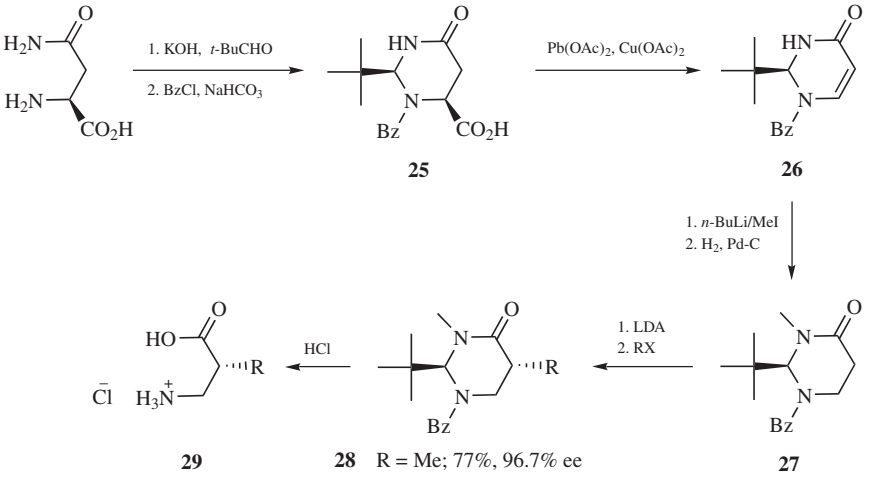


NaHMDS = sodium salt of hexamethyldisilazane

Scheme 11.7

11.1.5 Alkylation of Perhydropyrimidin-4-ones and Dihydropyrimidin-4-ones

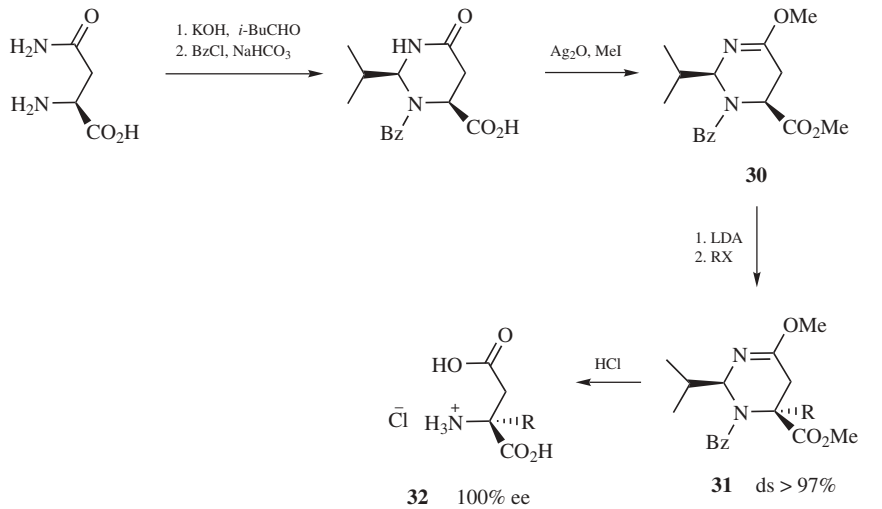
Perhydropyrimidin-4-ones and dihydropyrimidin-4-ones are an interesting class of heterocyclic compounds which represent a protected form of β-amino acids where the α- and β-position can be functionalized as desired. Thus the enantiomerically pure (2*S*,6*S*)-1-benzoyl-2-*tert*-butyl-6-carboxyperhydropyrimidin-4-one **25** was prepared[19] from the condensation of (*S*)-asparagine with pivaldehyde followed the benzoylation of the amino group (Scheme 11.8). The carboxyl side chain was removed by decarboxylation and the resulting enone **26** was reduced via catalytic



Scheme 11.8

hydrogenation. The perhydropyrimidinone **27** is a convenient substrate for the enantioselective synthesis of α-substituted β-aminopropanoic acid **28**, which can be obtained by LDA treatment of **27** followed by alkylation of the resulting enolate to afford **28**, whose acid hydrolysis leads to **29**.

Similarly, 6-methylperhydropyrimidin-4-ones were alkylated (LDA, RX) to afford the 5-substituted derivative, which upon hydrolysis afforded 2-substituted 3-aminobutanoic acids in high optical purity. Juaristi and co-workers[20] carried out the stereoselective transformation of (*S*)-asparagine into **30** (Scheme 11.9), which was alkylated with alkyl halides to yield trans adduct **31** in high diastereoselectivity.

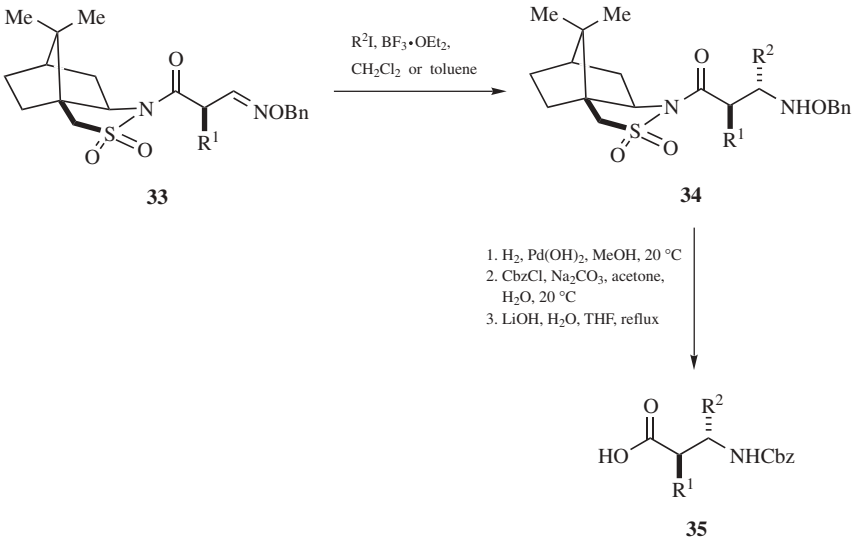


Scheme 11.9

Hydrolysis of the adduct **31** was accomplished under mild acidic conditions to afford enantiopure α-alkyl aspartic acids **32** in excellent yields.

11.1.6 Diastereoselective Radical Addition to Oxime Ethers

Alkyl radical addition to Oppolzer's camphorsultam derivatives of oxime ethers is a convenient method for the synthesis of enantiomerically pure α,β-dialkyl-β-amino acids. Miyabe and co-workers[21] have carried out a phase transfer catalyzed alkylation of *N*-(β-oximino)acyl derivatives of Oppolzer's sultam followed by $BF_3 \cdot OEt_2/Et_3B$-mediated alkyl radical addition on the alkylated adduct **33** leading to the diastereoselective formation of α,β-dialkyl-β-amino acid derivatives **34** which was transformed to the corresponding β-amino acid derivatives **35** by a sequential hydrogenolysis and alkaline hydrolysis protocol (Scheme 11.10). In another related approach, Miyabe and co-workers[22] have developed a tandem radical addition–cyclization involving oxime ethers for asymmetric synthesis of β-amino acids.

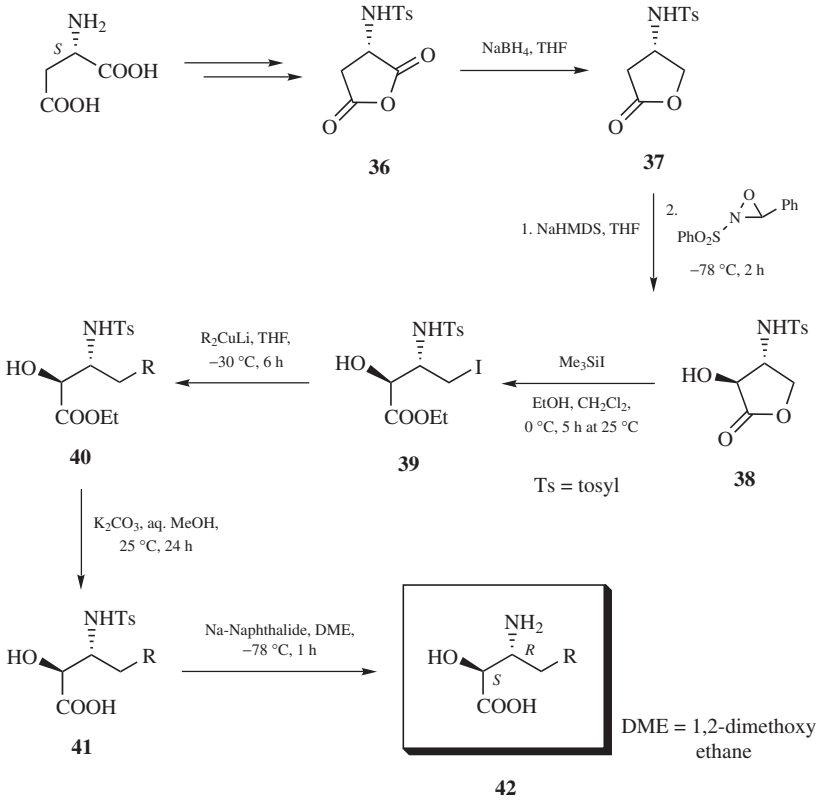


Scheme 11.10

11.1.7 Synthesis of α-Hydroxy-β-amino Acids

α-Hydroxy-β-amino acids are present in many natural products having significant biological activity. Among the best-known examples are the potent antineoplastic agent taxol,[23] bestatin,[2] and the well-known immune modifier microginin.[24] There are several procedures developed for the α-hydroxy-β-amino acid unit (β-phenylisoserine) present in taxol, but this chapter will focus only on the recent developments in the synthesis of other related β-amino acids. Jefford and co-workers[25]

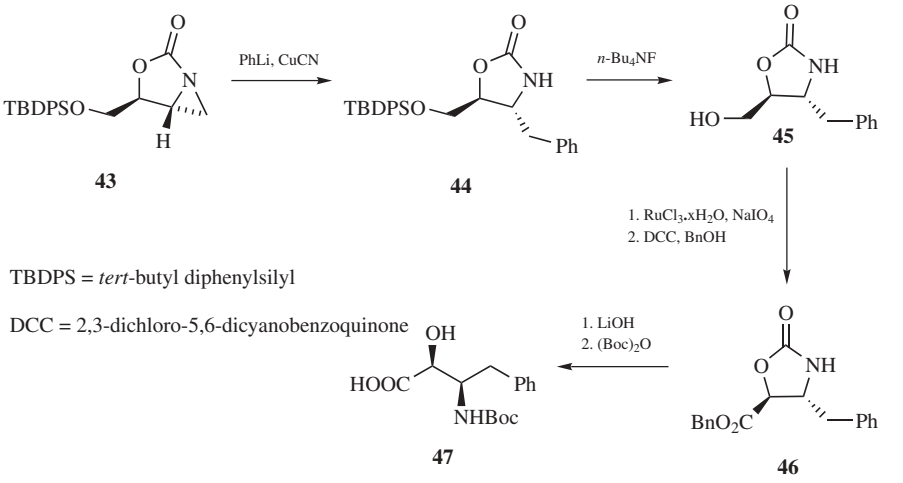
have developed a general route to the diastereospecific synthesis of 3-amino-2-hydroxy acids from L-aspartic acid. The cyclic anhydride **36** from aspartic acid was selectively reduced to give the lactone **37**, which underwent smooth oxidation by chiral oxaziridine to afford the α-hydroxy lactone **38** in a diastereoselective manner (Scheme 11.11). The lactone **38** was opened with trimethylsilyl iodide (TMSI) to



Scheme 11.11

give γ-iodo ester **39**, which was alkylated with alkyl cuprate leading to 3-amino-2-hydroxy acid derivatives **40**. Subsequent hydrolysis with alkali afforded **41**, which were deprotected with Na-naphthalide to furnish the corresponding α-hydroxy-β-amino acids **42** in high yields and diastereoselectivity.

A highly diastereoselective route to bestatin was developed[26] by selective cyanosilylation of the chiral amino aldehyde derived from phenylalanine. This procedure utilizes a chiral bifunctional catalyst to promote highly enantioselective cyanosilylation of aldehyde. This catalyst acts via a dual activation mechanism where aluminum metal and the phosphine oxide ligands act in tandem as Lewis acid and base. Bergmeier and Stanchina[27] have carried out an intramolecular acyl-nitrene-mediated aziridination to generate a key bicyclic aziridine **43** which can be



43 44 45 46 47

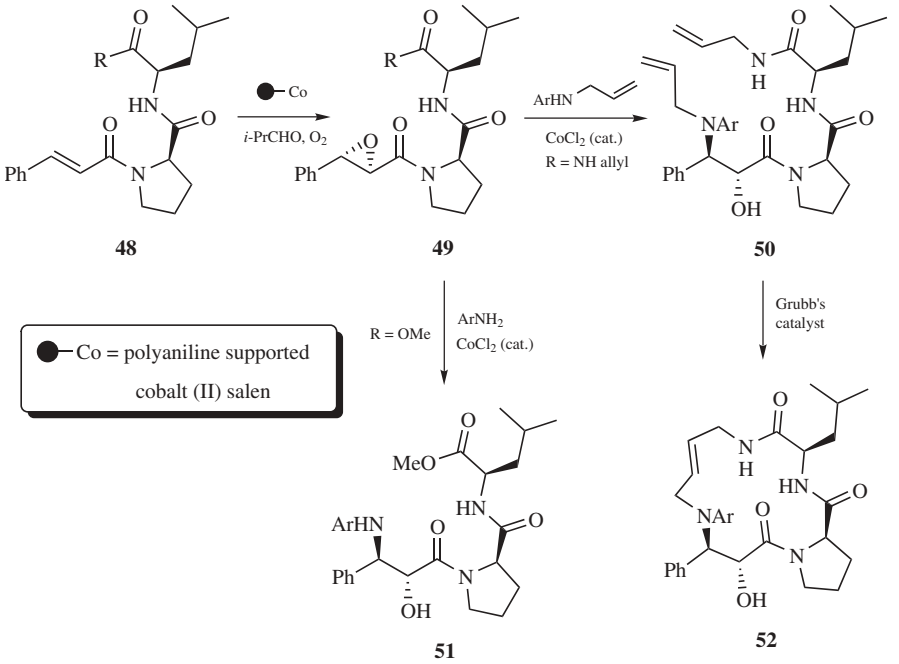
Scheme 11.12

opened with a number of organometallic reagents to provide a series of oxazolidinones (Scheme 11.12). The oxazolidinone **44** was deprotected to yield alcohol **45** which was transformed to the corresponding ester derivative **46** by ruthenium-catalyzed oxidation. Subsequent hydrolysis and Boc protection afforded the corresponding α-hydroxy-β-amino acid derivative **47**, which could be transformed to bestatin and its analogs.

Iqbal and co-workers[28] have synthesized α-hydroxy-β-amino acid derivatives on peptide templates by a novel aerobic epoxidation of cinnamoyl peptides followed by cobalt-catalyzed opening of the latter with several aromatic amines. The cinnamoyl peptides **48** were epoxidized in the presence of oxygen and polymer-supported Co(II) salen catalyst and the resulting epoxides **49** were opened with *n*-allyl amine stereoselectively to afford the corresponding α-hydroxy-β-amino acid–derived tripeptides **50** in high optical purity (Scheme 11.13). The tripeptide was cyclized by Grubb's catalyst to afford the corresponding cyclic peptide **52** as a conformational constrained analog of aspartyl protease inhibitors. On the other hand, the epoxide **49** was stereoselectively opened with aromatic amines to afford the structural analog **51** of bestatin.

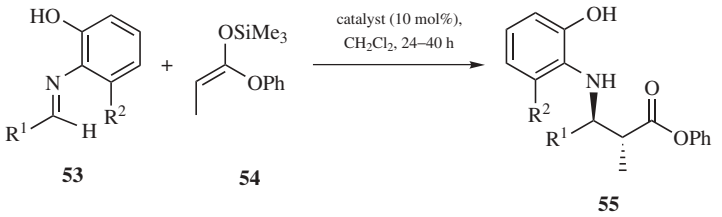
11.1.8 Catalytic Enantioselective Synthesis of β-Amino Acids

11.1.8.1 Mannich Reaction The Mannich reaction is a classic method for the preparation of β-amino ketones and aldehydes and therefore a very important carbon–carbon bond-forming reaction in organic synthesis. The first diastereoselective method reported[29] employed the addition of preformed enolates to preformed imines using stoichiometric amounts of chiral auxiliaries. Recently Kobayashi and co-workers[30] reported a highly enantioselective synthesis of *anti*-α-methyl-β-amino



Scheme 11.13

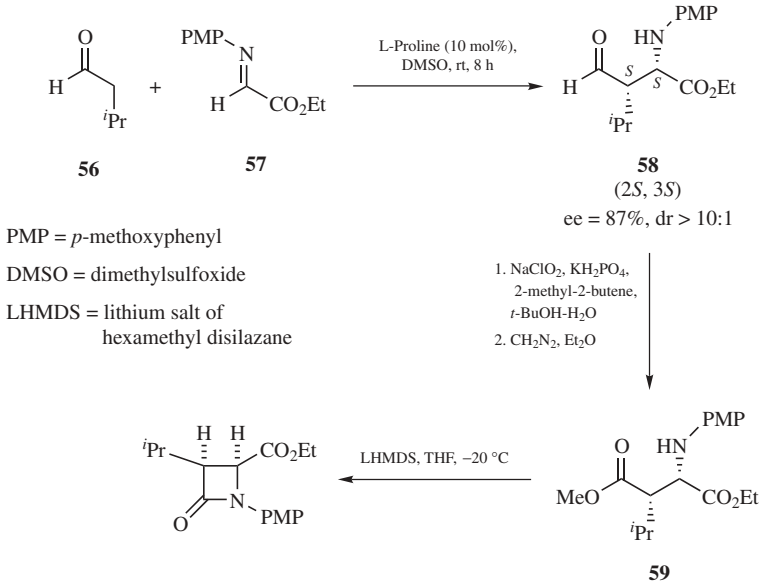
acid derivatives **55** using catalytic enantioselective addition of ketene (*E*)-silyl acetals **53** to imines **54**, derived from 2-aminophenol, using a chiral zirconium catalyst (Scheme 11.14). It is interesting to note that isomeric (*Z*)-ketene silyl acetal also gave high anti selectivity in 83% ee. In the reactions with aliphatic



Scheme 11.14

substrates, aldimines were prepared in situ from the corresponding aldehydes and 2-amino-*m*-cresol instead of 2-aminophenol. The phenol residue on nitrogen was a useful control element and protecting group, as amines were unmasked on ceric ammonium nitrate (CAN) treatment in high yields.

In a significant development, Córdova and co-workers[31] demonstrated that an unmodified donor aldehyde could be used in catalytic Mannich reactions. They



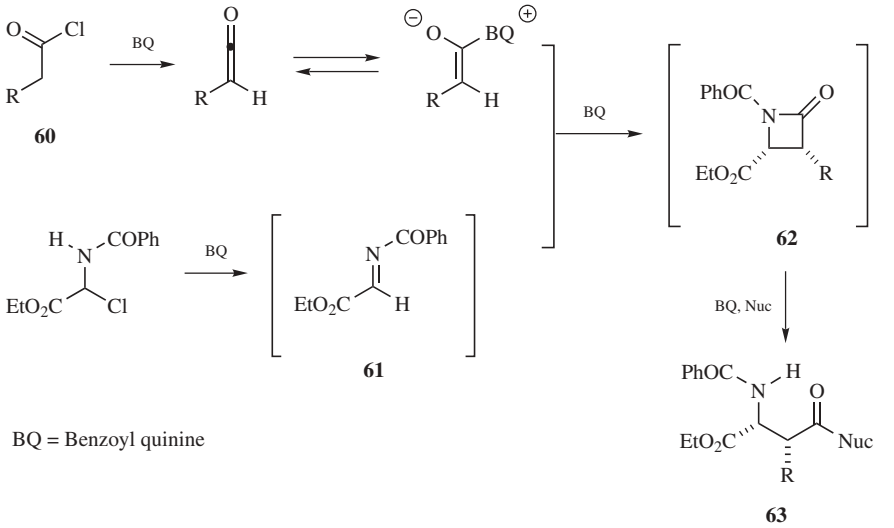
56 **57** **58** (2*S*, 3*S*) ee = 87%, dr > 10:1 **59**

Scheme 11.15

have carried out a coupling between aliphatic aldehyde **56** and α-imino ethyl glyoxylate **57** in the presence of catalytic L-proline leading to the synthesis of 3-formyl-α-L-amino acids **58** (Scheme 11.15). The aldehyde group of Mannich product **58** can be readily oxidized ($NaClO_2$) and subsequently esterified (CH_2N_2) to give aspartic acid derivative **59** in high enantiomeric excess.

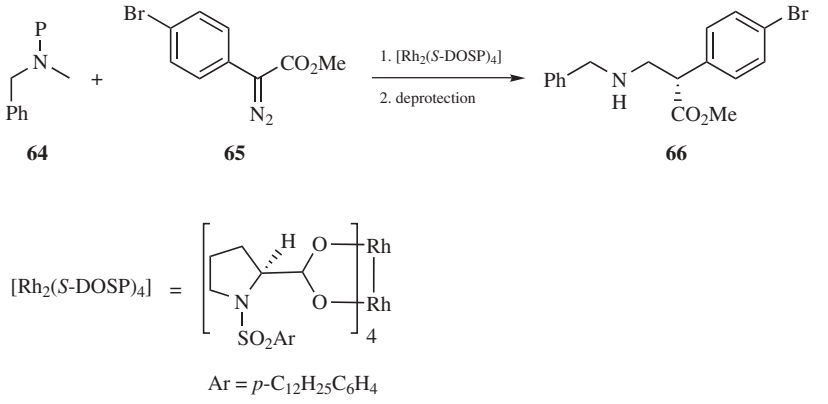
11.1.8.2 Staudinger Reaction Taggi and co-workers[32] have developed an elegant enantioselective β-lactam synthesis by employing a Staudinger type of reaction. They have demonstrated that β-substituted amino acid **63** can be obtained from β-lactams **62** (Scheme 11.16), which can be obtained by reacting acid chloride **60** with α-imino ester **61** in the presence of catalytic amounts of benzoyl quinine (BQ) and a proton sponge. This reaction was extended for the synthesis of β-substituted aspartic acid derivatives in which the chiral nucleophilic catalyst played four distinct roles in a one-pot procedure. Mechanistically this reaction is fascinating as catalytic dehydrogenation of acid chloride to form ketene, [2 + 2]-cycloaddition to produce intermediate acyl β-lactams **62**, and finally nucleophilic ring opening to afford optically enriched β-substituted aspartic acid derivatives **63** take place in tandem in a one-pot procedure.

11.1.8.3 Rhodium-Catalyzed Asymmetric C–H Activation In their attempt to develop the C–H activation of allylamines as a surrogate to the Mannich reaction, Davies and Venkataramani[33] discovered that [Rh_2(*S*-DOSP)$_4$]-catalyzed enantioselective insertion of methyl-*p*-bromophenyl diazoacetate **65** on Boc-protected *N*-methyl-crotoylamine has occurred in methyl C–H instead of the



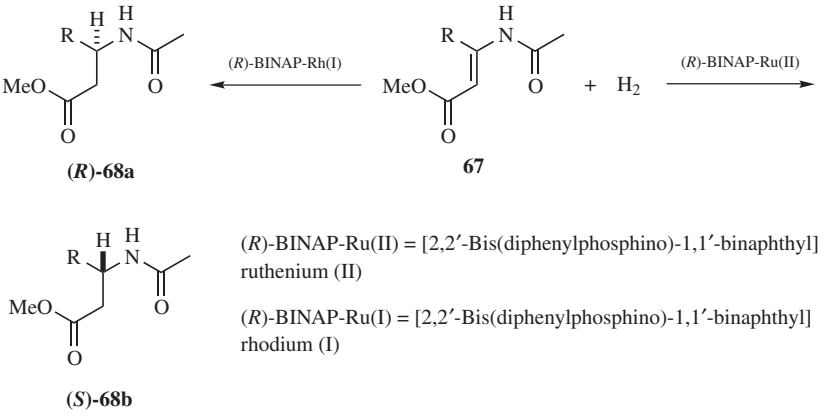
Scheme 11.16

expected allylic C–H bond. They developed this intermolecular C–H insertion into a general process for the synthesis of a range of β-substituted amino esters **66** (Scheme 11.17). They showed that benzyl amine **64** is the optimum substrate, which turned out to be an attractive methodology as the resulting products were readily converted to useful β-amino acids.



Scheme 11.17

11.1.8.4 Ruthenium-Catalyzed Enantioselective Hydrogenation Lubell and co-workers[34] have demonstrated the BINAP-Ru(II)-catalyzed hydrogenation of β-substituted methyl (*E*)-β-(acylamino)acrylates **67** to afford the corresponding β-amino esters **68a** and **68b** (Scheme 11.18) in high enantioselectivity. The (Z)



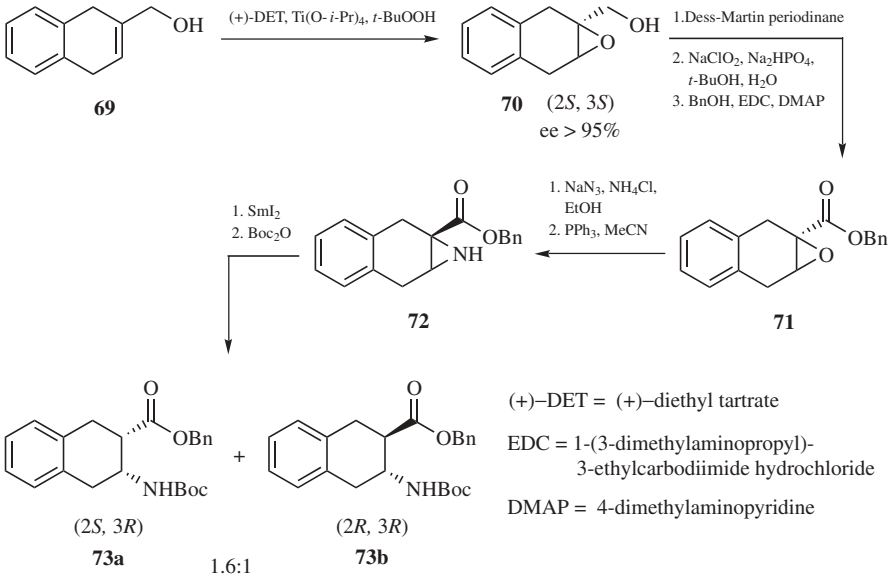
Scheme 11.18

double-bond isomers possessing an intramolecular hydrogen bond between amide and ester groups were hydrogenated with poor selectivity whereas BINAP-Rh(I) afforded β-amino ester in moderate stereoselectivity with opposite enantioselectivity.

11.2 CYCLIC AND CONFORMATIONALLY CONSTRAINED β-AMINO ACIDS

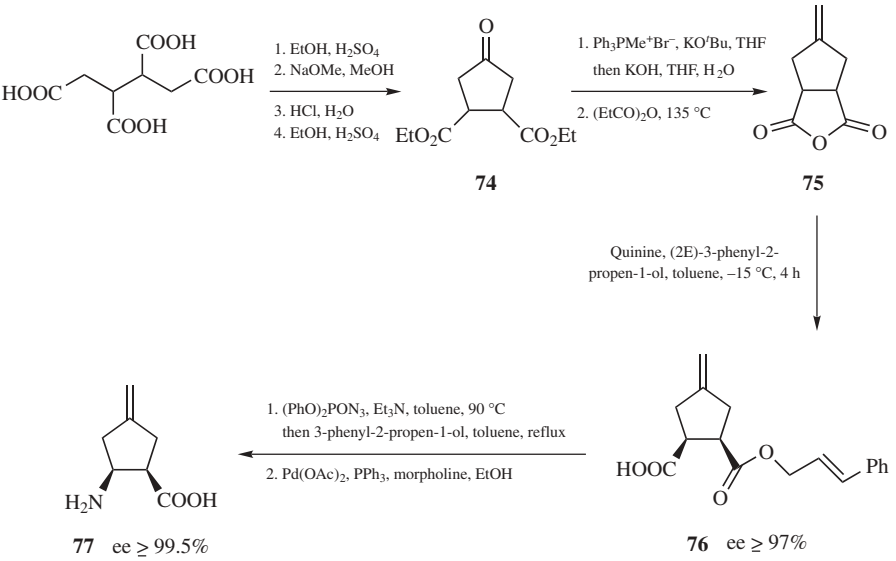
It is well known that conformationally constrained peptides exhibit increased stability and biological activity. Accordingly, several research groups have mimicked naturally occurring amino acids and biologically active peptides to address the problems related to potency, receptor selectivity, and pharmacokinetic properties. Thus structural modifications with decreased conformational flexibility may possibly be achieved from cyclic or constrained amino acids, and accordingly several groups have focused their attention on synthetic protocols for accessing cyclic and conformationally constrained β-amino acids. Kawahata and Goodman[35] have developed a procedure for the synthesis of orthogonally protected β-amino acid 3-*tert*-butoxycarbonylamino-1,2,3,4-tetrahydro-2-naphthonoic acid benzyl ester **73**. These constrained phenylalanine analogs are obtained by Sharpless asymmetric epoxidation on cyclic allyl alcohol **69** followed by the conversion of the epoxy alcohol **70** by a sequence of reactions (Scheme 11.19) to the epoxy ester **71**, which was converted to the corresponding aziridine **72** in a diastereoselective manner. SmI_2-mediated cleavage of the aziridine **72** then led to the corresponding β-amino esters **73** in high diastereoselectivity.

The Bayer group[36] has reported an efficient synthesis of 2-aminocyclohexane caboxylic acid as an antifungal agent. They have also synthesized the cyclic β-amino acid in a high diastereoselectivity by a quinine-mediated alcoholysis of the meso anhydride **75** (obtained from 3,4-dicarboethoxycarbonyl cyclopentanone **74**)

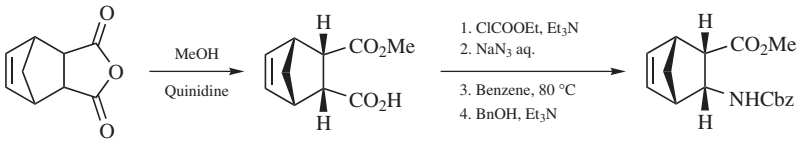


Scheme 11.19

by cinnamoyl alcohol with ee $> 97\%$ (Scheme 11.20). Subsequent Curtius rearrangement and Pd-catalyzed removal of the cinnamoyl protecting group on **76** afforded the corresponding cyclic β-amino acid **77** with ee $> 99.5\%$.



Scheme 11.20

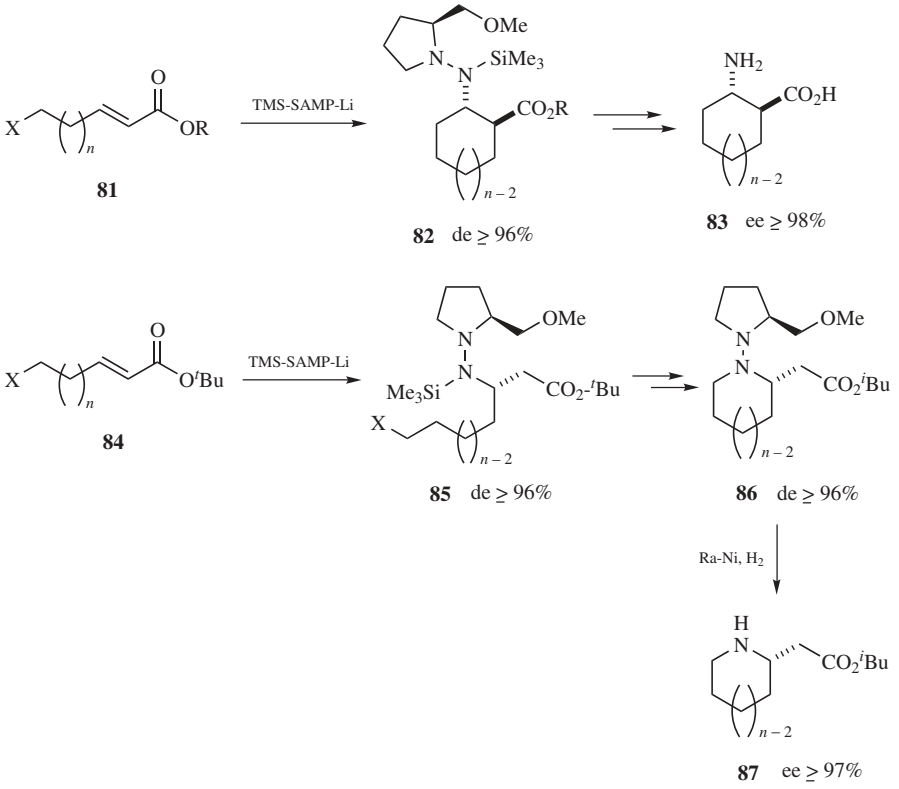


78 **79** **80**

Scheme 11.21

A similar approach[37] using methanolysis of cyclic meso anhydrides **78** mediated by cinchona alkaloids afforded (Scheme 11.21) a variety of dicarboxylic acid monomethyl esters **79** with up to 99% ee. Subsequently, unnatural *N*-protected β-amino esters **80** were obtained by means of Curtius degradation of the corresponding acyl azides.

In another elegant approach, Enders and co-workers[38] have carried out conjugate addition of lithiated TMS-SAMP to ω-halide-substituted enoates leading to the synthesis of cyclic β-amino acids via intramolecular Michael addition followed by ring closure (Scheme 11.22). When the methyl ester of ω-halo enoate **81** was a



81 **82** de ≥ 96% **83** ee ≥ 98%

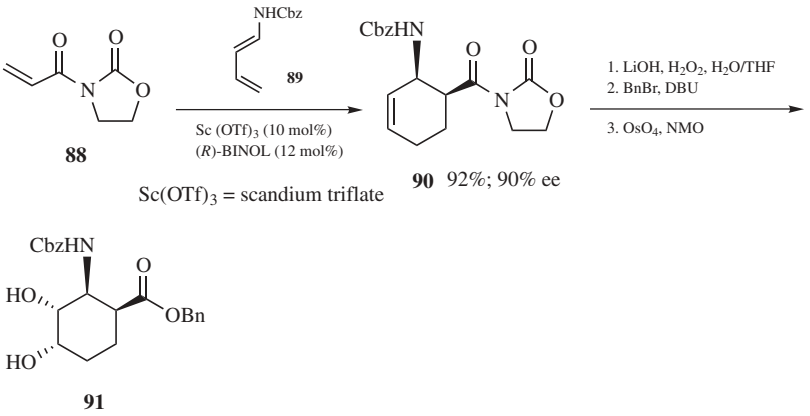
84 **85** de ≥ 96% **86** de ≥ 96%

87 ee ≥ 97%

Scheme 11.22

substrate, the intermediate enoate derived by addition of TMS-SAMP underwent intramolecular cyclization to afford the cyclized adduct **82** which could be transformed to the cyclic β-amino acid **83** on treatment with Raney Ni in high enantiomeric excess. On the other hand, the *tert*-butyl ester **84** underwent addition to give the adduct **85** which was cyclized to give the cyclic β-amino acid derivative **86**. A Raney Ni treatment on **86** afforded the corresponding cyclic β-amino acid **87** in high enantiomeric excess.

A novel approach[39] to ring-functionalized cyclic β-amino acid was carried out using the catalytic asymmetric Diels–Alder reaction with aminodiene **89** and acyl-1,3-oxazolidin-2-one **88** (Scheme 11.23). The Diels–Alder reaction was performed using scandium catalyst in the presence of (*R*)-BINOL and the double bond in the resulting cyclohexene derivative **90** was dihydroxylated to give highly functionalized cyclic β-amino acids **91** in high diastereomeric excess.



Scheme 11.23

11.3 CONCLUSION

In summary, this chapter describes an update on the recent synthetic methodologies developed for enantiopure β-amino acids. It is clearly apparent from the foregoing sections that there now exists a plethora of efficient routes for accessing acyclic as well as cyclic β-amino acids in high diastereomeric excess. This development has clearly paved the way for the access to a wide range of chiral β-amino acids required as key intermediate in the synthesis of novel therapeutics and β-peptides.

Experimental Procedure for Some Select β-Amino Acids

Preparation of **3** The *n*-BuLi (2.95 eq.) was added dropwise to a stirred solution of (*S*)-**1** (3.0 eq.) in anhydrous THF at −78°C and stirred for 30 min under nitrogen. A solution of the bis-α,β-unsaturated ester (1.0 eq.) in anhydrous THF at −78°C

was added dropwise via cannula and stirred at −78°C for 12 h before the addition of saturated NH_4Cl solution and was warmed to room temperature (rt). The resultant solution was partitioned between brine and CH_2Cl_2–Et_2O (1 : 1). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure and purified by column chromatography to afford pure **2**.

To a solution of **2** (0.14 mmol) in degassed MeOH (5 mL) in a Fischer–Porter bottle was added $Pd(OH)_2$ on C (150 mg) and the black suspension was stirred under a hydrogen atmosphere (5 atm) for 16 h. The reaction mixture was then filtered through a plug of Celite and concentrated. Purification on silica gel of the residue afforded **3**.

Preparation of **32** To a solution of (*S*)-asparagine (15 g, 113.5 mmol) in dry methanol (150 mL) a solution of KOH (6.4 g, 113.5 mmol) in methanol (35 mL) was added and the resulting mixture was stirred at ambient temperature until complete dissolution of the amino acid. Isobutyraldehyde (10.8 mL, 113.5 mmol) was then added slowly, and the reaction mixture was heated to reflux for 10 h. The reaction mixture was cooled in an ice bath followed by successive addition of sodium bicarbonate (4.76 g, 67 mmol) and benzoyl chloride (13.2 mL, 113.5 mmol). The reaction mixture was stirred at ambient temperature overnight before treatment with 6 N HCl until pH 3.0. The precipitate was filtered and the filtrate was concentrated to give pale yellow oil. The oil was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), and concentrated. Crystallization from ether–hexane (95 : 5) yielded the cyclized carboxylic acid (14.3 g, 50%).

To a mixture of the above carboxylic acid (5.0 g, 17.2 mmol) and silver oxide (8.2 g, 35.3 mmol) in THF (50 mL) methyl iodide (3.2 mL, 51.6 mmol) was added and was stirred for 32 h at ambient temperature. The reaction mixture was filtered through a Celite bed and was purified by flash chromatography (hexane–ethyl acetate 9 : 1) to afford the imino ether **30** (4.1 g, 74.2%).

To a cooled (−20°C) solution of diisopropyl amine (1.0 eq.) in THF *n*-BuLi (1.0 eq., 1.8 M in hexane) was added and was stirred for 20 min and then cooled to −78°C followed by the addition of **30** (1.0 eq.) in THF. The reaction mixture was stirred for 1 h at that temperature. The alkylating agent (1.15 eq.) was then added dropwise and the reaction mixture was stirred at −78°C for 2 h and at ambient temperature overnight. The reaction was quenched by saturated NH_4Cl solution and extracted with three portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure below 30°C to give **31**. A suspension of **31** (approximately 1 mmol) in 17% HCl (10 mL) was heated in a sealed ampule to 95°C (in a Thermolyne 21100 oven). The solution was then allowed to cool to ambient temperature and was extracted three times with CH_2Cl_2. The aqueous phase was evaporated to afford amino acid hydrochloride **32**.

*Preparation of (S)-***68b** (*E*)- and (*Z*)-Enamido esters **67** (1.0 mmol) were dissolved in MeOH (5 mL) and the solution was degassed three times, then treated with $Ru(OCOCH_3)_2$[(*R*)-binap] (0.005 mmol) and degassed two more times. The solution was transferred under a positive pressure of argon via stainless steel

cannula into a pressure vessel that was filled, vented, and refilled with hydrogen atmosphere five times. The solution was stirred for 24 h. Methanol was removed to give β-amido ester **68b**.

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CHAPTER 12

Asymmetric Synthesis of Phosphonic Analogs of β-Amino Acids

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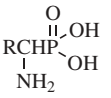
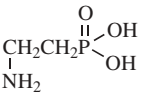
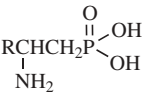
Aminophosphonic acids are phosphorus analogs of amino acids in which the carboxylic group is replaced by a phosphonic acid moiety. This class of compounds attracted considerable interest because of a wide spectrum of biological activities. Some aminophosphonic acids have found commercial applications in agriculture and medicine. Although α-aminophosphonic acids **A**—direct analogs of natural α-amino acids—occupy a special place among the diverse structures of aminophosphonic acids, the first aminophosphonic acid discovered in nature was β-aminoethanephosphonic acid **B** named ciliatine. The isolation of ciliatine and other related β-aminophosphonic acids **C** from natural sources has led to intense interest in this group of aminophosphonic acids, which in turn may be considered as analogs of unnatural β-amino acids.



A



B



C

As in the case of other classes of chiral bioactive compounds, the biological activity of aminophosphonic acids depends on the absolute configuration of the stereogenic carbon atom bearing the amino group. For this reason, the synthesis of chiral, nonracemic aminophosphonic acids is a challenging task. However, in contrast to the widely investigated α-aminophosphonic acids, the synthetic approaches to enantiomeric β-aminophosphonic acids are few in number and in many cases of limited applicability. The purpose of this chapter is to give an

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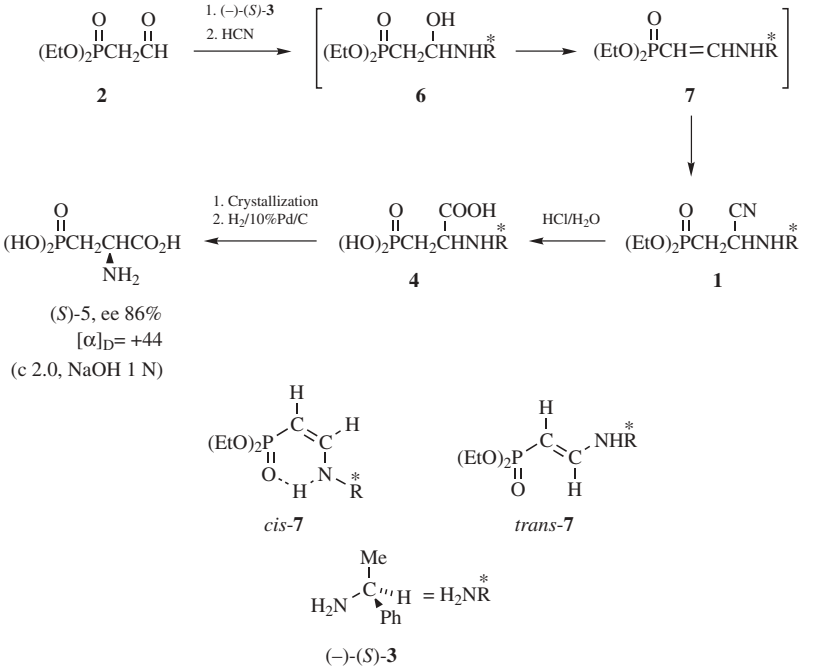
up-to-date account of asymmetric syntheses of β-aminophosphonic acids. This subject has been treated in a cursory manner in a recent monograph on aminophosphonic and aminophosphinic acids.[1] For the sake of clarity the various methods of asymmetric synthesis of β-aminophosphonic acids are grouped according to the type of bond formed: C–C, C–N, and C–H.

12.1 ENANTIOSELECTIVE C–C BOND-FORMING REACTIONS

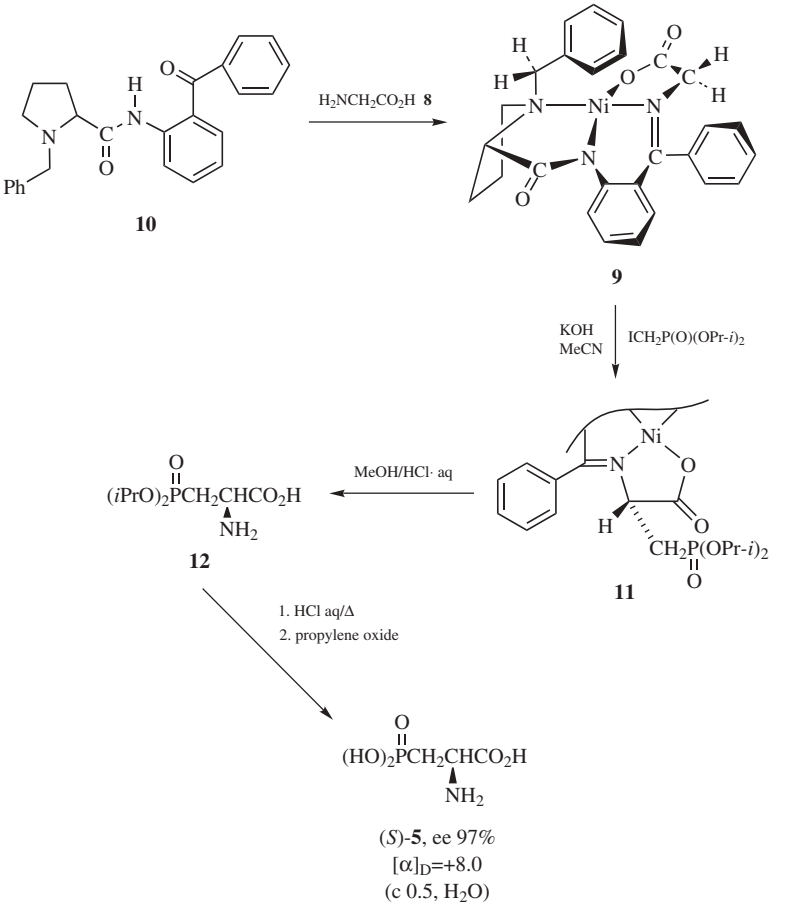
The oldest protocol for the asymmetric synthesis of β-aminophosphonic acids involving an asymmetric C–C bond-forming reaction utilizes the diastereoselectivity of the addition of hydrogen cyanide to β-aminovinylphosphonates. This protocol, which has been reported as early as 1983,[2] constitutes simultaneously the first example of asymmetric synthesis of an optically active β-aminophosphonic acid analog ever described. It started from the generation (direct or sequential) of the optically active aminonitrile **1** in the reaction of diethyl α-formylmethanephosphonate **2** with (−)-(*S*)-α-methylbenzylamine **3** in the presence of hydrogen cyanide. The aminonitrile **1** was produced with 50% diastereomeric purity [^{31}P nuclear magnetic resonance (NMR) assay]. Acid hydrolysis, enrichment of the diastereomers by fractional crystallization from an ethanol/ethyl acetate solution, and debenzylation led to the isolation of optically active (β-amino-β-carboxy)-ethanephosphonic acid **5** with 86% ee (Scheme 12.1).



Scheme 12.1

The sequential formation of β-hydroxyaminophosphonate **6** and β-aminovinylphosphonate **7** on the way from the starting aldehyde **2** to the final aminophosphonic acid **5** was suggested by the infrared (IR) and ^{31}P NMR spectra of the reaction mixture. These spectra indicated also that the *cis*-vinylphosphonate **7** was formed predominantly (92%).

More recently, the efficient asymmetric synthesis of the (*S*)-enantiomer of the acid **5** by the alkylation of glycine **8** in its chiral Schiff's base Ni(II) complex **9** with a chiral auxiliary, (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone **10**, has been reported by the Kukhar and Belokon groups.[3] The sequence of reactions used to achieve this goal is shown in Scheme 12.2.

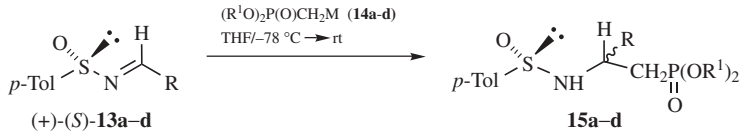


Scheme 12.2

The Ni(II) complex **9** was prepared as reported earlier[4] by the reaction of Ni(II) ions and glycine **8** in the presence of the chiral auxiliary **10**. Alkylation of the complex **9** with diisopropyl iodomethanephosphonate **11** using powdered KOH as a

base was found to give the diastereomerically pure complex **11**, which contains the (*S*)-2-amino-3-phosphonopropanoic acid **5** moiety, as it was established according to the shape of the optical rotatory dispersion (ORD) curve of the complex **11**. Decomposition of the diastereomerically pure complex **11** afforded the novel aminophosphonate **12** having the free carboxy and esterified phosphonic groups. Its hydrolysis with hydrochloric acid in the presence of propylene oxide furnished finally the optically pure amino acid (+)-(*S*)-**5**.

Two novel asymmetric syntheses of β-aminophosphonic acids, which are based on a highly diastereoselective addition of achiral or chiral α-phosphonate carbanions to chiral or achiral imines, have been elaborated in the author's[5] and Hanessian's[6] laboratories. Our group used as a chiral auxiliary the enantiomerically pure sulfinimines **13a–d** prepared from (−)-(*S*)-menthyl-*p*-toluenesulfinate according to the procedure described by Davis et al.[7] The reaction of **13a–d** with 1.5 eq. of the lithium(sodium) salt of dialkyl methanephosphonates **14a–d** was found to afford a mixture of the diastereomeric sulfinamides **15a–f** in 75–80% yield. The diastereomeric ratio of the adducts **15a–f** was determined by ^{31}P NMR spectroscopy (Scheme 12.3).



(+)-(*S*)-**13a–d** **15a–d**

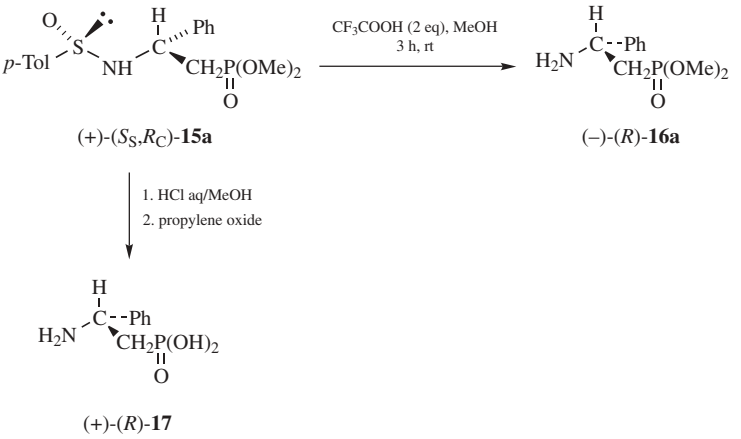
13		14				15		
No	R	No	R^1	M	Solvent	No	R^1	Dr
a	Ph	**a**	Et	Li	THF	**a**	Et	7.8:1
a	Ph	**b**	Et	Na	Et_2O	**a**	Et	4.7:1
a	Ph	**b**	Et	Na	THF	**a**	Et	4.8:1
a	Ph	**c**	Me	Li	THF	**b**	Me	10.3:1
a	Ph	**d**	i-Pr	Li	THF	**c**	iPr	6.6:1
b	PhCH=CH	**a**	Et	Li	THF	**d**	Et	4.9:1
c	α-furyl	**a**	Et	Li	THF	**e**	Et	6.6:1
d	α-thienyl	**a**	Et	Li	THF	**f**	Et	9.2:1

Scheme 12.3

Analysis of the results collected in Scheme 12.3 reveal that the use dimethyl methanephosphonate and lithium hexamethyldisilazane (LiHMDS) as a base (the reagent **14c**) led to the highest diastereomeric ratio (10.3 : 1 for **15b**). The major diastereomers of β-(*N*-sulfinylamino)phosphonates **15a–c** were isolated by flash chromatography on silica gel.

The aminophosphonate (+)-**15a** isolated in this way was subsequently converted to β-aminophosphonate (−)-**16a** by trifluoroacetic acid–catalyzed methanolysis,[8] resulting in a selective deprotection of the amino group and to (+)-β-amino-β-phenylethanephosphonic acid (+)-**17** by heating under reflux for 7 h in a mixture

of glacial acetic acid and hydrochloric acid.[9] The chirality at the β-carbon atom in (+)-**17** was established as (R) by a single-crystal X-ray analysis. Since in the conversion of (+)-**15a** to (−)-**16a** and (+)-(*R*)-**17** the bonds around the stereogenic β-carbon atom are not broken, it is possible to assign the (S_S,R_C)-configuration to the major diastereomer of (+)-**15a** and the (R)-configuration to the β-aminophosphonate (−)-**16a**, as depicted in Scheme 12.4.



Scheme 12.4

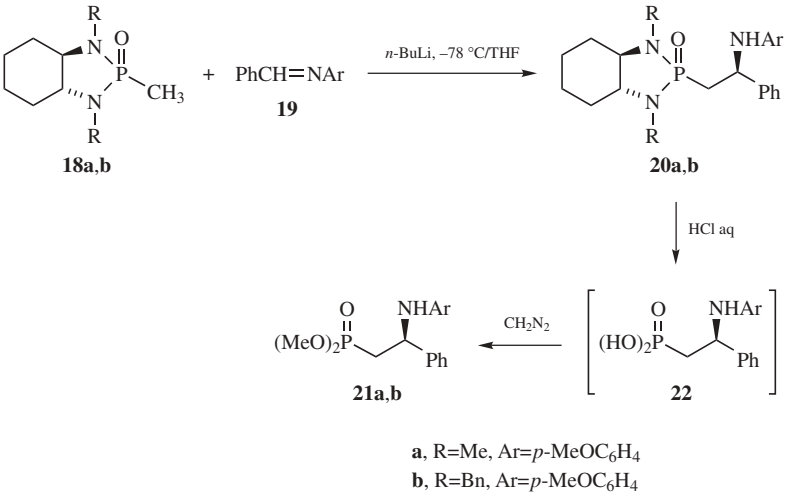
Analysis of the ^{31}P NMR chemical shifts of the diastereomeric adducts **15** revealed that all major diastereomers resonate at lower field in comparison with the minor ones. This clear relationship was taken as an indication that the newly created stereogenic β-carbon atom in all major diastereomeric adducts **15** has the absolute configuration (R).

Starting from the sulfinimine (−)-(*R*)-**13a**, the diastereomer (−)-**15a** was obtained in a similar way and converted to the aminophosphonic acid (−)-(S)-**17**.[5]

Hanessian's group[6] studied the addition of chiral phosphonamide α-carbanions to *N*-substituted benzylideneimines. The reaction of the lithium anion of **18a** generated using diisopropyllithium-amine (LDA) in tetrahydrofuran (THF) with *N*-*p*-methoxyphenylbenzylideneimine **19** was found to give the β-aminophosphonamide derivative **20a** in 80% yield together with its diastereomer (88 : 12 ratio). Acid hydrolysis of **20a** followed by esterification gave the corresponding enantiomeric, dimethyl phosphonate analog **21a** (Scheme 12.5).

The use in the above-discussed reaction sequence of *N*,*N*′-dibenzyl phosphonamide **18b** afforded the β-aminophosphonamide derivative **21b** with greater than 95 : 5 diastereoselectivity. The absolute configuration at the newly created stereogenic carbon atom in **20b** was established by single-crystal X-ray analysis.

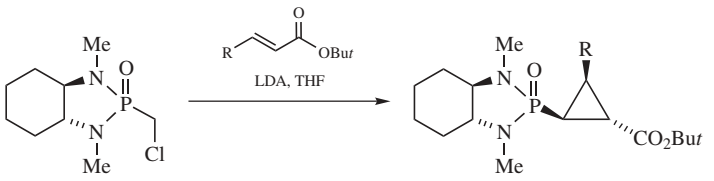
Since the design and synthesis of conformationally constrained peptidomimetics has recently been an important strategy in modern drug discovery,[10] the asymmetric synthesis of aminocyclopropanephosphonic acids, which are conformationally



Scheme 12.5

constrained analogs of acyclic aminophosphonic acids, presents a challenging area of research. The first approach to optically active β-aminocyclopropanephosphonic acids is based on a highly diastereofacial addition of the α-carbanion derived from the α-chloromethanephosphonamide **23** to α,β-unsaturated esters followed by cyclization leading to the corresponding cyclopropyl derivatives **24** (Scheme 12.6).[11]

Starting from **24h**, the absolute stereochemistry of which was established by single-crystal X-ray analysis, Hanessian et al.[11] accomplished the synthesis of the

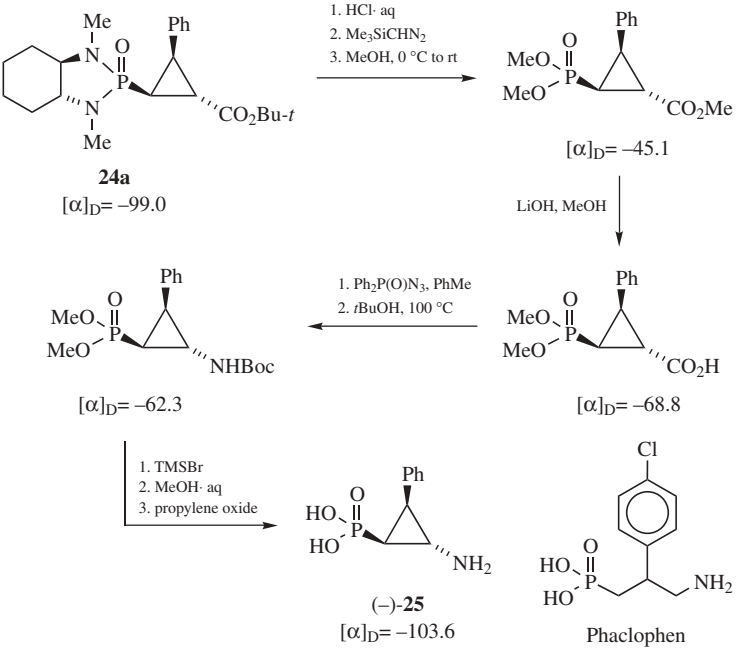


	R	Yield (%)	Ratio **a** : **b**
a	H	49	1.5:1
b	Me	70	5:2
c	*i*Pr	78	21:1
d	c-Hex	80	60:1
e	2,4-F_2Ph	70	19:1
f	Me_3Si	75	10:1
g	MeCH=CH	46	only **a**
h	Ph	72	only **a**

Scheme 12.6

enantiopure, levorotatory (2*S*)-amino-(3*S*)-phenyl-(1*S*)-cyclopropanephosphonic acid **25** depicted in Scheme 12.7. The latter is a constrained analog of the gamma-aminobutyric acid (GABA) antagonist phaclophen.

Interestingly, the synthesis of the dextrorotatory enantiomer of **25**, that is, (2*R*)-amino-(3*R*)-phenyl-(1*R*)-cyclopropanephosphonic acid, was based on a completely

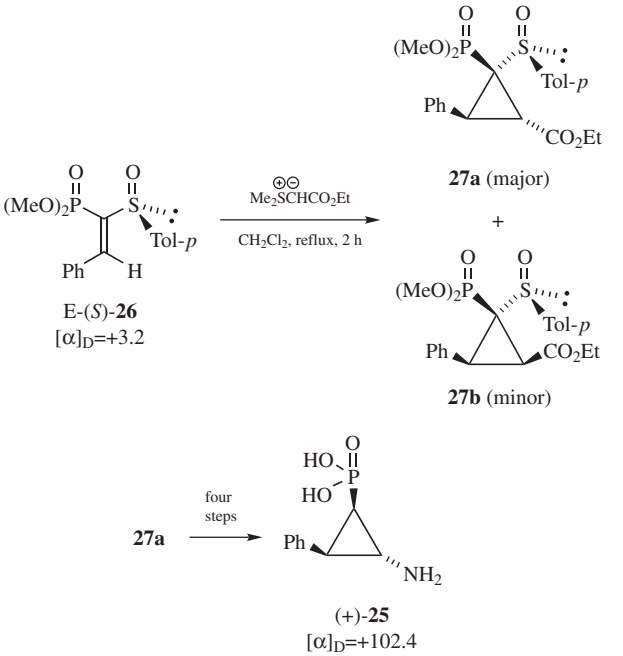


Scheme 12.7

different methodology developed by Midura and Mikołajczyk.[12] A key reaction was the asymmetric cyclopropanation reaction of *E*-(*S*)-(α-dimethoxyphosphoryl-β-phenyl)vinyl *p*-tolyl sulfoxide **26** with ethyl (dimethylsulfuranylidene)acetate, which resulted in the formation of only two diastereomers of the cyclopropane **27** in an 8 : 1 ratio. The isolated major diastereomer **27a** was then converted in four steps into (+)-**25** (Scheme 12.8).

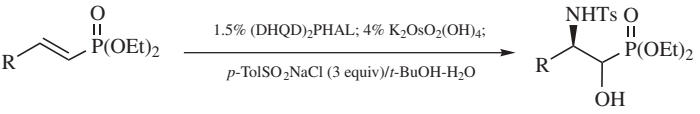
12.2 ENANTIOSELECTIVE C–N BOND-FORMING REACTIONS

The chemical literature contains only two very recent reports devoted to the asymmetric synthesis of β-aminophosphonic acid derivatives in which the new stereogenic β-carbon atom is created by a C–N bond-forming reaction. Both procedures are based on the Sharpless aminohydroxylation reaction of β-substituted vinylphosphonates as a prochiral substrate.



Scheme 12.8

Cravotto et al.[13] submitted a series of vinylphosphonates **28** to the aminohydroxylation reaction with potassium osmate (VI) dihydrate, $K_2OsO_2(OH)_4$, (4% mol) as a catalyst, chloroamine T hydrate (3 eq.) as an amination reagent, and dihydroquinidine 1,4-phthalazinediyl diether $(DHQD)_2PHAL$ (5% mol) as a chiral auxiliary and reaction accelerator. It was reported that under such conditions the reaction carried out in *t*-BuOH–H_2O (1 : 1 v/v) at room temperature required 2–24 h to reach >95% conversion and gave the β-amino-α-hydroxy derivatives **29a–e** with no detectable amounts of the regioisomers (^1H and ^{13}C NMR assay) (Scheme 12.9).

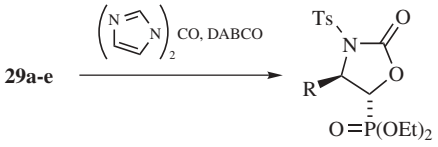


28a–e **29a–e**

29	R	Yield [%]	ee [%]
a	H	55	15
b	Ph	65	60
c	4-BrC_6H_4	71	75
d	4-NO_2-C_6H_4	75	92
e	4-MeO-C_6H_4	72	45

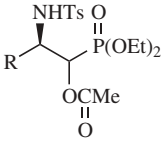
Scheme 12.9

The threo configuration was assigned to β-amino-α-hydroxyphosphonates based on a combination of coupling constants and NOE experiments on the oxazolidin-2-one derivatives **30a–e** easily prepared by exposure of **29a–e** to *N*,*N*′-carbonyldiimidazole (CDI) in the presence of diazabicyclooctane (DABCO) as a basic catalyst:



30a–e (12.1)

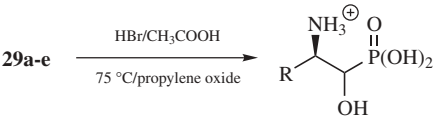
The enantiomeric excess (ee) values were determined by the analysis of ^{1}H NMR spectra of the corresponding acetoxy derivatives **31a–e** recorded in the presence of Eu(hfc)$_3$ as a chiral shift reagent.



31a-e

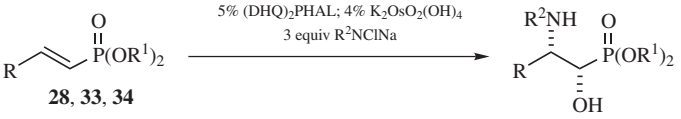
The results presented in Scheme 12.9 indicate that a double bond functionalized with an aromatic substituent having an electron-withdrawing group gave the highest ee value. It is interesting to note that in the case of **29b** the sample of high enantiomeric excess (ee $>95\%$) could be obtained after two recrystallizations of the crude aminohydroxylation product from *i*-Pr$_2$O–CH$_2$Cl$_2$. The absolute stereochemistry of the isolated β-aminophosphonates was not determined. The authors suggested, however, that (DHQD)$_2$PHAL should direct, as in the case of α,β-unsaturated esters, the addition to the β-face of **28a–d** (*re*, *si* approach) giving rise to a (1R, 2S)-threo configuration.

The isolated optically active β-aminophosphonates **29a–e** were hydrolyzed in excellent yields to the corresponding β-amino-α-hydroxyphosphonic acids **32a–e** by treatment with HBr (5.7 M solution in acetic acid) at 75°C in the presence of phenol as a scavenger of bromine followed by neutralization with propylene oxide:



32a–e (12.2)

Soon thereafter the Sharpless group[14] reported the results of independent work on the aminohydroxylation reaction of a richer family of vinylphosphonates. In addition to the phosphonates **28b**, **28d**, **28c**, and **28f**, they examined unsaturated substrates **33** and **34** using chloramine T and *N*-chloro-*N*-sodioethylcarbamide (Scheme 12.10) as a source of the *N*-amino group.



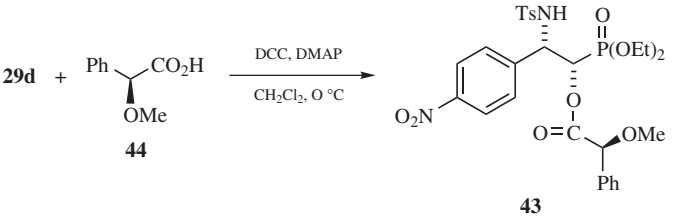
28, **33**, **34** → **29**, **35**–**42**

Substrate			R^2NClNa	Product		
No	R	R^1	R^2	No	Yield	ee [%][a]
28b	Ph	Et	Ts	**29b**	21	54(91)
28b	Ph	Et	EtO_2C	**35**	32	93
28d	$4\text{-}NO_2C_6H_4$	Et	Ts	**29d**	40	92(99)
28d	$4\text{-}NO_2C_6H_4$	Et	EtO_2C	**36**	53	97
28e	$4\text{-}MeOC_6H_4$	Et	Ts	**29e**	31	76(99)
28e	$4\text{-}MeOC_6H_4$	Et	EtO_2C	**37**	45	98(99)
28f	$2\text{-}C_{10}H_7$	Et	Ts	**29f**	30	62(93)
28f	$2\text{-}C_{10}H_7$	Et	EtO_2C	**38**	53	98(99)
33	$4\text{-}MeOC_6H_4$	Me	Ts	**39**	35	88
33	$4\text{-}MeOC_6H_4$	Me	EtO_2C	**40**	53	98(99)
33	$4\text{-}MeOC_6H_4$	*i*-Pr	Ts	**42**	21	32
33	$4\text{-}MeOC_6H_4$	*i*-Pr	EtO_2C	**42**	35	93(99)

[a]the ee values in parentheses after a single recrystallization

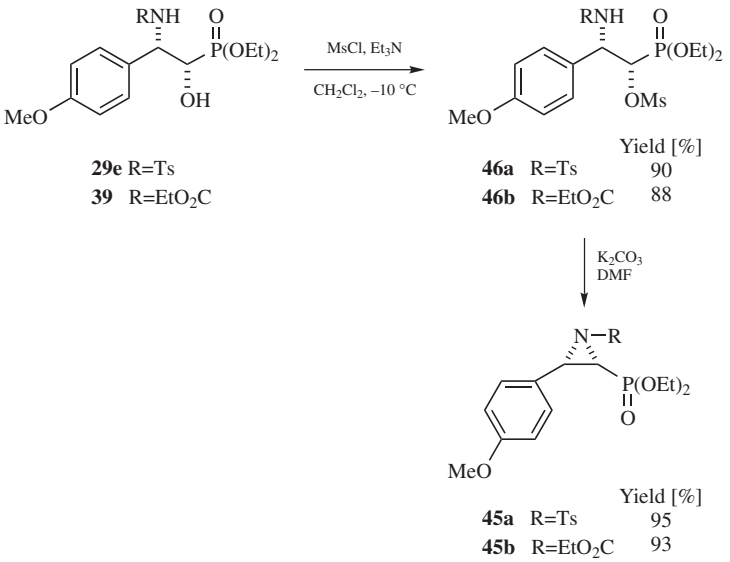
Scheme 12.10

It is interesting to note that the parent vinylphosphonate **28a** failed to react even upon prolonged heating and that several by-products were formed during aminohydroxylation reactions (^{31}P NMR assay), including some diol (5–25% of major isomer for sulfonamides and 15–30% for carbamates) and regioisomers (15–30% of major isomer for sulfonamides and 5–15% of major isomer for carbamates). The amounts of regioisomer and a diol present varied by substrate and with changes in reaction conditions. Analysis of the results collected in Scheme 12.10 indicates that the enantiomeric excess values of the sulfonamide products were generally lower than those of the corresponding carbamates; however, the sulfonamide derivatives could be isolated much more easily by recrystallization. The relative and absolute configuration of the aminophosphonate **29d** was assigned via an X-ray crystal structure of **43**—a diastereomeric derivative of this compound obtained from (*S*)-*O*-methyl madelate **44** in the presence of dicyclohexyl-carbodiimide (DCC) and dimethylaminopyridine (DMAP) (Equation 12.3). It was suggested that the other aminophosphonates listed in Scheme 12.10 should have similar stereo and regiochemistries.



(12.3)

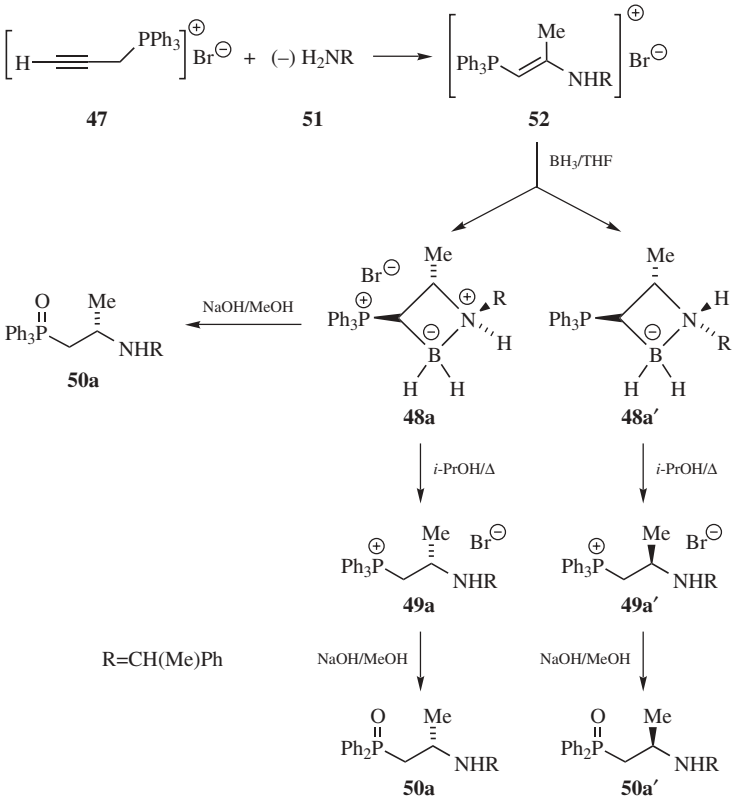
To demonstrate the utility of the prepared aminophosphonates, the compounds **29e** and **37** were converted into the corresponding *N*-tosyl or *N*-ethoxycarbonyl aziridines **45a** and **45b**, respectively (Scheme 12.11), by a two-step process involving initial mesylation of the hydroxyphosphonates followed by treatment of the isolated mesylates **46a** with K_2CO_3 in dimethylformamide (DMF).



Scheme 12.11

The recent literature also contains two papers reporting the asymmetric synthesis of optically active, diastereomeric β-aminophosphonium salts and β-aminophosphine oxides. The reaction sequence leading from prop-2-ynyl(triphenyl)phosphonium bromide **47** to (1*S*,3*R*,4*S*,1′*S*)-4-methyl-3-triphenylphosphonium-1-[1′-methylphenyl)]-2-hydrido-2-borazetidinium bromide **48a** and its transformation into β-aminophosphonium salts **49** and β-aminophosphine oxides **50** is shown in Scheme 12.12.[15]

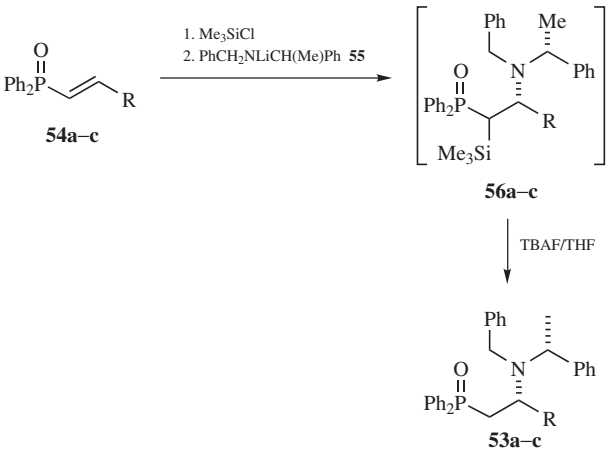
Reaction between **47** and primary, optically active α-methylbenzylamine (−)-**51** gave the salt **52**. Its hydroboration with a large excess of BH_3–tetrahydrofuran



Scheme 12.12

(THF) gave the novel borazetidinium salts **48a** and **48a′** as an approximate 1 : 1 mixture of diastereomers. In the case of the compound **48a** it was possible to isolate crystals suitable for single-crystal X-ray analysis by careful crystallization from propan-2-ol. It indicated that the salt **48a** represents the novel C–B–N–C heterocyclic ring system with two stereogenic carbons and a stereogenic nitrogen center having the (1S,2R,4S,1′S) absolute configuration. The diastereomer (1*R*,3*S* 4*R*,1′*S*)-**48a′** was also recovered in an almost pure state from the mother liquor. Upon heating in propan-2-ol the diastereomers **48a** and **48a′** decompose into the corresponding acyclic products **49a** and **49a′**. Subsequent heating of the phosphonium salts **49** with 30% NaOH solution in MeOH afforded the phosphine oxides **50a** and **50a′**. On the other hand, treatment of the pure diastereomer **48a** with 30% aqueous NaOH gave the pure diastereomer (1*S*,1′*S*)-**50a** in 93% yield.

A few β-aminophosphine oxides **53a–c** were isolated as single diastereomers upon treatment of the vinylphosphine oxides **54a–c** with the chiral lithium amide **55** in the presence of trimethylsilyl chloride followed by protodesilylation of α-silylphosphine oxides **56a–c** most conveniently achieved by reacting the

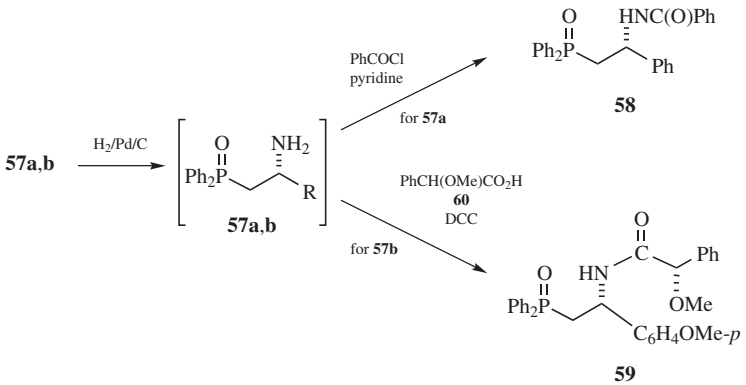


48	R	Yield [%]	dr
a	Ph	65	98:2
b	p-MeOC$_6$H$_4$	76	>99:1
c	2-furyl	34	>99:1

Scheme 12.13

crude reaction mixture with tetrabutylammonium fluoride (TBAF) in THF (Scheme 12.13).[16]

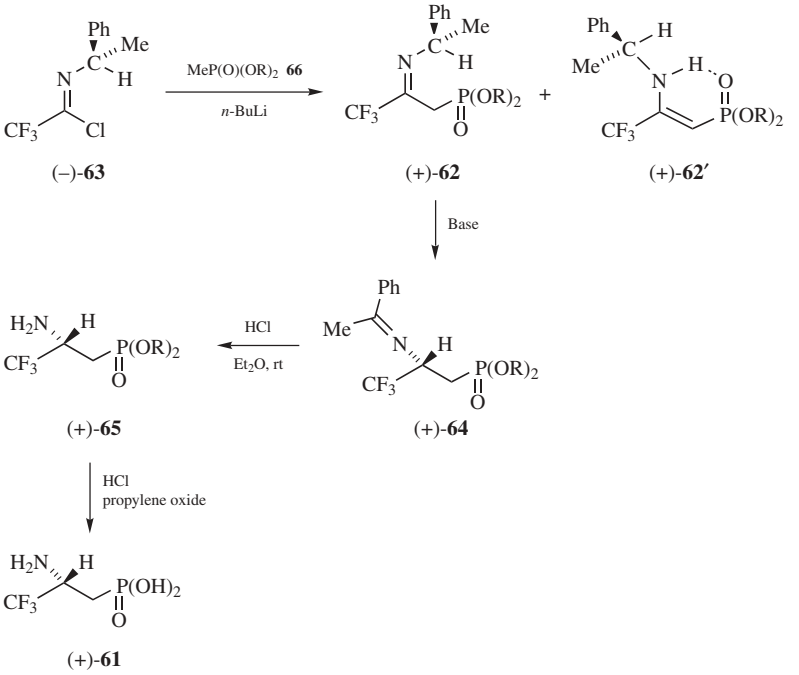
The benzyl groups were removed from the β-aminophosphine oxides **53a**,**b** hydrogenolytically to give the amines **57a**,**b**. The amine **57a** was characterized as the benzamide **58** and the amine **57b** as the amide **59** (Scheme 12.14).



Scheme 12.14

12.3 ENANTIOSELECTIVE C–H BOND-FORMING REACTIONS

Xia and Yuan[17] have reported a practical and efficient synthesis of optically active 2-amino-3,3,3-trifluoropropanephosphonic acid **61** of high enantiomeric purity utilizing a base-induced [1,3]-proton shift reaction of the intermediate 2-imino-3,3,3-trifluoropropanephosphonates **62**. The synthetic route leading to the amino acid **61** starting from easily available *N*-(−)-α-methylbenzyl-acetimidoyl chloride (−)-**63** is outlined in Scheme 12.15.



Scheme 12.15

The reaction of the chloride **63** with the α-phosphonate carbanions derived from methanephosphonates **66** furnished the first intermediate products, that is, imines (+)-**62** and their isomeric enamines (+)-**62′**, which were stabilized by

TABLE 12.1 Isomerization of (+)-62 and (+)-62′ to (+)-64

Compound	R	Base	Yield (%)	ee (%)
(+)-**64a**	Et	DBU (1 eq.)	50	60
(+)-**64a**	Et	DBU (2 eq.)	75	70
(+)-**64b**	*n*-Pr	DBU (2 eq.)	72	83
(+)-**64c**	*i*-Pr	DBU (2 eq.)	83	80
(+)-**64d**	*n*-Bu	DBU (2 eq.)	73	72

TABLE 12.2 Preparation of Aminophosphonates (+)-65 and Acid (+)-61

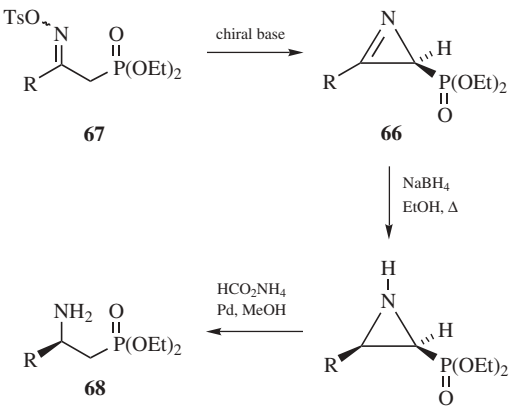
Compound	R	Yield (%)	$[\alpha]_D^{22}$
65a	Et	90	+18.8
65b	*n*-Pr	80	+16.3
65c	*i*-Pr	85	+26.9
65d	*n*-Bu	88	+17.1
61		90	+21.0

intramolecular hydrogen bonds. Although these mixtures were difficult to separate by column chromatography, the ratio of both isomeric products was determined by ^{1}H and ^{19}F NMR spectroscopies (the range from 0/100 to 6/8). When these mixtures were treated with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), the efficient isomerization into the corresponding Schiff bases **64** occurred (Table 12.1).

Schiff bases (+)-**64a–d** were then hydrolyzed under mild conditions to give 2-amino-3,3,3-trifluoropropanephosphonates (+)-**65a–d**, which in turn were converted to the free acid (+)-**61** by hydrolysis in concentrated hydrochloric acid (Table 12.2).

12.4 MISCELLANEOUS

In 2000 Palacios et al.[18] described an efficient asymmetric synthesis of 2*H*-azirines **66** substituted with a phosphonate group. The key step involved a base-mediated Neber reaction of *p*-toluenesulfonyloximes **67** derived from phosphonates (Scheme 12.16). When chiral bases (sparteine, quinidine, hydroquinidine, quinine) were used, the enantioenriched azirines **66** were obtained with enantiomeric excess values up to 69%.



Scheme 12.16

The azirines prepared in such a way were used as intermediates in the synthesis of enantioenriched β-aminophosphonates **68** (Scheme 12.16). Although the above-mentioned authors utilized this conversion for the configurational assignments, the reaction sequence depicted in Scheme 12.16 represents also a new synthetic approach to chiral β-aminophosphonic acids.

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CHAPTER 13

Asymmetric Synthesis of α-Substituted-β-Amino Phosphonates and Phosphinates and β-Amino Sulfur Analogs

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13.1 INTRODUCTION

Because the biological activity of one enantiomer of a substance can differ completely from that of the mirror-image substance, the pharmaceutical industry pays careful attention to the separation and purity of enantiomers of chiral drugs. The asymmetric synthesis of organophosphorus and organosulfur compounds is a relatively new field which has developed mostly during the past two decades. The rapid growth of the asymmetric synthesis of *P*-chiral organophosphorus compounds is connected not only with their great practical value as ligands in the catalyst for asymmetric organic synthesis but also because organophosphorus compounds are important substrates in the study of biochemical processes.[1] Chiral trivalent and tetracoordinate pentavalent compounds play a key role in the area of organophosphorus stereochemistry. These compounds are widely used as biologically active compounds and enantioselective reagents, and tetracoordinate organophosphorus compounds are required in optical form to be effective synthetic tools for asymmetric carbon–carbon bond formation. The key role of naturally occurring amino acids in the chemistry of life and as structural units in peptides, proteins, and enzymes has led to intense interest in the chemistry and biological activity of synthetic analogs. For a long time, the so-called phosphorus analogs of the amino acids, in which the carboxylic acid group is replaced by a phosphonic, $P(O)(OH)_2$,

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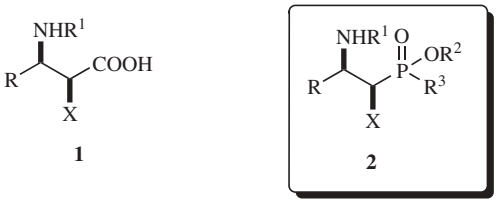


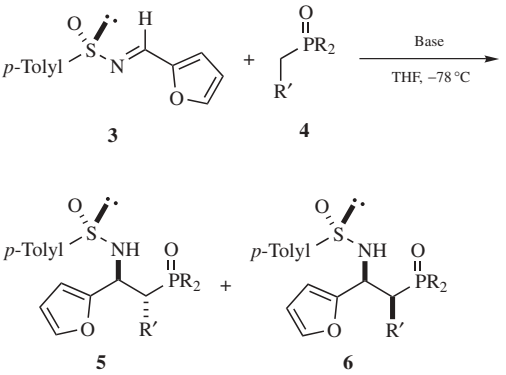
Figure 13.1

or a phosphinic acid group, P(O)(OH)R (in which R may be H, alkyl or aryl), as well as a phosphonate group, $P(O)(OR)_2$ (in which R may be alkyl or aryl), have attracted particular interest in the preparation of isosteric or bioisosteric analogs of numerous natural products.[2] β-Amino phosphonic acids **2** ($R^2 = H$, $R^3 = OH$), isosteres of β-amino acids **1** (Fig. 13.1), reveal diverse and interesting biological and biochemical properties: antibacterial agents,[3] enzyme inhibitors,[4] haptens for catalytic antibodies,[5] or anti-HIV (human immunodeficiency virus) agents.[6]

This chapter will focus on the asymmetric synthesis of α-substituted β-amino phosphonic ($R^3 = OR$) and α-substituted β-amino phosphinic acids ($R^3 = H$, R) and their derivatives **2**. The first section (13.2) outlines the presence of alkyl group substitution besides the β-amino phosphorus moiety. In the next sections (13.3–13.5) attention is drawn to the presence of additional functionality such as hydroxy, halogen, or amine groups in the α-position of the β-amino phosphonic and phosphinic acid derivatives. β-Amino phosphono- and phosphinopeptides, β-amino phosphorus derivatives with peptide bond formation, will also be discussed in Section 13.6.

13.2 SYNTHESIS OF α-ALKYL-β-AMINO PHOSPHORUS DERIVATIVES

Chiral enantiopure sulfinimines have been used in the preparation of β-amino phosphonic acids. Addition of α-phosphonate carbanions (Scheme 13.1, R = OEt,



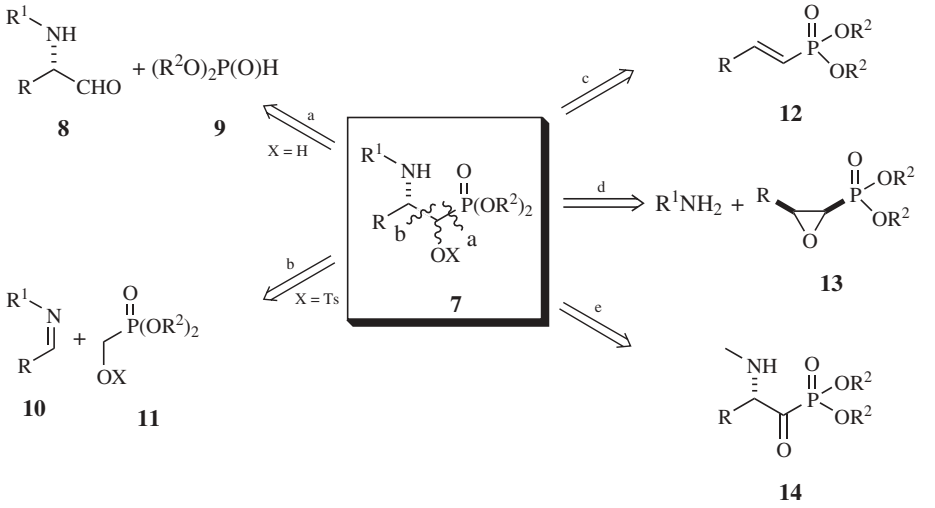
Scheme 13.1

R′ = H) to sulfinimines afforded α-unsubstituted *N*-sulfinyl-β-aminophosphonates in good yield.[7] The process can also be extended to the addition of α-phosphine oxide carbanions (Scheme 13.1, R = Ph, R′ = Me) to enantiopure sulfinimines.[8] The addition of carbanion derived from ethyl diphenyl phosphine oxide **4** to sulfinimine **3** proceeded to give *anti*-(S_S,1*R*,2*R*)-**5** and *syn*-(S_S,1*S*,2*R*)-*N*-sulfinyl-α-alkyl-β-aminophosphine oxide **6**, with a higher proportion of the anti isomer.

Opening of azirines derived from phosphonates constitutes an alternative for the preparation of β-aminophosphonates. In this way, the asymmetric synthesis of *N*-substituted and unsubstituted-β-aminophosphonates[9] was recently disclosed by means of regioselective ring opening of the N–C2 single bond of the azirine ring.[10]

13.3 SYNTHESIS OF β-AMINO-α-HYDROXY PHOSPHONIC AND PHOSPHINIC ACID DERIVATIVES

β-Amino-α-hydroxy phosphonic and phosphinic acid derivatives **7** have attracted a growing interest due to their potent and selective activities in many biological fields. Nucleophilic addition of phosphites to aldehydes constitutes one of the simplest entries to α-hydroxy phosphonic acid derivatives **7** (X = H, Scheme 13.2, route a) and involves C–P bond construction. These derivatives **7** can also be obtained either by C–C bond formation (Scheme 13.2, route b) or by Sharpless asymmetric aminohydroxylation (AA) of α,β-unsaturated phosphonates **12** (Scheme 13.2, route c) as well as by ammonolysis of oxiranes **13** (Scheme 13.2, route d) involving C–N bond formation and by reduction of β-amino-α-keto phosphonates **14** (Scheme 13.2, route e).

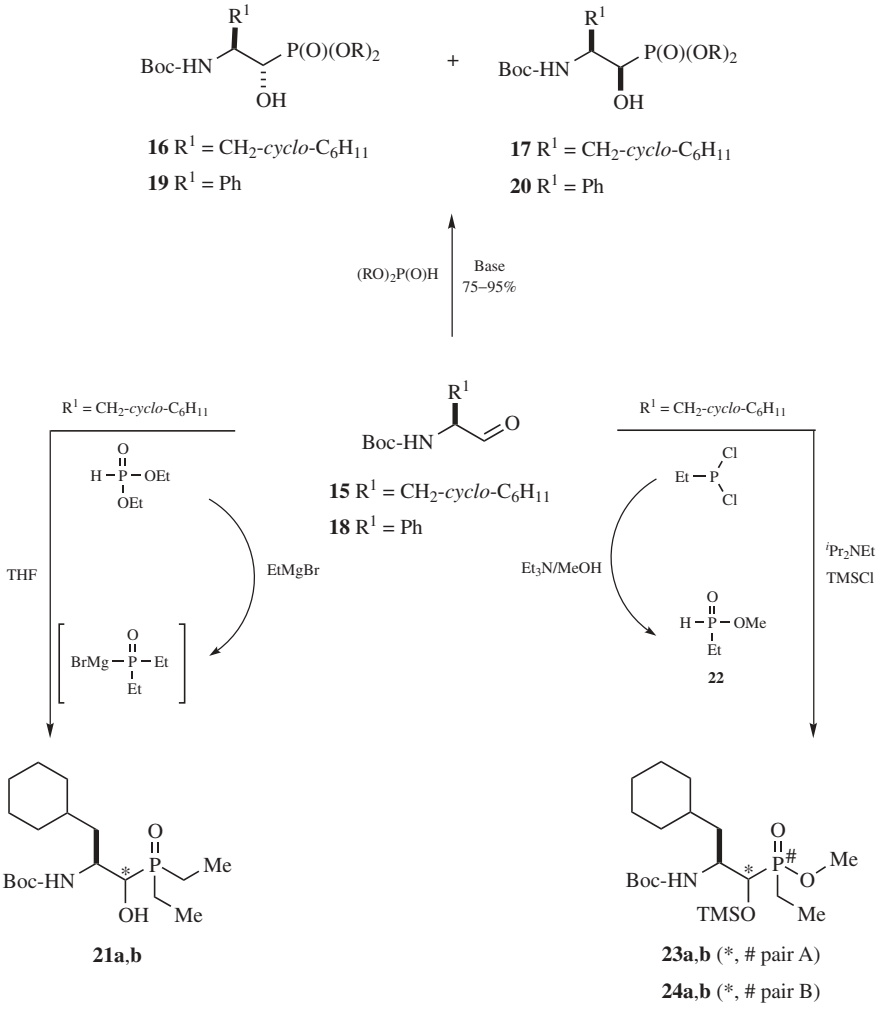


Scheme 13.2

13.3.1 Hydrophosphinylation of α-Amino Aldehydes

Stereogenic carbon–phosphorus bond formation processes are of great interest in the stereoselective synthetic sequences of the β-amino alcohol moiety by the reaction of α-amino aldehydes with phosphinic nucleophiles, since the stereochemistry of β-amino alcohol is known to be an important factor to show highly potent protease inhibitory activity.

The coupling of dialkyl phosphites and chiral aminoaldehydes **8** in the presence of a base seems to be the most straightforward method for the preparation of β-amino-α-hydroxy phosphonates because the addition of phosphites to aldehydes usually proceeds quantitatively and optically active α-aminoaldehydes[11] can be obtained from the respective amino acids. β-Amino-α-hydroxy phosphonates are



Scheme 13.3

TABLE 13.1 Diastereoselectivity of Addition of Dialkyl Phosphites to 15

Entry	R	Base	Solvent	Ratio **16/17**
1	Me	DBU	DMF	55 : 45
2	Me	NMM	DMF	88 : 12
3	Me	*i*-Pr_2NEt	DMF	84 : 16
4	Me	*i*-Pr_2NEt	MeOH	80 : 20
5	Me	*i*-Pr_2NEt	CH_2Cl_2	88 : 12
6	Me	KF	DMF	92 : 8
7	Me	KF	MeOH	88 : 12
8	Me	KF	CH_2Cl_2	80 : 20
9	Et	KF	CH_2Cl_2	80 : 20

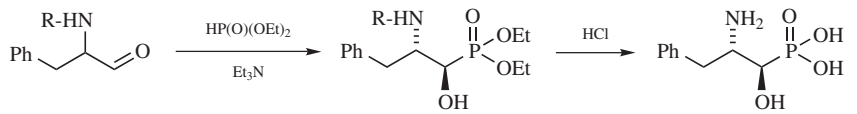
obtained as a mixture of syn and anti diastereoisomers. Furthermore, the reaction stereochemistry at C-1 in chiral α-hydroxyphosphonates can be tuned by proper selection of the catalyst used to promote the addition. Hydrophosphinylation of *N*-Boc-L-cyclohexylalanal **15** with dimethyl phosphite (R = Me) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethylformamide proceeded well and gave, essentially, an equimolecular ratio of the syn and anti diastereoisomers **16** and **17**, respectively[12] (Scheme 13.3, Table 13.1, entry 1). Stereoselection in favor of *anti*-**16** isomer was optimized by employing potassium fluoride as a base in dimethylformamide (DMF) (95% yield, **16/17** = 92 : 8) (Table 13.1, entry 6). The stereochemistry of the addition did not change when diethyl phosphite (R = Et) was used instead of the dimethyl derivative (77% yield, **16/17** = 80 : 20)[13] (Scheme 13.3, Table 13.1, entry 9). For absolute stereochemical assignment, diastereoisomers **16** and **17** were converted to the corresponding oxazolidinones. Based on proton nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR data and NOE experiments in oxazolidinones, diastereoisomer **16** was designated as having the (S)-anti stereochemistry.

This process has been recently extended to racemic *N*-Boc-phenylglycinal **18** (racemic *N*-Boc-phenylglycinal **18** was used because these are especially easily racemized in the presence of bases)[14] to give 2-amino-2-phenyl-1-hydroxy phosphonates as a mixture of the *anti*-**19** and the *syn*-**20** isomers with a higher proportion of the syn isomer.[15] Enantiomerically pure *N*-Bz-substituted (1*S*,2*S*)-**20** and (1*R*,2*R*)-**20** were obtained in good yield by resolution via *O*-methylmandelate derivatives. (For ammonolysis of β-amino-α-hydroxy phosphonates from their carboxylic esters, see Ref. 16.) When using *N*-Bz-phenylglycinal,[15b] the diastereoselectivity of the addition changed significantly, increasing the anti isomer amount compared to that observed when *N*-Boc-phenylglycinal was used. However, the stereochemistry of the addition did not change when dimethyl phosphite was used instead of diethyl derivative.[15c]

In the same way, hydrophosphinylation of *N*-protected α-aminoaldehyde **15** was achieved using phosphine oxides and alkyl alkylphosphinates.[13] When the bromomagnesium phosphine oxide generated in situ by treatment of diethyl phosphite with 3 eq. of ethylmagnesium bromide was trapped directly with aldehyde **15**, β-amino-α-hydroxy phosphine oxide **21** was obtained in high yield (87%) as a 1 : 1

mixture of diastereomers (Scheme 13.3). Alternatively, the preparation of phosphinate reagent **22** required for synthesizing the phosphinate analogs **23** and **24** was attempted by treatment of ethyldichlorophosphine ($EtPCl_2$) with 2 eq. of methanol and 1 eq. of triethylamine. Upon condensation of phosphinate **22** with aldehyde **15** in the presence of *i*-Pr_2NEt and chlorotrimethylsilane (TMSCl), a mixture of silyl-protected hydroxy phosphinates **23** and **24** was obtained in good yields (Scheme 13.3). The reaction of phosphinate **22** with aldehyde **15** generates two new contiguous chiral centers because of the chirality of phosphorus, resulting in the formation of four possible diastereoisomers. The two pairs of diastereoisomers were separated on silica gel and the individual diastereomeric content of each isomer pair was roughly 1 : 1. β-Amino-α-hydroxy phosphonates, phosphinates, and phosphine oxides as building blocks for the synthesis of novel peptidyl phosphorus derivatives as inhibitors of human calpain I have also been synthesized through hydrophosphinylation of Boc-Leu-H with dialkyl phosphites or dialkylphosphine oxides employing KF as base.[17] Potassium fluoride–promoted addition of dialkyl phosphites to *N*-Boc-α-aminoaldehyde derivatives has also been reported for the preparation of β-amino-α-hydroxy phosphonates with high diastereoselectivity. These β-amino-α-hydroxy phosphonates are valuable intermediates for the preparation of *cis*-aziridines[18] or more elaborate compounds as phosphorus norstatine inhibitors.[19]

A highly diastereoselective synthesis of 2-amino-1-hydroxy-3-phenylpropyl phosphonic acids **27** was achieved by triethyl amine–catalyzed simple addition of diethyl phosphite to optically active *N*-blocked amino aldehydes derived from phenylalanine **25** (Scheme 13.4).[20] The use of L- or D-*N*-protected amino aldehydes gave practically one diastereoisomer of product **26** in 95% de. Acid hydrolysis of the adduct **26** yielded the desired acid **27** also with 95% de and anti configuration. The good agreement between calculated and simulated spectra data strongly supports the hypothesis that acids **27** derived from L-**25a** or L-**25b** and acids **27** derived from D-**25a** or D-**25b** are enantiomers.



D- or L-**25a**: R = Cbz

D- or L-**25b**: R = Boc

26 **27**

Scheme 13.4

Several literature reports[21] noted the predominance of the anti products in nucleophilic additions to *N*,*N*-disubstituted α-amino aldehydes opposite to *N*-monosubstituted analogs, which afforded syn isomers as the major products. The synthesis of phosphonates (1*R*,2*S*)-**20** (R^1 = Ph) and *N*-Bz-substituted (1*R*,2*S*)-**20** (R^1 = Ph) and their methyl ester derivatives can also be accomplished via addition of dialkyl phosphites to *N*,*N*-dibenzylphenylglycinal[22] when triethylamine was chosen to catalyze the addition affording mixtures of *syn*- and *anti*-β-amino-α-hydroxy phosphonates with a higher proportion of the anti isomer (syn/anti ratio

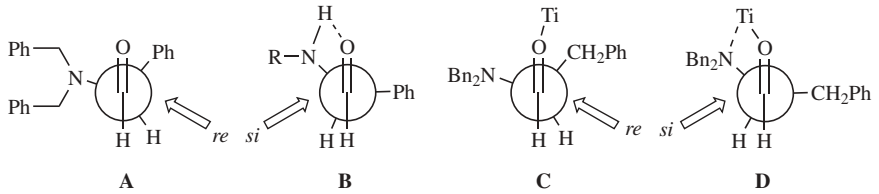
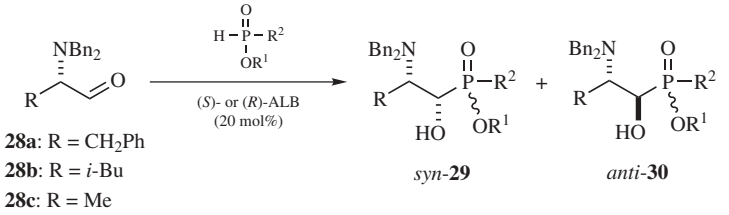


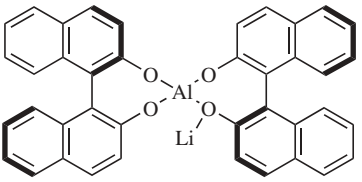
Figure 13.2

22 : 78 for methyl ester and 20 : 80 for ethyl ester). Dimethyl phosphite approaches the *re* face of the carbonyl group in *N*,*N*-dibenzylphenylglycinal preferentially because chelation is not possible in the presence of Et_3N (model **A**) (Fig. 13.2). On the other hand, in *N*-monosubstituted α-amino aldehydes (*N*-Boc) the intramolecular hydrogen bond stabilizes conformation **B** and the dialkyl phosphite attacks the *si* face of the carbonyl group, thus leading to the formation of syn adducts.

A highly diastereoselective synthesis of β-amino-α-hydroxy phosphonic acid derivatives was achieved by Lewis acid–mediated hydrophosphinylation of α-dibenzylamino aldehyde derived from L-phenylalanine.[23] As before, diastereofacial differentiation could be controlled in either a chelation or nonchelation manner (Fig. 13.2) by simple tuning of the nature of phosphonic nucleophiles. Thus, hydrophosphinylation of α-dibenzylamino aldehyde derived from L-phenylalanine using diethyl *t*-butyldimethylsilylphosphite [*t*-$BuMe_2SiOP(OEt)_2$] or triethyl phosphite [$P(OEt)_3$] as nucleophile employing $TiCl_4$ as a catalyst gave the anti and syn isomer via the nonchelate complex **C** in ratios of 98 : 2 and 81 : 19, respectively. However, treatment of α-dibenzylamino aldehyde with diethyl phosphite [$HP(O)(OEt)_2$] and $TiCl_4$ gave high diastereoselectivity (7 : 93) in favor of syn isomer. These differences in the stereochemical course might arise from the higher nucleophilicity of trivalent than pentavalent phosphorus. The nonchelate complex **C** can be assumed to be less reactive than the chelate complex **D** but to be of greater equilibrium concentration (Fig. 13.2). The anti selectivity obtained for hydrophosphinylation with trivalent phosphorus reagents might be attributed to the fact that these reagents are nucleophilic enough to capture the major and less reactive complex **C**. Nevertheless, pentavalent phosphorus reagents are less nucleophilic and are capable of reacting with more reactive chelate complex **D** but not with the less reactive nonchelate complex **C**, inducing syn selectivity.

High diastereoselectivities have also been observed by hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes **28** catalyzed by (*S*)- or (*R*)-ALB [AlLi-bis(binaphthoxide)] (Scheme 13.5). The stereochemical outcome of the reaction can be controlled in either anti- or syn-selective manner by tuning the chirality of ALB. Thus, hydrophosphinylation of aldehyde **28a** with ethyl ethylphosphinate in the presence of (*R*)-ALB gave adducts **29** and **30** with poor selectivity (Table 13.2, entry 1).[24] On the other hand, employing (*S*)-ALB anti selectivity was observed (Table 13.2, entry 2). These results indicated that the combination of (*S*)-ALB and **28a** was suitably matched for inducing diastereofacial selectivity. The extension of this procedure employing ethyl phosphinate and aldehyde **28a**,**b** (Scheme 13.5, Table 13.2, entries 3–6) for the synthesis of β-amino-α-hydroxy-*H*-phosphinates **29**





(*R*)-ALB

Scheme 13.5

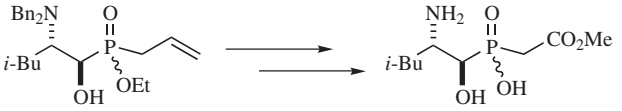
and **30** gave rise to high syn selectivity when performing the reaction with (*R*)-ALB (entries 3 and 5).[24,25] On the other hand, the use of (*S*)-ALB proceeded with inverse stereoselection to afford *anti*-**30** with high diastereoselectivity (entries 4 and 6). The hydrophosphinylation products *syn*-**29** and *anti*-**30**, separable by column chromatography on silica gel, were obtained as a 1 : 1 mixture of diastereoisomers arising from the chirality of the phosphinate group.

In the above-mentioned cases, diastereofacial selectivity was found to be controlled predominantly by the chirality of the asymmetric catalyst rather than by that of the α-amino aldehydes. Although the exact reason for high selectivities in (*R*)-ALB-catalyzed hydrophosphinylation using ethyl phosphinate in comparison with ethyl ethylphosphinate remains unclear, it seems to be associated with a steric disposition for phosphonic nucleophile.

TABLE 13.2 Diatereoselectivity to Addition of Alkyl Alkylphosphites or Alkylphosphinates to 28a–c

Entry	Substrate	R^1	R^2	ALB	syn/anti Ratio	Yield (%)
1	**28a**	Et	Et	(*R*)-ALB	43 : 57	55
2	**28a**	Et	Et	(*S*)-ALB	11 : 89	51
3	**28a**	Et	H	(*R*)-ALB	87 : 13	66
4	**28a**	Et	H	(*S*)-ALB	6 : 94	56
5	**28b**	Et	H	(*R*)-ALB	94 : 6	54
6	**28b**	Et	H	(*S*)-ALB	2 : 98	71
7	**28a**	Et		(*R*)-ALB	50 : 50	74
8	**28a**	Et		(*S*)-ALB	7 : 93	63
9	**28b**	Et		(*R*)-ALB	58 : 42	71
10	**28b**	Et		(*S*)-ALB	5 : 95	51
11	**28c**	Et		(*R*)-ALB	24 : 76	48
12	**28c**	Et		(*S*)-ALB	6 : 94	52

β-Amino-α-hydroxy(allyl)phosphinates **29** and **30** (Scheme 13.5, Table 13.2, entries 7–12) can also be obtained through hydrophosphinylation of aldehydes **28a–c** with ethyl allylphosphinates.[26] While syn selectivity was not observed when using (*R*)-ALB as catalyst (entries 7, 9, and 11), preferable formation of anti adducts was given by using (*S*)-ALB (entries 8, 10, and 12). This trend is consistent with the previous results of ALB-catalyzed hydrophosphinylation of aldehyde **28a** with ethyl ethylphosphinate. In addition, *anti*-β-amino-α-hydroxy(allyl)-phosphinates **30** are a useful intermediate for the stereoselective synthesis of *anti*-β-amino-α-hydroxy(methoxycarbonylmethyl)phosphinic acid **31**, which would be applicable as a building block for peptidic transition-state analog inhibitors of protease (Scheme 13.6).[26]



anti-**30b** **31**

Scheme 13.6

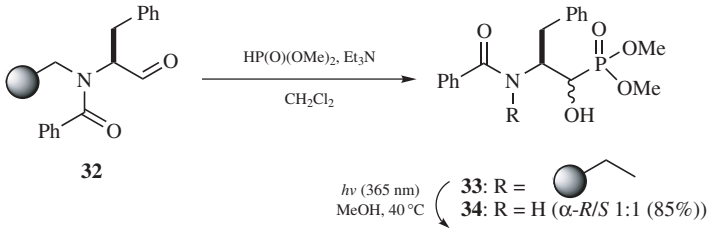
Solid-phase synthesis of β-amino-α-hydroxy phosphonates **34–38** by hydrophosphinylation of resin-bound *N*-acylated amino aldehydes **32** has recently been reported.[27] Treatment of resin-bound aldehyde **32** with dimethyl phosphite using Et_3N as base followed by photolysis furnished the α-hydroxy dimethyl phosphonates **34** as a 1 : 1 mixture of diastereoisomers. A survey of the reaction of other amino acid aldehydes (e.g., alanine, leucine, substituted phenylalanine acylated with electron-rich/deficient aroyls, heteroaroyls, substituted acyls) with commercially available dialkyl and dibenzyl phosphites gave similarly clean conversions to β-amino-α-hydroxy phosphonates **35–38** with diastereomeric ratios ranging from 1 : 1 to 3 : 1 (Scheme 13.7).

13.3.2 Addition of Methylphosphonate Anions to Enantiopure Sulfinimines

Davis et al.[28] have also recently described an approach for the synthesis of β-amino-α-*O*-*p*-toluenesulfonyl phosphonates **41** and **42** (Scheme 13.8). The synthesis of these phosphonates **41** and **42** was achieved by addition of the anion derived from diethylphosphonomethoxytosylate **40** to benzaldehyde-derived sulfinimines (*S*)-**39**. The ratio of *syn*-**41**/*anti*-**42** in the crude reaction mixture was 69 : 31.[28]

13.3.3 Asymmetric Dihydroxylation and Sharpless Asymmetric Aminohydroxylation

Asymmetric aminohydroxylation,[29] which utilizes Os(VIII) and the cinchona alkaloid ligands as catalysts, provides straightforward access to optically active



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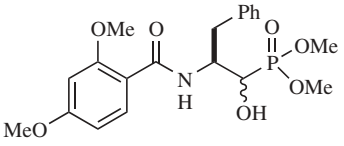
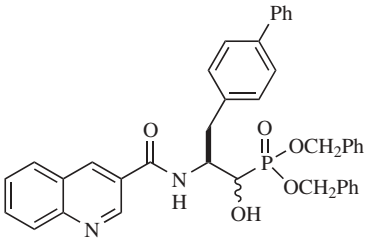
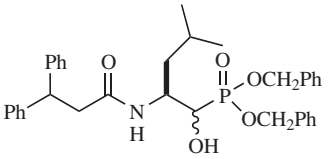


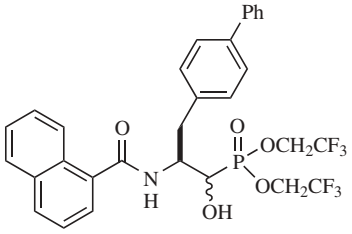
35: α-*R*/*S* 1:1
(85%)



36: α-*R*/*S* 1:1
(90%)

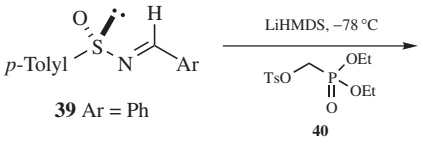


37: α-*R*/*S* 3:1
(92%)



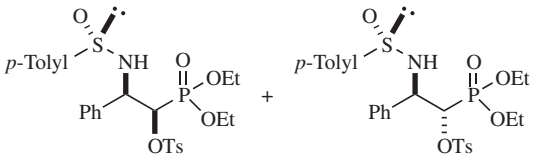
38: α-*R*/*S* 1:1
(87%)

Scheme 13.7



39 Ar = Ph

40

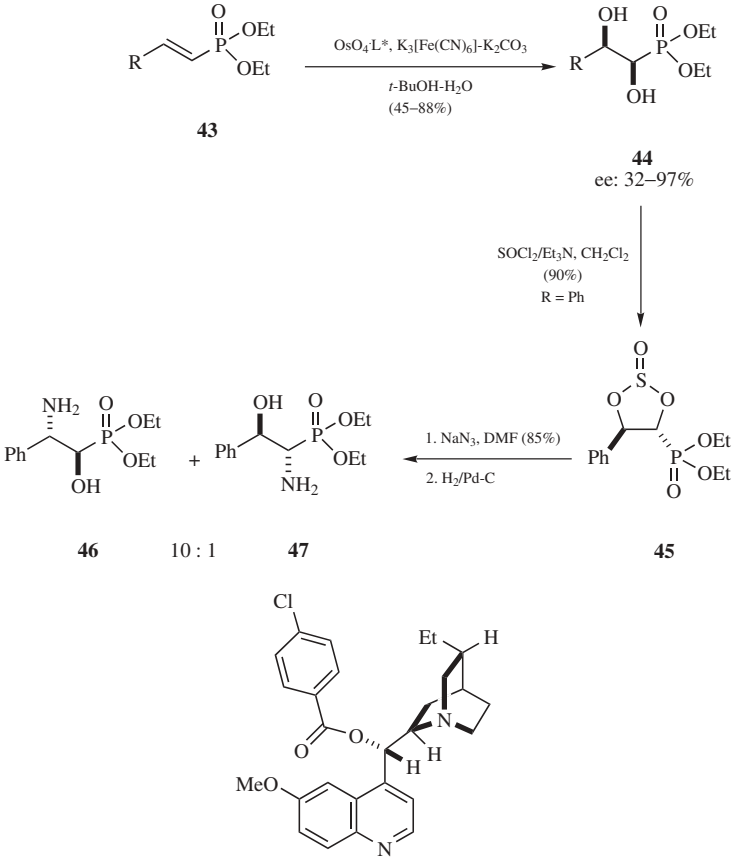


syn-(S_S,1*S*,2*R*)-**41** *anti*-(S_S,1*R*,2*R*)-**42**

Scheme 13.8

β-amino-α-hydroxyphosphonate diesters in high enantiomeric excess. Both AA and asymmetric dihydroxylation (AD)[30] of α,β-unsaturated carbonyls have been thoroughly investigated with a great deal of success; however, the study of their phosphonated analogs still remains undeveloped. The AA[31] and AD[32] reactions were applied to dialkyl vinylphosphonates to give the corresponding β-amino-α-hydroxyphosphonates or α,β-dihydroxy derivatives, respectively.

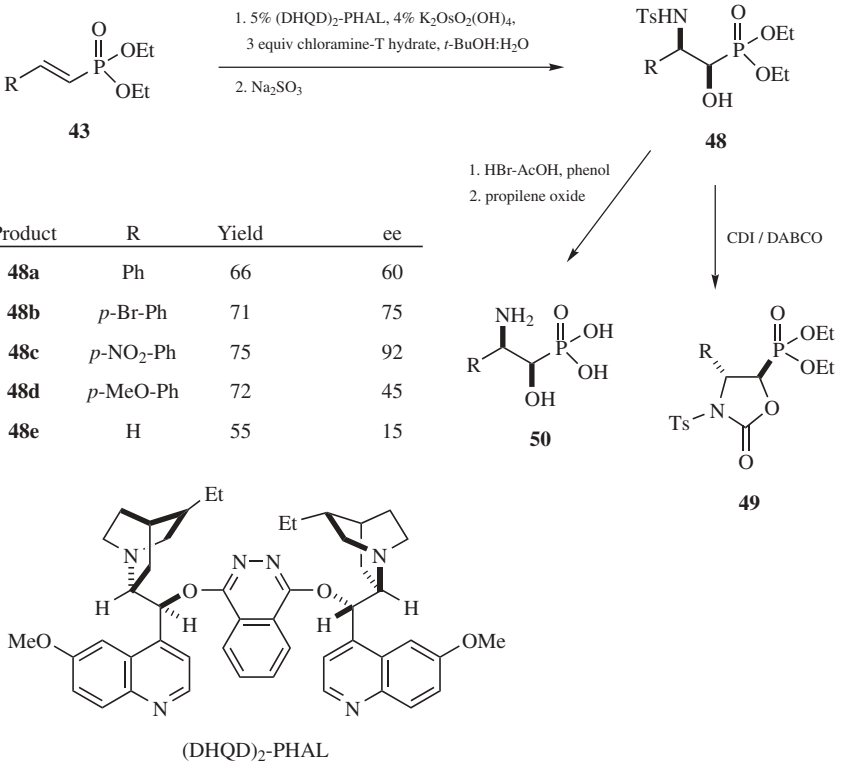
α,β-Unsaturated phosphonates **43** were subjected to osmium tetroxide–catalyzed AD using dihydroquinidine and dihydroquinine derivatives as chiral ligands to furnish the optically active diols **44**, which were converted into the corresponding cyclic sulfites **45** as a diastereomeric mixture (3 : 1) by treatment with thionyl chloride. Upon treatment with NaN_3, the latter afforded the azidohydroxyphosphonates, which were reduced with H_2/Pd–C to give the optically pure hydroxyaminophosphonic acid derivatives **46** and **47** in almost quantitative yield (Scheme 13.9).[32] The stereochemical assignments were made by comparison of the optical



Scheme 13.9

rotations of known compounds and also by assuming that the reaction of cyclic sulfite proceeds via complete inversion at the reacting stereogenic center.

Diethyl-substituted α,β-unsaturated phosphonates **43** were successfully oxyaminated using Os(VIII) and the cinchona alkaloid ligand hydroquinidine 1,4-phthalazinediyl diether $(DHQD)_2$-PHAL as the asymmetric inductor and reaction accelerator, and chloramine T hydrate in *t*-BuOH-H_2O (1 : 1 v/v) at room temperature (Scheme 13.10).[31a] The reaction required about 2–24 h to reach >95%



Product	R	Yield	ee
48a	Ph	66	60
48b	*p*-Br-Ph	71	75
48c	*p*-NO_2-Ph	75	92
48d	*p*-MeO-Ph	72	45
48e	H	55	15

Scheme 13.10

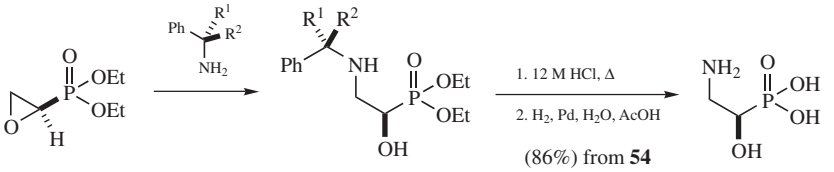
conversion and gave the β-amino-α-hydroxy derivatives **48a–e** with no detectable amounts of the other regioisomer. The syn assignment to **48** stemmed from a combination of coupling constants and NOE experiments on the oxazolidin-2-one derivatives **49**, easily obtained by exposure of **48** to *N*,*N*′-carbodiimidazole (CDI) in the presence of catalyst 1,4-diazabicyclo[2.2.2]octane (DABCO), strongly suggesting a trans-relative stereochemistry. Although the absolute stereochemistry was not assessed, it seems reasonable to speculate that $(DHQD)_2$-PHAL should direct, as in the case of α,β-unsaturated esters, the addition to the β-face of **43a–d** (*re*, *si* approach), giving rise to a (1R,2R) syn configuration. Purification with enantioselectivity enrichment was found possible by recrystallyzation. β-Amino-

α-hydroxyphosphonates **48a–d** could be hydrolyzed in excellent yields to the corresponding β-amino-α-hydroxyphosphonic acids **50** with HBr in AcOH at 75°C in the presence of phenol as a scavenger of bromine followed by neutralization with propylene oxide (Scheme 13.10).

The pseudoenantiomeric ligand hydroquinine 1,4-phthalazinediyl diether $(DHQ)_2$-PHAL as the asymmetric inductor in the AA reaction has also been used employing *N*-chloro-*N*-sodioamides derived from *p*-toluenesulfonyl and ethoxycarbonyl *N*-amino groups, affording *syn*- β-amino-α-hydroxyphosphonates in high enantiomeric excess (values arise from 32 to 99% ee).[31b] The corresponding alkyl-substituted unsaturated phosphonates **43** (R = Alk) failed to react even upon prolonged heating. Purification with enantioselectivity enrichment proved possible by recrystallization. Several by-products were formed during AA reactions, including some diol and regioisomer, whose concentration varied by substrate and with changes in reaction conditions. In addition, cleavage of the α-hydroxyphosphonate products to give an aldehyde and dialkyl phosphite was also observed.

13.3.4 Ammonolysis of Oxiranes

Another method for the preparation of β-amino-α-hydroxyphosphonic esters was demonstrated by ammonolysis of oxiranes.[33] Epoxide (*R*)-**51** reacted with (*S*)- and (*R*)-1-phenylethylamine giving two single diastereomeric amino alcohols **52** and **53** as judged by ^{31}P NMR (Scheme 13.11).[34] Likewise, the formation of the natural product phosphonic acid **55** can be performed by hydrolysis of the phosphonate ester into acid and subsequent deprotection of the amino group in phosphate **54**, obtained from (*R*)-(+)-epoxide **51**.



(*R*)-**51**

52 R^1 = Me, R^2 = H (74%)
53 R^1 = H, R^2 = Me (97%)
54 R^1 = R^2 = H (77%)

55

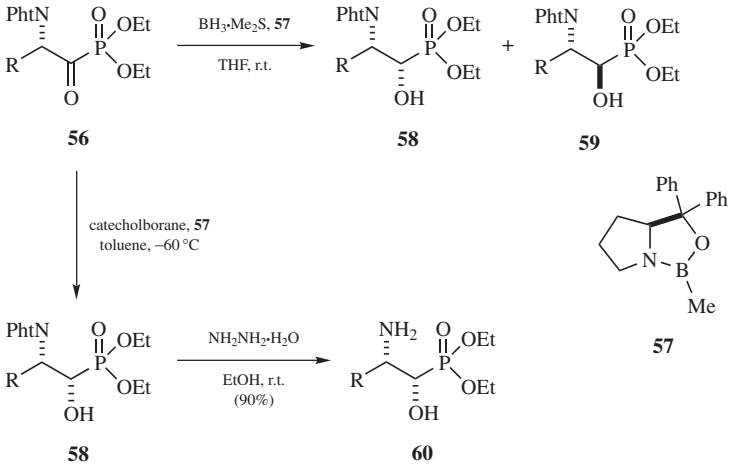
Scheme 13.11

13.3.5 Reduction of β-Amino-α-keto Phosphonates

β-Amino-α-hydroxyphosphonic ester derivatives can also be obtained by reduction of β-phthalimido-α-keto phosphonates **56**. Oshikawa and Yamashita[35] reported the reduction of β-phthalimido-α-keto phosphonates **56** (R = Me, *i*-Bu) with sodium cyanoborohydride, giving to the formation of β-amino-α-hydroxyphosphonates **58** and **59** in almost quantitative yield but in low diastereoselectivity (ratio of 2 : 1 to 3 : 1).[35] Reduction of **56** (R = *i*-Pr) with sodium cyanoborohydride has also been

described by Ziora et al.,[36] giving rise to a mixture of diastereoisomers in a ratio of 5.7 : 1.

However, a highly diastereoselective synthesis of β-amino-α-hydroxyphosphonates **58** and **59** from β-phthalimido-α-keto phosphonates has been reported by means of the reduction with boranes in the presence of oxazaborolidine (Scheme 13.12).[37] Reductions with the borane–dimethylsulfide complex in the presence of catalytic amount (12 mol %) of oxazaborolidine **57** afforded mixtures of diastereoisomers **58** and **59** (R = alkyl, aryl) in a ratio of 8 : 1 to 10 : 1 in favor



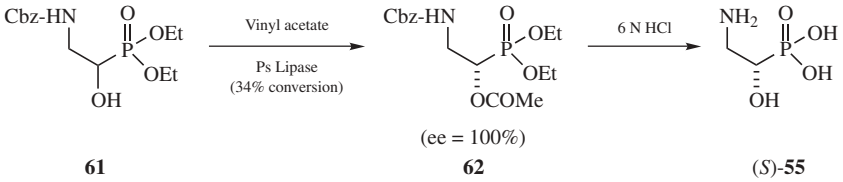
Scheme 13.12

of syn diastereoselectivity. On the other hand, the highest diastereoselectivities were achieved when catecholborane as the reductant in the presence of catalytic amounts of reductions fit with Corey's model, which involves a transition state where the phosphonate moiety represents the large group. The hydride attack occurring preferentially from the *re* face produces the (S)-configuration at the newly created stereogenic center.[38] β-Amino-α-hydroxyphosphonates **60** were produced by reacting hydroxyphosphonates **58** with hydrazine in almost quantitative yields.

13.3.6 Enzymatic Resolutions

Up to now the asymmetric synthesis of β-amino-α-hydroxy phosphonic esters has been applied for their optically active preparation (see previous sections). Few diastereomeric resolutions using direct liquid chromatography employing quinine-derived chiral anion exchangers[39] or stereoselective capillary electrophoresis[40] have been reported. However, chemoenzymatic methods have not been widely used for the preparation of optically pure β-amino-α-hydroxy phosphonic esters. Selectivity of the lipases toward isoserine phosphonate derivative **61** has been reported by Heisler et al.[41] Vinyl acetate transesterification of **61** mediated by *Candida*

cylindracea, *Porcine pancreatic*, *Pseudomonas*, *Rhizopus*, and *Mucor* lipases produced slow but very enantioselective reactions (Scheme 13.13). *Pseudomonas* lipase produced 34% conversion of **61** to ester **62** within 7 days of incubation. After separation of the ester **62** and the remaining alcohol, the two compounds were hydrolyzed separately using 6 N HCl. The enantioselectivity observed in the unprotected β-amino-α-hydroxy phosphonic acid **55** obtained from the ester **62** was very close to 100% showing an (S)-configuration.



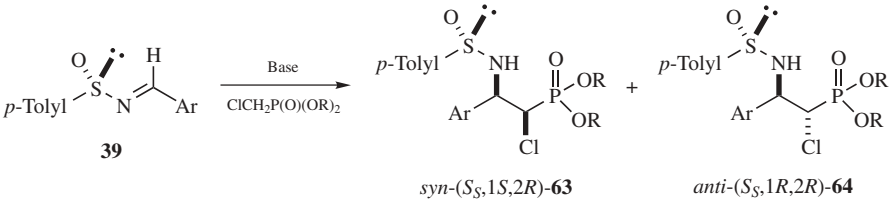
Scheme 13.13

Lipases are known to catalyze not only transesterification but also transamidation reactions. Selectivity of the lipases toward transesterification of *N*-unprotected isothreonine phosphonate derivatives has also been described for the same group.[42] Using vinyl acetate, *Candida rugosa* lipase first induced the *N*-acylation reaction giving a conversion of ~100% with very good chemoselectivity and diastereoselectivity. This reaction, which proceeded without any enantioselectivity, was followed by the slow transesterification leading to the *N*,*O*-diacetylated compounds. Small amounts of other polyacetylated compounds were also present.

13.4 SYNTHESIS OF β-AMINO-α-HALOGENATED PHOSPHONATES

Most of the investigations into the synthesis of β-amino-α-halogenated phosphonates and derivatives have dealt with the addition of carbanions of α-halomethyl phosphorus derivatives to imines or sulfinimines. For example, Hanessian et al.[43] have reported an asymmetric synthesis of β-amino-α-chloro phosphonamides involving the stereoselective addition of carbanions of chiral α-chloromethyl bicyclic phosphonamides to imines.

Davis et al.[28,44] have also recently described an elegant approach to the synthesis of β-amino-α-halogenated phosphonates **63** and **64** employed for the asymmetric synthesis of azirinyl phosphonates (Scheme 13.14). The synthesis of diethyl



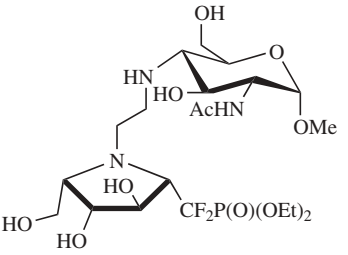
Scheme 13.14

chlorophosphonates (R = Et) **63** and **64** was achieved by addition of carbanions derived from chloromethyl phosphonate (R = Et) to benzaldehyde-derived sulfinimines (*S*)-**39** (Ar = Ph). The ratio of (+)-**63**/(+)-**64** in the crude reaction mixture was 59 : 41.[44a] Interestingly, the exclusive (R)-absolute induction at C-2 in the formation of **63** and **64** is opposite to that found in the analogous carboxylic ester case,[45] and the same as that observed for the addition of phosphites[46] and α-phosphonates carbanions[7] to (*S*)-**39**. Whereas the selectivity for metal enolate additions to sulfinimines has been rationalized in terms of chairlike transition states where the metal is coordinated to both the sulfinyl oxygen and imine nitrogen,[45,47] transition-state rationales for phosphine and α-phosphonate carbanion additions to (*S*)-**39** have these species reacting from the least hindered direction, that is, opposite to the *p*-tolylsulfinyl group.[7,46] This difference may reflect the greater steric bulk of metal phosphonate anions compared to enolates as well as their tetrahedral structure.

Carbanions derived from dimethyl chloromethyl phosphonate (R = Me) in the addition to sulfinimines **39** (Ar = Ph, *p*-MeO-Ph) have been reported for the same group, giving rise to better diastereoselectivities for the β-amino-α-chloro phosphonates **63** and **64** (72 : 28).[44b] Also, α-alkyl-β-amino-α-chloro phosphonates have been obtained by addition of carbanions derived from diethyl chloroethyl phosphonate to sulfinimines **39** (Ar = Ph).[48] However, three diastereoisomers were isolated: (S_S,1R,2R) in 56% yield and also an inseparable mixture of (S_S,1S,2R) and (S_S,1S,2S) (68 : 32) in 23% isolated yield. Very recently, the process has been extended by the same group to the preparation of β-amino-α-iodo phosphonates with very good yields.[44c] Likewise, difluoromethylphosphonate azadisaccharide **65** designed as inhibitors for glycosyl transferases (Fig. 13.3) has been prepared from imines derived from D-arabinose and from L-xylose with diethyl (lithiodifluoromethyl)phosphonate.[49]

13.5 SYNTHESIS OF α,β-DIAMINO PHOSPHONATES AND PHOSPHINATES

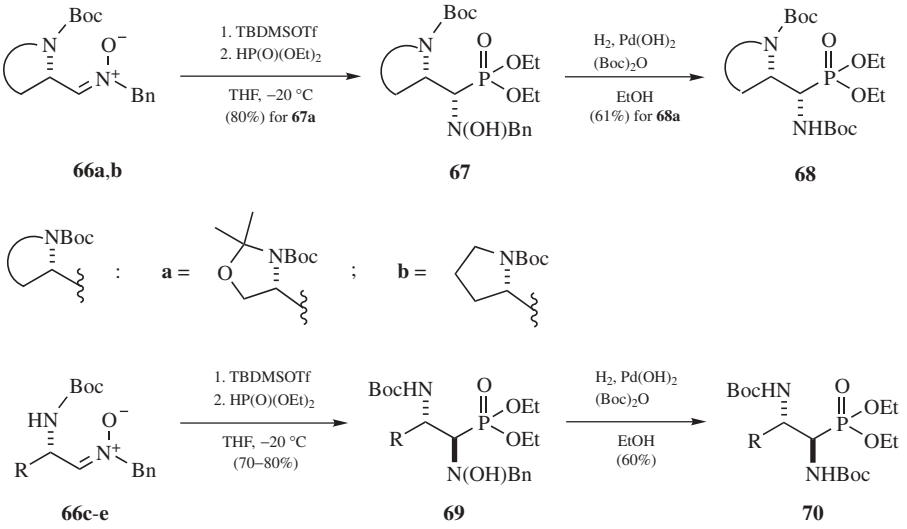
While the α,β-diamino acids[50] have been investigated widely in both their biological activities and their preparation, there have been very few reports about



65

Figure 13.3

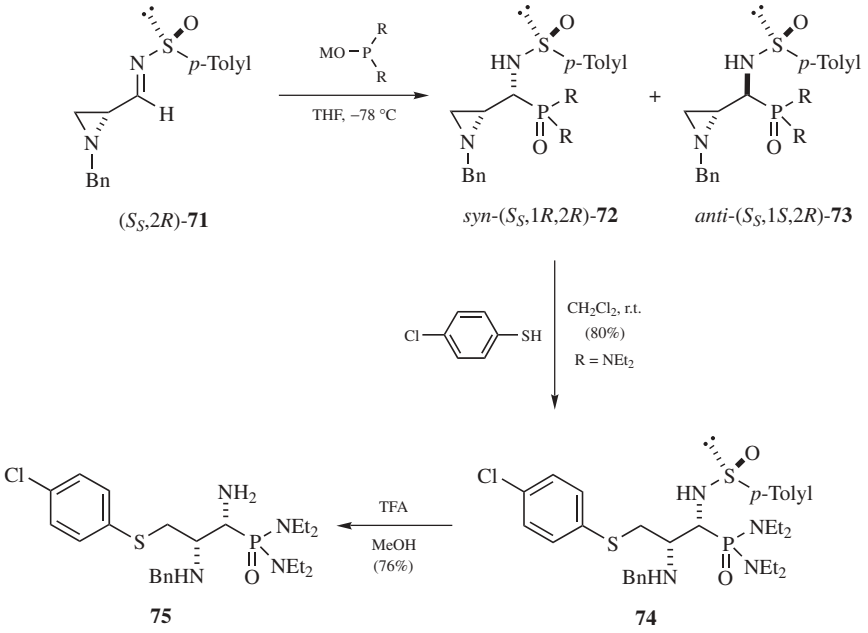
the synthesis and biological studies of their isosteres α,β-diamino phosphonic acids. Access to chiral α,β-diamino phosphonates **68** and **70** with high levels of diastereoselectivity was achieved via a stereoselective carbon–phosphorus bond-forming process through addition of diethyl phosphite to *O*-silylated *N*-benzyl nitrones **66** derived from chiral α-amino aldehydes (Scheme 13.15).[51] Treatment of the *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf)–precomplex nitrone **66a**,**b** with diethyl phosphite afforded exclusively the syn-adduct **67**.



Scheme 13.15

The diastereoselectivity of the addition reaction to α-amino nitrones can be tuned by monoprotection of the amino group. Thus, the reaction of *N*-monoprotected α-amino nitrones **66c**-**e**, whose progenitors were alanine, phenylalanine, and leucine, respectively, afforded the corresponding *anti*-*N*-hydroxy α-amino phosphonates **69** in good yields (Scheme 13.15). The same stereochemical outcome in the addition reaction of 2-lithiothiazole to the nitrone derived from *N*-monoprotected serinal has been observed.[52] Finally, the removal of both the benzyl and hydroxy groups from the nitrogen atom of **67** and **69** with concomitant protection of the amino group was carried out in one step by hydrogenation over $Pd(OH)_2$ in the presence of $(Boc)_2O$ to give *N*-Boc protected α,β-diamino phosphonates **68** and **70**, respectively.

The addition of phosphite anions to enantiopure 2-aziridinesulfinimines **71** constitutes a synthetic route to α-amino-2-aziridinemethan phosphonates **72** and **73**, which are a kind of α,β-diamino phosphonate and also the intermediates that allow easy access to a variety of α,β-diamino phosphonates by ring opening of the aziridine with various nucleophiles (Scheme 13.16).[53] The reaction of (S_S,2*R*)-**71** gave the syn isomer as the major product, while in the reaction of (S_S,2*S*)-**71**, the



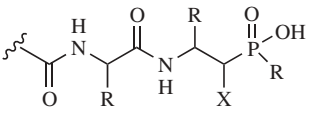
Scheme 13.16

anti isomer is predominant; however, the configuration of the newly formed chiral carbon center of major products for both reactions is (R). These results also suggested the operation of a double-stereodifferentiation effect, but the chirality of the sulfinyl group dominated the asymmetric induction.[54]

A ring-opening reaction of the aziridine system in compound *syn*-**72** was carried out by nucleophilic addition of *p*-chlorothiophenol, giving the corresponding α-(*N*-sulfinylamino)-β-amino phosphonamide **74**, which was treated with TFA to remove the *N*-sulfinyl group to give α,β-diamino phosphonamide **75** (Scheme 13.16). Proton NMR showed that two amino groups were at the syn position, which was confirmed by single-crystal X-ray analysis of **74**.

13.6 β-AMINO-α-SUBSTITUTED PHOSPHORUS DERIVATIVES WITH PEPTIDE BOND FORMATION: β-AMINO-α-SUBSTITUTED PHOSPHONO- AND PHOSPHINOPEPTIDES

The preceding sections delineated the preparation of β-amino-α-substituted phosphorus derivatives. In a similar way, some works documented the utility of these compounds as intermediates for the synthesis of medium or large β-amino-α-substituted phosphonopeptides. Among peptidomimetics, considerable attention is paid to the peptides obtained by the introduction of aminophosphonic acid residues into the peptide molecule. β-Amino-α-hydroxy phosphonopeptides are well-recognized key components for a variety of protease inhibitors. Introduction of



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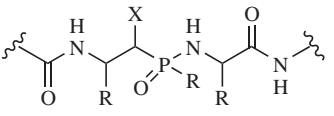

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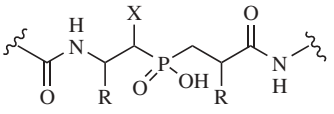

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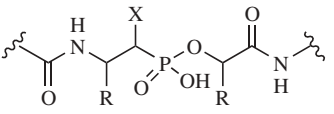

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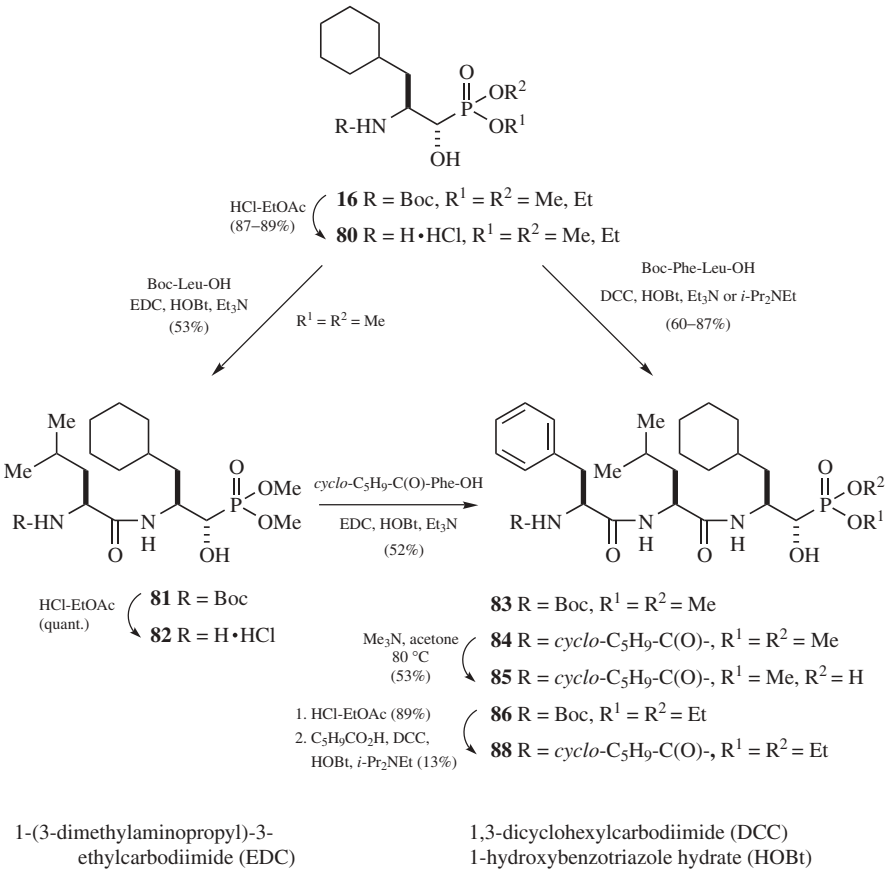
Figure 13.4

an aminophosphonate into the peptide molecule offers several structural possibilities (Fig. 13.4). The most common are β-amino-α-substituted phosphonopeptides **76** containing a P-terminal aminophosphonate unit. Although peptides **77**, containing a phosphonamidate bond, are of special interest because the planar amide is replaced by the tetrahedral phosphonamide structure, no reports have described the synthesis of such peptides. Similar features are present in peptides **78** and **79** containing an β-aminophosphonic acid unit, but only some peptides **78** have been reported in the literature.

Patel et al.[12,13] have reported the synthesis of β-amino-α-hydroxy phosphonopeptides as inhibitors of human renin (Scheme 13.17). The synthesis of dipeptides **81**, **82** and tripeptides **83**–**85** is based on a coupling of protected amino acids with β-amino-α-hydroxy phosphonate **80**. As indicated in Section 13.3.1, **80** was prepared by potassium fluoride–promoted addition of dimethyl phosphite to *N*-Boc-α-aminoaldehyde derivative followed by deprotection of the *N*-Boc group. Subsequent coupling of **80** with Boc-Leu-OH and with Boc-Phe-Leu-OH afforded phosphonodipeptide **81** and phosphonotripeptide **83**, respectiely.[12,13] Alternatively, the cyclopentyl analogs of tripeptide **83** were synthesized in a sequential fashion by first coupling **80** with Boc-Leu-OH to obtain phosphonodipeptide **81**, which was deprotected to give **82**. Coupling of **82** with *cyclo*-C_5H_9CO-Phe-OH yielded analog **84**. Upon treatment with anhydrous trimethylamine in acetone at 80°C, **84** could be cleanly monodealkylated to provide the phosphinotripeptide **85**.[13] The same coupling strategy has also been reported by this group for the synthesis of diethyl phosphonate tripeptides **86** and **88** (Scheme 13.17). The synthesis comprises a coupling of Boc-Phe-Leu-OH with a 4 : 1 mixture of diastereoisomers of **16** ($R^1 = R^2 = Et$) providing the tripeptidic hydroxy phosphonates as a separable mixture of two diastereoisomers, **86** in 73% yield and **87** (not shown) in 14% yield. Removal of the *N*-Boc group from **86** followed by coupling of the resulting amine with cyclopentanecarboxylic acid gave **88** in 13% yield.[13]

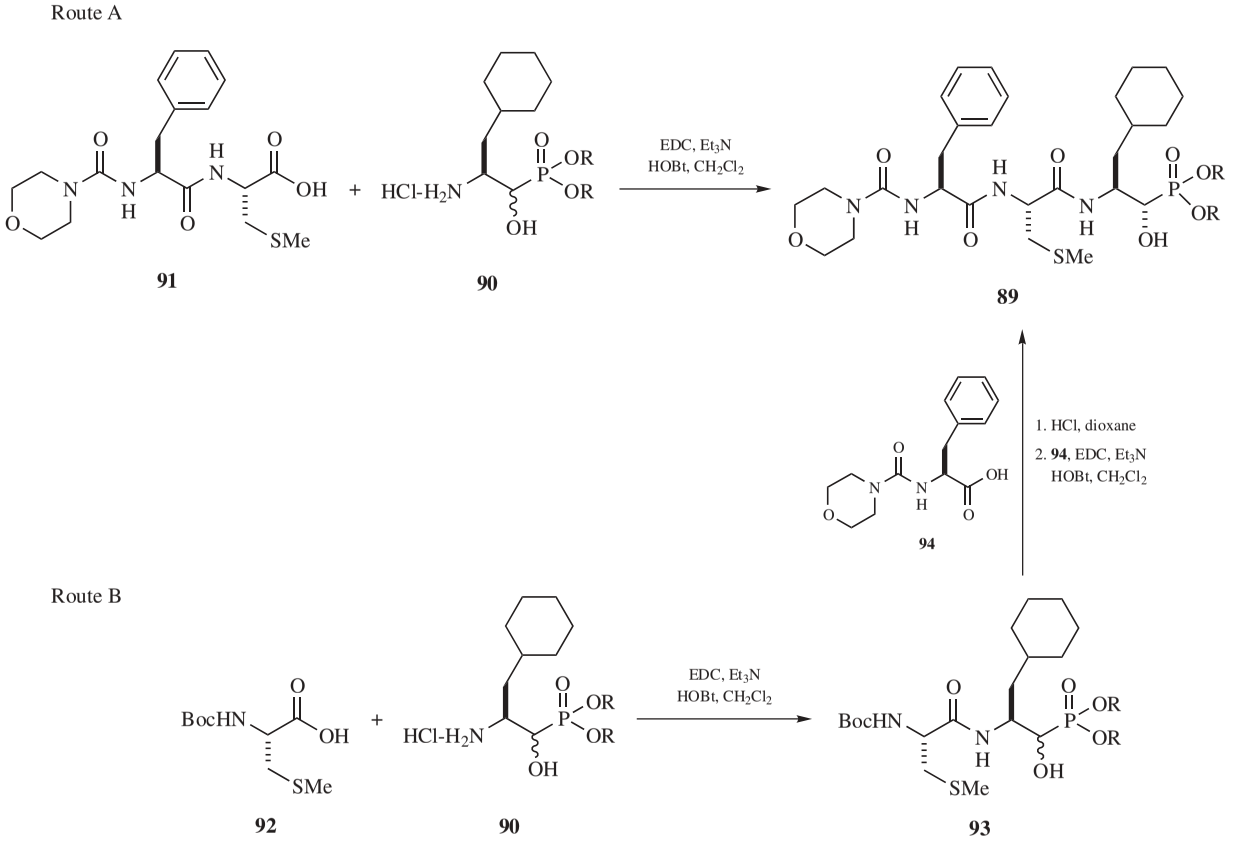
Another example is the replacement of the C-terminal isopropyl ester in the orally active norstatine renin inhibitor terlakiren with dialkyl phosphonate groups, providing a novel series of phosphorus norstatine inhibitors **89**.[19] As Scheme 13.18



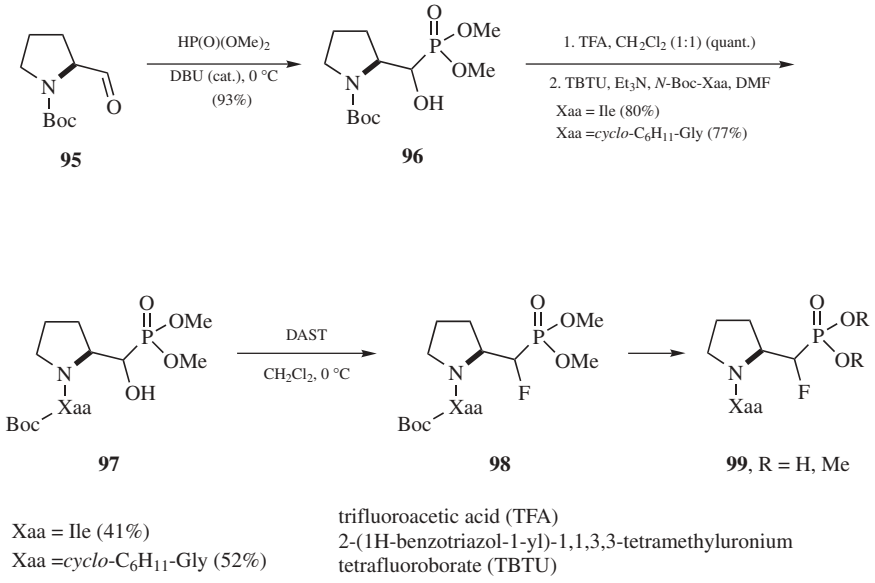
Scheme 13.17

illustrates, the synthesis of **89** could be accomplished starting from Boc-L-cyclohexylalanal. Potassium fluoride–promoted addition of dialkyl phosphites to Boc-L-cyclohexylalanal afforded, after deprotection, 3–4 : 1 mixtures of inseparable epimeric phosphonates **90** with (S)-configuration (desired) for the major isomer. The final phosphonopeptide **89** was prepared as a mixtures of diastereoisomers from **90**, either by coupling to dipeptide **91** (route A) or via intermediates **93** (route B). Route B ultimately proved advantageous in obtaining products of higher diastereomeric purity allowing the separation of epimers in intermediate **93**.

β-Amino-α-fluorinated phosphono- and phosphinopeptides have also been recently reported as potential transition-state inhibitors for proline-selective serine dipeptidases.[55] For the preparation of fluorophosphono- and phosphinopeptides **99**, *N*-Boc-prolinal **95** was subjected to Pudovik–Abramov condensation providing hydroxyphosphonate **96** as a mixture of two diastereoisomers in a ratio of 2 : 1 (Scheme 13.19). The use of DBU catalysis resulted in a very fast reaction with only moderate diastereoselectivity compared to KF or other catalysts reported in Section 13.3.1. Since the potential biological activity differences for both isomers was


Route A
EDC, Et3N
HOBt, CH2Cl2
91
90
89
1. HCl, dioxane
2. 94, EDC, Et3N
HOBt, CH2Cl2
94
Route B
EDC, Et3N
HOBt, CH2Cl2
92
90
93

Scheme 13.18



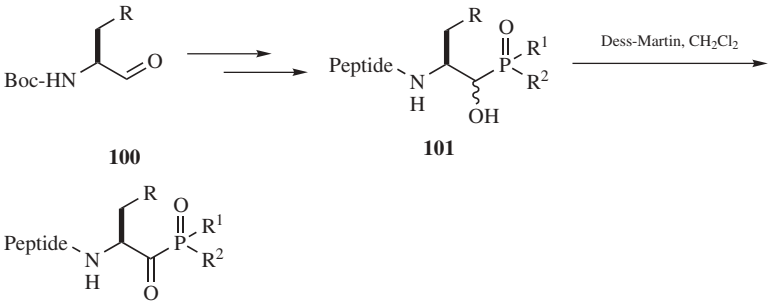
95 **96** **97** **98** **99**, R = H, Me

Scheme 13.19

fundamental in this study, the use of reaction conditions with low diastereoselectivity was considered beneficial. Deprotection of **96** and coupling with *N*-Boc-Ile or *N*-Boc-*cyclo*-C_6H_{11}-Gly afforded dipeptides **97**, which were fluorinated with (diethylamino)sulfur trifluoride (DAST) to give β-amino-α-fluorinated phosphonopeptides **98** in moderate yield. Separation of diastereoisomers was possible by column chromatography. Finally, different deprotecting steps were then used to obtain the deprotected β-amino-α-fluorinated phosphono- and phosphinopeptides **99**.

β-Amino-α-hydroxy phosphopeptides as intermediates for the synthesis of α-ketophosphonates, phosphinates, and phosphine oxides **102**, potent inhibitors of human calpain I (calcium-dependent cysteine protease), have been reported.[17] The synthesis of the peptidyl phosphonates, phosphinates, and phosphine oxides **101** (Scheme 13.20) was accomplished by hydrophosphinylation of protected aldehydes **100** with dialkyl phosphites or dialkyl phosphine oxides. Subsequent deprotection and amino acid coupling chemistry gave dipeptide α-hydroxy phosphonate and phosphine oxide **101**. Oxidation of **101** with Dess–Martin reagent in methylene chloride gave α-ketophosphonates and phosphine oxides **102**.

The results reported above showed the feasibility of using β-amino-α-hydroxy phosphonates for the preparation of phosphonopeptides by coupling of amino acids to the amino group of the β-amino-α-hydroxy phosphonates. For a more general application, it would be desirable to insert amino acid or peptidic fragments at both the amino and phosphorus terminis of the α-hydroxy phosphinic moiety of a particular transition-state mimic. Thus, a suitable methodology has been developed for modifications at the phosphorus terminus of the α-hydroxy phosphinic moiety in **16** (Scheme 13.21).[56] For the preparation of phosphinodipeptide **107**, it was found necessary to protect the β-amino-α-hydroxy phosphonate **16** in order to direct

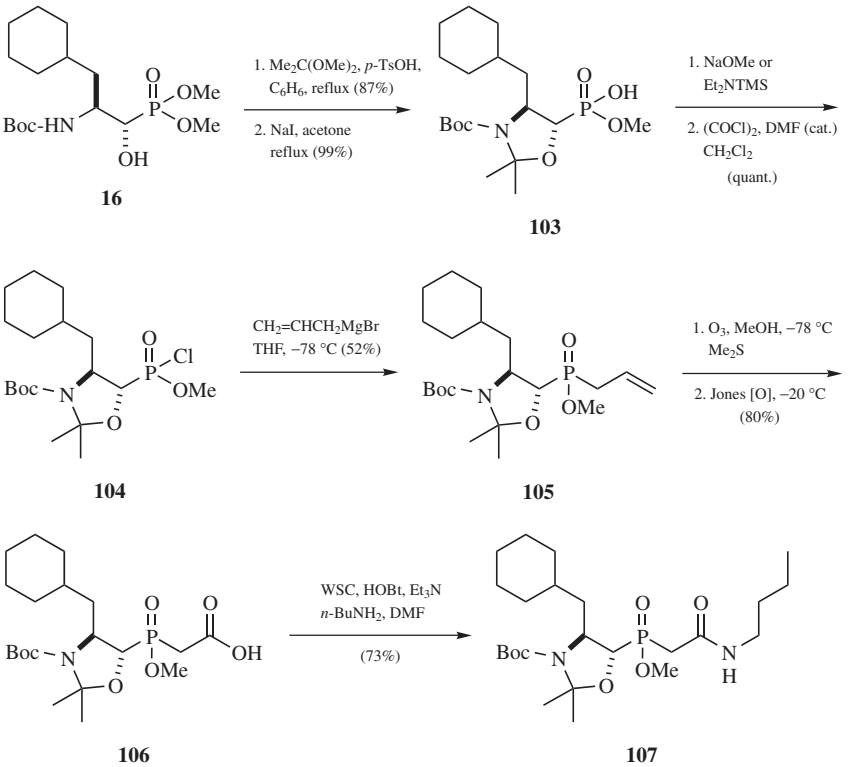


100 **101**

102

R = *i*-Pr, Peptide = Cbz-Leu
R = Ph, Peptide = Cbz-Val

Scheme 13.20



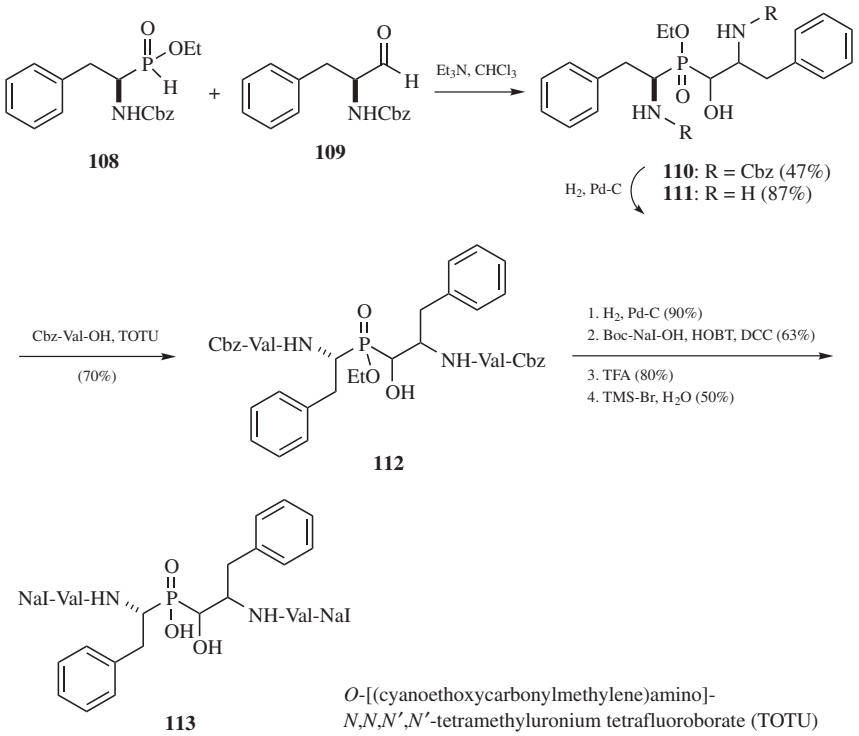
16 **103** **104** **105** **106** **107**

N,*N*-diethyltrimethylsilylamine (Et_2NTMS)
Tetrahydrofuran (THF)
Water-sol. carbodiimide (WSC)

Scheme 13.21

reactions specifically at the phosphorus center and minimize side reactions. Thus, compound **16** was converted to the fully protected oxazolidine derivative by following the special procedure of Garner and Park,[57] wherein it was treated with a large excess of 2,2-dimethoxypropane and the MeOH being produced was continually removed by slow distillation of the reaction mixture. Selective mono-dealkylation of the resulting oxazolidine afforded the monoester monoacid **103**, which was converted to its phosphonochloridate **104** under neutral conditions, followed by reaction with oxalyl chloride and catalytic amounts of DMF in CH_2Cl_2. To insert amino acid residues at the C-terminal of the α-hydroxyphosphinyl group, the chloridate **104** reacted with allylmagnesium bromide to give the allylic phosphinate **105**, which under ozonolysis and with a reductive workup followed by low-temperature Jones oxidation of the crude aldehyde afforded the acid **106**. This can now serve as a versatile intermediate for the incorporation of various amino acids, peptides, or other functionalities as required for specific application to a particular enzyme. For example, coupling of **106** with *n*-butyl amine gave the amide **107**, an advanced intermediate for the preparation of novel renin inhibitors. Authors also reported the insertion of oxygen and nitrogen at the phosphorus center of intermediate **103**.[56]

Stowasser et al.[58] have also described the synthesis of β-amino-α-hydroxy phosphinopeptide **113** (Scheme 13.22). Phosphinopeptide **113** is a powerful



Scheme 13.22

inhibitor of HIV protease. The synthesis of **113** is based on a coupling of protected amino acids with the central building block β-amino-α-hydroxy phosphinate analog **111**. This latter compound was prepared by nucleophilic addition of phosphinic acid derivative **108** to Cbz-protected (*S*)-phenyl alaninal **109**. Base catalysis with Et_3N gave the desired coupling product **110** as mixture of three major diastereoisomers in a ratio of 3.4 : 1.7 : 1. Subsequent deprotection of the Cbz group to give β-amino-α-hydroxy phosphinopeptide **111** and coupling with L-Cbz-valine afforded phosphinopeptide **112**. The resulting phosphinopeptide product **112**, on reductive deprotection of the Cbz group, was next coupled with L-Boc-naphthylalanine. Finally, deprotection of the Boc group and hydrolysis of the ester group gave **113**.

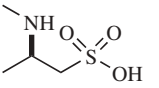
13.7 β-AMINO SULFUR ANALOGS

13.7.1 Introduction

The sulfur atom is chiral and possesses different electronic and polarity characteristics, so stereogenic sulfur groups can efficiently control the relative and absolute stereochemistry of organic processes. For this reason the sulfur atom represents a versatile element in organic chemistry. Sulfur demonstrates pyramidal bonding in sulfinic acid derivatives, sulfoxides, and sulfonium salts; however, in sulfonic acid derivatives, although the sulfur atom is tetrahedral, two of the substituents are always oxygen, and therefore there is no chirality.[59] However, when there is an amino group as substituent in a β-position, these compounds play an important role in asymmetric synthesis and in peptidomimetics derivative preparation through the so-called sulfonyl and sulfinyl chloride strategy. Earlier methods for the synthesis and chemistry of optically active sulfur derivatives have been reviewed previously.[60] The purpose of the present chapter is to provide an overview of the asymmetric synthesis of chiral β-amino sulfur derivatives, β-amino sulfonic acid **114**, β-amino sulfinic acid **115**, and their functional derivatives (Fig. 13.5), interesting substrates due to their application in total synthesis through the synthetic versatility associated with sulfinyl moieties. The end of the chapter is focused on the preparation of sulfonopeptides, oligopeptides, or peptidomimetics from these β-amino sulfur precursors.

13.7.2 Synthesis of Building Blocks: β-Amino Sulfinic and Sulfonic Acid Derivatives

A correlation exists between the absolute configuration of sulfinyl derivatives and their chiroptical properties,[61] whose chirality has allowed the extention of the



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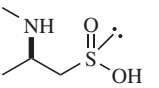
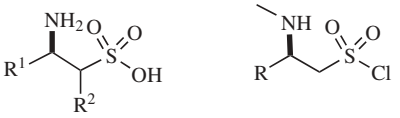


115

Figure 13.5



116 $R^1 = R^2 = H$ **119**
117 $R^1 = CO_2H$, $R^2 = H$
118 $R^1 = Me$, $R^2 = H$

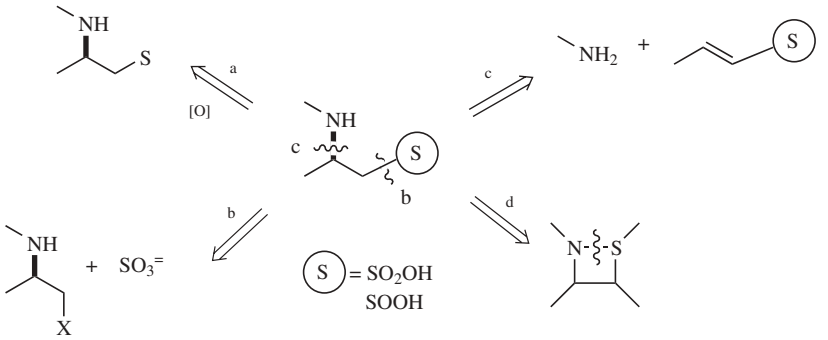
Figure 13.6

synthetic utility of the sulfinyl group to the field of asymmetric synthesis.[62] Diastereomerically pure, optically active, β-functionalized sulfinyl compounds with two stereogenic centers constitute an interesting class of chiral building blocks for the construction of various important compounds.[59e] However, the respective β-amino derivatives are rather scarcely used because they are usually prepared in a multistep synthesis from the other nonracemic compounds.

Enantiopure β-amino sulfonic acids possess an important role in physiological processes. Some of these compounds are taurine (2-aminoethanesulfonic acid) **116** ($R^1 = R^2 = H$) and cysteic acid (2-amino-3-sulfopropionic acid) **117** ($R^1 = COOH$, $R^2 = H$) (Fig. 13.6). Their conformational preferences in aqueous solution under conditions similar to physiological environments may be of importance in investigating their functional activity. Recently the study of the two enantiomers of 2-methyltaurine **118** ($R^1 = Me$, $R^2 = H$) showed that the (S)-enantiomer is the most effective in mimicking the hypotensive activity of taurine, thus suggesting that this effect could be receptor mediated.[63] β-Amino sulfonic acids which undergo electrophilic substitution in the α-position[64] are used as intermediaries in the synthesis of β-lactams.[65]

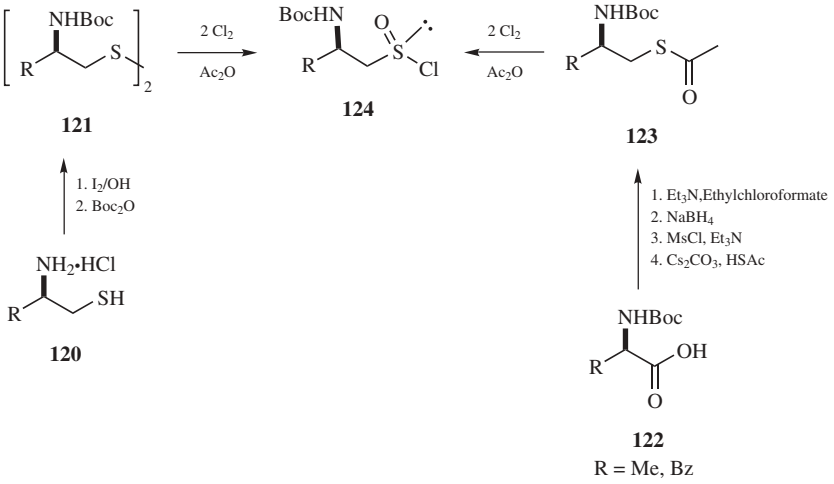
The synthesis of peptidomimetics incorporating the β-aminoethane sulfinamide or sulfonamide moiety have been developed by using β-aminoethane sulfonylchlorides **119** as building blocks[66] and also has been successfully applied to the synthesis of receptor molecules,[67] catalysts,[68] and oligopeptidosulfonamides.[69] The preparation of these building blocks has been developed by several routes starting from a wide variety of substrates. In the next sections, the preparation of these building blocks will be examined by four different types of reactions (Scheme 13.23): the oxidation of sulfur derivatives (route a), nucleophilic substitution with sulfites (route b), Michael addition of nitrogen derivatives to vinyl sulfones (route c), and hydrolysis of β-sultams (route d) as well as the use of these substrates for the preparation of sulfur-containing pseudopeptides.

13.7.2.1 Oxidation of Sulfur Atom The synthesis of sulfur derivatives from sulfides by oxidation has been widely used. This reaction involves the S–O bond formation (Scheme 13.23, route a). The oxidant selected plays an important role. Specific oxidants could stop the oxidation in the sulfinic acid derivatives, and subsequent oxidation of sulfinic to sulfonic acid derivatives can be performed with powerful oxidant reagents.



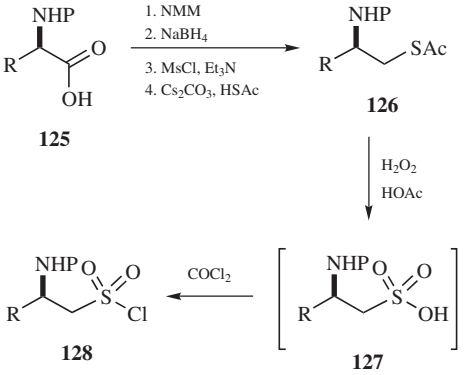
Scheme 13.23

β-Amino sulfinyl chlorides **124** can be prepared by selective oxidation of sulfides when starting from cysteamine hydrochloride **120**[70] or from amino acids **122**.[71] The system chlorine (2 eq.)–acetic anhydride (1 eq.) was employed for the oxidation of disulfides **121** or thiols **123** into a mixture of diastereomeric sulfinyl chlorides **124** (Scheme 13.24). Therefore, this process involves the enantioselective preparation of β-amino sulfinyl chlorides **124**, interesting substrates in the preparation of sulfonamide peptides from amino acids. The most simple aminosulfinic acid which can be incorporated into the sequence of sulfonamide-containing peptides is β-aminoethane sulfonic acid or taurine (Tau) (R = H) via its sulfinyl chloride.[72]



Scheme 13.24

A similar strategy was employed for the preparation of sulfonyl derivatives. Starting from α-amino acids **125**, Liskamp et al.[66] have reported the synthesis of enantiomerically pure β-amino sulfonic derivatives **128** by using hydrogen peroxide



P: protecting group
N-methylmorpholine (NMM)

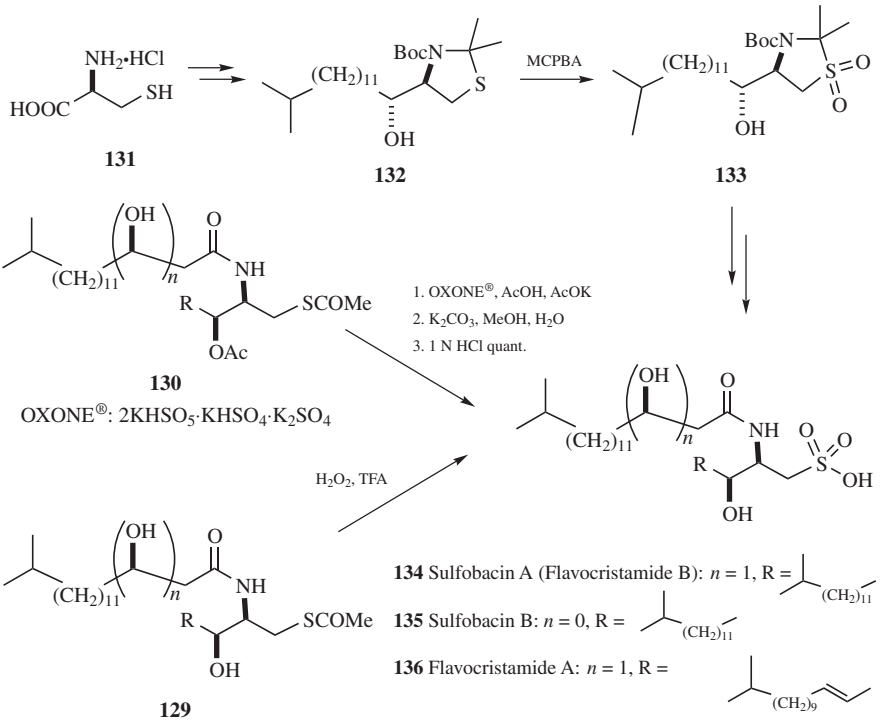
Scheme 13.25

and acetic acid as the oxidant system. Subsequent treatment with phosgene affords the expected β-amino sulfonyl chlorides **128** (Scheme 13.25).[66]

However, the sulfonyl chloride derivative **128** was not always obtained under the oxidation conditions. Even after exposures to excess chlorine for relatively long periods, the sulfonyl chloride derivatives **128** were invariably contaminated with the sulfinyl chlorides **124**. Likewise, the oxidation of sulfinyl to sulfonyl compounds can be applied in the formation of sulfonamides[70,71] by oxidation of sulfinamides using $RuCl_3/NaIO_4$.

The oxidation of functionalized β-amino sulfide derivatives has been used for the synthesis of sulfonic acid sphingosine relatives as Sulfobacin A (Flavocristamide B) **134** and B **135** and Flavocristamide A **136** (Scheme 13.26), sulfonolipid relatives having an aminosulfonic acid moiety, which have inhibitory activity against deoxyribonucleic acid (DNA) polymerase α. A structurally similar sulfonolipid was previously synthesized by Ohashi et al.[73] Afterward, the first total syntheses of Sulfobacin A **134** (Flavocristamide B) and the synthesis of Sulfobacin B **135** were simultaneously achieved in different effective stereoselective manner by two groups. Shioiri and Irako[74] have performed the oxidation of the sulfur atom of thiol **129** using peroxytrifluoroacetic acid as oxidant agent. On the other hand, Takikawa et al.[75] have prepared the natural compounds starting from L-cysteine hydrochloride **131** through the thiazolidine ring **132** and *m*-chloroperbenzoic acid (MCPBA) as oxidant. For the synthesis of Flavocristamide A **136**, the oxidation of compound **130** was accomplished with potassium monoperoxysulfate (OXONE).

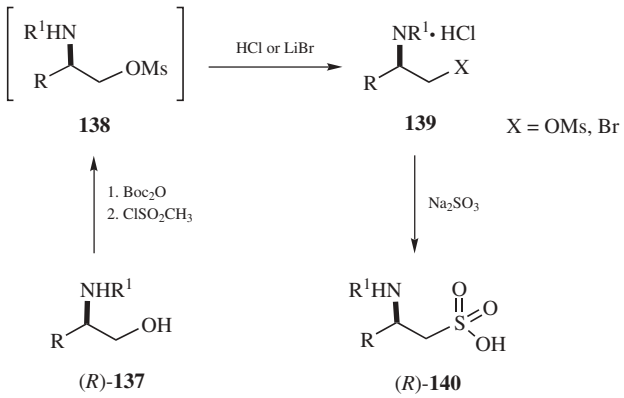
13.7.2.2 Nucleophilic Substitution Compounds which have good leaving groups are excellent starting material for C–S bond formation through attack by sulfite ion (Scheme 13.23, route b). Likewise, chiral 2-aminoalkanesulfonic acids have been prepared by nucleophilic substitution of chiral β-aminoalcohols or amino acids. Enantiomerically pure 2-substituted taurines **140** were synthesized by two



Scheme 13.26

routes, through mesylates **139** (X = OMs) or through halogeno derivatives **139** (X = Br) with total absence of racemization when starting from the optically pure substrates **137**[76] (Scheme 13.27, Table 13.3).

The reaction sequence was performed starting from both (R) and (S) optically pure compounds. The key step is the reaction of hydrochloride **139** with sodium



Scheme 13.27

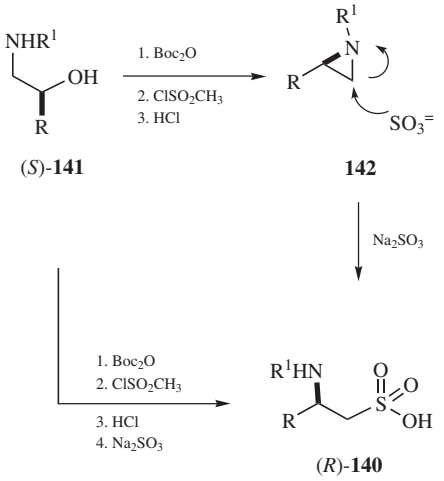
TABLE 13.3 β-Amino Sulfonic Acids 140 Obtained from Primary 137 and Secondary β-Amino Alcohols 141

Compound	R	R^1	Starting Alcohol	R/S (ee, %)	Yield (%)	Reference
140a	Me	H	(*S*)-**137a**	S	82	76a
140b	Me	H	(*R*)-**137b**	R	67	76a
140c	*i*-Pr	H	(*S*)-**137c**	S	89/86	76a
140d	*i*-Pr	H	(*R*)-**137d**	R	67	76a
140e	Bz	H	(*S*)-**137e**	S	72	76a
140f	Bz	H	(*R*)-**137f**	R	83	76a
140g	Ph	H	(*R*)-**137g**	R	79	76a
140h	$PhCH_2OCH_2$	H	(*S*)-**137h**	S	76	76a
140i	*t*-Bu	H	(*S*)-**137i**	S	79/84	76a,b
140j	*t*-Bu	H	(*R*)-**137j**	R (>99)	81	76b
140k	$-(CH_2)_3-$		(*R*)-**137k**	R (>99)	81	77
140l	$-(CH_2)_3-$		(*S*)-**137l**	S (>99)	83	77
140m	Et	H	(*R*)-**137m**	R (>99)	89	76b
140n	Et	H	(*S*)-**137n**	S (>99)	86	76b
140o	*t*-Bu	H	(*R*)-**137o**	R (>99)	81	76b
140b	Me	H	(*S*)-**141a**	R (>99)	—	78
140a	Me	H	(*R*)-**141b**	S (>99)	—	78

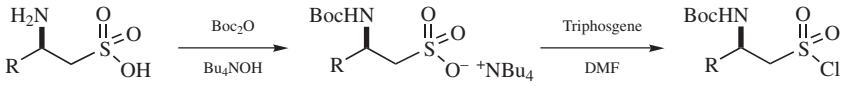
sulfite, which occurs either by a rearrangement or by a simple nucleophilic substitution in a molecule with a group with an unshared pair of electrons β to the leaving group. The same methodology was applied for the asymmetric synthesis of (*R*)- and (*S*)-2-pyrrolidinemethanesulfonic acid starting from a cyclic alcohol as (*R*)- and (*S*)-2-pyrrolidinemethanol **137** ($R^1R = -(CH_2)_3-$, Scheme 13.27) affording the corresponding compounds with an enantiomeric purity >99%.[77]

However, when starting from chiral β-amino secondary alcohols **141**, the asymmetric synthesis of the β-aminoalkanesulfonic acids **140** was carried out following the same methodology, but in this case an inversion of configuration was observed[78] (Scheme 13.28, Table 13.3). Along with these observations, Xu[79] has proposed a mechanism based on a neighboring-group-assisted cyclization to a 2-alkylaziridine **142** formed from both primary β-amino alcohol **137** or secondary β-amino alcohol **141** (Scheme 13.28). The sodium bisulfite generated attacks the aziridine at the less hindered carbon atom to yield a sodium β-amino alkanesulfonate with the same configurations as the corresponding β-amino primary alcohols but with inverse configurations with respect to the secondary alcohols.

Two groups, Gude et al.[80] and deBont et al.,[81] have prepared the corresponding sulfonyl chlorides taking as starting material the β-amino sulfonic acids **143** obtained from primary and secondary alcohols previously reported. Reaction of **144** with phosgene in the presence of catalytic amounts of DMF yielded after purification sulfonylchlorides **128** exclusively (no sulfinyl chloride formation is observed) (Scheme 13.29).



Scheme 13.28



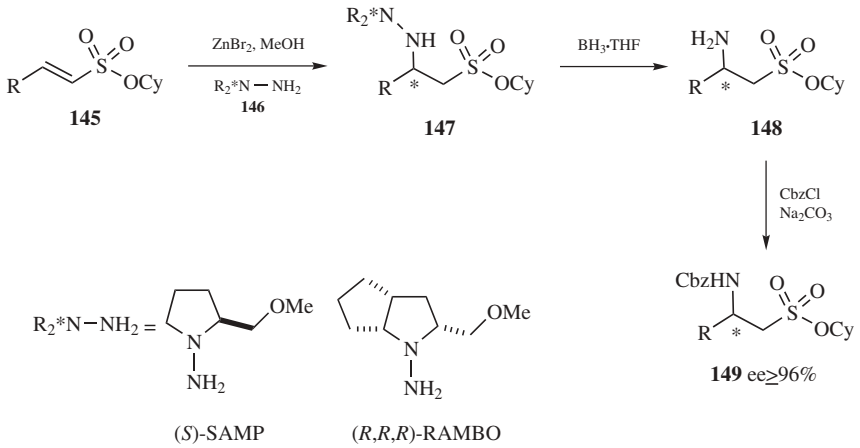
Scheme 13.29

13.7.2.3 Michael Addition of Nitrogen Derivatives to Vinyl Sulfonates

The Michael reaction can provide an efficient access to sulfonic acid derivatives through C–N bond formation (Scheme 13.23, route c). The 1,4-addition of (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP) **146** to (*E*)-alkenylcylohexyl sulfonates **145** in the presence of catalytic amounts of zinc bromide (ZnBr) gave in moderate to good yields and moderate diasteromeric excesses β-hydrazinocyclohexylsulfonates **147**[82] (Scheme 13.30, Table 13.4, entries 1–11). Epimers were separated by high-performance liquid chromatography (HPLC). The use of (*R*,*R*,*R*)-1-amino-2-(methoxymethyl)-1-azabicyclo[3.3.0]octane (RAMBO) instead of SAMP had a significant effect on the diastereomeric excesses, which increased from 50–60% up to 80–90% de. Posterior N–N bond cleavage utilizing BH_3–THF and direct protection with CbzCl yielded *N*-Cbz-protected β-amino-cyclohexyl sulfonates **149** in moderate to good yields and high enantiomeric excesses (Scheme 13.30, Table 13.4, entries 12–22).

13.7.2.4 Hydrolysis of β-Sultams

β-Sultams are the sulfonyl analogs of β-lactams, widely used in the amino acid chemistry. Analogous to β-lactams, cleavage of the N–S bond led to β-amino sulfonic acids (Scheme 13.23, route d).[83] Baldoli et al.[84] have reported the first stereoselective synthesis of β-sultams from

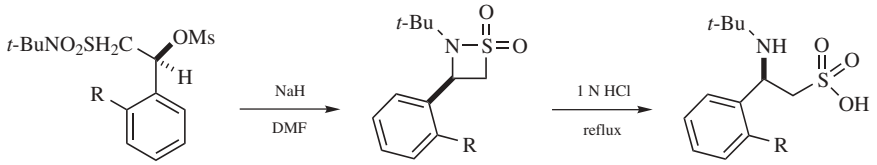


Scheme 13.30

sulfone derivatives **150** and have proved that these 3-substituted β-sultams are precursors of taurine analogs. Hydrolysis of β-sultams **151** with 1 N HCl afforded the corresponding optically pure β-amino sulfonic acid **152** (R = Cl, Scheme 13.31) in good yield.

TABLE 13.4 β-Amino Sulfonic Acids 147 and 149 Obtained by Michael Addition

Entry	Compound	R	Yield	de (%)
1	(*R*,*S*)-**147a**	Me	78	44 (≥96)
2	(*R*,*S*)-**147b**	Et	74	55 (≥96)
3	(*R*,*S*)-**147c**	*n*-Pr	73	58 (≥96)
4	(*R*,*S*)-**147d**	*i*-Pr	41	80 (≥96)
5	(*R*,*S*)-**147e**	$Ph(CH_2)_2$	66	60 (≥96)
6	(*S*,*R*,*R*,*R*)-**147f**	Me	77	64 (≥96)
7	(*S*,*R*,*R*,*R*)-**147g**	Et	85	77 (≥96)
8	(*S*,*R*,*R*,*R*)-**147h**	*n*-Pr	62	82 (≥96)
9	(*S*,*R*,*R*,*R*)-**147i**	*i*-Pr	44	90 (≥96)
10	(*S*,*R*,*R*,*R*)-**147j**	$Ph(CH_2)_2$	63	78 (≥96)
11	(*S*,*R*,*R*,*R*)-**147k**	*n*-Bu	65	80 (≥96)
12	(*R*)-**149a**	Me	68	≥96
13	(*R*)-**149b**	Et	53	≥96
14	(*R*)-**149c**	*n*-Pr	43	≥96
15	(*R*)-**149d**	*i*-Pr	52	≥96
16	(*R*)-**149e**	$Ph(CH_2)_2$	53	≥96
17	(*S*)-**149a**	Me	56	≥96
18	(*S*)-**149b**	Et	53	≥96
19	(*S*)-**149c**	*n*-Pr	38	≥96
20	(*S*)-**149d**	*i*-Pr	57	≥96
21	(*S*)-**149e**	$Ph(CH_2)_2$	56	≥96
22	(*S*)-**149f**	*n*-Bu	63	≥96



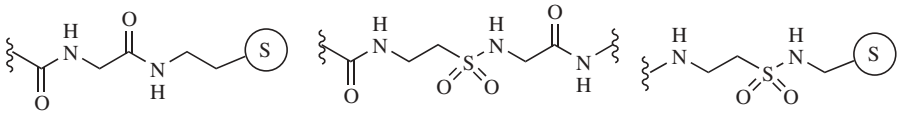
150 **151** **152**

Scheme 13.31

13.7.3 β-Sulfur Peptides: Foldamers

Despite the important biological application of peptides, their use as drugs is limited by the poor bioavailability and rapid enzymatic degradation in vivo. Therefore, there is a growing interest in the design and synthesis of nonnatural biopolymer scaffolds (carbamates, peptoids, ureas, sulfonamides, β-peptides, etc.) as modified peptides or peptidomimetics which present an improved stability against degradation by proteases[85] and affinities and specificities toward biological receptors. A sulfonamide N–H is more acidic (pK_a is approximately 11–12) and is therefore a stronger hydrogen bond donor than a carbamate or an amide N–H. Hydrogen-bonding acceptor scale is RCON $\approx$*t*-BuOCON > COOMe $\geq$ RSO_2N.[80a,86] The very poor acceptor ability of the sulfonamide group has been confirmed by recent theoretical studies.[87] X-rays indicate that the N–H–O=S=O hydrogen bond is much weaker than the N–H–O=C hydrogen bond.[88] Furthermore, the sulfonamido bond is more flexible than the amide bond and should show significant increase in polarity, enhanced metabolic stability, and structural similarity to the tetrahedral transition state involved in the amide bond enzymatic hydrolysis,[89] which is interesting for the development of catalytic antibodies and new drugs.[90]

To develop peptidosulfonamides stables against enzymatic hydrolysis, three types of peptide derivatives have been designed (Fig. 13.7). Depending on the position of sulfonamide moiety into the peptidic chain, different binding activities are observed. Replacement of the C-terminal amides by a sulfonamide moiety (ΨCH_2SO_2) (type I, Fig. 13.7) resulted in nearly equipotent compounds, but replacement of other amide bonds closer to the amino terminus (type II, Fig. 13.7) resulted in a decreased and complete loss of its inhibitory activity, as was monitored by an inhibition enzyme-linked immunosorbent assay (ELISA) for *anti*-β-endorphin monoclonal antibody.[81,91] On the other hand, substitution of an amide bond of the protease cleavage site by a sulfonamide moiety resulted in



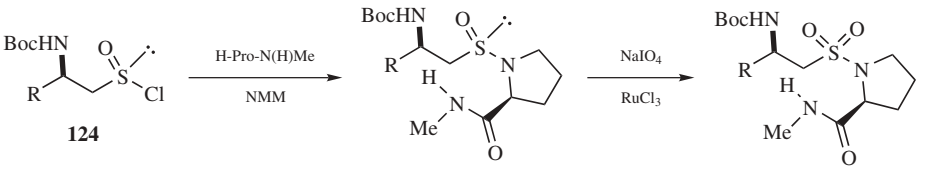
I **II** **III**

Figure 13.7

peptidosulfonamides, whose resistance to protease-catalyzed degradation suggests that they will have a similar stability with regard to degradation by proteases encountered in biological fluids.[80b,91,92]

The ability to efficiently assemble large synthetic oligomers provides an opportunity to generate unnatural polymers with defined secondary and tertiary structures. To designate these type of compounds, Borman and Gellman[93] introduced the concept of the *foldamer*. A "Foldamer," defined by Gellman,[94] is any polymer with a strong tendency to adopt a specific compact conformation, which indicates that its members have been shown to fold into defined three-dimensional structures similar to those of natural peptides. For a foldamer to favor a single tertiary structure, the molecule must be a heteropolymer (composed of two or more types of monomers). The class of peptides studied by Albert and Seebach[95] and Wang et al.[96] represents the most important class, but relatively little is known about pseudopeptides characterized by the presence of the sulfonamido bond.[72,91] β-Sulfonamidopeptides have a covalent framework that should be essential for the formation of well-defined folded structures by intramolecular hydrogen bonding; the repeating backbone structure contains both hydrogen bond donors (N–H) and hydrogen bond acceptors (C=O and S=O).

De Bont et al. have carried out a positional scan in which specific amide bonds in Leu-enkephalin were replaced by sulfonamide isosters.[91] Peptidosulfonamides **I** (Fig. 13.7) were prepared by a solid-phase strategy consisting of a reaction of a Boc or Fmoc-protected β-substituted aminoethane sulfonyl chloride with an amino acid or peptide attached to a solid support.[81] Analogously, the preparation of sulfonopeptides **II** (Fig. 13.7) was performed by the use of the same procedure: deprotection followed by coupling. The most simple aminosulfonic acid which can be incorporated into the sequence of sulfonamide-containing peptides is β-aminoethane sulfonic acid or taurine (Tau) via its sulfinyl chloride **124** (R = H).[72] Coupling of chlorides **124** (R = H) to H-Pro(N)HMe in the presence of 4-methylmorpholine as base led to the peptide sulfinamides **153** (R = H) (Scheme 13.32). Diastereomers isolated in equal amounts and oxidated with $RuCl_3/NaIO_4$ gave the corresponding sulfonamides **154**. This sulfonamide substitute connected to a proline **154** (R = H) does not present the cis–trans isomerism observed in the analog *N*-acetyl-β-alanyl-proline, which may influence the secondary structure of sulfonopeptide formed. Also, White and Paik designed β-sulfonopeptides as inhibitors of D-alanyl-D-alanine transpeptidases containing a taurine instead of a penultimate amino acid.[97] With this strategy it could be feasible to employ every

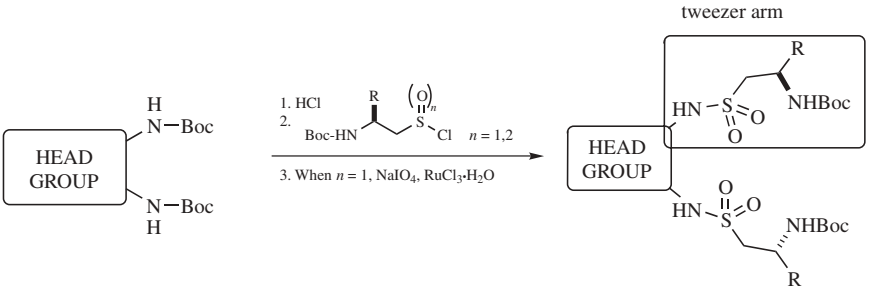


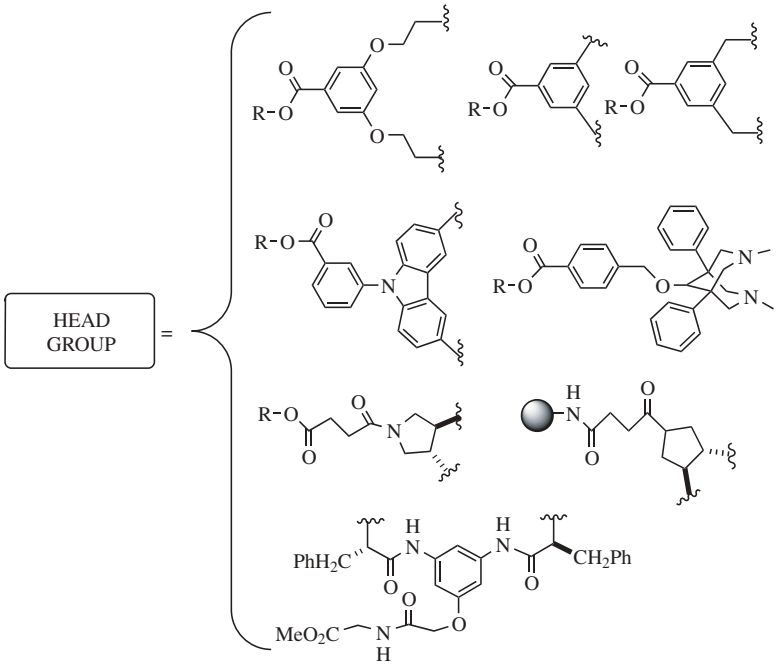
124 **153** **154**

Scheme 13.32

possible α-amino acid in the preparation of sulfinamide **153** or sulfonamide **154** transition-state analog containing peptides.[70,71]

This strategy has beeen used for the design of two-armed, or tweezer, receptors, a class of receptors for peptides. During the last decade several peptidosulfonamide-containing tweezerlike molecules have been shown to bind to a particular ligand for catalysis[68a]: amino acid residues[67b] and peptides.[67c] The tweezerlike synthetic receptor consists of two parts: a head group where two side arms are attached and tweezer arms consisting of sulfonamide peptides (Scheme 13.33).

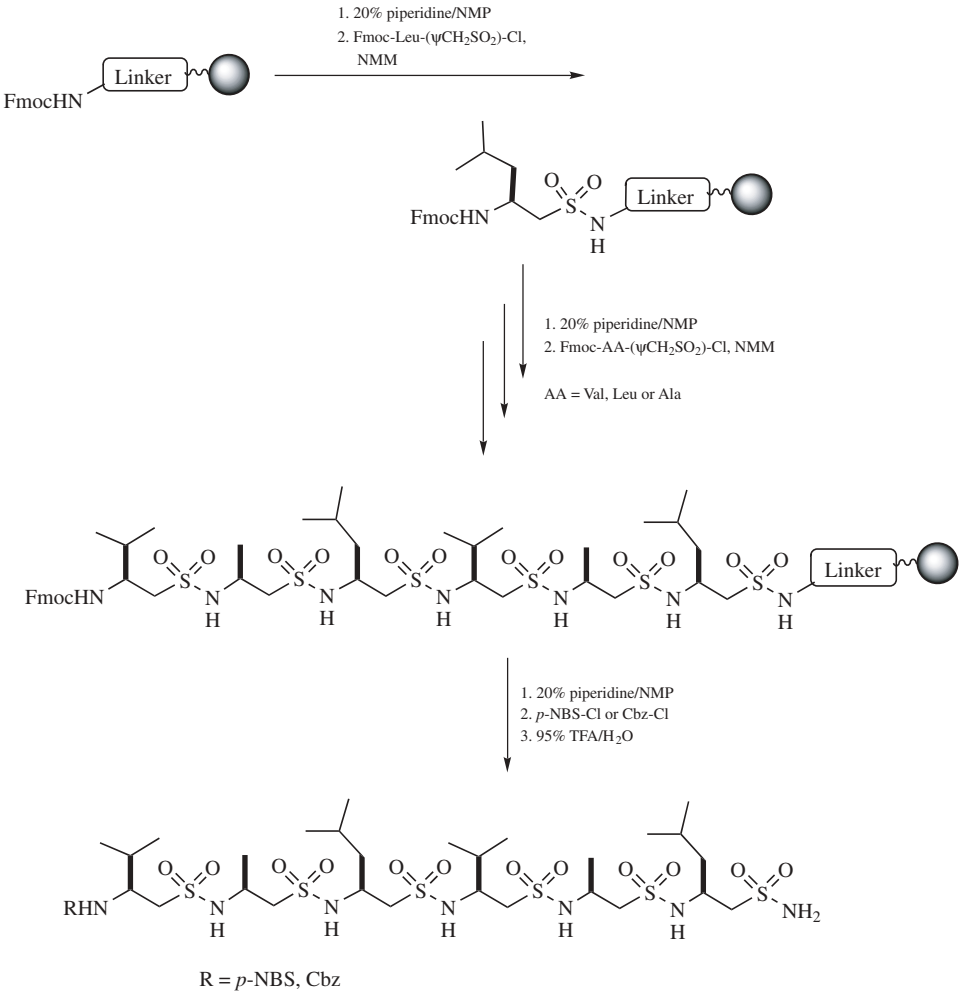




Scheme 13.33

The peptido sulfonamide arms were introduced into a head group through the treatment of the unprotected amino acid with sulfinylchloride in the presence of Et_3N followed by oxidation using $RuCl_3/NaIO_4$[67b] or directly coupling with sulfonyl chloride through a solution[68b] or solid-phase[68a,98] methodology.

Finally, oligopeptidosulfonamide foldamers of type **III** (Fig. 13.7) were also prepared to see if these large oligomers present secondary and tertiary structures similar to those of natural peptides. Taking advantage of solid-phase strategy, the synthesis of β-sulfonamidopeptides (Scheme 13.34) is possible via an iterative process.[80b] In this case computer modeling studies showed a strong tendency for β-sulfonopeptides to form well-defined folded structures via intramolecular hydrogen bonding. However, peptidosulfonamide oligomers consisting of six or nine



Scheme 13.34

residues prepared by Monnee et al.[69,99] for their study as a new class of foldamer did not show any indications of secondary-structure formation, even closely resembling β-peptides with respect to the number of atoms per residue, but a single β-aminoethane sulfonamide residue was capable of disordering the foldamer behavior of β-peptides and in the middle of a medium-sized β-peptide was practically detrimental and significantly reduced its helicity when present at the N-terminus.[100]

13.8 CONCLUSION

In summary, it is evident from the results presented in this chapter that different methodologies have been applied as effective tools for the construction of β-amino phosphonic acid derivatives with differing substitution patterns at the α-position and for the construction of β-amino sulfinic and sulfonic acid derivatives. Although the application of the nucleophilic addition of phosphites to *N*-protected α-aminoaldehydes has become a useful and versatile method for the synthesis of α-hydroxy-β-amino phosphonic acid derivatives, there appear to be few reports on the preparation of other α-substituted β-amino phosphonic acid derivatives. Therefore, it is reasonable to expect, in the near future, research into new methodologies for the preparation of asymmetric β-amino phosphonic acid derivatives bearing substitution patterns at the α-position. Some works have documented the utility of these compounds as intermediates for the synthesis of β-amino-α-substituted phosphonopeptides. Because β-amino-α-hydroxy phosphonopeptides are well-recognized key components for a variety of protease inhibitors, introduction of an aminophosphonate into the peptide molecule offers several structural possibilities. Although the most common are β-amino-α-substituted phosphonopeptides **76** containing a P-terminal aminophosphonate unit, no reports have described the synthesis of peptides containing a phosphonamidate bond **77** or a β-aminophosphonic acid unit **79**. We believe that the growing importance of enantiopure α-substituted β-amino phosphonic acid derivatives should stimulate further achievements in this area.

Sulfinic and sulfonic acid derivatives have proven to be potential building blocks in the preparation of peptido sulfonamide peptidomimetics, and the demonstrated versatility of the sulfonamide moiety as amide transition-state isostere opens up possibilities to investigate their behavior as a new class of foldamers. The extension of these chemistries to solid-phase synthesis and the preparation of combinatorial libraries will allow the construction of larger oligopeptidosulfonamide foldamers as well as of oligopeptidosulfonamides containing functionalized aminosulfonic acid residues with biological properties.

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CHAPTER 14

Stereoselective Synthesis of Fluorine-Containing β-Amino Acids

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14.1 INTRODUCTION

The synthesis and reactivity of 1,3-difunctionalized derivatives, especially those aspects related to the stereoselective synthesis of β-amino acids, represent active areas of investigation in organic chemistry.[1] The special value of these products comes from not only their potential therapeutic applications but also their use as valuable intermediates in the design and construction of novel molecules of biological and pharmacological interest.[2] In essence, β-amino acids are an important class of organic molecules appearing free in nature or as part of peptides or depsipeptides.[3] In contrast to their nonfluorinated derivatives, very little is known about the chemistry and biological activity of fluorine-containing β-amino acids.[4]

Considering the benefits of fluorine substitution of hydrogen in organic compounds, the development of new synthetic methodologies for preparing enantiomerically pure β-amino acids containing fluorine is of particular interest. Two main strategies have been used to synthesize these products, the direct fluorination strategy and the building block approach, with most of the described processes for the synthesis of fluorinated β-amino acids being based on the building block approach.

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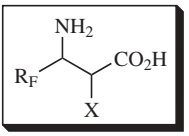


X = OH, SH, HaI

Figure 14.1

14.2 ACYCLIC FLUORINATED α,β-DISUBSTITUTED β-AMINO ACIDS

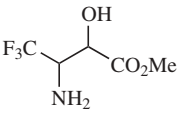
14.2.1 Acyclic α-Functionalized β-Fluoroalkyl β-Amino Acids

α-Functionalized β-fluoroalkyl β-amino acids, in particular the β-amino-α-hydroxy acid derivatives, represent crucial substructures of medicinally valuable molecules such as taxol[5] and the antitumoral agent bestatin (Fig. 14.1).[6] Despite the biomedicinal benefits of hydrogen replacement by fluorine in strategic positions of a molecule, little is known about the chemistry and biological activity of fluorine-containing α-functionalized β-amino acids, probably because there are few methods available for their preparation.

In 1996, for example, Abouabdellah et al. described the first successful preparation of methyl *syn*-3-trifluoromethyl isoserinate **1** (Fig. 14.2).[7]

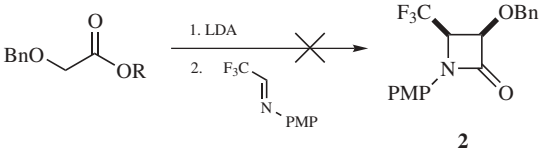
The strategy used in this case was based on opening the ring of the requisite *cis*-β-lactam **2**. To this end, the known cyclocondensation of an ester enolate with an imine was first explored, but this only yielded the starting imine and several ill-defined products (Scheme 14.1).

Another alternative consisted of a [2+2] ketene–imine cycloaddition. Although the ketenes derived from propionyl, butyryl, phenylacetyl, and phenylpropionyl



1

Figure 14.2

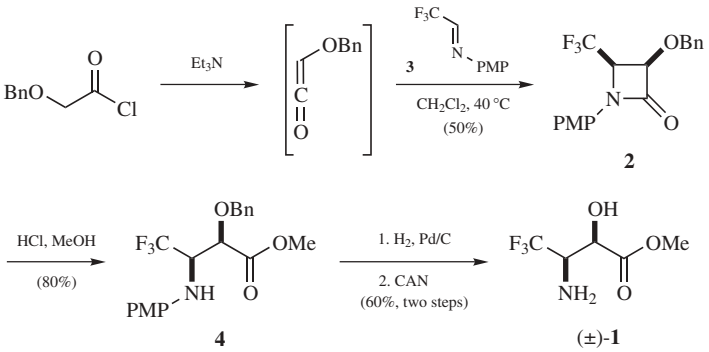


2

(PMP = *p*-Methoxyphenyl, LDA = lithium diisopropylamide)

Scheme 14.1

chlorides did not provide the desired products, the ketene generated in situ from α-benzyloxyacetyl chloride in the presence of triethylamine was successfully condensed with the fluorinated aldimine **3** at 40°C in dichloromethane to selectively provide the racemic *cis*-β-lactam **2** in 50% yield (Scheme 14.2).



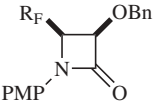
Scheme 14.2

The acidic methanolysis of **2** led to the α-benzyloxy amino ester **4** in 80% yield. Finally, the cleavage of the benzyl group by means of hydrogenolysis with Pd/C as catalyst followed by removal of the PMP with ceric ammonium nitrate (CAN) gave the desired racemic CF_3–isoserine ester **1** in a yield of 60% for the two deprotection steps combined.

This method was extended to the preparation of other fluoroalkyl β-lactams ($R_F = CF_3$, CF_2H, CF_2Cl); the preparation of chiral nonracemic β-lactams and isoserinates was also explored.

As before, the cycloaddition of a ketene derived from α-benzyloxyacetyl chloride and fluorinated aldimines afforded the corresponding β-lactams **2** in a stereoselective manner with yields ranging from 55 to 72%, depending on the nature of R_F (Fig. 14.3).

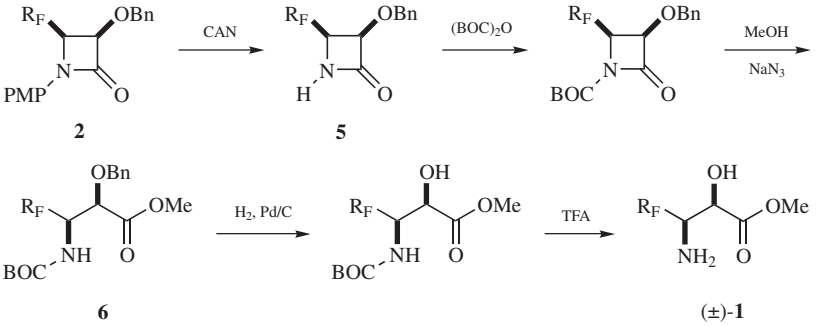
The transformation of the β-lactams into isoserinate was accomplished in several steps. The acid-catalyzed ring-opening methanolysis proved to be very slow and not reproducible. For that reason, these authors chose to remove the PMP group first treating compounds **2** with CAN to yield azetidinones **5**. The reaction was carefully



2a $R_F = CF_3$ (65%)
2b $R_F = CF_2H$ (72%)
2c $R_F = CF_2Cl$ (55%)

Figure 14.3

monitored and stopped as soon as the starting material had disappeared, as azetidinones **2** degraded rapidly in the presence of an excess of CAN. The resulting azetidinones were first BOC protected, after which a sodium azide–catalyzed ring-opening reaction caused by methanol provided esters **6**. Debenzylation through hydrogenolysis on Pd/C followed by BOC cleavage led to the isoserinates **1** (Scheme 14.3).



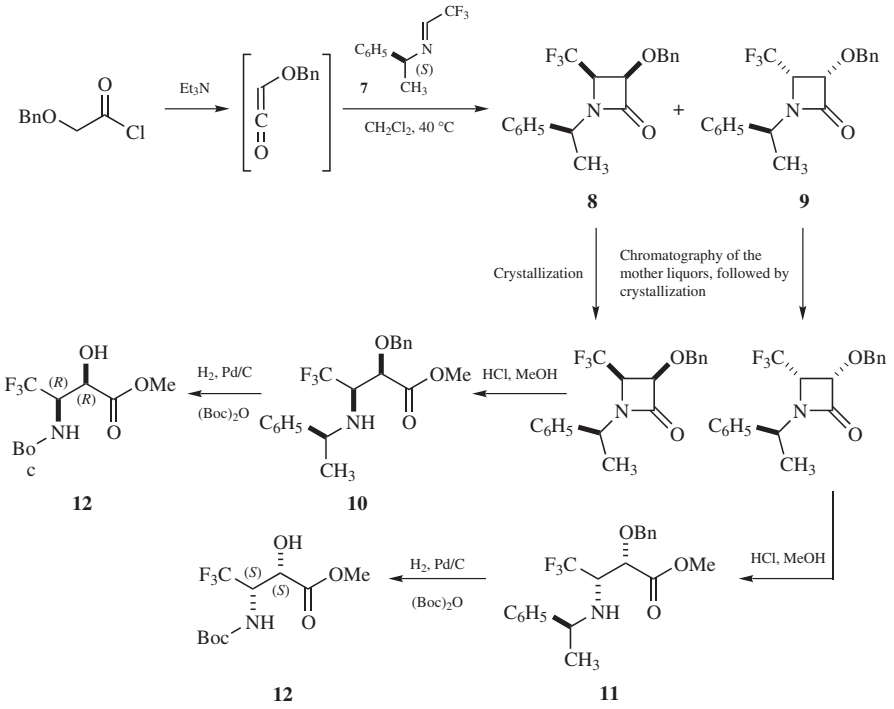
TFA = trifluoroacetic acid

Scheme 14.3

To prepare chiral nonracemic azetidinones, the authors first attempted the use of the lithium ester enolate–imine cyclocondensation protocol. The yields, however, were disappointingly low. They then tried the [2+2] ketene–imine cycloaddition strategy once more, examining the reaction with the chiral imine **7**, which had been prepared from the trifluoroacetaldehyde hemiacetal and (*S*)-phenethylamine. The cycloaddition reaction afforded a mixture of *cis*-azetidinones **8** and **9** in 90% yield, together with only 5% of the *trans*-azetidinone. While the chirality transfer was low (only 15% de), the diastereomers were easily separated by means of crystallization followed by column chromatography on silica gel. Thus, stereoisomer **8** was obtained with excellent diastereomeric purity (>99%), while **9** was isolated of 95% diastereomeric purity. The azetidinones **8** and **9** easily underwent acid-catalyzed ring opening by means of methanolysis to yield the isoserinates **10** and **11**. Finally, a catalytic hydrogenolysis in the presence of $(BOC)_2O$ provided the two nonracemic *N*-BOC isoserinates **12** (*R,R*) and (*S,S*), which are new fluoro analogs of the C-13 side-chain taxoids (Scheme 14.4).

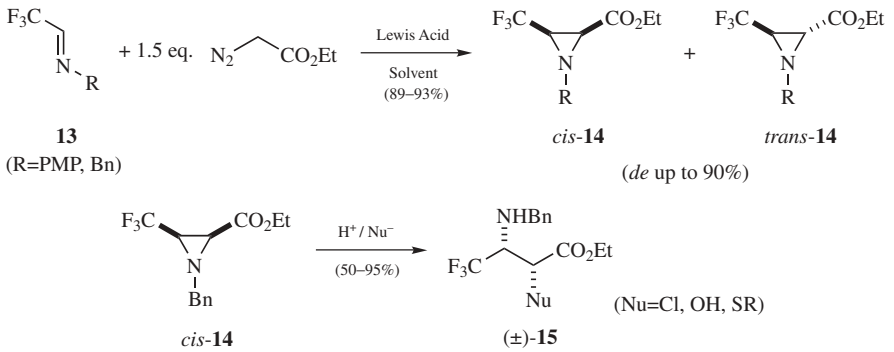
Aziridine-2-carboxylates are potentially useful synthetic precursors of nonproteogenic α- and β-amino acids, which are important building blocks for enzyme inhibitors. In this context, the same authors have recently reported a new strategy for the synthesis of these compounds based on the reaction of ethyl diazoacetate with CF_3–imines under Lewis acid catalysis followed by ring opening of aziridine intermediates with different heteronucleophiles.[8]

When the imines **13** were treated with 1.5 eq. of ethyl diazoacetate with 10% mol. eq. of a Lewis acid in various solvents and at different temperatures, the corresponding aziridines **14** were obtained in variable yields. The best results

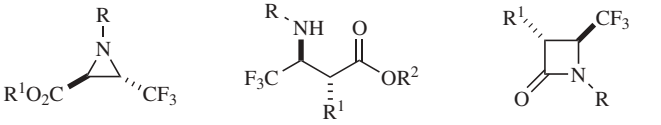


Scheme 14.4

(90% de for compounds **14**) were obtained under $BF_3 \cdot Et_2O$ catalysis and with ether as solvent. These aziridines (i.e., *cis*-**14**) underwent a regio- and diastereoselective ring-opening reaction upon treatment with various heteronucleophiles (e.g., HCl, CF_3CO_2H, RSH/CF_3SO_3H) to afford racemic α-functionalized-β-amino esters **15**. Of particular interest within this group of compounds are the novel trifluoromethyl-α-sulfide-β-amino esters (Scheme 14.5).



Scheme 14.5



16
R = H, Bn
R^1 = H, Me, Et

17
R = H, Bn, $COCF_3$
R^1 = H, Cl, Br, OH
R^2 = Me, Et

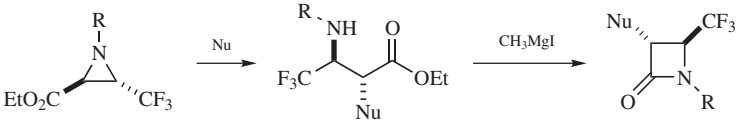
18
R = H, Bn
R^1 = H, OTBDMS

Figure 14.4

The ring opening occurs with complete inversion of the configuration at C-2 and provides a simple syn diastereomer despite the acidic catalysis. In the nonfluorinated series, C-3 regioselectivity was observed for the ring opening of 3-alkyl-aziridine-2-carboxylic esters. In contrast, in the case of 3-CF_3–aziridine-2-carboxylic ester, the nucleophilic attack occurred in C-2, which indicates that the regioselectivity of the ring opening is governed by the CF_3 group rather than the ester group.

Before the publication of these results, Davoli et al.[9] had already described the regio- and stereoselective nucleophilic ring opening of *trans*-1-benzyl-3-trifluoromethyl-2-ethoxycarbonyl aziridines **16** to afford chiral β-amino acids, such as *anti*-α-halo-β-trifluoromethyl-β-alanine **17** (R^1 = Cl, Br), β-trifluoromethyl-β-alanine **17** (R^1 = H), *anti*-3-(trifluromethyl)isoserinates **17** (R^1 = OH), as well as the synthesis of the fluorinated *trans*-β-lactams **18** (Fig. 14.4).

Racemic aziridine **16** was resolved by means of enzymatic hydrolysis with *Candida antarctica* lipase as catalyst. The ester function was hydrolyzed with high enantioselectivity (ee > 99%). The ring-opening reactions on the aziridines (−)-**16** were performed with Brønsted acids such as HCl, $MgBr_2$ in H_2SO_4, and TFA. The ring-opening reaction proceeded with high regio- and stereoselectivity: The nucleophilic attack occurred only at C-2 of the aziridine to afford only one regioisomer, a β-amino ester **17**, in a single anti diastereomeric form (Scheme 14.6).



(−)-**16**
(R = H, Bn)

17

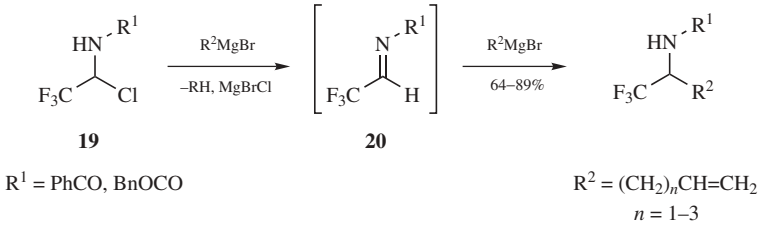
18

Scheme 14.6

The β-lactams **18** were prepared according to a well-known procedure that involves a Grignard-mediated intramolecular cyclization. When Nu = OH, it was necessary to protect this group as a TBDMS ether with TBDMSCl in

dichloromethane in the presence of DMAP. Since the optically active starting aziridines are easily prepared and enzymatically resolved, this method provides a convenient entry into the stereoselective preparation of optically active anti-α-functionalized β-trifluoromethyl β-amino acids and β-lactams (Scheme 14.6).

Sergeeva et al. described a new synthesis of ω-trifluoromethyl ω-amino acids from *N*-acyl-1-chloro-2,2,2-trifluoroethylamines **19**.[10] Compounds **19**, in contrast to the acylimines of trifluoroacetaldehyde, which polymerize easily at high temperatures, are reputed to be relatively stable crystalline compounds, easy to handle, and easily stored for months at low temperatures as long as there is no moisture. For that reason, compounds **19** were generated in situ. The amino acid backbone was built by reacting Grignard reagents of the type $CH_2{=}CH(CH_2)_n$ MgBr, where $n = 1, 2, 3$, with **19**. Since many branches and linear bromoalkenes are readily available, this method provides access to a variety of ω-trifluoromethyl ω-amino acids with a variable framework. Two equivalents of the Grignard reagent are necessary for the reaction, as one is used in the generation of the acylimines **20** from **19** (Scheme 14.7).



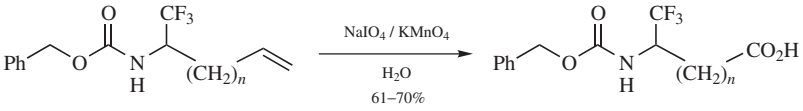
19 **20**

R^1 = PhCO, BnOCO

$R^2 = (CH_2)_nCH{=}CH_2$, n = 1–3

Scheme 14.7

In a second step, standard oxidation methods were used to transform the C=C double bond into a carboxyl group to give *N*-protected β-trifluoromethyl β-amino ($n = 1$), γ-trifluoromethyl γ-amino ($n = 2$), and δ-trifluoromethyl δ-amino acids ($n = 3$) **21** (Scheme 14.8).

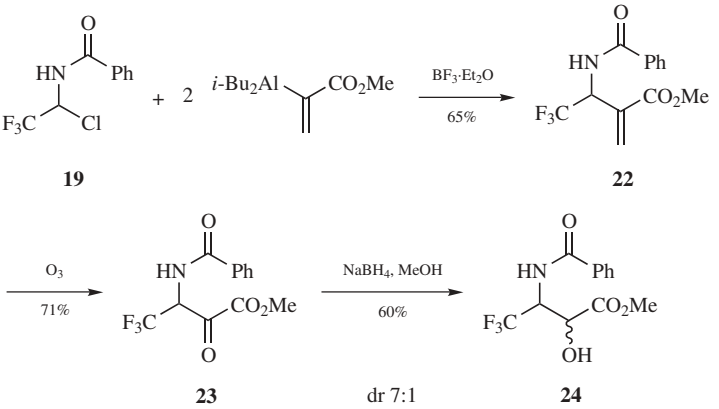


n = 1–3 **21**

Scheme 14.8

Another application for compounds **19** consists of reacting them with two equivalents of an [α-(alkoxycarbonyl)vinyl]diisobutylaluminum in the presence of $BF_3 \cdot Et_2O$ to give the addition compound **22**. This reaction thus permits the introduction of additional functional groups in the α-position. By way of example, compound **22** has been treated with ozone to prepare the α-keto ester **23**, which was

then reduced to the α-hydroxy ester methyl 3-(*N*-benzoyl)amino-4,4,4-trifluoro-2-hydroxy butanoate **24** as a mixture of diastereomers in a ratio of 7 : 1 (Scheme 14.9). L-4-Fluorothreonine, produced by *Streptomyces cattleya*, is one of the few examples of naturally occurring organofluorine compounds.



Scheme 14.9

The proposed stereochemistry of the main diastereomer is based on NOE experiments performed on a racemic mixture of the five-membered ring system **25**, obtained by reaction with triphosgene. These NOE data unequivocally indicate a cis configuration for **25**; consequently, the main product **24** has an anti configuration (Fig. 14.5).

In 1998, Uneyama et al. reported a similarly efficient and novel strategy for the synthesis of α-hydroxy-β-imino-γ-fluorinated esters **26** using intramolecular Wittig-type rearrangement of imino ethers **27**.[11] These authors went on to apply their approach successfully to the preparation of racemic *anti*-β-trifluoromethyl isoserine derivatives **28** (Fig. 14.6).

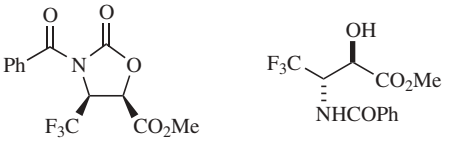


Figure 14.5

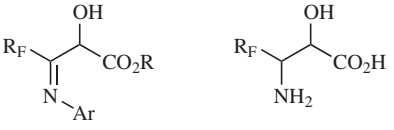
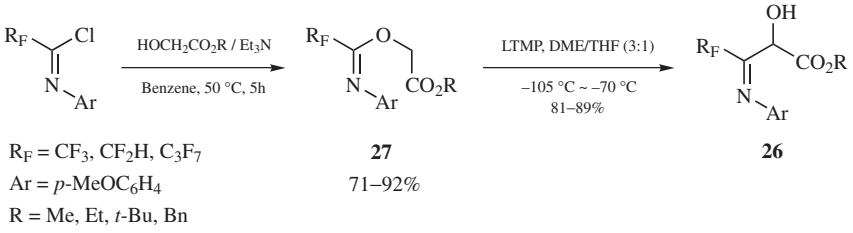


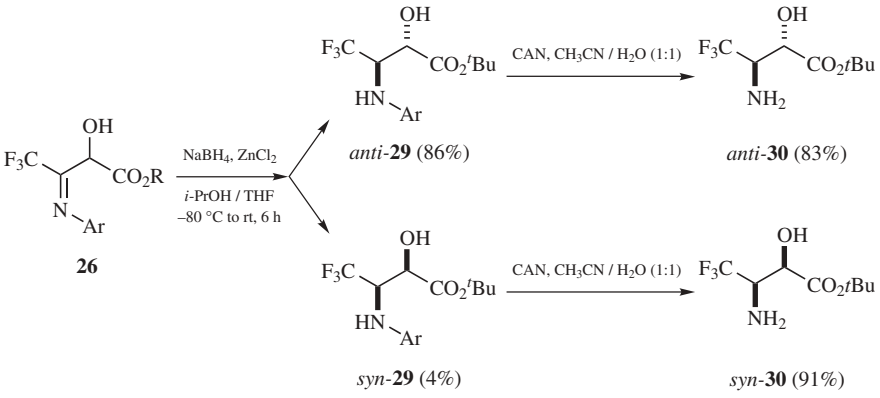
Figure 14.6

The imino ethers **27** were prepared from the fluorinated imidoyl chlorides with commercially available glycolate compounds under basic conditions in good yields and then converted into **26** by means of a lithium 2,2,6,6-tetramethylpiperidine (LTMP)–catalyzed intramolecular addition–elimination reaction. The yields resulting from the use of the base were on average 10% higher than those obtained when LDA was used. Several esters, for example, methyl, ethyl, benzyl, and *t*-butyl, were prepared in this way in yields ranging from 81% to 89% (Scheme 14.10).



Scheme 14.10

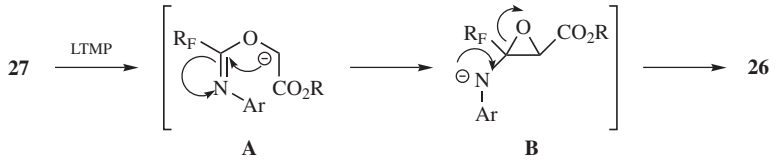
The diastereoselective reduction of the imine esters **26** with $NaBH_4$–$ZnCl_2$ in isopropanol–tetrahydrofuran (THF) (1 : 1) predominantly afforded the corresponding anti products. The two diastereomers **29** were separated with column chromatography to provide pure anti and syn products in 86 and 4% isolated yields, respectively. Finally, amine deprotection with CAN in acetonitrile–water afforded the final products **30** in good yields (Scheme 14.11). These compounds are direct precursors to the important α-hydroxy-β-amino acids **28**.



Scheme 14.11

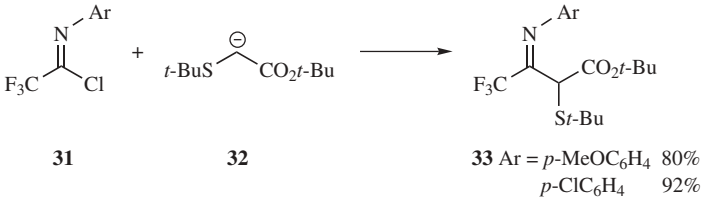
The authors provide a possible explanation for the rearrangement that transforms compounds **27** into **26**, namely that the LTMP-generated carbanion intermediate (**A**) of the imino ether may undergo a nucleophilic attack to the electrophilic imino carbon to form the epoxy intermediates (**B**). Subsequent regeneration

of the imino bond and a ring-opening reaction of the epoxide moiety would lead to the formation of the α-hydroxy-β-imino esters **26** after work-up (Scheme 14.12).



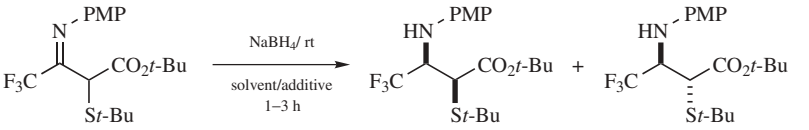
Scheme 14.12

Several well-known amino acid drugs (i.e., Captopril and its trifluoromethylated analog) contain a thiol group. With this in mind and in light of the important biological activity of isoserine derivatives, the synthesis of the corresponding isocysteine is of significant interest, especially in order to examine its biological activity. Thus, Okhura et al. succeeded in the synthesis of both diastereomers of *S-tert*-butyl-β-(trifluoromethyl)isocysteine in a stereoselective manner[12] by coupling fluorinated imidoyl chloride **31** with the enolate **32** to provide β-imino esters **33** in good yields. To suppress the desulfurination during the Wittig-type rearrangement, *S-tert*-butyl protection of the sulfur moiety was necessary[13] (Scheme 14.13).



Scheme 14.13

The conversion of compounds **33** into the corresponding fluorinated β-amino acid diastereomers *syn*- and *anti*-**34** was achieved by means of stereocontrolled reduction with hydride via the chelated intermediate and the nonchelated Felkin–Ahn intermediate, respectively. For this purpose, $NaBH_4$ in the presence of either $ZnBr_2$ or ZnI_2 and CH_2Cl_2 as solvent led to the preferential reduction of the imino moiety, affording the syn product exclusively. Stopping the reaction when approximately 20% of the starting material was still present was deemed convenient, as prolonged reaction times led to the appearance of a certain quantity of alcohol arising from the ester group reduction. In contrast, reduction of compounds **33** with $NaBH_4$ in a solvent such as di(ethylene glycol) dimethyl ether (DGDE)/THF that traps sodium ions to generate naked borohydride gave a mixture of both diastereoisomers, with the anti being predominant, in a ratio of 11 : 89 syn/anti



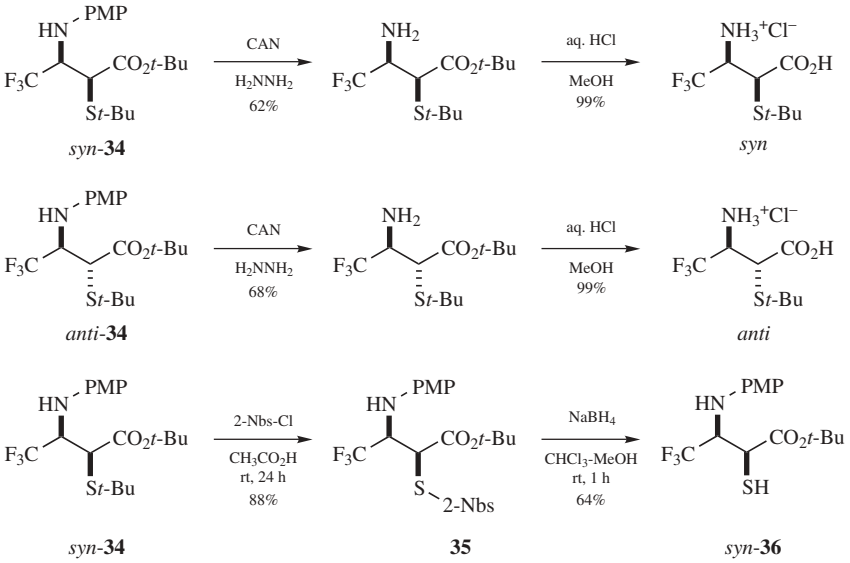
33 *syn*-**34** *anti*-**34**

solv	additive	*syn/anti*	yield(%)
CH_2Cl_2	$ZnBr_2$	>99/1	70
CH_2Cl_2	ZnI_2	>99/1	50
THF	DGDE	11/89	81

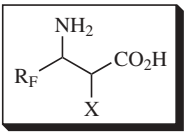
Scheme 14.14

(Scheme 14.14). The configurations of the *syn*- and *anti*-β-amino esters were confirmed by means of X-ray crystallographic analysis.

Both diastereomers were easily deprotected by first removing the PMP group by means of CAN oxidation followed by *t*-butyl group removal through acid-catalyzed hydrolysis. In addition, the deprotection of the *S-tert*-butyl group was achieved in two steps. First, the C–S bond was cleaved with *o*-nitrobenzenesulfenyl chloride to give the unsymmetrical disulfide **35** in 88% yield. This compound was then reduced with $NaBH_4$ to provide the thiol **36** in 64% yield (Scheme 14.15).



Scheme 14.15



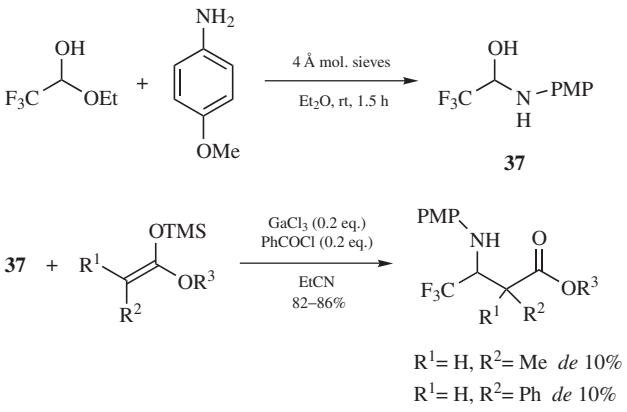
X = Alkyl, Aryl

Figure 14.7

14.2.2 Acyclic α-Alkyl-β-fluoroalkyl β-Amino Acids

One especially attractive class of β-amino acids is the α-methyl derivatives. Examples of these (e.g., 2-methyl-3-amino pentanoic acid) have been identified as framework components for several biologically active cyclic peptides which have been isolated from marine organisms and which have antifungal, antineoplasic, or cytotoxic properties.[14] Although useful synthetic approaches have already been reported for the synthesis of α-substituted β-amino acids, descriptions of methods for preparing α-substituted β-(fluoroalkyl) β-amino acids are particularly rare (Fig. 14.7).

In 1993, Kaneko et al. reported the first example of a racemic α-alkyl β-(difluoromethyl)-β-amino acid synthesis which entailed the condensation of difluoroacetaldimine with enol silyl ethers.[15] More recently, Takaya et al.[16] described a racemic synthesis of an α-methyl and α-phenyl β-trifluoromethyl-β-amino ester involving a Mannich-type reaction of silyl enolates and an *N*,*O*-hemiacetal, derived from the commercially available trifluoroacetaldehyde ethyl hemiacetal and *p*-anisidine, in the presence of $GaCl_3$ as catalyst. The process occurs with excellent yields but very low distereoselectivity (10%) (Scheme 14.16). The authors found that the *N*,*O*-hemiacetal **37**, which is easily prepared by simply mixing

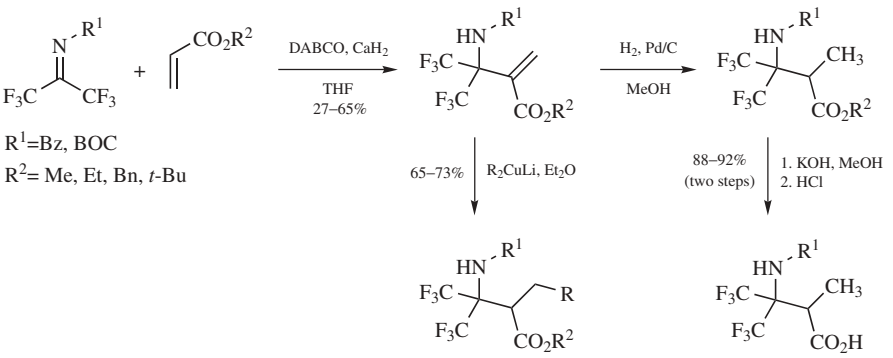


Scheme 14.16

trifluoroacetaldehyde ethyl hemiacetal and an amine, is indefinitely stable at low temperatures. The Mannich-type reaction with *N*,*O*-hemiacetal proceeded smoothly under the influence of $GaCl_3$ to give α-substituted β-trifluoromethyl β-amino esters in excellent yields. The use of $GaCl_3$ provided much higher yields than the other Lewis acids used, including $TiCl_4$, $InCl_3$, $BF_3 \cdot Et_2O$, and ZnI_2. The PMP group was easily removed with CAN in aqueous acetonitrile to afford good yields.

The configuration of the major diastereomer was not determined. It was possible to reduce the amount of $GaCl_3$ used when it was combined in equimolecular amount with PhCOCl (0.2 eq. of each). The yields were slightly lower and the diastereomeric ratios similar to those obtained when the reaction was performed in the absence of PhCOCl.

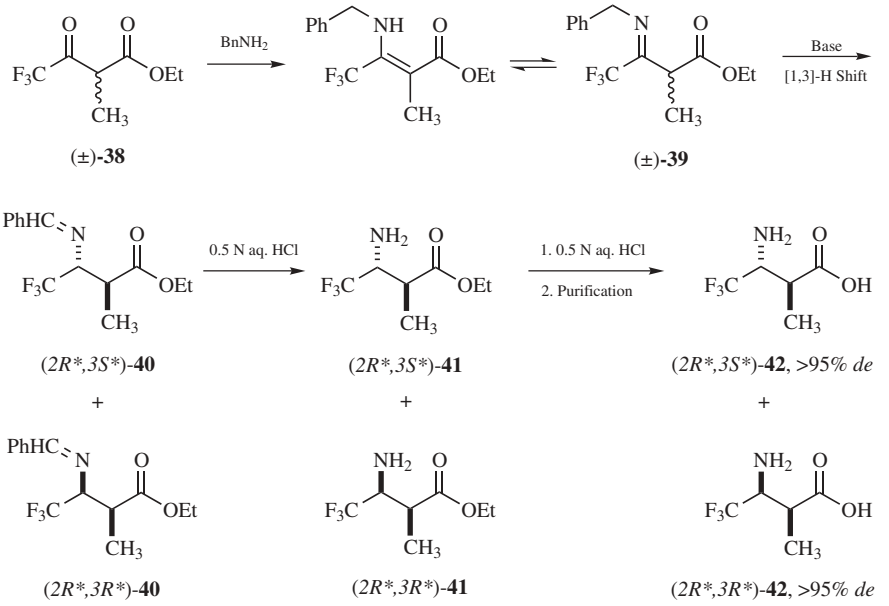
Sergeeva et al.[17] reported a new and efficient two-step synthesis of racemic α-alkyl β,β-bis(trifluoromethyl) β-amino acids. The key step is a Morita–Baylis–Hillman (MBH) reaction of hexafluoroacetone imines with acrylic esters followed by functionalization of the double bond by hydrogenation or cuprate addition (Scheme 14.17).



Scheme 14.17

These β-amino acids have been used for preparing several dipeptides, albeit in low chemical yields (below 30%).

In 1998, Soloshonok et al. reported an elegant chemoenzymatic approach to chiral nonracemic α-alkyl β-fluoralkyl β-amino acids, in particular to α-methyl-β-(trifluoromethyl)-β-alanine derivatives.[18] This strategy relies on a diastereoselective biomimetic transamination of α-alkyl β-keto carboxylic esters to generate the required fluorinated α-methyl β-amino moiety followed by enantioselective biocatalytic resolution in the presence of penicillin acylase (PA). The synthesis begins with a base-catalyzed [1,3]-proton shift reaction (PSR) of β-imino esters **39**, which can be easily prepared by having the commercially available β-keto ester **38** undergo condensation with benzyl amine. Using the PSR under the proper reaction conditions and in the presence of various bases such as Et_3N, Et_2NH, DABCO, DBN, and DBU, it is possible to obtain compounds **40** as a mixture of diastereomers (Scheme 14.18). The PSR provides an intramolecular reduction–oxidation



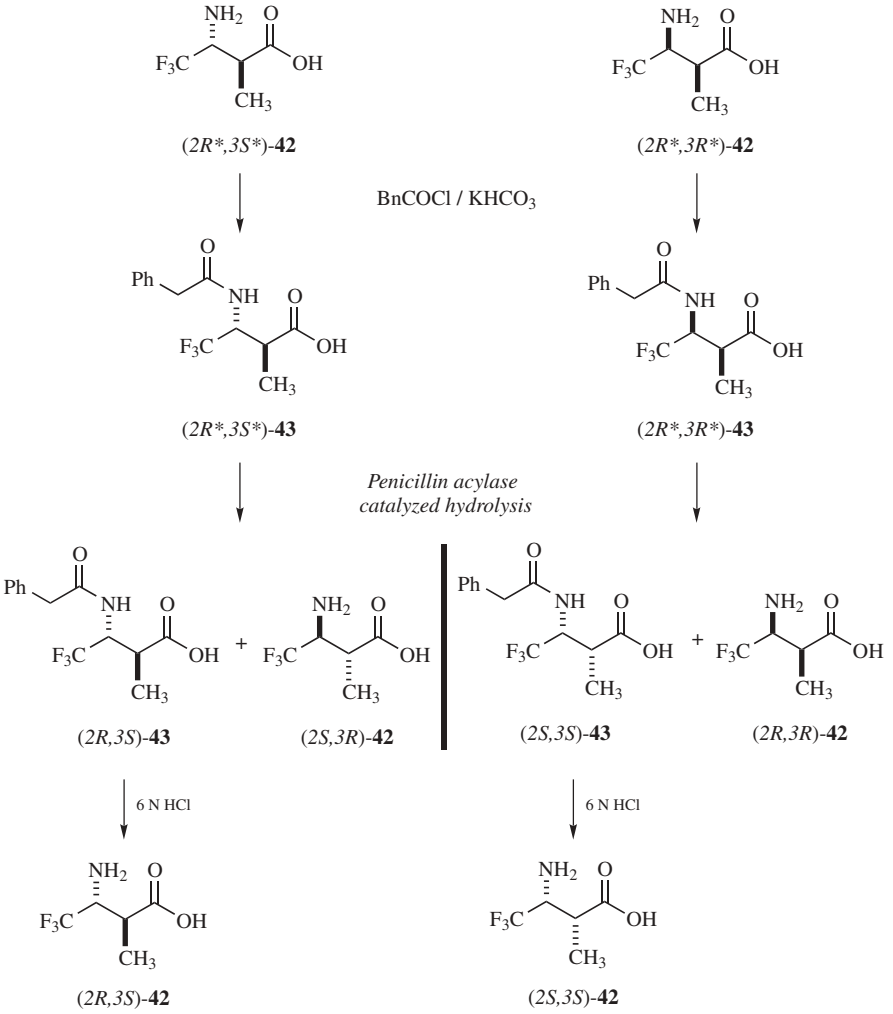
Scheme 14.18

process via biomimetic transposition of the imine functionality. The isomerization occurs with a high conversion grade and the diastereoselectivity of the reaction can be controlled to a certain extent by carefully choosing the base: while Et_3N and Et_2NH favored the syn diastereomer (*2R**,*3S**) with de 35–40%, the bases DBN and DBU preferentially gave the anti diastereomer (*2R**,*3R**) (de 35–40%). DABCO was the least stereoselective, with only 9% de for the syn diastereomer.

Diastereomers **40** are then mildly hydrolyzed with diluted aqueous acid to yield β-amino esters **41**, which in turn can be hydrolyzed with a higher acid concentration to furnish compounds **42**. Mixtures of the amino acids (*2R**,*3S**)-**42** and (*2R**,*3R**)-**42**, with approximately 40% de of each compound, were successfully crystallized from acetone–ether solutions to afford amino acids (*2R**,*3S**)-**42** and (*2R**,*3R**)-**42** with >95% diastereomeric purity.

Preparation of all four enantiomeriaclly pure optical isomers of **42** was accomplished by means of biocatalytic resolution. The enzymatic resolution of these amino acids was achieved on their *N*-phenylacetyl-protected derivatives **43**, which were prepared in high yields via a Schotten–Baumann reaction of their respective water–acetone solutions with phenylacetyl chloride in the presence of potassium bicarbonate. In both cases, when these compounds were subjected to hydrolysis separately in the presence of PA from *Escherichia coli*, only one of the enantiomers reacted in each case, which allowed for easy separation from the unreacted starting enantiomer. Thus, the optically pure enantiomers (>95% ee)

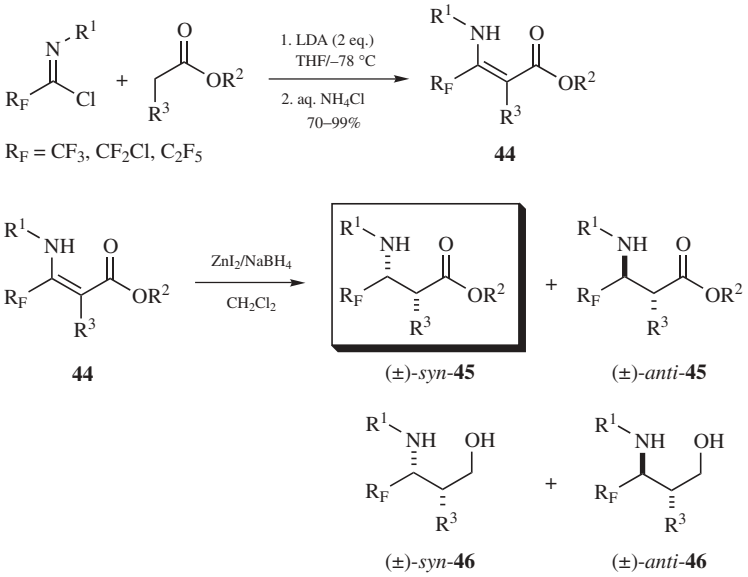
(*2S*,*3R*)-**42** and (*2R*,*3R*)-**42** were prepared separately. The enantiomers that had not been affected by the enzyme were then easily hydrolyzed with 6 N aqueous HCl to furnish the fluorinated β-amino acids (*2R*,*3S*)-**42** and (*2S*,*3S*)-**42** (Scheme 14.19).



Scheme 14.19

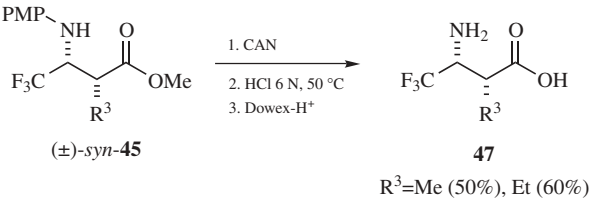
Another simple and attractive route to enantiopure β-amino acids involves the chemo- and stereoselective reduction of chiral nonracemic β-enamino ester derivatives. However, although these compounds are well-known intermediates in organic synthesis, very few examples have been reported in connection with this strategy for preparing enantiopure fluorinated β-amino acids. In fact, only two reports regarding the synthesis of *racemic* α-fluorinated β-amino acids whose key step involves the use of reductive methods have been described.[11,19] One exception

is Fustero et al.'s description in 1999 of an efficient new two-step procedure for the diastereoselective synthesis of racemic and chiral nonracemic *syn*-α-alkyl-β-fluoroalkyl-β-amino esters **45**.[20] This approach is based on the chemical reduction of fluorinated β-enamino esters **44**, which can be easily prepared from imidoyl chlorides and lithium ester enolates, with $NaBH_4/ZnX_2$ in a nonchelated aprotic medium as reducing agent. The process takes place with high syn diastereoselectivity (up to 98% de) and in 30–92% yield (Scheme 14.20).



Scheme 14.20

The best results were achieved by using 3 eq. of anhydrous ZnI_2 as the chelating agent and $NaBH_4$ as reducing agent in dry dichloromethane as solvent. Other zinc salts such as $ZnBr_2$ and $ZnCl_2$ proved to be less effective. The use of $Zn(BH_4)_2$ as reducing agent instead of $ZnI_2/NaBH_4$ yielded slightly lower diastereomeric ratios and chemical yields. On some occasions, especially when higher temperatures were used or with long reaction times, the reduction of the ester to the corresponding alcohol was observed as a side reaction. When this occurred, the alcohol had a syn configuration almost exclusively (98% de). Compounds **45** and **46** were easily



Scheme 14.21

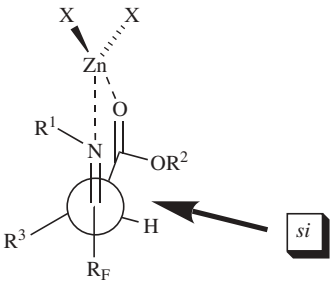


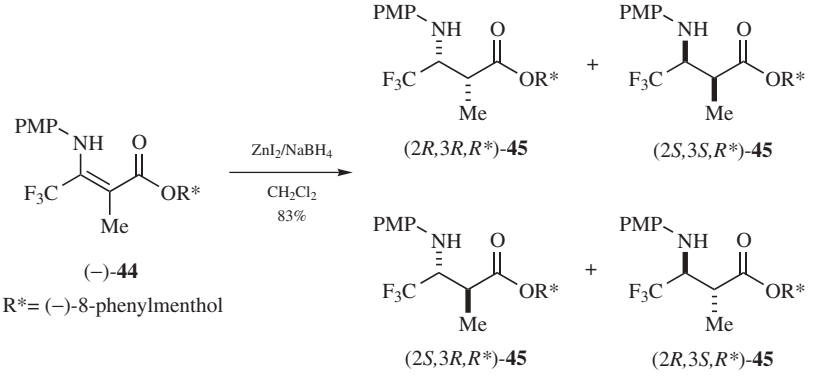
Figure 14.8

separated with column chromatography, and the PMP protecting group was easily removed in high yield with CAN in aqueous acetonitrile. Isolation and purification of the free racemic β-amino acids **47** were achieved by means of acidic hydrolysis (HCl 6 N) followed by ion exchange chromatography (Dowex-50, H^+ form) (Scheme 14.21).

A metal-chelated six-membered model has been suggested to explain the stereochemical outcome of the reduction reaction. The hydride thus attacks the imino double bond from the opposite side (*si* face) to the α-alkyl group (*ul*-1,2-addition) (Fig. 14.8).

These optimal reduction conditions were also used for the synthesis of chiral nonracemic γ-fluorinated β-enamino esters (−)-**45**. For this purpose, several chiral α-alkyl-γ-fluorinated β-enamino esters bearing the chiral auxiliary group at the nitrogen atom [e.g., (*S*)-methyl benzyl amine] and in the ester moiety, for example (−)-menthol, (−)-8-phenylmenthol, (−)-8-(2-naphthyl)menthol, and (−)-8- (4-iodo)-phenylmenthol, were examined. The best results in regard to the diastereoselective reduction of chiral β-enamino esters **44** occurred when (−)-8-phenylmenthol was used as a chiral auxiliary. The process took place in high yields (75–90%) and with moderate to good diastereoselectivity.[21]

Since in this case two new stereogenic centers are created at C-2 and C-3, four diastereomers are possible (Scheme 14.22). The nuclear magnetic resonance (NMR)



Scheme 14.22

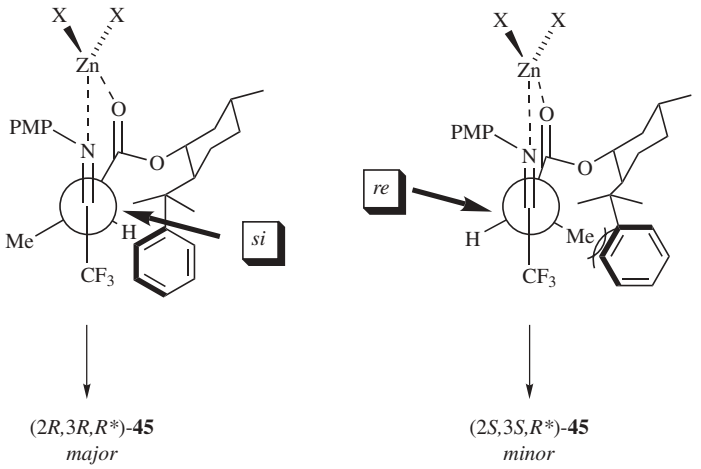
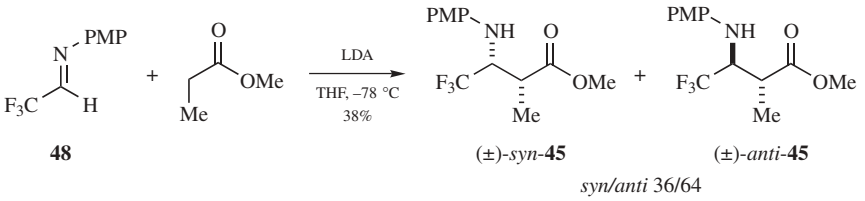


Figure 14.9

analysis from the crude reduction mixture, however, indicated the presence of only three compounds in a ratio of 78 : 18 : 4. The syn diastereomers (2*R*,3*R*,*R**)-**45** and (2*S*,3*S*,*R**)-**45** (overall 96% of the crude reaction mixture) were isolated and purified as white solids by means of silica gel flash chromatography.

One explanation for the stereochemical outcome of the reduction of chiral β-enamino esters **44** could involve the participation of two diastereomeric chelate models similar to the one described above but in which the hydride attack is now conditioned by the presence of the 8-phenyl group of the chiral auxiliary (1,5-asymmetric induction) (Fig. 14.9).

An alternative one-step method for the preparation of the compounds **45** involving the Mannich-like addition of lithium enolates of esters to trifluoromethyl imines **48** was also explored. Thus, treatment of imine with lithium enolate of methyl propionate led to a racemic mixture of β-amino esters **45** in low yield and with low anti diastereoselectivity (de 28%) (Scheme 14.23). Using a chiral ester did not improve the yield or diastereoselectivity. In light of these results, then, the procedure of choice for the diastereoselective synthesis of fluorinated β-amino esters seems to be the reduction of β-enamino esters **44**.

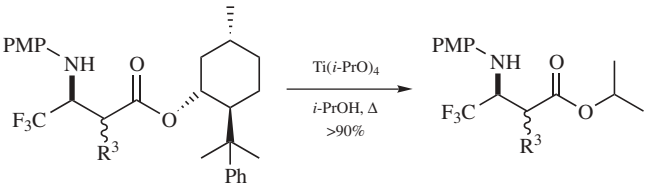


48 (±)-*syn*-**45** (±)-*anti*-**45**

syn/anti 36/64

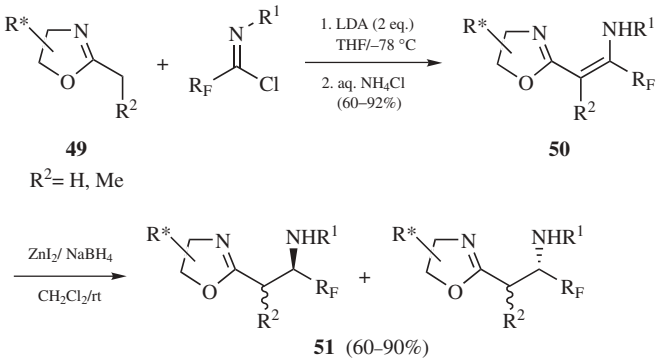
Scheme 14.23

Removal of the chiral auxiliary was carried out by means of Ti(IV) isopropoxide-catalyzed transesterification to isopropyl esters (Scheme 14.24).[22] This methodology has also been applied to fluorinated α-unsubstituted β-amino esters with similar results.



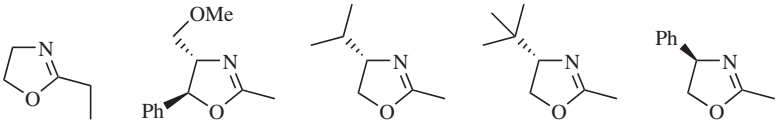
Scheme 14.24

These same authors have also developed an alternative and novel approach to racemic and chiral nonracemic β-fluoroalkyl-β-amino acids starting from 2-alkyl-Δ^2-oxazolines **49**. (For a similar synthesis of racemic nonfluorinated β-amino acids, see Ref. 23.) The strategy is based on the reaction of α-metalated 2-alkyl-Δ^2-oxazolines with acylimidoyl species to furnish masked β-enamino acid derivatives **50**. Subsequent chemo- and stereoselective reduction to the target fluorinated β-amino acid derivatives **51** was carried out with the system $ZnI_2/NaBH_4$ in CH_2Cl_2 as solvent.[24] The reduction took place with high yields, total regioselectivity, and moderate to good stereocontrol (de ranging between 10 and 94%) (Scheme 14.25).



Scheme 14.25

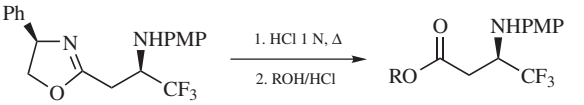
To study the diastereoselectivity of the process, a series of 2-alkyl-Δ^2-oxazolines **49** was investigated. The best results were obtained with chiral oxazolines **49b** and **49e** (dr up to 4 : 1). The reaction with racemic nonchiral oxazoline **49a** provided the syn diastereomer as the major product (syn/anti 97/3) (Fig. 14.10).



49a *de* 94 *syn* **49b** *de* 60 **49c** *de* 30 **49d** *de* 10 **49e** *de* 60

Figure 14.10

The oxazoline moiety can be easily removed by means of acid-catalyzed hydrolysis to provide the corresponding *N*-protected fluorinated β-amino acids [i.e., (*R*)-**52** from (2′*R*,2*R*)-**51**] (Scheme 14.26).



(2′*R*,4*R*)-**51** (*R*)-**52**

R= Me (65%), *i*-Pr (60%)

Scheme 14.26

14.3 CYCLIC FLUORINATED α,β-DISUBSTITUTED β-AMINO ACIDS

Cyclic β-amino acids represent an interesting class of compounds not only from a synthetic point of view but also because of their potential use as therapeutic agents (Fig. 14.11). Cyclic β-amino acids are also useful intermediates in the synthesis of natural products, β-peptides, and peptidomimetics. While the chemistry of their nonfluorinated derivatives has received a great deal of attention in the past few years,[25] very little is known about their fluorinated counterparts. Although the literature includes several examples of β-amino acids with seven-membered rings, no fluorinated seven-membered β-amino acids have been described until extremely recently.

Thus, in 2003, Fustero et al.[26] reported the first diastereoselective preparation of seven-membered β-amino acid derivatives via a ring-closing metathesis. The synthesis begins with the condensation between imidoyl chlorides and ester

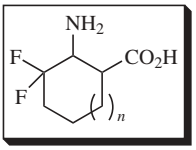
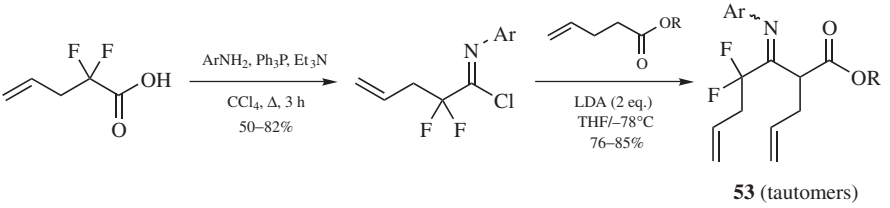


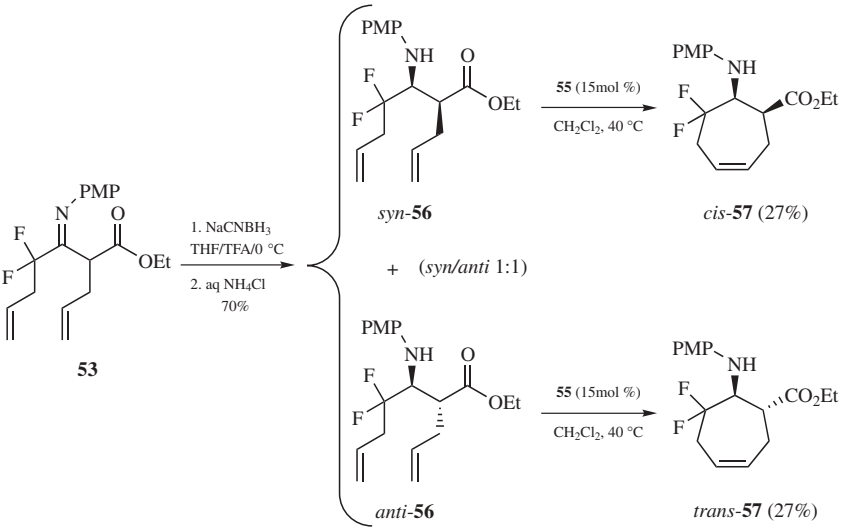
Figure 14.11

enolates. This gives compounds **53**, which appear as a mixture of enamino and imino tautomers (Scheme 14.27). Using a variety of reagents (i.e., $NaCNBH_3$/TFA, $NaBH_4/ZnI_2$/dry CH_2Cl_2, LAH, etc.), the authors then attempted to reduce compound **53** (R = Et, Ar = PMP), but stereoselectivity could not be achieved in this way (**56** syn/anti 1 : 1). However, column chromatography easily separated both the syn and anti diastereomers, which were then submitted to a ring-closing metathesis (RCM) reaction with the second-generation Grubbs catalyst **55** to yield the respective seven-membered amino esters **57** in low yields (27%) (Scheme 14.28).

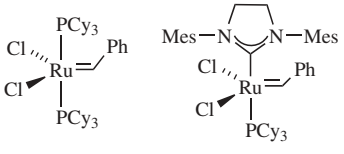


53 (tautomers)

Scheme 14.27



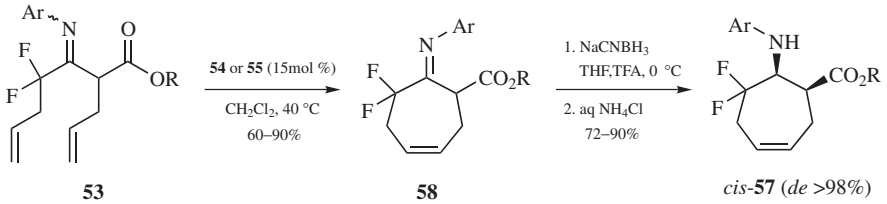
53



54 **55**

Scheme 14.28

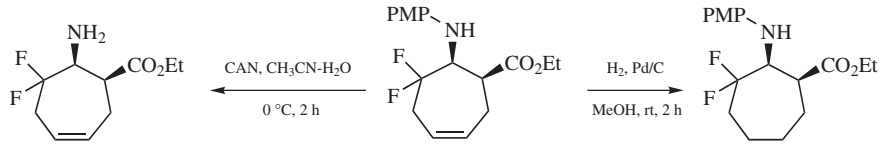
Since neither the diastereoselectivity nor the yields for this approach were particularly satisfactory, the order of reactions was inversed in the hope that this would improve the results. Thus, compound **53** reacted with either catalyst **54** or **55** (**55** gave slightly better yields under milder conditions) to give the cyclized imino ester **58** in 60–90% yield, depending on the substituents. This compound was then reduced with $NaCNBH_3$/TFA in a completely stereoselective fashion to give the cis diastereomer **57** in 72–90% yield (Scheme 14.29).



53 **58** *cis*-**57** (*de* >98%)

Scheme 14.29

Finally, it was possible to either deprotect the amino group by means of PMP removal with CAN or hydrogenate the double bond with hydrogen and palladium on a charcoal catalyst, with very high yields in both cases (Scheme 14.30).



95% 99%

Scheme 14.30

14.4 α-FLUOROALKYL β-AMINO ACIDS

Another interesting, and until now virtually unexplored, route for the synthesis of fluorinated β-amino acids is based on the asymmetric Michael addition of ammonia or amines to fluorinated substituted α,β-unsaturated esters or amides (Fig. 14.12). In

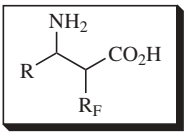
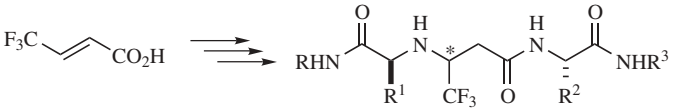


Figure 14.12

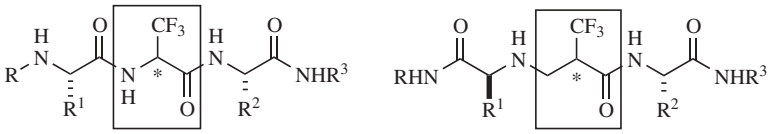
this way, Volonterio et al. have described novel peptidomimetic structures that incorporate a trifluoromethyl group in the β-position of β-amino acids within the framework of a research project aimed at the development of fluorine-containing protease inhibitors (Scheme 14.31).[27]



Scheme 14.31

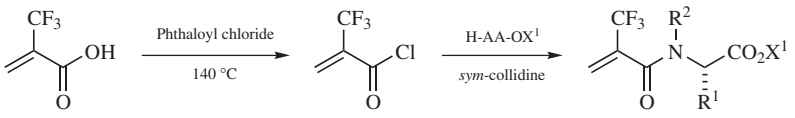
α-Trifluoromethyl β-amino acids are also interesting molecules, especially as analogs of natural β-alanine. In addition, since they are methylene homologs of proteinogenic amino acids, they may serve as valuable building blocks in the study of natural peptides. Unfortunately, the incorporation of a 3,3,3-trifluoroalanine (TF-Ala) unit into a peptide to give a modified peptide **59** has proven to be a challenging endeavor since many peptides have low chemical and configurational stability at pH > 6 (Fig. 14.13).

In light of this fact, the groups of Zanda in Milan and Fustero in Valencia jointly reported recently the synthesis of partially modified retro (PMR) Ψ[$NHCH_2$] peptidomimetics **60**, which incorporate a chemically stable and stereodefined $CH_2CH(CF_3)CO$ surrogate for TF-Ala.[28] The synthesis is based on a *tandem* asymmetric aza-Michael addition–enolate protonation of α-amino esters to *N*-(α-trifluoromethyl)acryloyl-α-amino esters **61**. The strategy starts with the commercially available trifluorometacrylic acid, which is transformed into its chloride. Michael acceptors **61** were obtained, with generally high yields, upon treatment of the appropriate α-amino ester H-AA-OX^1 with (α-trifluoromethyl)acryloyl chloride (Scheme 14.32).



59 **60**

Figure 14.13

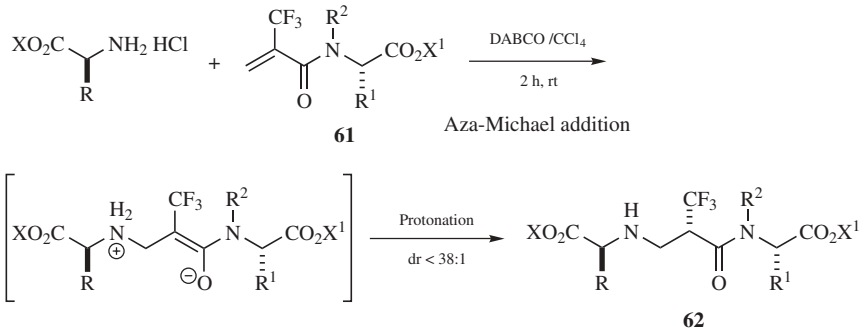


AA = Gly, Val, Pro, Ala, Phe, Leu...

61

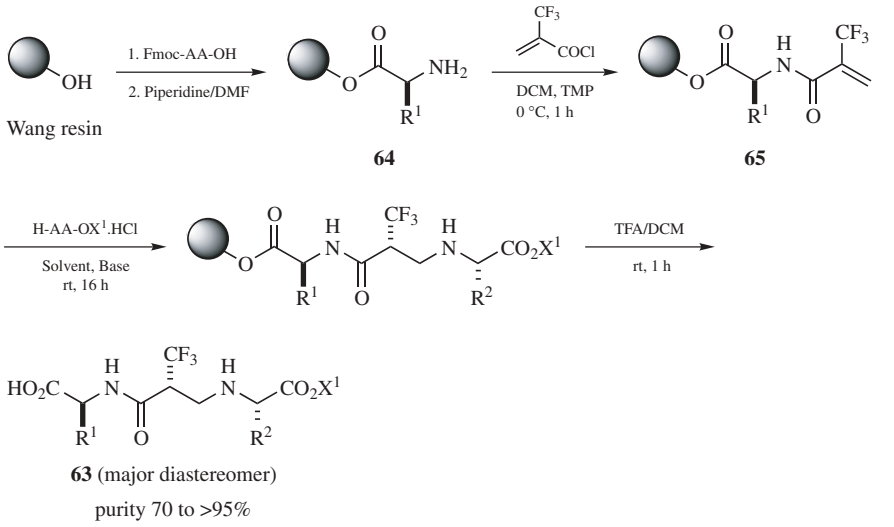
Scheme 14.32

These compounds were next reacted with a variety of α-amino esters to give the PMR-tripeptides **62**, which were isolated in yields of 75–98%. The process takes place with good to excellent 1,4-asymmetric induction (up to 95%), depending on the substrate. Very high stereocontrol was achieved after careful adjustment of key reaction parameters, including the solvent and base used. While side chains (R and R^1) and chirality (matched/mismatched pairs) of both reaction partners were also found to have an influence on the diastereoselectivity, concentration and reaction temperature had negligible effects on the stereocontrol. Thus, when the reaction parameters were carefully chosen, the diastereomeric excess of this reaction was increased from 0 to 95%. The best results were achieved with 1,4-diazabicyclo[2,2,2]octane (DABCO) as base and CCl_4 as apolar solvent. Other solvents such as CH_2Cl_2, CH_3CN, THF, toluene, and bases such as triethylamine, diisopropylethylamine, *sym*-collidine, 4-dimethyl-aminopyridine (DMPA), quinidine, and cinchonine provided less efficient results (Scheme 14.33).



Scheme 14.33

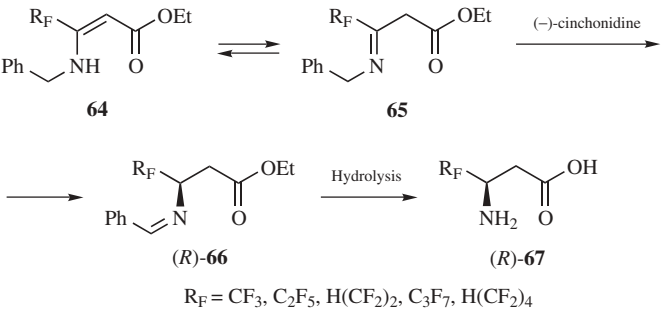
The same authors have also described the efficient, stereocontrolled, solid-phase synthesis of a library of PMR Ψ[$NHCH_2$]-peptides **63** incorporating a stereochemically defined and stable TF-Ala mimic by means of a *tandem* asymmetric aza-Michael/enolate protonation of α-amino esters with chiral Wang resin-supported *N*-(2-Tfm)-propenoyl-α-amino ester acceptors.[29] In the first step, Wang resin was loaded with *N*-Fmoc α-amino acids to afford the Fmoc-resins **64**, which were *N*-deprotected upon treatment with piperidine/dimethylformamide (DMF). Next, the resins were reacted with an excess of 2-trifluoromethyl-propenoyl chloride in CH_2Cl_2 to provide the chiral Michael acceptors **65**. The crucial aza-Michael reactions were carried out with the addition of 3 eq. of the appropriate α-amino ester to a suspension of resin **65** in the appropriate solvent in the presence of 6 eq. of base. The stereocontrol can be dramatically improved (up to 15 : 1) by using apolar solvents such as CCl_4 and DABCO as base. Release of the PMR peptides from the solid support was achieved by treatment with TFA in CH_2Cl_2 (Scheme 14.34).



Scheme 14.34

14.5 β-FLUOROALKYL β-AMINO ACIDS

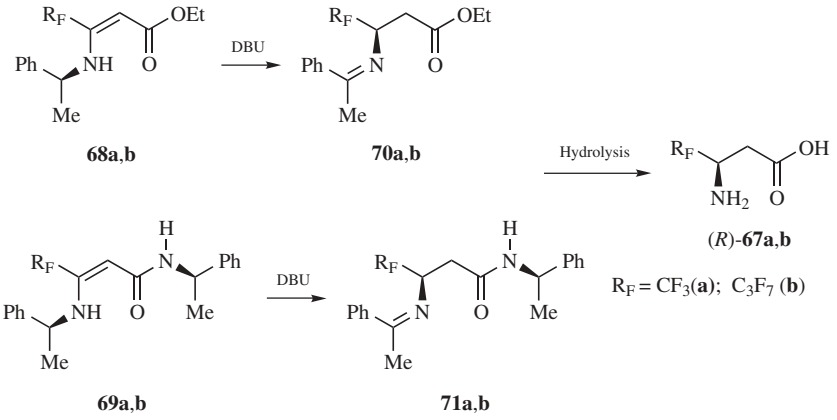
As mentioned above in Section 14.2.1, the biomimetic reductive amination of fluorine-containing carbonyl compounds developed by Soloshonok et al.[30] was applied efficiently to the preparation of enantiomerically α-unsubstituted β-fluoroalkyl-β-amino acids. In an earlier report from this group the authors studied 1,3-proton shift isomerization of *N*-benzylenamines **64** to Schiff bases **66** in the presence of chiral amines (Scheme 14.35).[31]



Scheme 14.35

While this isomerization occurred in enantioselective fashion in the presence of 10 mol % of (−)-cinchonidine, the level of asymmetric induction was too low to be synthetically useful, ranging from 15 to 36% ee, depending on the nature of the fluoroalkyl group. The authors suggested that enamines **64** first underwent a

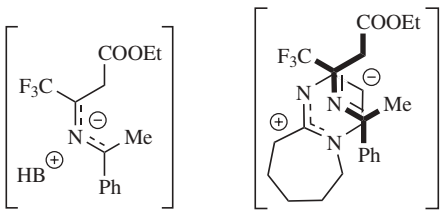
reversible 1,3-proton shift to give rise to imines **65**, which then experienced an additional, irreversible 1,3-proton shift to afford the Schiff bases **66**. Compounds **66** were readily hydrolyzed to the target amino acids **67** in good overall chemical yield. A more practical application of this methodology was achieved by using α-methylbenzyl amine as a stoichiometric chiral auxiliary to control the stereoselectivity of the 1,3-proton shift transfer (Scheme 14.36). Thus, chiral enamines **68** and **69**, derived from the corresponding ester and amide, respectively, underwent a 1,3-proton shift in the presence of DBU to afford imines **70** and **71**, which were then hydrolyzed to yield the target amino acids **67a**,**b**.[32]



68a,**b** **70a**,**b** **69a**,**b** **71a**,**b**

Scheme 14.36

The isomerization of esters **68** occurred at a substantially higher rate than that of amides **69**; however, the enantioselectivity of the 1,3-PST was found to be similar, ranging from 87 to 96% ee. The highest asymmetric induction value (96% ee) was registered for the isomerizations of **68a** and **68b**, in both of which R_F is a bulky perfluoropropyl group. To account for the observed stereochemical preferences, the authors proposed transition state **72**, in which the phenyl of the amine residue and the trifluoromethyl group are assumed to be the stereocontrolling substituents (Fig. 14.14).

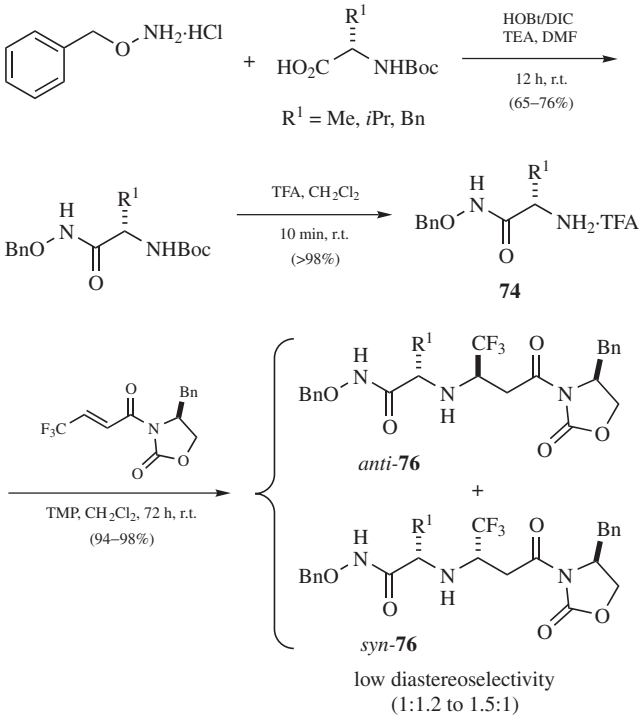


72 **73**

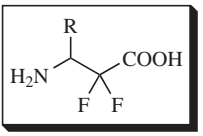
Figure 14.14

As an alternative, and to rationalize the particular role of DBU as a catalyst for this isomerization, transition state **73** was suggested. In this transition state the 1,3-azaallylic carbocation, which is derived from the starting imine, is perfectly matched with the delocalized anion of the base. In general, this method features operationally convenient conditions as well as optimal chemical and stereochemical outcomes. In addition, this technique may be generalized for the synthesis of various β-fluoroalkyl-β-amino acids. The recently reported protocol for the highly regioselective large-scale preparation of the starting compounds **68** and **69**[33] only serves to enhance the synthetic value of this approach.

Between 2000 and 2002, Volonterio et al. published three papers that describe the synthesis of a family of partially modified peptidomimetics, both in solution and in solid phase.[27] The key step in this synthesis is the Michael-type *N*-addition of free or polymer-bound α-amino hydroxamates **74** to 3-[(*E*)-enoyl]-1,3-oxazolidin-2-ones **75**. This reaction took place in high yields (94–98%), although with low stereocontrol. The products thus formed, *syn*-**76** and *anti*-**76**, include a β-trifluoromethyl-β-amino acid moiety in their structures (Scheme 14.37).



Scheme 14.37



77

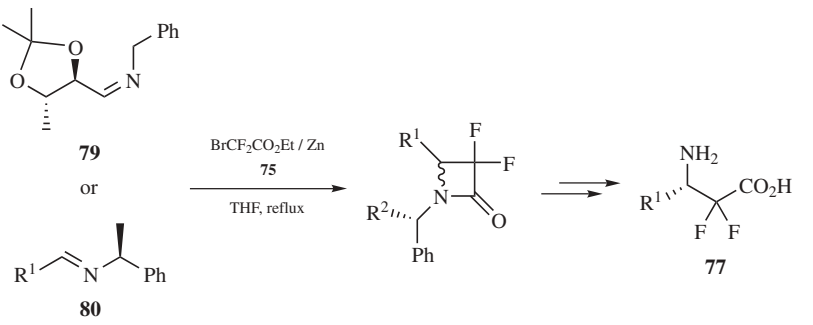
Figure 14.15

14.6 β-SUBSTITUTED α,α-DIFLUORO-β-AMINO ACIDS

Considering the potential application of fluorine-containing β-amino acids in the design of the corresponding β-peptides, β-substituted α,α-difluoro-β-amino acids **77** are of particular interest[34] (Fig. 14.15). These amino acids could give rise to a type of folded β-peptides with a fluorinated inner surface in which a β-substituent R could be rationally introduced to control numerous characteristics, including lipophilicity/hydrophobicity, acid/base properties, and the desired three-dimensional structure of the target β-peptide.

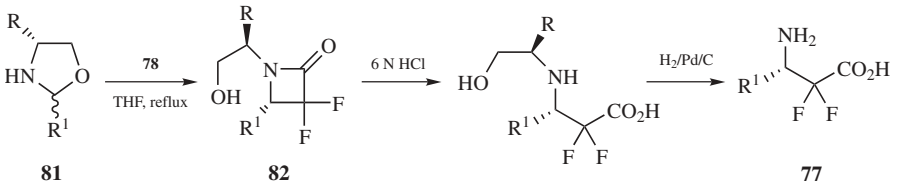
Curiously, despite the considerable interest in enantiomerically pure α,α-difluoro-β-amino acids of the type **77**, especially as precursors to a particular class of fluorinated β-lactam antibiotics,[35] the literature contains only a handful of reports that deal with the asymmetric synthesis of β-amino acids **77**. In an earlier report by Taguchi et al.,[36] the authors studied the Reformatsky addition between in situ–generated $XZnCF_2COOR$ **78** (X = halogen) and either *N*-benzylimine of (*R*)-glyceraldehyde acetonide **79** or a series of aromatic aldimines derived from (*S*)- or (*R*)-α-methylbenzylamine **80** (Scheme 14.38). In both cases the stereochemical outcome was disappointingly low (de <50%).

In a recent paper, Marcotte et al.[37] reported a similar Reformatsky-type reaction using chiral 1,3-oxazolidines **81** as stable equivalents of the required imines



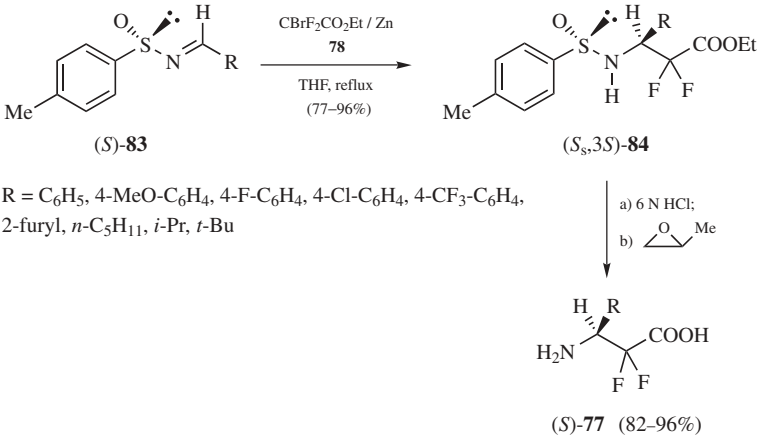
Scheme 14.38

(Scheme 14.39). The reactions proceeded with high diastereoselectivity, furnishing the corresponding azetidin-2-ones **82** with up to 99% de. However, the chemical yields were less satisfactory, ranging from 32 to 69%. Furthermore, the additional two to three steps required for the transformation of the azetidin-2-ones **82** to the target α,α-difluoro-β-amino acids **77** led to low overall yields, thus rendering this approach synthetically problematic.

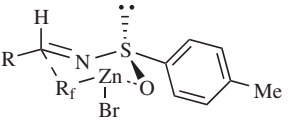


Scheme 14.39

Recently, Sorochinsky et al.[38] reported on the application of Davis's chiral sulfinimines **83** in an addition reaction with in situ–generated $BrZnCF_2COOEt$ (**78**) as a generalizable method for the preparation of enantiomerically pure α,α-difluoro-β-amino acids **77** (Scheme 14.40). The reactions, conducted in THF at reflux between imines **83** derived from aromatic aldehydes, furnished the corresponding addition products **84** in high chemical yields (77–96%) and with a synthetically useful level of diastereoselectivity (80 to >98% de). Addition products **84** were then readily hydrolyzed and the target amino acids **77** were isolated in good chemical yields (82–96%). The only exception was the hydrolysis of furyl-derived **84**, which failed to furnish the target product, presumably due to the instability of



Scheme 14.40



85

$R_f = CF_2\text{-}COOEt$

Figure 14.16

the furane ring under acidic conditions. Application of those sulfinimines **83** derived from aliphatic aldehydes in the addition reaction with the $BrZnCF_2COOEt$ (**78**) was relatively less successful. In fact, both the chemical yields and the diastereoselectivity of the addition reactions were noticeably lower as compared with those observed in the aromatic series. Thus, under the same reaction conditions, sulfinimines **83** which contained *normal*-, *iso*-, and *tert*-alkyl groups gave the addition products **84** in 59–65% chemical yield and with 72–96% de. Moreover, hydrolysis of these derivatives to the target amino acids **77** was not as clean as in the aromatic series, giving rise to the target amino acids **77** in chemical yields ranging from 56 to 70%.

To account for the asymmetric induction observed in these reactions, the authors proposed transition state **85**. In **85** the sulfinimine moiety is of the stereochemically favorable E-configuration while the reagent **78** is in the corresponding carbon–metal form.[39] The authors propose that the steric interactions between the imine R-substituent and difluoromethylene group in transition state **85** can explain the intriguing differences observed in the diastereoselectivity of the aromatic and aliphatic series. Thus, when the R-substituent is a phenyl group, it can minimize the unfavorable steric interactions by virtue of its flat shape. On the other hand, if the R-group is a bulky alkyl group, it may experience repulsive steric interactions with the difluoromethylene group, thereby destabilizing the proposed transition state **85** (Fig. 14.16).

More recently, Staas et al. reported a similar approach, albeit limited to the reactions of aromatic derivatives.[40] This work employed the more costly *N*-*t*-butylsulfinimines instead of *p*-phenylsulfinimines **83**, but with no advantage in terms of the stereochemical outcome and chemical yields.

Among the other techniques and approaches available in the literature that lead to the enantiomerically enriched/pure amino acids **77**, several are worth mentioning: (a) separation of racemic derivatives by means of preparative chiral high-performance liquid chromatography (HPLC)[41]; (b) conversion of enantiomerically enriched β,β-difluoro-β-hydroxy derivatives to the corresponding β-amino acids via Mitsunobu protocol[42]; (c) separation of diastereomeric derivatives[43]; (d) solid-phase synthesis of *N*-alkyl-substituted derivatives[44]; and (e) enzymatic separation of the *N*-phenylacetyl derivatives of **77**.[45] This last approach will be discussed more fully in Chapter 17 of this book.

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CHAPTER 15

Enantioselective Synthesis of β-Amino Acids via Conjugate Addition to α,β-Unsaturated Carbonyl Compounds

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15.1 INTRODUCTION

There has been significant attention focused on the development of stereoselective syntheses to access optically pure β-amino acids owing to the fact that they can be found as substructures in numerous natural products, possess interesting biological activity, and are potential precursors to β-lactam synthons.[1,2] Oligomers of β-amino acids have potential in the design of biostable peptidomimetics for drug discovery[3] as well as in the design of β-peptide "foldamers," which have been shown to exhibit stable secondary structures in organic and aqueous solutions.[4] Of the many methods available to the organic chemist for stereoselective synthesis of these interesting compounds, conjugate addition of either nitrogen- or carbon-based nucleophiles to an appropriately functionalized α,β-unsaturated carbonyl compound is an attractive approach. The stereoselective conjugate addition disconnection can be accomplished in the forward direction by three typical methods: (1) addition of a nitrogen nucleophile to a chiral acceptor (i.e., chiral ester); (2) addition of a chiral nitrogen nucleophile to an achiral acceptor; and (3) asymmetric catalysis of nitrogen- or carbon-based nucleophiles. This review will attempt to discuss these various stereoselective conjugate addition strategies as well as highlight applications of these methods in the synthesis of more complex targets.

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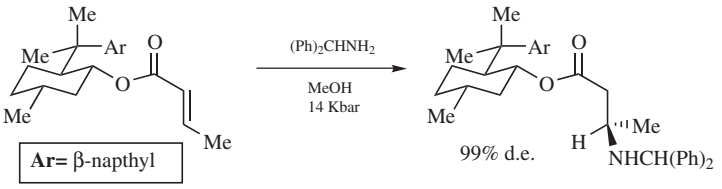
15.2 DIASTEREOSELECTIVE ADDITIONS TO CHIRAL MICHAEL ACCEPTORS

One potential strategy for the synthesis of optically enriched β-amino acid derivatives is through the use of chiral Michael acceptors as substrates in conjugate addition reactions with nitrogen nucleophiles. This strategy requires the judicious use of an appropriate chiral auxiliary that governs the sense of asymmetric induction and can be subsequently removed under mild conditions. (For examples of nonauxiliary-based diastereoselective additions, see Ref. 5.) This can be an attractive approach to access β-amino acids, especially if the auxiliary can be recovered for repetitive use.

Dumas and co-workers have shown that alcohols derived from β-pinene are effective chiral auxiliaries for diastereoselective conjugate addition of diphenylmethaneamine under high pressures[6]:



1.1 **1.2** (15.1)

Ester **1.1** is treated with diphenylmethaneamine in methanol at 14 kbars to effect conjugate addition to give product **1.2** with high diastereoselectivity (99% de). Critical for high diastereoselectivity is the aromatic substituent on the auxiliary. This aromatic group serves to block one face of the ester through a π-stacking interaction, thereby leading to high stereoselectivities (Fig. 15.1). Addition takes place on the less hindered face of the *s*-trans conformer of substrate **1.1**. Evidence to support this model includes proton nuclear magnetic resonance (^{1}H NMR) analysis of the olefinic protons, which indicates shielding by the ring current of the aromatic ring, as well as an X-ray crystal structure of a simplified model substrate that clearly illustrates the π-stacking interaction.

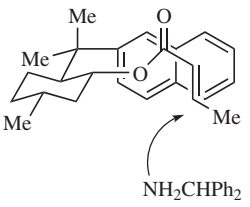
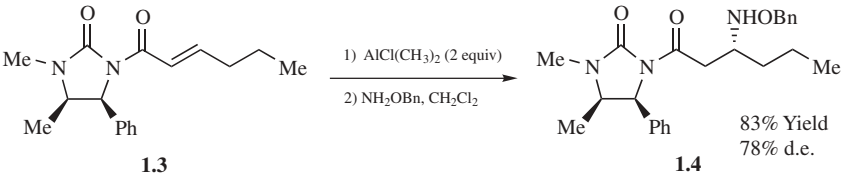
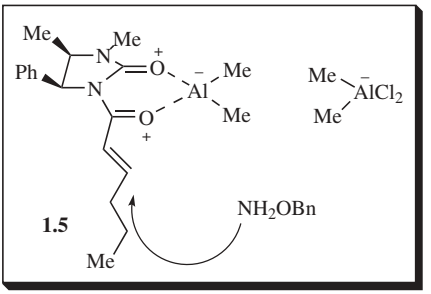


Figure 15.1 Conformation of chiral Michael acceptor **1.1** illustrating aromatic π-stacking interaction.

Another approach involves the incorporation of optically pure heterocycles as auxiliaries to yield chiral imide scaffolds for diastereoselective conjugate addition.[7] In this manner, Cardillo and co-workers have developed a Lewis acid–promoted conjugate addition of *O*-benzylhydroxylamine to chiral imides[8]:



1.3 **1.4**



1.5

(15.2)

Imide **1.3** is first complexed with 2 eq. $AlCl(CH_3)_2$, then is treated with *O*-benzylhydroxylamine in dichloromethane to effect the conjugate addition to provide product **1.4**. The desired product is obtained in 83% isolated yield and was found to be of 78% de. The use of a Lewis acid as a complexation agent serves two purposes, the first being to increase the electrophilicity of the substrate, thereby enhancing reactivity. In addition to reactivity enhancement, the Lewis acid acts to form a chelated salt **1.5** which serves to stabilize a single substrate *s*-cis conformation. The nucleophile then adds to the less hindered diastereoface to afford the observed product. While the authors propose a free hydroxylamine as the nucleophile, it seems likely that under these reaction conditions an aluminum amide may be acting as the nucleophilic species.

In 1997 Matsuyama and co-workers developed an exceptionally simple protocol for the addition of ammonia to (*E*)-2(*p*-tolylsulfinyl)cinnamate substrate **1.6** to afford adduct **1.7**.[9] Upon reductive removal of the sulfoxide auxiliary, the subsequent β-amino ester was obtained in 68% yield and 81% ee (Fig. 15.2). Other amines also add with good diastereoselectivity (up to 89% de), although the simplicity of using ammonia as the nucleophile has obvious advantages. A model to account for the observed diastereomer was developed by X-ray crystal structure analysis of the substrate. The nucleophile attacks anti to the bulky *t*-butyl ester and phenyl substituents which lie below the plane of the olefin.

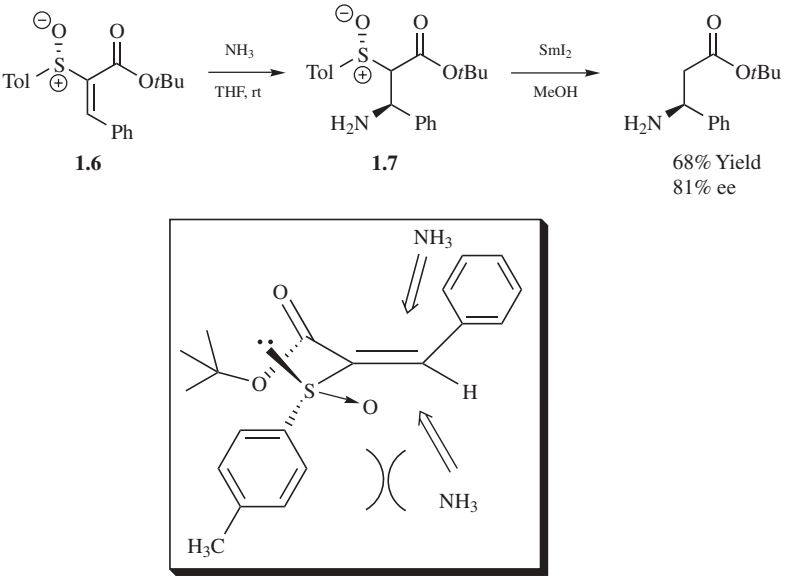


Figure 15.2 Diastereoselective conjugate addition of ammonia to vinyl sulfoxides.

Another approach for diastereoselective conjugate addition is the incorporation of the Michael acceptor into a chiral heterocyclic scaffold. The rigidity of the resulting heterocyclic substrate allows for highly diastereoselective additions. Dechoux and co-workers have designed a system whereby pyrimidone substrate **1.8** is treated with various cuprate reagents (R = alkyl) in the presence of TMSCl to afford the corresponding addition product **1.9** in good yield and excellent diastereoselectivity (>95% de; Fig. 15.3).[10] A model was proposed to account for the observed diastereoselectivity whereby the nucleophile adds to the olefin of the relatively planar heterocycle anti with respect to the phenyl controlling group. This methodology was useful in the preparation of α,β-substituted β-amino acids via diastereoselective enolate alkylation of products **1.9** followed by reductive and hydrolytic removal of the chiral auxiliary to afford the corresponding amino acid **1.10**.

An intriguing, yet nonobvious approach to access novel β-amino acid scaffolds was developed by Masanao and Meyers through the development of a stereoselective addition of lithiated amides to chiral napthyloxazolines (Scheme 15.1).[11] Treatment of oxazoline **1.11** with lithium amine derivatives followed by quenching with CH_3I leads to the disubstituted product **1.12** in excellent yield and diastereoselectivity (96%, >98% de). Product **1.12** can then be converted to the desired amino acid utilizing a simple three-step protocol. It is of note that this method appears to be limited to a restricted set of β-amino acid targets.

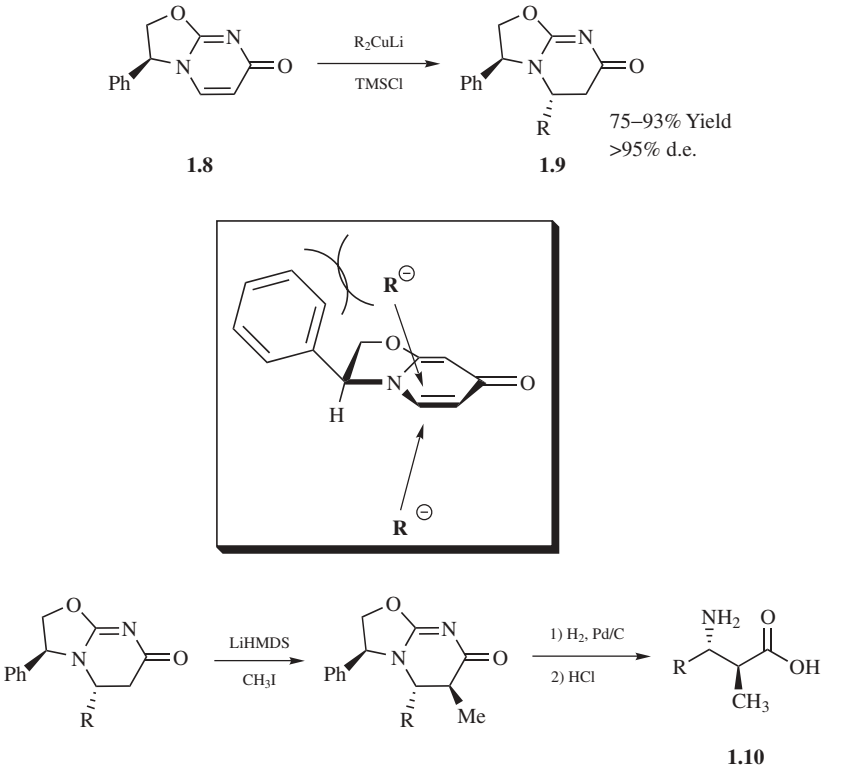
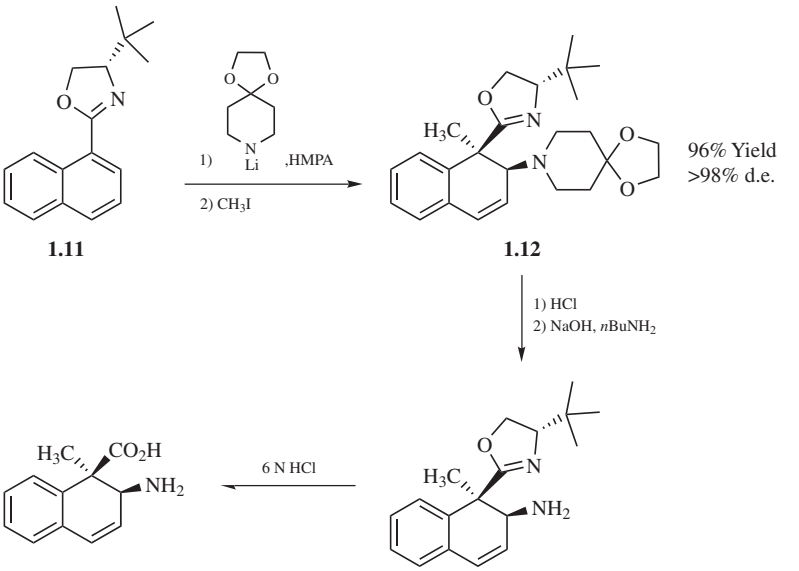


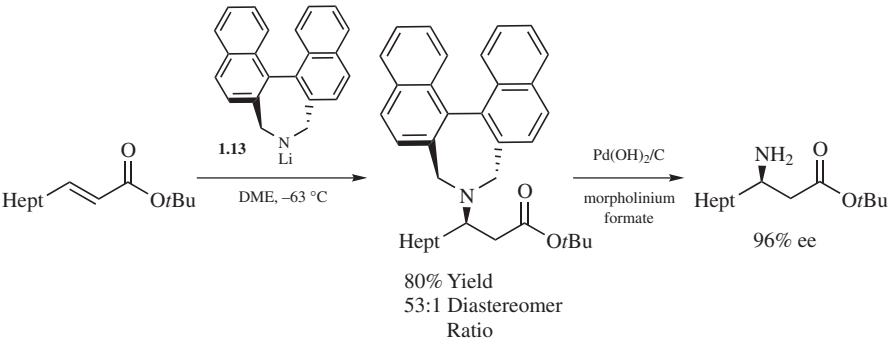
Figure 15.3 Diastereselective cuprate addition to assemble substituted β-amino acid synthon.



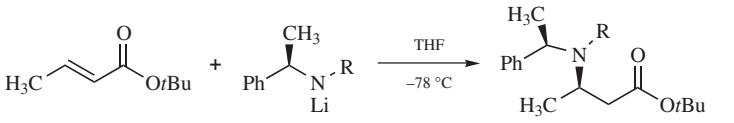
Scheme 15.1

15.3 ADDITIONS OF CHIRAL AMMONIA EQUIVALENTS TO MICHAEL ACCEPTORS

An early example of a chiral "NH_3" equivalent for diastereoselective conjugate addition was developed by Hawkins et al. and is based on a chiral binapthyl lithium amide.[12] Lithiated binapthyl–derived amide **1.13** was treated with various α,β-unsaturated esters to afford the corresponding adducts in good yield and diastereoselectivity (Scheme 15.2). Notable is the fact that the corresponding free



Scheme 15.2



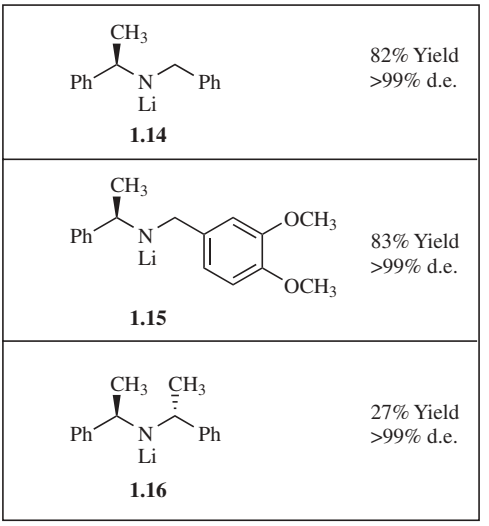


Figure 15.4 Diastereoselective addition of α-methyl benzylamine derivates to enoates.

amine is a competent nucleophile for addition; however, the diastereoselectivities are much lower, and elevated temperatures are required. Conversion to the lithium amide is therefore preferred for reactivity as well as selectivity enhancement. The desired β-amino esters are obtained in good yields after transfer hydrogenolysis conditions employing $Pd(OH)_2/C$ and morpholinium formate. While this method represents one of the early examples of a successful asymmetric β-amino acid synthesis, the lack of atom economy is a disadvantage.

There has been significant interest in the development of chiral NH_3 synthons derived from optically pure α-methylbenzylamine owing to the fact that both enantiomers are readily available and relatively inexpensive. Davies[13a,14] and coworkers have had a significant interest in this area and have developed highly efficient methods for β-amino acid synthesis based on this concept. Simple crotonate esters react with several lithium amides derived from (*R*)-α-methylbenzylamine to afford the conjugate addition products in high yields and excellent diastereoselectivities (Fig. 15.4).[13a,14] (See also Refs. 13b,c. For an excellent discussion of a proposed stereochemical model to account for the observed diastereoselectivities, see Ref. 14). Lithium amides **1.14**, **1.15**, and **1.16** all add to *t*-butyl crotonate within minutes at low temperature to afford product with total diastereocontrol. This methodology was effectively applied to the synthesis of the β-amino acid side chain of taxol (Fig. 15.5).[15]

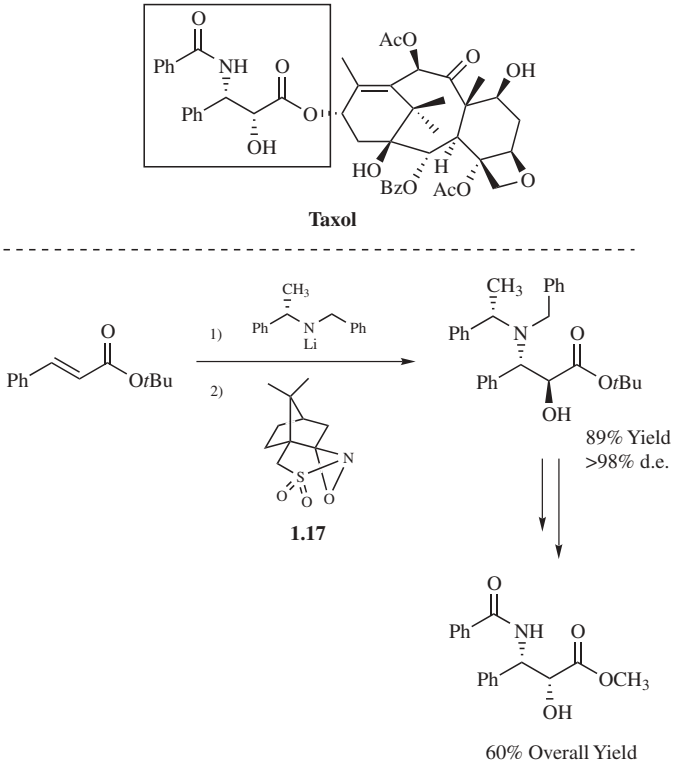
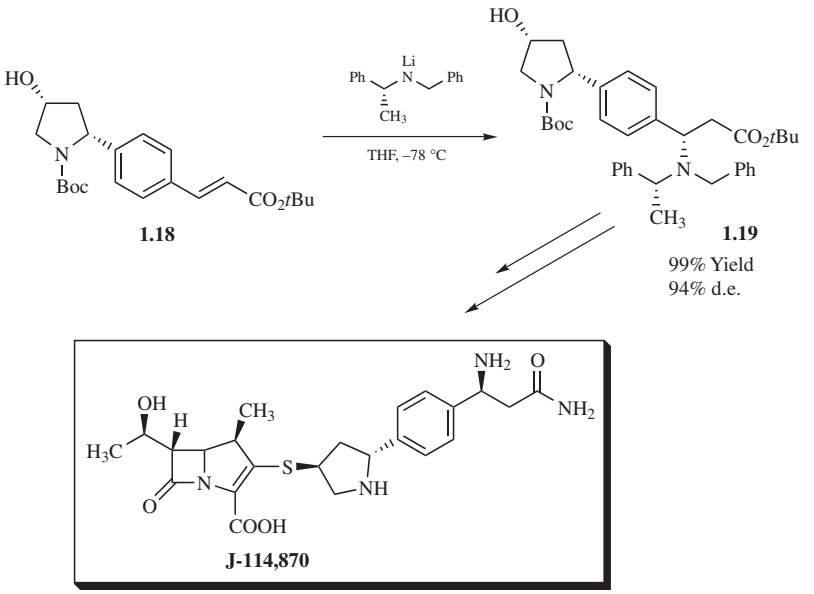


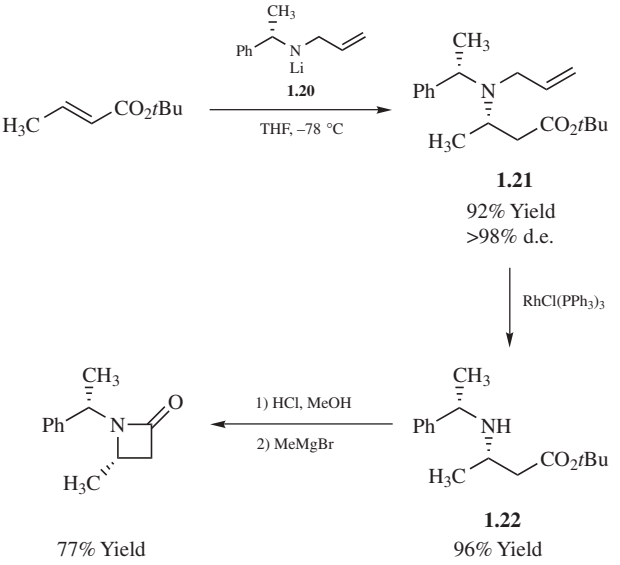
Figure 15.5 Application of α-methyl benzylamine additions to the Taxol side chain.

Diastereoselective conjugate addition to *t*-butyl cinnamate followed by treatment of the resulting lithium enolate with oxaziridine **1.17** affords the resultant *anti*-β-amino-α-hydroxy acid as a single diastereomer, which upon subsequent derivatization affords the taxol side chain in 60% overall yield. Another example of an application of this methodology in total synthesis involves the conjugate addition of the lithium salt of (*R*)-*N*-(α-methylbenzyl)benzylamine to the complex unsaturated ester **1.18** (Scheme 15.3)[16] and subsequent incorporation into the broad-spectrum 1β-methylcarbapenem antibiotic J-114,870. (Other notable examples of applications in the synthesis of complex β-amino acid derivatives are given in Ref. 17.) Addition to ester **1.18** proceeded smoothly in tetrahydrofuran (THF) at −78°C to afford **1.19** in 99% yield and 94% de, which was then carried on to provide J-114,870.



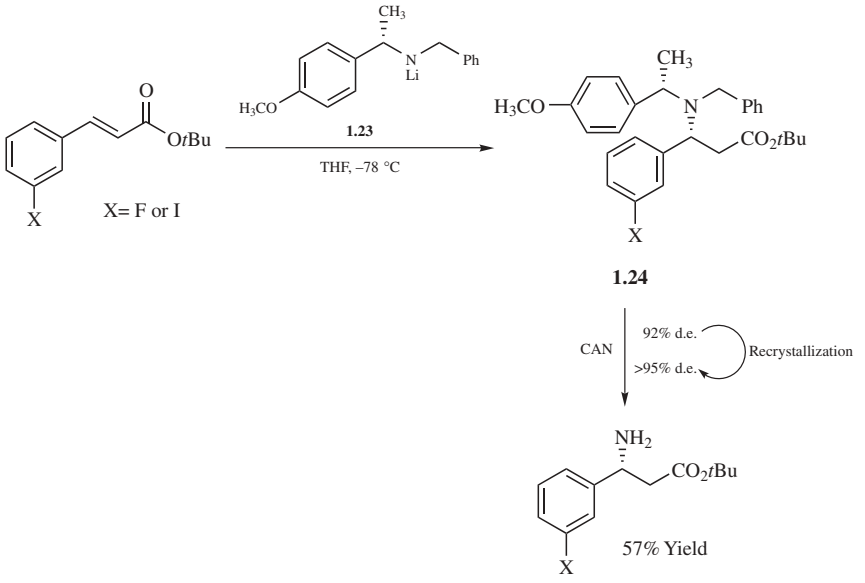
Scheme 15.3

In an attempt to develop chiral NH_3 equivalents that were differentially protected in such a way as to allow for selective removal of one of the *N* protecting groups in the presence of the other, Davies and Fenwick developed lithium (α-methylbenzyl)-allylamide as a reagent for diastereoselective conjugate addition.[18] Treatment of *t*-butylcrotonate with **1.20** in THF at −78°C afforded adduct **1.21** in 92% yield and >98% de (Scheme 15.4). The allyl group on adduct **1.21** can be selectively cleaved using Wilkinson's catalyst to afford the monoprotected amine **1.22** in high yield (96%). Subsequent derivatization affords access to the β-lactam in good yield (77%). (Other examples of the use of this reagent in synthetic applications are given in Ref. 19.)



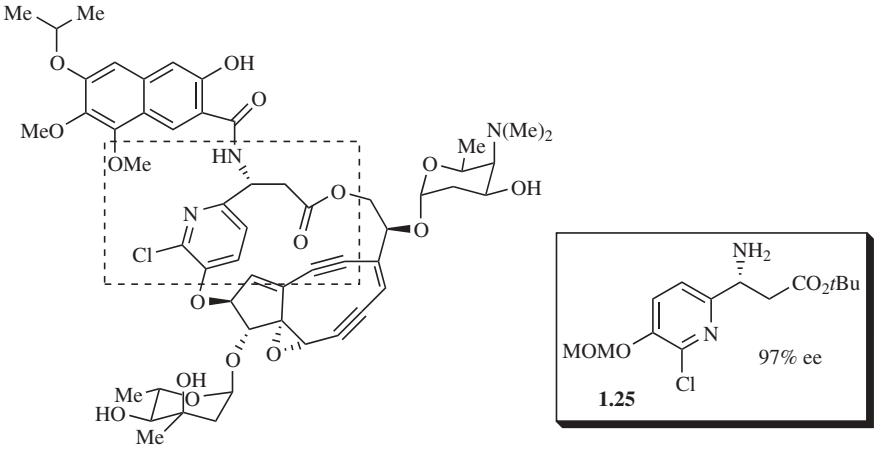
Scheme 15.4

In efforts to develop methodology to access β-haloaryl-β-amino acids, Davies et al. designed a chiral ammonia equivalent that can be deprotected under oxidative, rather than the typical hydrogenolytic conditions that are incompatible with sensitive haloaryl functionality within the substrate (Scheme 15.5)[20a] (see also



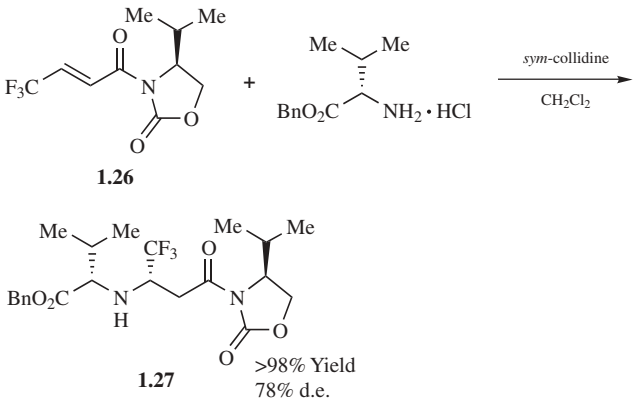
Scheme 15.5

Refs. 20b,c). In this method, *t*-butyl cinnamate is treated with lithium amide **1.23** to afford adduct **1.24** in 92% de which can be enhanced to >95% de after a single recrystallization. Subsequent deprotection using aqueous cerium ammonium nitrate (CAN) affords the desired β-haloaryl-β-amino ester in good yield. The usefulness of this methodology is illustrated in the synthesis of the β-amino acid subunit of the antitumor natural product kedarcidin. The protected β-amino acid subunit **1.25** was synthesized by conjugate addition of **1.23** and subsequent oxidative deprotection with CAN to afford **1.25** in 97% ee.[21]



Kedarcidin

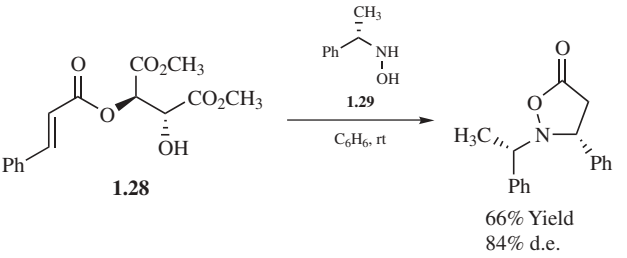
Volonterio et al. have shown that simple α-amino esters can serve as chiral ammonia equivalents in conjugate addition reactions with chiral imide acceptors (Scheme 15.6).[22] Imide **1.26** was treated with the hydrochloride salt of valine *O*-benzyl ester in the presence of the hindered base *sym*-collidine in methylene chloride to afford adduct **1.27** in >98% yield and 78% de. Diastereoselectivities are a function of both the chirality of the amino ester and imide acceptor, an



Scheme 15.6

example of double stereodifferentiation.[23] Control experiments indicate that the stereogenic center of the amino ester is responsible for the majority of the asymmetric induction. Addition to achiral imides proceeds with good diastereoselectivities (up to 65% de); however, introduction of an imide stereogenic center of the appropriate absolute stereochemistry enhances selectivity (matched case). Functionalization of the resulting adducts utilizing traditional methods of imide hydrolysis with lithium hydroperoxide afforded the desired β-amino acid derivatives.[24]

Ishikawa and co-workers have developed another protocol exploiting the effect of double stereodifferentiation in the addition of chiral hydroxylamines to chiral ester substrates (Scheme 15.7).[25] (For an early example, see Ref. 26.) Ester **1.28**, derived from (*R*,*R*)-dimethyl tartrate and cinnamic acid, is treated with hydroxylamine **1.29** to deliver the corresponding adduct in 66% yield and 84% de. It was found that both the chiral hydroxylamine and chiral ester were essential for high diastereoselectivities, revealed by preliminary experiments with simple *N*-benzyl hydroxylamine affording products with minimal diastereoselectivity (1–10% de). Not only is the tartrate ester critical for diastereoselectivity, it also enhances overall reactivity of the addition and subsequent cyclization steps due to the presence of the electron-withdrawing α-ester substituent. Simple N–O bond cleavage under reductive conditions (H_2, Pd/C) affords the corresponding β-amino acids.



Scheme 15.7

One of the potential drawbacks of the methods described above is the fact that, upon deprotection of the amine, the stereogenic center of the auxiliary is destroyed, eliminating the possibility of recovery and reuse. Ishikawa and co-workers[27] addressed this problem by developing what they refer to as a Lewis acid–hydroxylamine hybrid reagent (LHHR), which allows for the recovery and reuse of the chiral auxiliary. This concept focuses on the design of a hybrid reagent where a chiral Lewis acid is tethered to the hydroxylamine nucleophile via alkoxide ligation to the metal center (Fig. 15.6).[27] The metal acts as a Lewis acid which will activate the substrate toward conjugate addition. Subsequent addition and cyclization affords product, while the metal complex of the chiral auxiliary could be potentially recovered for further use. In this manner, imide **1.30** is treated with hybrid reagent **1.31** in THF to afford the desired isoxazolidinone in 59% yield and 71% ee.

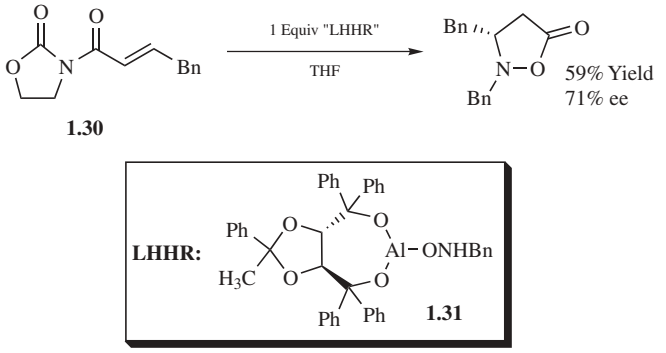
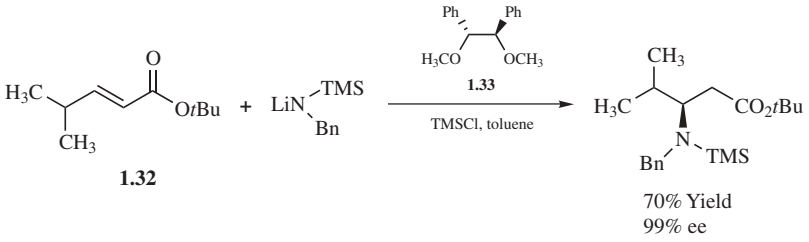


Figure 15.6 Application of chiral aluminum complex to the asymmetric conjugate addition hydroxylamines.

Recently, Doi et al. have developed a similar approach utilizing lithium amides as nucleophiles for conjugate addition, where asymmetric induction is a function of lithium ion chelation by a chiral bis-ether ligand.[28] Ester **1.32** was treated with the lithium amide of *N*-trimethylsilyl-benzylamine in the presence of ligand **1.33** and TMSCl in toluene solvent to afford the desired adduct in 70% yield and 99% ee (Scheme 15.8). To ensure high enantioselectivities, ligand **1.33** is used in slight

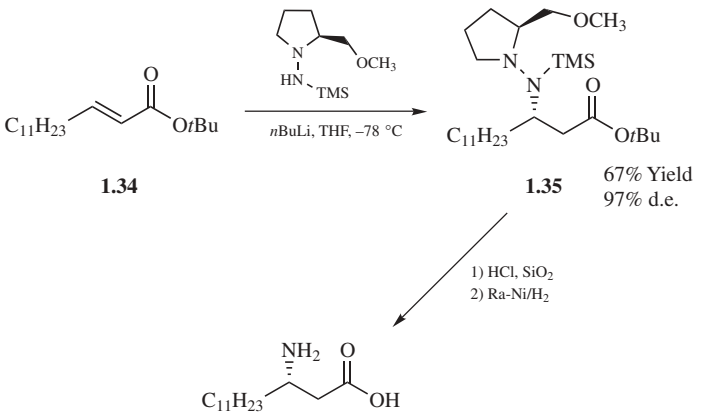


Scheme 15.8

excess relative to lithium amide reagent so that there is no free lithium amide that may undergo conjugate addition in a racemic sense. As an additive, TMSCl improves reaction efficiency by silylating the intermediate enolate, thereby preventing the formation of higher order lithium aggregates. Preliminary results indicate that this reaction can be performed using a catalytic amount of ligand **1.33**. It was shown that this reaction is rather sluggish in the absence of ligand, indicating a ligand-accelerating effect on reactivity. Using 30 mol % of ligand **1.33**, product is obtained in 75% yield and 70% ee, indicating that a catalytic reaction is viable.

Job et al. have developed a chiral ammonia equivalent based on the widely used (*S*)-2-methoxymethyl-1-aminopyrrolidine (SAMP) chiral auxiliary.[29] The required reagent is synthesized by lithiating SAMP followed by silylation with TMSCl to

afford TMS-SAMP in good yield. The silylation step is critical; otherwise the 1,2-addition product is formed exclusively. Then TMS-SAMP is lithiated and treated with ester **1.34** in THF at −78°C to afford adduct **1.35** in excellent diastereoselectivity (97% de, Scheme 15.9). Again, to minimize competing 1,2-addition, a *t*-butyl ester substrate is used. Subsequent desilylation using a HCl/SiO_2 system followed by hydrogenolytic N–N bond cleavage (with concomitant ester hydrolysis) affords the corresponding β-amino acids. An advantage to this methodology is that the expelled pyrrolidine by-product may be isolated and converted



Scheme 15.9

to SAMP for further use. Utilizing this methodology, Job et al. have developed a protocol to access carbocyclic and heterocyclic β-amino acids via a tandem conjugate addition/cyclization strategy (Fig. 15.7).[30] In this protocol, conjugate addition to substrate **1.36**, which possesses a pendant halide, followed by desilylation and *N*-alkylation affords the heterocyclic framework, while C-alkylation of the resulting enolate affords the carbocycle. Both of these processes after subsequent auxiliary removal afford products in high yields and diastereoselectivities.

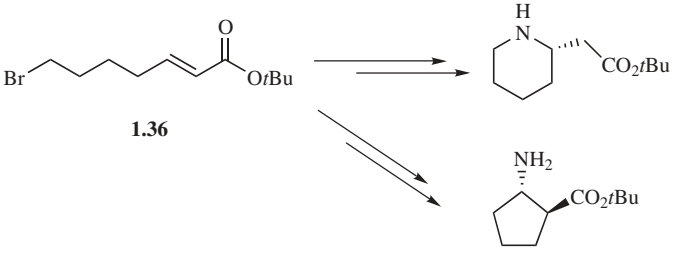
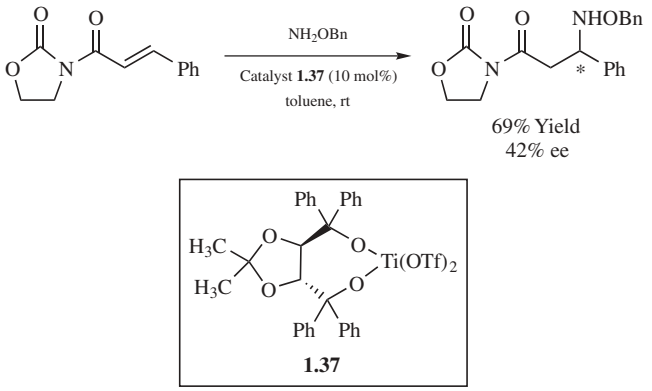


Figure 15.7 Tandem conjugate addition/cyclization.

15.4 METHODS BASED ON ASYMMETRIC CATALYSIS

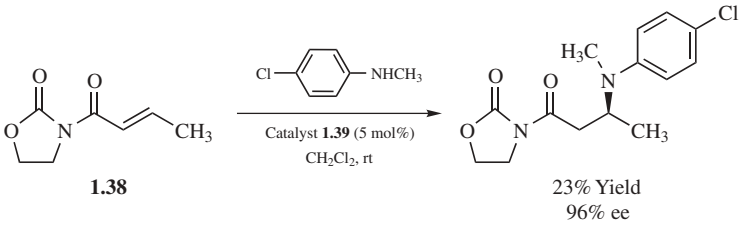
In an attempt to develop an asymmetric, catalytic approach to access β-amino acid derivatives, Falborg and Jørgensen developed a titanium–TADDOL-catalyzed addition of *O*-benzylhydroxylamine to achiral imide substrates.[31] Oxazolidinone-derived imides are treated with *O*-benzylhydroxylamine in the presence of 10 mol % of titanium–TADDOL complex **1.37** to afford product in 69% yield and 42% ee (Scheme 15.10). The adducts can be converted to the desired β-amino acid

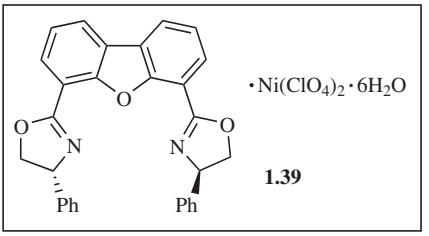


Scheme 15.10

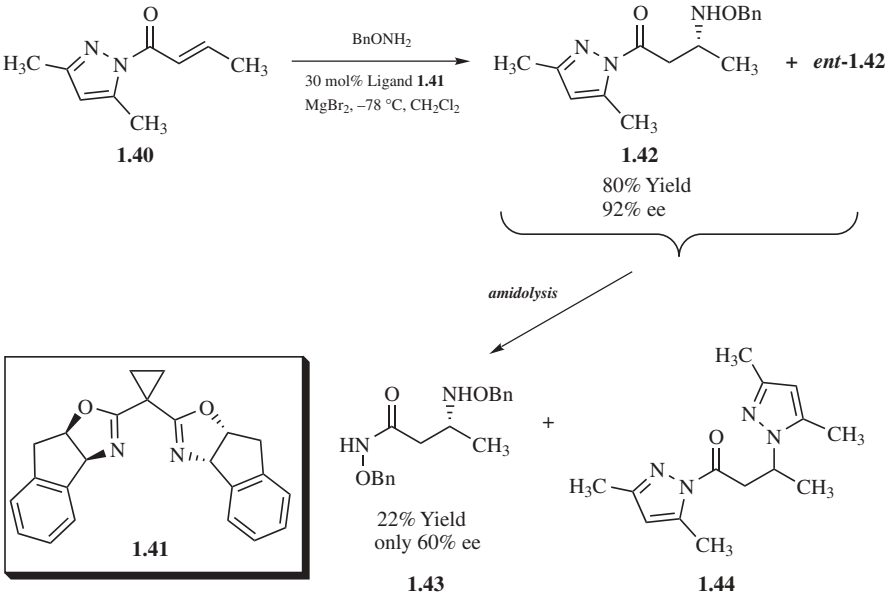
derivative via typical N–O bond cleavage using SmI_2. An improved procedure was later developed by Zhuang et al. whereby the amine nucleophile was changed to a secondary aromatic amine and a nickel–bisoxazoline complex was used as the catalyst.[32] Imide **1.38** was treated with *p*-chloro-*N*-methyl aniline in the presence of 5 mol % of nickel complex **1.39** to afford product in 23% yield and 96% ee (Scheme 15.11). For a similar protocol using aldoximes as the nucleophile, see Ref. 33.

Sibi and co-workers have developed a magnesium-based Lewis acid–catalyzed addition of *O*-benzylhydroxylamine to various unsaturated crotonamide substrates.[34] Substrate **1.40**, when treated with *O*-benzylhydroxylamine in the presence of 30 mol % of magnesium dibromide and bisoxazoline ligand **1.41**, affords product **1.42** in 80% yield and 92% ee (Scheme 15.12). Interestingly, enantioselectivities are enhanced if the reaction is allowed to proceed to greater conversions. This can be explained by careful analysis of the minor products isolated from the reaction. Product **1.43** resulting from amidolysis of **1.42** is obtained in moderate enantiomeric excess (60%), while product **1.44** resulting from conjugate addition of expelled pyrazole was formed in low yields (3–5%). The fact that **1.43** is obtained in low enantiomeric excess (although with the same enantiomer in excess, 60% ee)





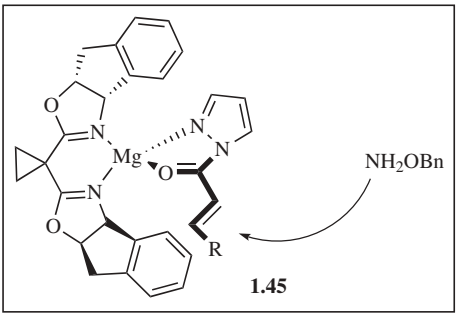
Scheme 15.11



Scheme 15.12

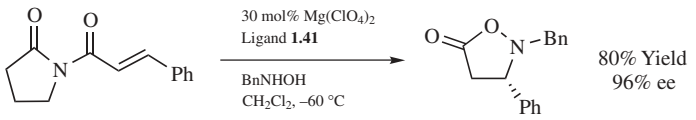
indicates that the minor enantiomer of **1.42** reacts faster to give the amidolysis product, resulting in a kinetic resolution reaction to enhance the enantioselectivity of **1.42**. The sense of asymmetric induction can be explained by model **1.45**. A *re* face addition of *O*-benzylhydroxylamine to a *s*-cis-substrate Lewis acid complex

1.45 where the magnesium either has a tetrahedral or cis octahedral arrangement accounts for the observed product stereochemistry.



1.45

This methodology has been adapted to the synthesis of β-aryl-β-amino acid synthons, a previously difficult product class to access using catalytic methods.[35] Due to the fact that β-aryl-substituted Michael acceptors are not as electrophilic as their β-alkyl counterparts, a variety of achiral heterocyclic templates were screened in an attempt to find acceptable reactivity for conjugate addition. In addition to substrate screens, the more nucleophilic *N*-benzylhydroxylamine was chosen in an attempt to increase reactivity as well. 2-Pyrrolidinone substrate **1.46** was found to undergo efficient conjugate addition with *N*-benzylhydroxylamine in the presence of the $Mg(ClO_4)_2$ complex of ligand **1.41** to afford isoxazolidinone in 80% yield and 96% ee (Scheme 15.13). Although the authors do not convert these synthons to



1.46 **1.47**

Scheme 15.13

the corresponding β-amino acids, reductive N–O bond cleavage should provide access to these compounds. This reaction can be improved by utilizing achiral templates that have functional groups that may participate in ''chiral relay'' to enhance enantioselectivities (Fig. 15.8).[36] When complexed to a chiral Lewis acid, imide **1.48** derived from an achiral pyrazolidinone will exist in either conformation **A** or **B**, depending on the chiral ligand used. The relay group (Z) then enhances the asymmetric influence of the chiral Lewis acid, resulting in higher enantioselectivities compared to when an achiral template devoid of the potential for chiral relay is used. Interestingly, by changing to a zinc-based Lewis acid catalyst **1.49**, the opposite enantiomer is obtained, although in somewhat lower enantioselectivities

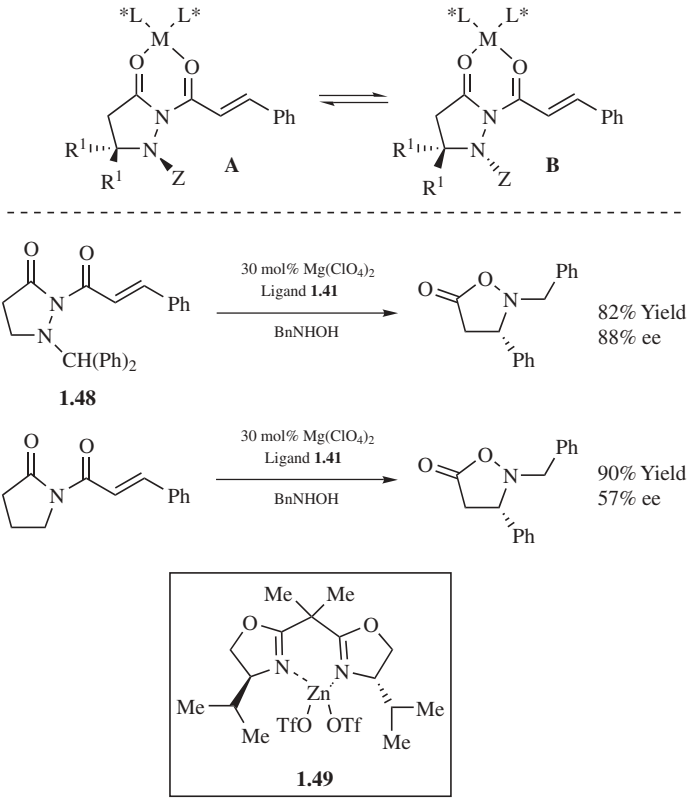
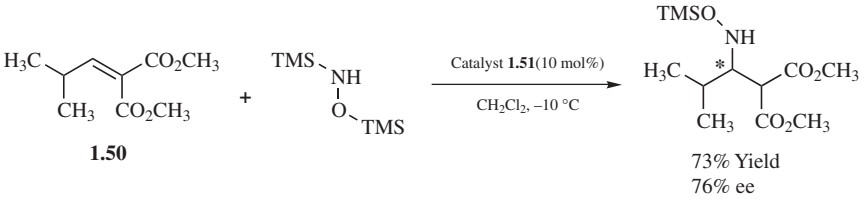


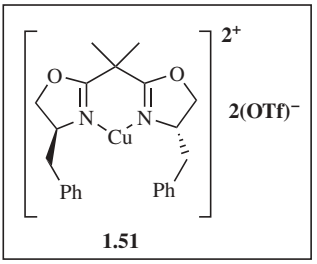
Figure 15.8 Application of ''chiral relay'' concept to asymmetric conjugate addition.

(up to 83%). (See Ref. 37a for an example of temperature-dependent reversal of stereochemistry and Ref. 37b for a recent review of reversal of selectivity.)

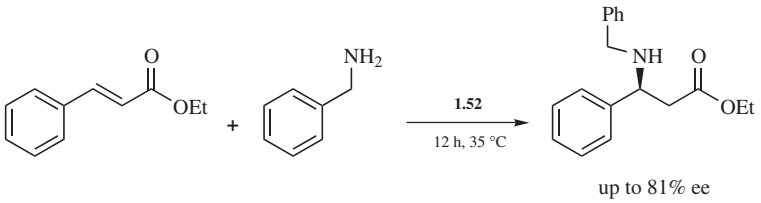
Cardillo and co-workers have developed a Cu(II)-catalyzed conjugate addition of *N*,*O*-bis-trimethylsilylhydroxylamine to alkylidene malonates.[38] Alkylidene malonate **1.50** reacts with *N*,*O*-bis-trimethylsilylhydroxylamine in the presence of 10 mol % of Cu(II) bisoxazoline complex **1.51** to afford product in 73% yield and 76% ee (Scheme 15.14). While the authors do not carry the products on to β-amino acids, one can imagine that a Krapcho-type decarboxylation followed by reductive N–O cleavage would afford the desired products.

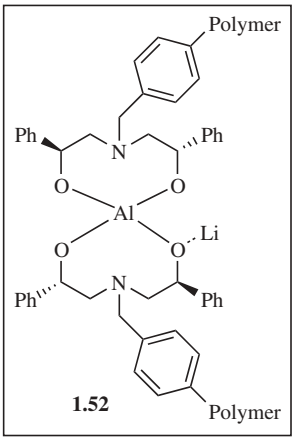
The use of insoluble support-bound catalysts for asymmetric catalysis has received increased attention owing to the possibility of facile recovery and recycling. Sundararajan and Prabagaran have developed an asymmetric Michael addition of various nucleophiles using a polymer-anchored heterobimetallic catalyst.[39] Using this methodology, benzylamine can be added to *trans*-ethyl cinnamate in the presence of catalyst **1.52** to give product in 60% yield and 81% ee (Scheme 15.15). Notably, the polymeric catalyst may be recovered by simple filtration and





Scheme 15.14



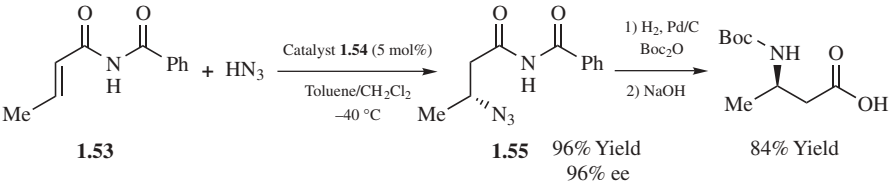


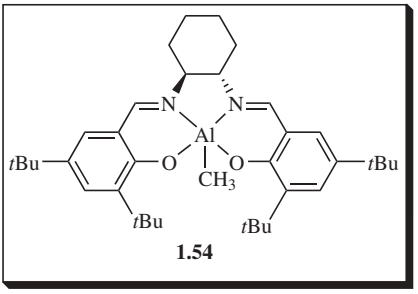
Scheme 15.15

reused in subsequent conjugate addition reactions after being reactivated by treating with lithium aluminum hydride. However, the reactions performed with recycled polymer suffer from lower enantioselectivities.

Myers and Jacobsen have developed a method whereby hydrazoic acid (HN_3) is added selectively to a range of imide substrates with high yields and selectivities by

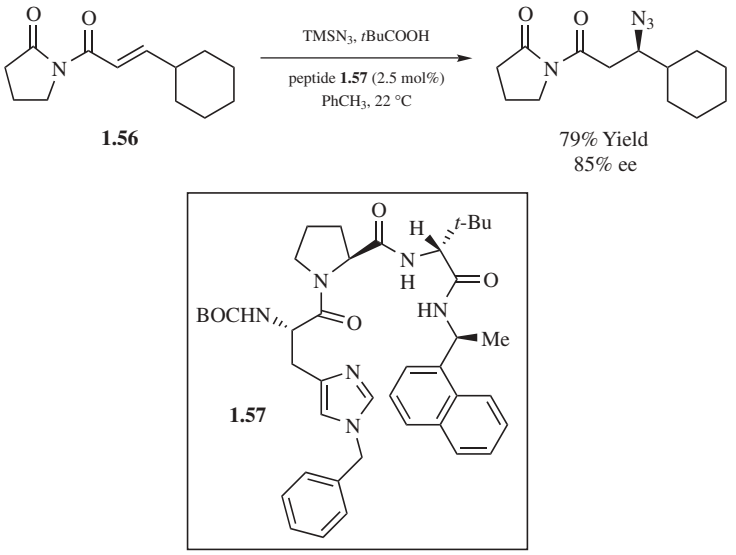
using a readily available chiral (salen) Al(III) complex.[40] Imide **1.53** is treated with hydrazoic acid in the presence of 5 mol % of aluminum complex **1.54** to afford adduct **1.55** in 96% yield and 96% ee (Scheme 15.16). After screening a host of readily available Michael acceptors, it was found that the imide functionality was critical for high selectivities (*N*-alkylmaleimides are excellent substrates as well). Product **1.55** can be converted to the desired β-amino acids in two simple steps; reduction of the azide in the presence of Boc_2O affords an intermediate carbamate which can be hydrolyzed using NaOH to afford the protected amino acid in 84% yield over two steps.





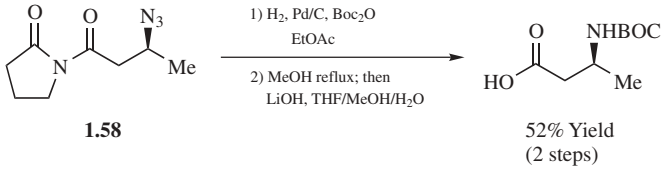
Scheme 15.16

In 1997 Lakshmipathi and Rama Rao developed a tertiary amine base-catalyzed (i.e., Et_3N) addition of hydrazoic acid to various crotonate esters.[41] Inspired by this method, our research group set out to develop a peptide-based asymmetric variant of this conjugate addition reaction. In addition, we wished to develop a variant of the process that would avoid the use of stock solutions of the highly toxic and shock-sensitive hydrazoic acid.[42] Our first goal was to investigate whether commercially available azidotrimethylsilane ($TMSN_3$) was a suitable reagent to generate HN_3 in situ. It was found that various α,β-unsaturated carbonyl compounds undergo facile conjugate addition of azide using $TMSN_3$, a carboxylic acid source, and a substoichiometric amount (20 mol %) of various tertiary amine catalysts.[43] With a potentially safer protocol in hand, we set out to develop an asymmetric variant utilizing peptidic catalysts that have been shown to form stable conformations in organic solvent and catalyze kinetic resolution reactions with good enantioselectivities.[44] Through efforts in both solid-phase and solution-phase catalyst synthesis and screening, catalyst **1.57** exhibited moderate to good enantioselectivities in the conjugate addition of azide to various imide substrates (Scheme 15.17).[45] (For X-ray and solution-phase structure determination of a



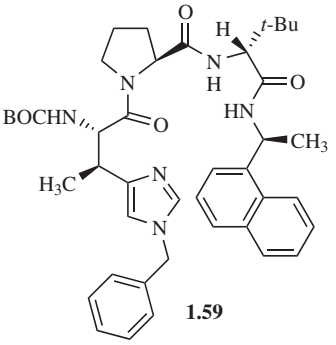
Scheme 15.17

related catalyst, see Ref. 46.) For example, imide **1.56** undergoes facile conjugate addition catalyzed by peptide **1.57** to give the corresponding β-azido imide in 79% yield and 85% ee. It was found that bulky substituents on the β-position of the imide enhanced enantioselectivity. The azido-imide products can be converted to the desired β-amino acid derivatives via a reduction followed by pyrrolidinone removal:



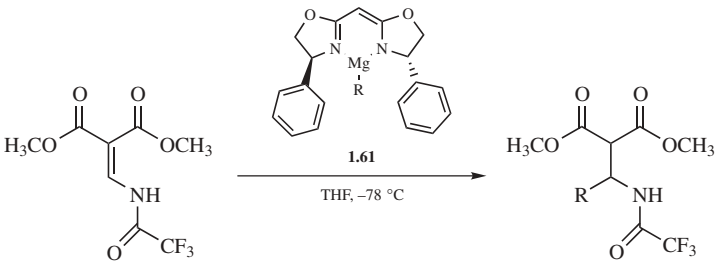
(15.3)

In this manner, imide **1.58** is reduced with H_2, Pd/C in the presence of BOC_2O, followed by methanolysis and LiOH hydrolysis to afford the corresponding protected β-amino acid derivatives. In an effort to increase enantioselectivities, a series of peptides which incorporated β-alkylated histidine residues was synthesized and screened for selectivity enhancement.[47] The goal was to develop conformationally constrained histidine analogs that, when incorporated into a peptide backbone, would serve to rigidify the overall secondary structure of the catalyst, thereby leading to higher enantioselectivities. (For an excellent review on the conformational design of open-chain compounds, see Ref. 48.) Rigidified catalyst **1.59** proved to be a more selective catalyst, delivering azide products with higher enantioselectivities than the parent unsubstituted peptide **1.57**.



1.59

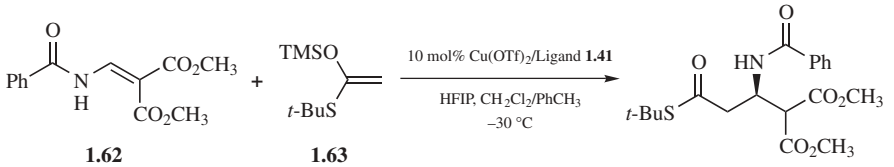
An alternative disconnection for the synthesis of β-amino acid derivatives would be via a conjugate addition of a carbon-based nucleophile to an α,β-unsaturated enamide substrate. Sibi and Asano have developed a protocol whereby chiral organomagnesium amides add to enamidomalonates in high yields and enantioselectivities.[49] Enamidomalonate substrate **1.60** reacts with organomagnesium reagent **1.61** to afford the corresponding adduct in good yields and up to 94% ee:



1.60 up to 94% ee (15.4)

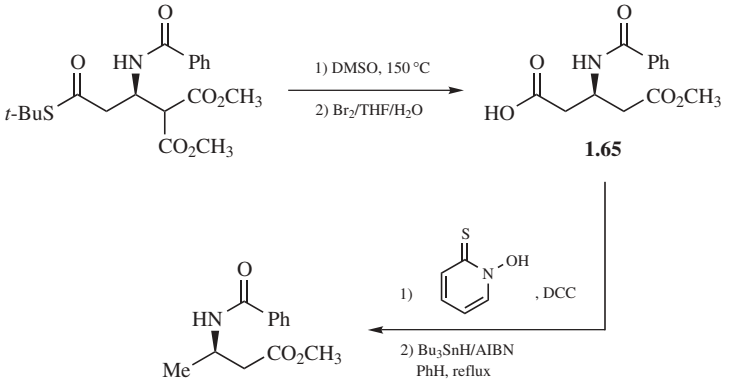
Experimental evidence indicates that the source of asymmetric induction is the result of the chiral nucleophile itself, rather than a substrate–magnesium complex that could form after amide deprotonation. Data that support this include an experiment where the chiral magnesium diamide is formed via amide deprotonation and reaction with **1.61** (R = Br). Upon treatment with EtMgCl, product in low enantiomeric excess is obtained (22% ee).

An alternative C–C bond-forming reaction involving a Mukaiyama–Michael-type addition to enamidomalonates was developed by Sibi and Chen.[50] Enamide substrate **1.62** was reacted with *O*,*S*-ketene silyl acetal **1.63** in the presence of $Cu(OTf)_2$/ligand **1.41** complex (10 mol %) to afford product in good yields and up to 89% ee.



1.62 **1.63** **1.64** 96% Yield 89% ee (15.5)

It was found that other enolsilanes add under these conditions, but with lower enantioselectivities. The conjugate addition products can be converted to the desired β-amino acid derivatives in an efficient manner (Scheme 15.18). Adduct **1.64** is treated under Krapcho decarboxylation conditions followed by thioester hydrolysis to provide desymmetrized glutarate derivative **1.65**. Radical decarboxylation following Barton's conditions affords the corresponding β-amino ester.



Scheme 15.18

The chemistry illustrated above includes a number of impressive advances in the field of stereoselective synthesis of β-amino acid derivatives. However, with the ultimate goal being an "ideal synthesis"[51]—use of simple precursors to afford the desired amino acid in one step and in optically pure form—there still exists the need for further development. With the rate of discovery in the field of asymmetric catalysis ever-increasing,[52] it may be possible in the future to synthesize any desired optically pure β-amino acid in one step from readily available starting materials. Until that goal is realized, new frontiers continue to exist in this exciting field.

General Preparation of Substrates* To a vigorously stirred solution of crotonic acid (8.71 mmol) in 10.0 mL of anhydrous CH_2Cl_2 was added pyridine (9.58 mmol) in one portion. The resulting solution was cooled to 0°C followed by addition of trimethylacetyl chloride (9.59 mmol) via syringe. The resulting cloudy solution was allowed to warm to room temperature and was stirred for a total of 30 min. The reaction mixture was poured into 75 mL of Et_2O and filtered through a cotton plug. Concentration of the filtrate provided crude, mixed anhydride which was used immediately without further purification.

To a vigorously stirred suspension of solid sodium hydride (10.02 mmol) in 20.0 mL of anhydrous CH_2Cl_2 at 0°C was added 2-pyrrolidinone (8.71 mmol) via syringe dropwise. The reaction was allowed to stir at 0°C for 30 min or until H_2 gas evolution ceased. The crude mixed anhydride was then added as a solution

*For detailed experimental procedures with spectral data for the described compounds see Ref. 45 and 47.

(10 mL/CH_2Cl_2) via syringe. The reaction mixture was allowed to stir at room temperature for 12 h, whereupon it was poured into distilled water and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to a crude oil which was purified via silica gel flash column chromatography (15–20% EtOAc/hexane) to provide analytically pure substrate.

General Procedure for Asymmetric Azidation with Peptide-Based Imidazoles To a stirred solution of unsaturated imide (0.141 mmol) in anhydrous toluene (0.470 mL) was added azidotrimethylsilane (0.536 mmol) at room temperature. Trimethylacetic acid (0.141 mmol) was then added in one portion followed by 2.5 mg of peptide catalyst (2.5 mol %). The reaction was capped and allowed to stir at room temperature for 24 h. The reaction mixture was then diluted with ether (10 mL) and washed with saturated. $NaHCO_3$ solution (1×10 mL) followed by a 10% aqueous citric acid solution (1×10 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to give the desired azido imides.

Synthesis of Peptide Catalysts All peptide catalysts were prepared employing standard solution-phase coupling techniques, utilizing commercially available amino acid derivatives with EDC [1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride] as the coupling agent and HOBt (1-hydroxybenzotriazole) as a racemization suppressant. The resulting peptides were then purified by silica gel flash column chromatography (2.5–5% MeOH/CH_2Cl_2).

Procedure for Conversion of Azide 1.58 to Corresponding BOC-Protected β-Amino Acid To a stirred solution of **1.58** (3.24 mmol) in 5.0 mL EtOAc was added BOC_2O (3.90 mmol). The reaction flask was purged with argon, and to this solution was added 10 mol % of 10% Pd/C. The reaction flask was purged 3 times with H_2 (balloon), then stirred under an H_2 atmosphere for 18 h at room temperature. The reaction mixture was then purged with argon and filtered through Celite. The filtrate was concentrated to an oil, then purified via silica gel chromatography using 15% EtOAc/hexane to give the resulting BOC-protected amino imide. This compound was then dissolved in high-performance liquid chromatography (HPLC) grade MeOH (2.60 mmol in 10.0 mL) and heated at reflux for 24 h. The reaction mixture was cooled to room temperature, then concentrated to an oil. The resulting oil was purified by silica gel chromatography to give the corresponding methyl ester. The resulting methyl ester (1.76 mmol) was then dissolved in THF/MeOH/H_2O (2:1:1, 5 mL). To this solution was added LiOH (3.53 mmol) and the resulting solution was stirred for 12 h at room temperature. The reaction mixture was then concentrated to remove the volatile organics, diluted with 10.0 mL of distilled H_2O, washed (2×10 mL of CH_2Cl_2), and acidified with 15 mL of a 10% aqueous citric acid solution. The aqueous layer was then extracted with 10 mL of CH_2Cl_2, salted with NaCl(s), and extracted again with 10 mL of CH_2Cl_2. The organic layers were combined, dried over sodium sulfate, and filtered. Concentration of the filtrate yielded the desired BOC-protected β-amino acid (0.328 g, 50% from **1.58**).

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CHAPTER 16

Preparation of Enantiopure β-Amino Acids via Enantioselective Conjugate Addition

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16.1 INTRODUCTION

During the last decade, stereoselective synthesis of β-amino acids has received considerable attention due to their biologically important properties, their occurrence in natural products, and their use as potential precursors for β-lactams.[1] The β-amino acids in free form show interesting pharmacological properties. Functionalized β-amino acids are also key components of a variety of bioactive molecules, such as taxol, one of the most active antitumor agents which contains phenylisoserine as its side chain.[1] Given the significance of β-amino acids, the development of their synthesis in optically pure form has become an important and challenging endeavor for organic chemists in recent years.

Among approaches available to date, conjugate addition of an amine nucleophile to α,β-unsaturated carboxylic acid derivatives represents one of the most attractive and versatile methods for the synthesis of enantiopure β-amino acids (Scheme 16.1).[2] There are three major ways to achieve asymmetric induction in conjugate addition reactions via the use of chiral acceptors, chiral nucleophiles, or chiral catalysts. In contrast to the large numbers of diastereoselective examples reported in the literature, only in the last 5 years have tremendous achievements been made in the area of enantioselective conjugate amine additions. This review will focus on recent progress of such examples from 1997 to the present with an emphasis on asymmetric catalysis.

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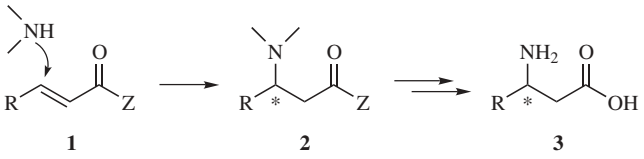
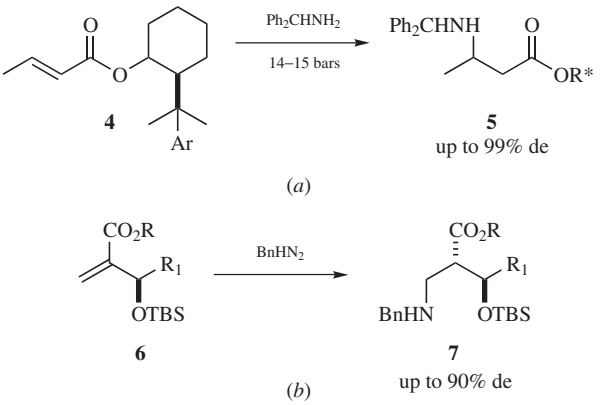


Scheme 16.1 Asymmetric synthesis of β-amino acid via conjugate amine additions.

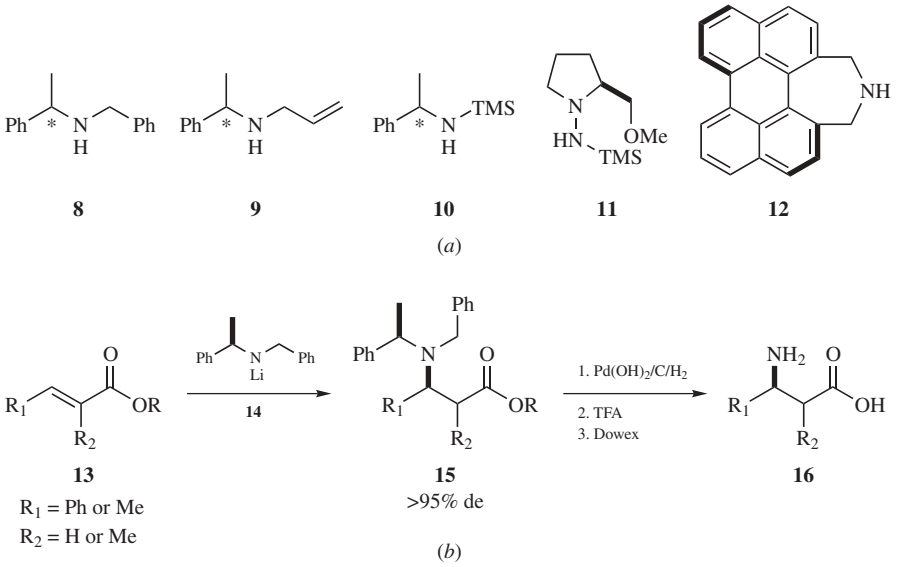
16.2 CONJUGATE ADDITION OF ALKYL OR AROMATIC AMINES

The addition of an achiral amine to chiral esters or imides has been reported in the literature most notably by Dumas et al. in the highly diastereoselective addition of diphenylmethanamine to 8-phenylmenthol-derived chiral crotonates under high-pressure conditions (Scheme 16.2*a*),[3] Perlmutter and Tabone's synthesis of anti-α-substituted β-amino esters via diastereoselective conjugate addition of $BnNH_2$ to chiral 2-hydroxyalkylpropenoates (Scheme 16.2*b*),[4] as well as some elegant work by others.[5]



Scheme 16.2 Conjugate addition to chiral esters: (*a*) Dumas et al.; (*b*) Perlmutter and Tabone.

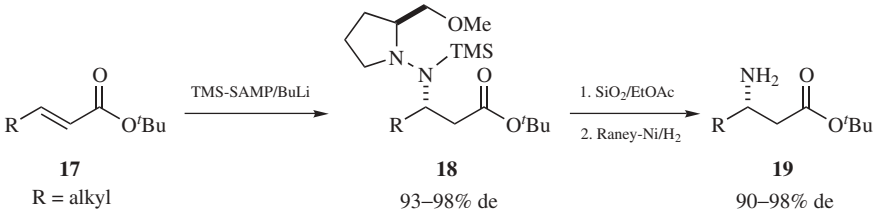
On the other hand, lithium amides, derived from readily available chiral amines **8–12**, have been extensively used as synthetic equivalents of ammonia in conjugate addition reactions (Scheme 16.3*a*). Davies et al.[6a] were among the first to demonstrate that lithium *N*-benzylphenylethylamine **14**, a chiral ammonia equivalent, added to different enoates with high diastereoselectivity, after debenzylation with $Pd(OH)_2$ and subsequent hydrolysis, gave enantiopure β-amino acids **16** in good yields (Scheme 16.3*b*).[6] The conjugate amine addition methodology has found broad utility in recent years, which was highlighted by some outstanding examples reported by Davies et al.[7] and others[8] in the stereoselective synthesis of many biologically interesting β-amino acids as well as natural products.



Scheme 16.3 Chiral lithium amide as ammonium equivalent in diastereoselective conjugate addition reactions: (*a*) Common lithium amide precursors; (*b*) (TFA = Trifluoroacetic acid).

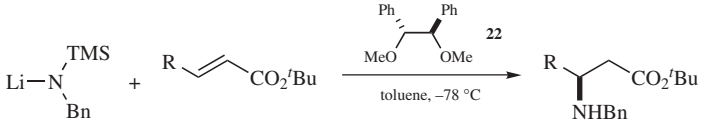
In a similar manner, Enders et al.[6a] and Davies and Fenwick[6b] have explored the use of tetramethylsilane–(*S*)-2-methoxymethyl-1-aminopyrrolidine (TMS-SAMP) as a nucleophile in an aza analogous Michael addition process, which yielded *N*-silylated β-hydrazinoesters **18** in up to 98% de (Scheme 16.4). To suppress the competing 1,2-addition pathway, silylated SAMP as well as *t*-butyl esters **17** were required in this transformation. Furthermore, hydrazinoesters **18** were converted to β-amino esters in two easy steps via silica gel–mediated desilylation followed by cleavage of the hydrazine linkage using Raney Ni.

Recently, Doi et al. have developed a highly efficient method for the synthesis of enantiopure β-amino acids via the conjugate addition of an achiral lithium amide



Scheme 16.4 Conjugate addition of chiral amine nucleophiles.

20.[9] In the presence of 3.6 eq. of chiral ligand **22**, lithium amide **20** added smoothly to enoates **21** at −78°C, providing the desired product with up to 98% ee (Scheme 16.5). The amount of **20** used was one of the crucial factors in determining the efficiency of the reaction: Lowering the amount of **20** from 3.0 eq. to 1.5 eq. produced **23** with a drop in enantioselectivity and yield (compare entries 1 and 2, Scheme 16.5). Another interesting observation of their study was that the addition of 5 eq. of TMSCl helped to regain the efficiency of the reaction (entry 3, Scheme 16.5), possibly via the conversion of lithium ester enolate to an inert silyl enol ether.



20 **21** R = aryl, alkyl **23** up to 98% ee

Entry	**20** (eqs)	**22** (eqs)	Time (h)	Yield (%)	ee (%)
1	3.0	3.6	0.7	92	93
2	1.5	1.8	2.0	81	82
3*	1.5	1.8	5.0	97	97

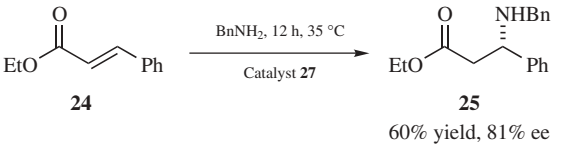
* 5 eq. of TMSCl was added together with **21**

Scheme 16.5 Enantioselective conjugate addition of lithium amide **20**.

Sundararajan and Prabagaran were able to add $BnNH_2$ to ethyl cinnamate (**24**) enantioselectively in the presence of a novel polymer-supported chiral catalyst (**27**) (Scheme 16.6).[10] It should be noted that only a simple filtration was needed for purification of the final product, and the catalyst could be easily recovered by washing with 1 N HCl and reactivated by reacting with lithium aluminum hydride.

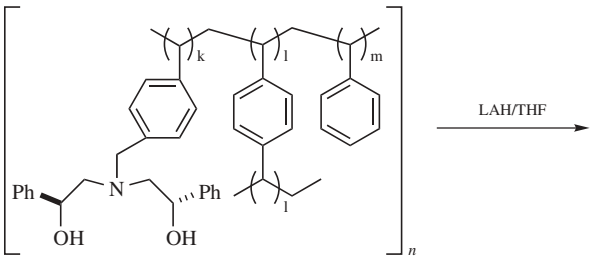
Sharma and co-workers have demonstrated the use of TBAF as an efficient base in promoting the aza-Michael reaction of $BnNH_2$ to sugar-based γ-alkoxy α,β-unsaturated esters **28**.[11] β-Amino ester **29** was obtained in up to 82% yield and 91% de. The presence of TBAF was important, as it not only enhanced the reactivity of the amine nucleophile but also helped to suppress the 1,2-addition pathway (Scheme 16.7).

Stereoselective addition of secondary aromatic amines **31** to acyl pyrrolidinones **30** has been investigated by Zhuang and co-workers.[12] A profound solvent effect was observed in these reactions; better conversions were obtained using CH_2Cl_2 as the solvent whereas only 19% conversion was observed using tetrahydrofuran (THF). The choice of Lewis acid as well as catalyst were also important. DBFOX-Ph (**33**) was the most effective in catalyzing the addition of substituted *N*-methyl



24 **25**

60% yield, 81% ee



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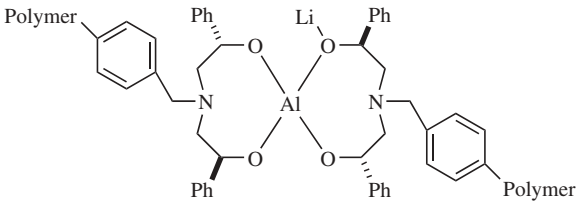

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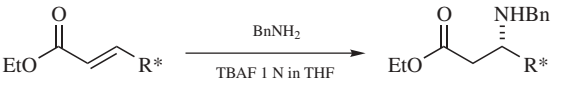
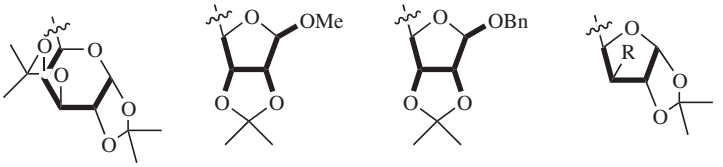
Scheme 16.6 Polymer-supported catalyst-mediated 1,4,-addition of $BnNH_2$ to ethyl cinnamate.



28 **29**



29a 82%, 91% de

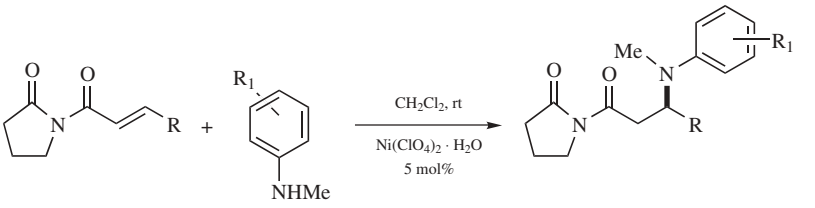
29b 80%, 83% de

29c 75%, 87% de

29d, R = OMe 75%, 87% de

Scheme 16.7 1,4-Addition of benzyl amine.

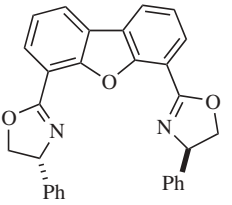
anilines to **30**, providing β-amino acid derivatives **32** in up to 90% ee (Scheme 16.8). The absolute configuration of the product was determined to be S, which agreed with a trigonal bipyramidal geometry around the metal, with ligand **33** occupying three sites and the substrate taking up the other two, leaving the *re* face of the alkene available for amine additions.



30 **31** **32**

Substrate	Amine R_1	Yield (%)	ee (%)
R = Me	R_1 = H	62	90
R = Me*	R_1 = H	19	84
R = Me	R_1 = *m*-MeO	73	89
R = Me	R_1 = *p*-Cl	23	96
R = Pr	R_1 = H	25	95
R = COOEt	R_1 = H	93	00

* THF was used as the solvent



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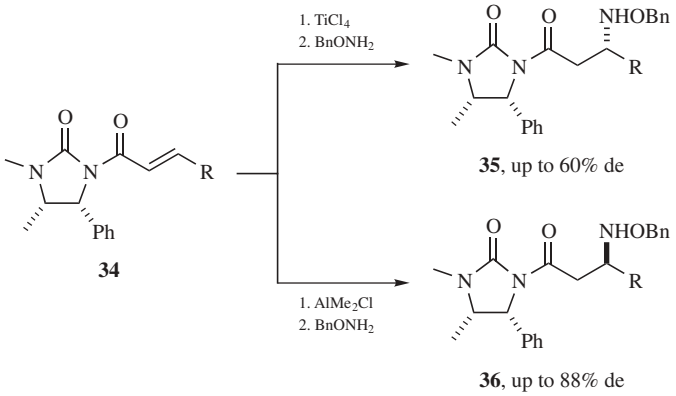
Scheme 16.8 Conjugate addition of aromatic amines.

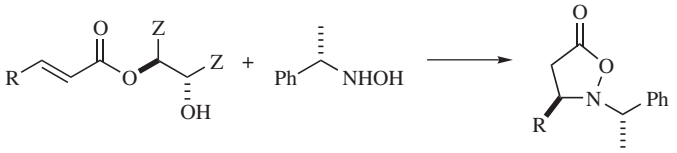
16.3 ADDITION OF HYDROXYLAMINE TO ENOATES

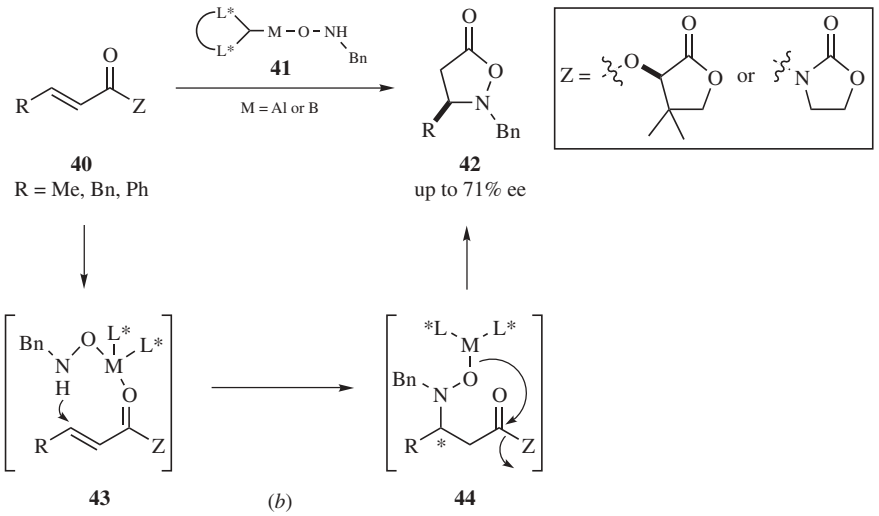
Hydroxylamines are soft nucleophiles and are known to undergo conjugate addition reactions more readily than simple alkylamines, which tend to generate 1,2-adducts as the major product. Cardillo and co-workers have developed an elegant protocol for the addition of *O*-benzylhydroxylamine to chiral imide **34** in the presence of a Lewis acid.[13] The role of the Lewis acid was twofold: to control the rotamer population and to enhance the reactivity of the substrate. Interestingly, an inversion of product stereochemistry was observed when changing the Lewis acid from $TiCl_4$ to $AlMe_2Cl$ (Scheme 16.9).

Ishikawa and co-workers have successfully demonstrated the use of more reactive *N*-substituted hydroxylamines as ''chiral ammonia'' equivalents in conjugate addition reactions. As illustrated in Scheme 16.10*a*, chiral methylbenzylhydroxylamine (**38**) added to chiral ester **37** with up to 84% de as a result of double diastereoinduction.[14] Lee et al. have applied a similar approach to the large-scale synthesis of α-substituted β-amino acids via conjugate addition to various acrylates.[15] Ishikawa et al. have also developed a novel recyclable chiral amine source called Lewis acid hydroxylamine hybrid reagent (LHHR) **41**, where a chiral



Scheme 16.9 Conjugate addition of $BnONH_2$ to chiral imide **34**.

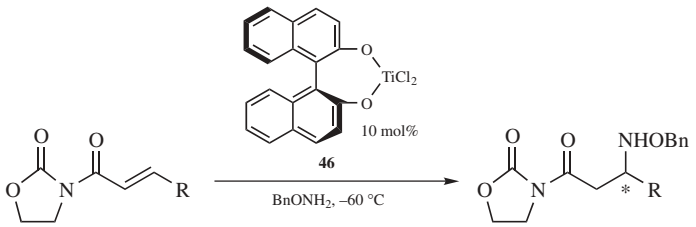




Scheme 16.10 Asymmetric synthesis of isoxazolidinones.

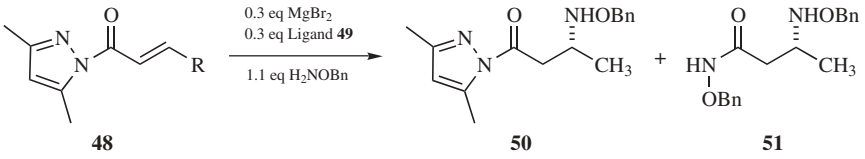
auxiliary was tethered to the hydroxylamine through a metal, which added to enoates **40** with up to 71% ee (Scheme 16.10*b*).[16] The isoxazolidinones (**42**) generated in these processes were transformed to β-amino acids in excellent yields by cleavage of the N–O bond.

The first catalytic example for enantioselective synthesis of β-amino acids via conjugate amine addition was reported by Falborg and Jørgensen in 1996.[17] In the presence of a titanium BINOL (**46**) catalyst, high conversions and moderate enantioselectivities (up to 42%) were obtained in the addition of $BnONH_2$ to *N*-acyloxazolidinones **45** (Scheme 16.11).



Scheme 16.11 $TiCl_2$–BINOL-catalyzed $BnONH_2$ conjugate additions.

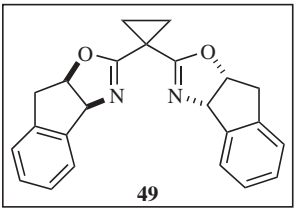
Following Fallborg and Jørgensen's pioneering work, Sibi et al. explored the conjugate addition of *O*-benzylhydroxylamine to 3,5-dimethylpyrazole-derived enoate (**48**) using catalytic amounts of a chiral Lewis acid prepared from $MgBr_2$•OEt_2 and a bisoxazoline **49**.[18] β-Amino acid derivatives (**50**) were synthesized in good chemical efficiency and excellent levels of enantioselectivity (Scheme 16.12). The high enantioselectivities obtained in this process were partially



R	yield (%)	ee (%)
Me	80	92 (*R*)
Ch_2Ph	80	95 (*R*)
i-Pr	76	87 (*S*)
Me[a]	67	59 (*S*)
Ph[b]	24	83

[a]1 equiv $Y(OTf)_3$ used

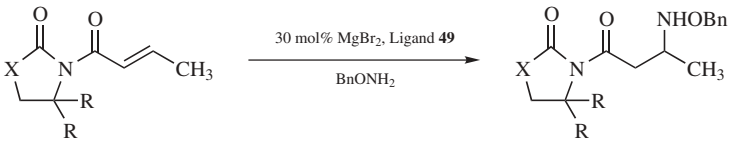
[b]60% of the starting material was recovered



Scheme 16.12 Enantioselective conjugate addition of $BnONH_2$.

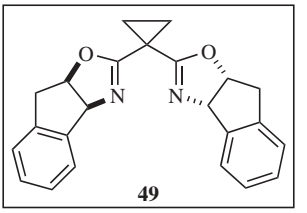
accounted for by a selective 1,2-addition of excess amine to the minor isomer (enantiomer-**50**) to give by-product **51**, thereby increasing the enantioselectivity of **50** by kinetic resolution. The configuration of the product was found to be dependent on the Lewis acid employed: Products with opposite configurations were obtained in 59% ee when a lanthanide Lewis acid $Y(OTf)_3$ was used in combination with the same ligand.

The same authors have studied the effect of achiral templates on enantioselectivity in these transformations. The addition of *O*-benzylhydroxylamine to oxazolidinone or pyrrolidinone-derived enoates provided product with only up to 71% ee in the presence of the same chiral Lewis acid (entries 1 and 2, Scheme 16.13) due to their less labile nature as compared to 3,5-dimethylpyrazole, and therefore no kinetic resolution was observed with these templates.[19] An interesting observation of this study was that changing the reaction temperature from 0 to −60°C led to a reversal of product stereochemistry in the addition of $BnONH_2$ to 4,4-dimethyl oxazolidinone crotonate (entry 3, Scheme 16.13).[20] Similar reaction outcomes were evident with any substrates having disubstitution at the 4-position. The size of the 4-substituent or the nature of the template (oxazolidinone or pyrrolidinone) was shown to have minimal impact on the selectivity of the reactions (compare entries 3–5, Scheme 16.13).



52 **53**

Entry	Substrate	ee (%), 0 °C	ee (%), –60 °C
1	R = H, X = O	66 (*R*)	66 (*R*)
2	R = H, X = CH_2	68 (*R*)	71 (*R*)
3	R = Me, X = O	50 (*R*)	43 (*S*)
4	R = Ph, X = O	37 (*R*)	44 (*S*)
5	R = Me, X = CH_2	30 (*R*)	25 (*S*)

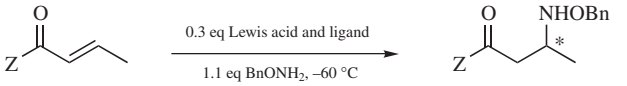


49

Scheme 16.13 An unusual reversal of stereochemistry at two different temperatures.

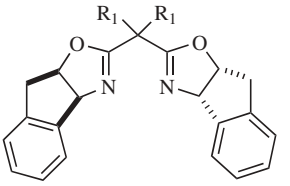
To further develop a more efficient method for the synthesis of enantiomeric products from the same chiral source, Sibi et al. have screened several chiral ligand–Lewis acid combinations as catalysts in the addition of *O*-benzylhydroxylamine to **54** and **55**, and some of the results are highlighted in Scheme 16.14.[19] A simple change of the bridge substitution of the indanol-derived box ligand **49** to dibenzyl group (**58a**) resulted in a reversal of product stereochemistry when pyrrolidinone crotonate **55** was used. In contrast, catalysts prepared from simple bisoxazolines (**59a**, **b**) and $MgBr_2$ were less efficient, with low enantioselectivities (up to 39%) obtained in all the cases and with no inversion of product

stereochemistry (Scheme 16.14). Surprisingly, when $Cu(OTf)_2$ was used as the Lewis acid, product **57** with S-configuration was generated in up to 93% ee in the conjugate addition to **55**. This represents the first efficient catalytic method for the preparation of both enantiomers of β-amino acid derivatives in high purity from the same chiral source.

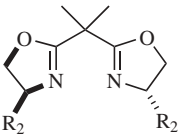


54: Z = 3,5-Dimethylpyrazole
55: Z = Pyrrolidinone

56: Z = 3,5-Dimethylpyrazole
57: Z = Pyrrolidinone



49, **58a**, **b**



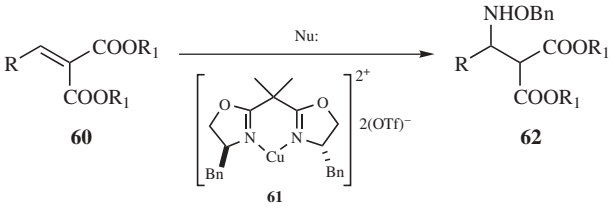
59a, **b**

Ligand	Lewis Acid	ee %, **57**	ee %, **58**
49, $R_1 = -CH_2-$	$MgBr_2$	92 (*R*)	71 (*R*)
58a, R_1 = Bn	$MgBr_2$	65 (*R*)	74 (*S*)
58b, R_1 = H	$MgBr_2$	54 (*R*)	38 (*R*)
59a, $R_2 = {}^{i}Pr$	$MgBr_2$	15 (*R*)	12 (*R*)
59b, R_2 = Bn	$MgBr_2$	39 (*R*)	08 (*R*)
59a, $R_2 = {}^{i}Pr$	$Cu(OTf)_2$	34 (*S*)	93 (*S*)
59b, R_2 = Bn	$Cu(OTf)_2$	30 (*S*)	75 (*S*)

Scheme 16.14 Effect of ligand on selectivity and product configuration in conjugate amine additions.

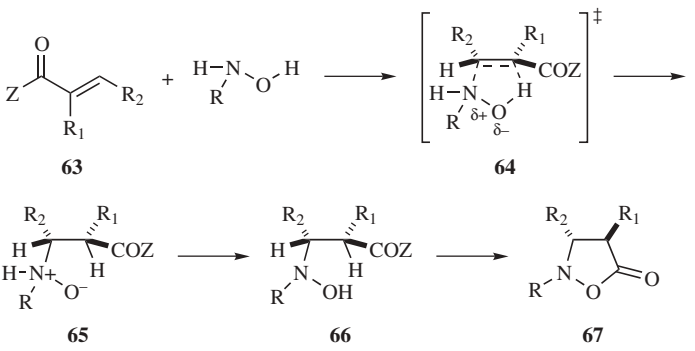
The conjugate addition of *O*-benzylhydroxylamine to doubly activated acceptors, alkylidene, or arylidene malonates **60** was recently investigated by Cardillo et al., where they reported low enantioselectivities (up to 29%) in the presence of a Cu(II)–box–complex **61**.[21] The selectivity could be increased to as high as 76% when a bulkier hydroxylamine, *N*,*O*-bis(trimethylsilyl)hydroxylamine, was used (Scheme 16.15).

As mentioned earlier, *N*-substituted hydroxylamines, which are more nucleophilic than *O*-substituted hydroxylamines, can undergo conjugate addition to α,β-unsaturated enoates to generate isoxazolidinones, precursors for β-amino acids.[22] (For the conversion of isoxazolidinones to β-amino acids, see Ref. 22d.) Niu and Zhao[23] and Moglioni et al.[24] have independently proposed a concerted mechanism for the conjugate addition of *N*-alkylhydroxylamine to enoates, which was confirmed by O'Neil and co-workers in their study of BnNHOH addition to nitriles, sulfones, and nitro compounds (Scheme 16.16).[25]



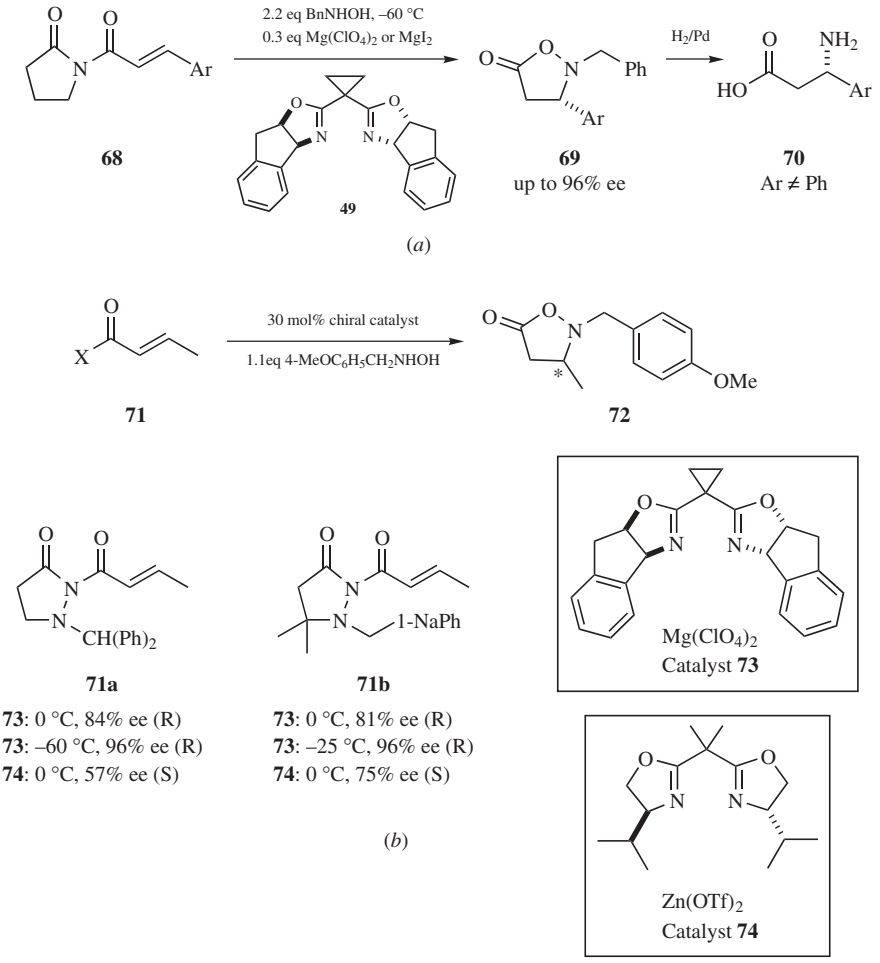
Substrate	Amine Nu:	Temp. (°C)	Yield (%)	ee (%)
R = Ph, R_1 = Me	$BnONH_2$	10	66	20
R = ^{i}Pr, R_1 = Me	$BnONH_2$	–10	60	00
R = ^{i}Pr, R_1 = Et	$BnONH_2$	–20	71	29
R = ^{i}Pr, R_1 = Me	TMSNHOTMS	–10	73	76
R = $CH_2{}^i$Pr, R_1 = Me	TMSNHOTMS	–10	52	74

Scheme 16.15 Conjugate additions to doubly activated substrates.



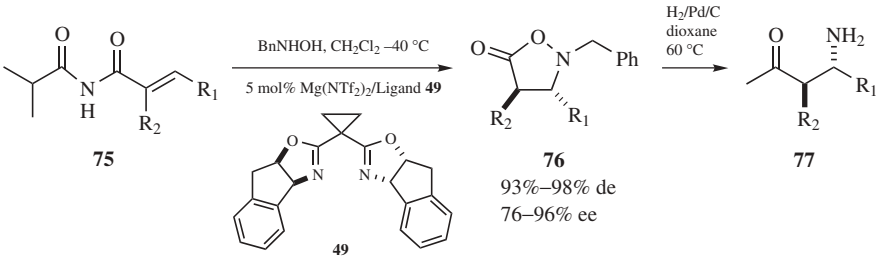
Scheme 16.16 Concerted mechanism of *N*-substituted hydroxylamine conjugate additions.

Taking advantage of the high reactivity of *N*-substituted hydroxylamines, Sibi and Liu have recently described a highly selective addition of BnNHOH to pyrrolidinone-derived enoates (**68**).[26] Their method provided the first effective catalytic route to enantiopure β-aryl-β-amino acid derivatives, which were otherwise difficult to obtain due to the intrinsic low reactivity at the β-carbon of the corresponding enoates (Scheme 16.17*a*). However, long reaction times (2–3 days) and low reaction temperature were still required to achieve >90% ee in these transformations. To overcome this difficulty and to increase the practicality of this methodology, the same authors have reported another interesting account of how to improve the selectivity of conjugate addition at moderate reaction temperatures and using simple ligands.[27] The use of a novel class of achiral templates, pyrazolidinones, to perform chiral relay[28] was the highlight of this report. Furthermore, catalysts **73** and **74** provided enantiomeric products with high purity at practical reaction conditions (Scheme 16.17*b*).



Scheme 16.17 Enantioselective conjugate addition of *N*-substituted hydroxylamines.

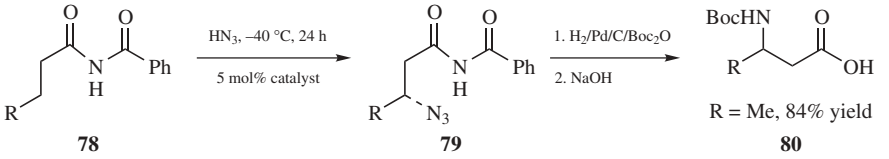
The conjugate amine addition strategy was also extended to the synthesis of α,β-disubstituted β-amino acids.[29] The use of an acyclic achiral imide substrate **75** for both reactivity and rotamer control was important in this transformation, as traditional templates such as oxazolidinone often gave poor rotamer control, leading to low selectivity of the reaction (Scheme 16.18). The effect of magnesium counterion was also investigated, with magnesium triflimide providing the highest enantioselectivity. Utilizing this methodology, a variety of disubstituted isoxazolidinones were prepared in high yields and excellent levels of enantio- and anti diastereoselectivity, which were converted to β-amino acids **77** via hydrogenolysis.



Scheme 16.18 A practical catalytic method for the synthesis of α,β-disubstituted β-amino acids.

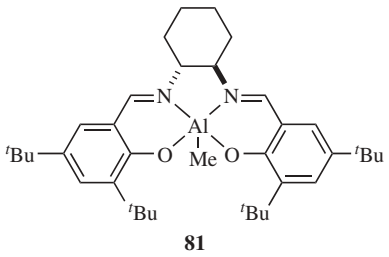
16.4 CONJUGATE ADDITION OF AZIDE

The use of azide as a nucleophile in conjugate addition reactions is well documented.[30] Readily available chiral (salen)Al(III) complex **81**–catalyzed conjugate addition of hydrazoic acid (HN_3) to α,β-unsaturated imides was recently described by Myers and Jacobsen.[31] This procedure provided access to a variety of enantiopure β-alkyl-β-azido compounds. However, the addition to cinnamate (**78**) (R = Ph) was inefficient, and the reaction was incomplete after 24 h at room temperature (Scheme 16.19). The azide group of **79** was then hydrogenated followed by in situ protection with Boc_2O and subsequent hydrolysis to give *N*-Boc-β-amino acid **80** in 84% yield in one single transformation.



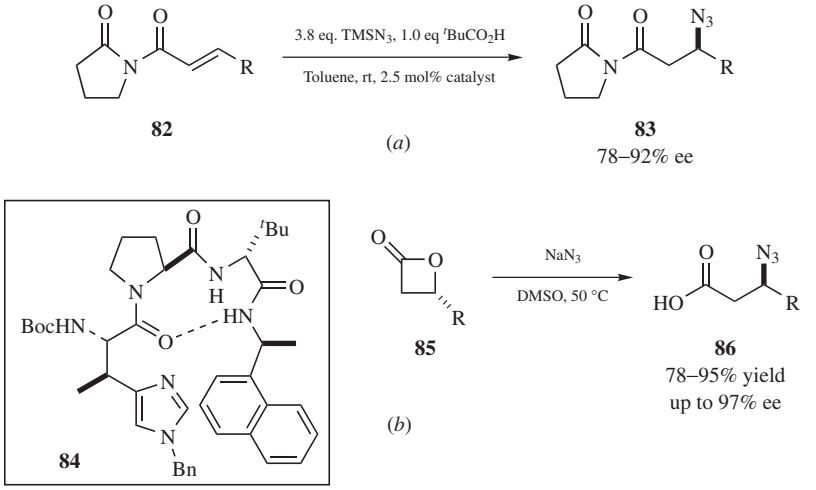
Substrate	yield (%)	ee (%)
R = Me	96	96
R = Pr	97	95
R = ^{i}Pr	98	97
R = ^{t}Bu	99	97
R = Bn	97	95
R = Ph	60	58*

*10 mol% catalyst, at rt



Scheme 16.19 Enantioselective conjugate addition of hydrazoic acid.

Recently, Miller and co-workers developed a milder reaction condition for azidation in which the azide was generated from a 3.8 : 1 mixture of $TMSN_3$ and *t*-BuCOOH in toluene.[32] A peptide-based catalyst (**84**)–mediated conjugate addition of azide to enoate (**82**) yielded β-amino acid derivatives (**83**) in up to 92% ee



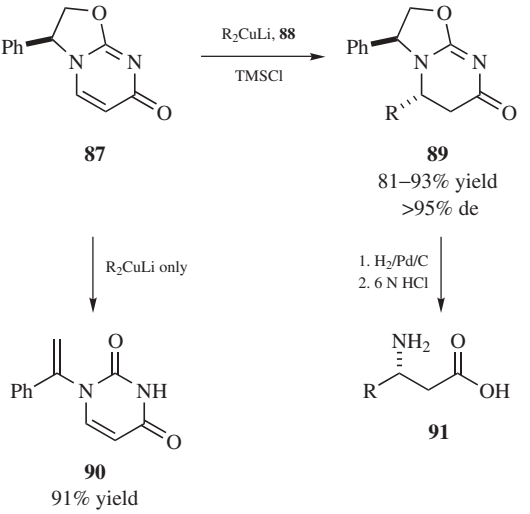
Scheme 16.20 Enantioselective synthesis of β-azido carboxylic acid derivatives. (*a*) Simple peptide-catalyzed azidation; (*b*) Azide-mediated ring opening of β-lactones.

(Scheme 16.20*a*). The optimal catalyst was found to have a β-turn conformation, appended with a τ-(benzyl)histidine residue to enhance the catalytic activity. Metal-free catalysis was another key feature of this process. Additionally, Nelson and Spencer have reported another method for the preparation of enantiopure β-substituted β-azido carboxylic acids (**86**) via the azide-mediated S_N2 ring opening of chiral β-lactones (**85**) (Scheme 16.20*b*).[33]

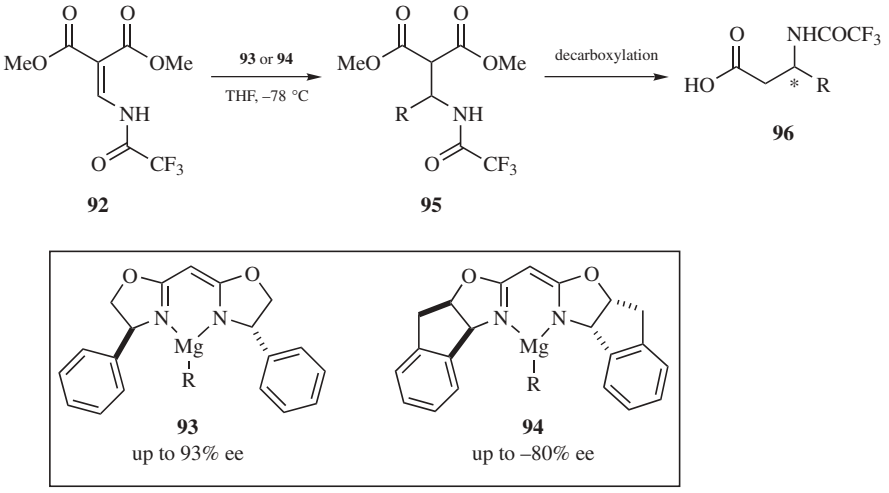
16.5 CONJUGATE ADDITION OF CARBON NUCLEOPHILES

An alternative strategy for the synthesis of β-amino acids is the conjugate addition of a carbon nucleophile to a substrate containing preinstalled nitrogen. Dechoux and co-workers have accomplished the asymmetric synthesis of β-amino acids by means of conjugate addition of organocuprates (**88**) to chiral acceptor **87**.[34] The anti addition of **88** to **87** proceeded with almost complete diastereocontrol, and the use of TMSCl as an additive was essential to prevent the formation of by-product **90** via a β-elimination process (Scheme 16.21). The resulting adducts were converted to β-amino acids **91** in two easy steps.

Sibi and Asano explored the 1,4-addition of chiral ionic nucleophiles to enamidomalonates (**92**).[35] The chiral organomagnesium amides (**93** and **94**) were prepared by treatment of the corresponding bisoxazoline ligand with 1 eq. of *n*-BuLi followed by different Grignard reagents. Their procedure allowed for the enantioselective preparation of a variety of β-amino acids after decarboxylation of the addition products **95** (Scheme 16.22). More importantly, the sense of stereo-induction was reversed with these two chiral nucleophiles.

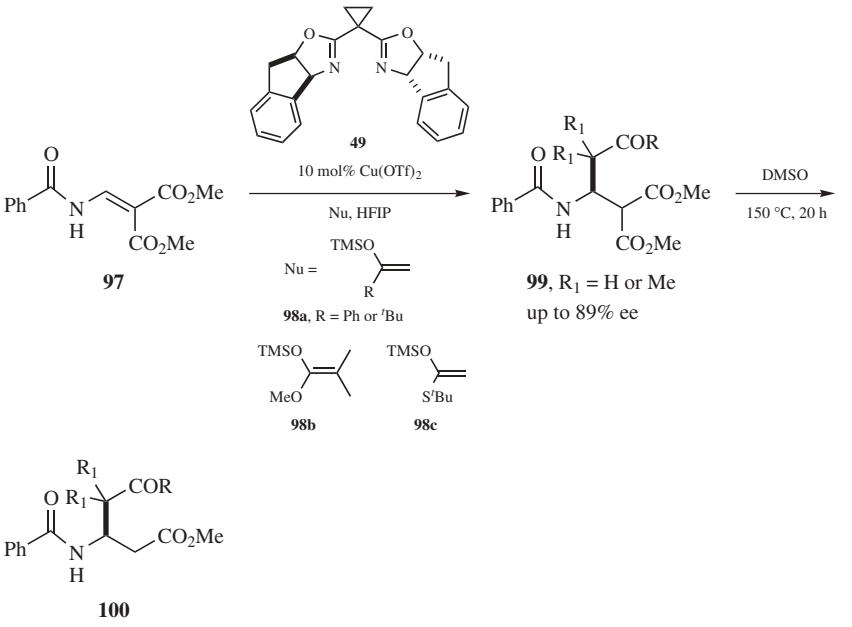


Scheme 16.21 Conjugate addition of organocuprates to chiral acceptor **87**.



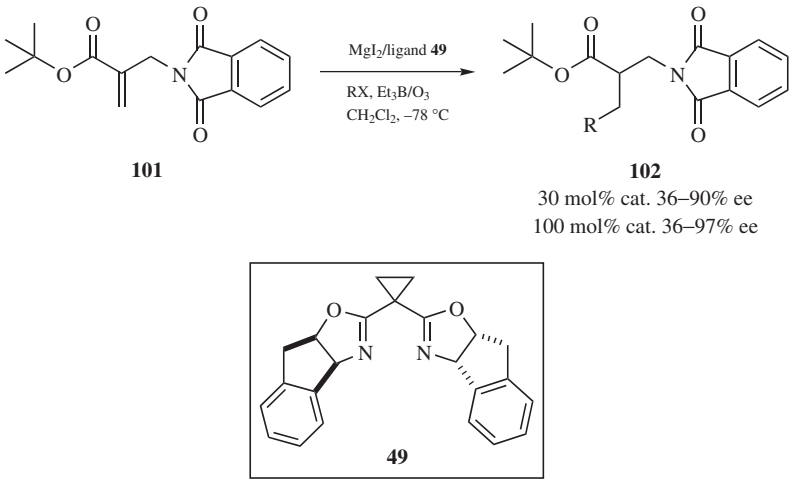
Scheme 16.22 Enantioselective addition of chiral ionic nucleophiles to enamidomalonates.

The reaction between neutral nucleophiles, silylketene acetals **98a–c**, and enamidomalonates **97** was also investigated by the same group.[36] As illustrated in Scheme 16.23, copper triflate– and ligand **49**–catalyzed conjugate addition of various *O*,*S*-ketene or *O*,*O*-ketene silyl acetals proceeded with excellent yields and good enantioselectivities. Monodecarboxylation of the conjugate addition product **99** under the Krapcho condition furnished the desymmetrized glutarate β-amino acid derivative **100** nearly quantitatively.



Scheme 16.23 Enantioselective addition of silylketene acetals to enamidomalonates.

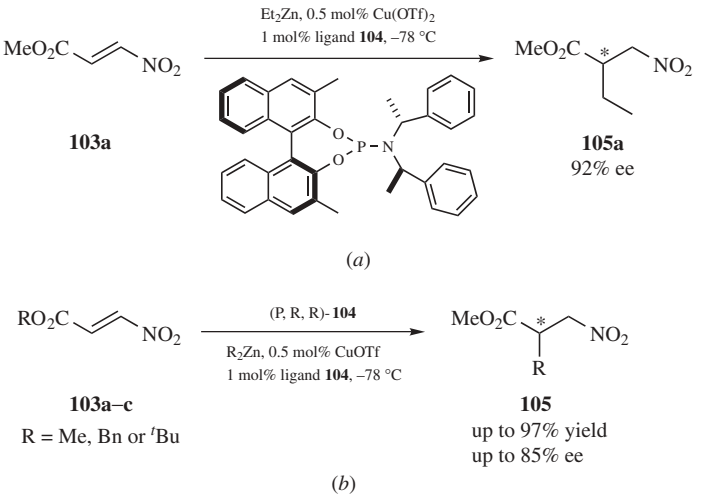
The synthesis of α-substituted β-amino acid derivatives has received extensive scrutiny in recent years. Sibi and Patil have developed an excellent protocol for the enantioselective preparation of β^2-amino acids involving conjugate radical addition to acrylates followed by asymmetric hydrogen atom transfer.[37] As depicted in



Scheme 16.24 Asymmetric synthesis of α-substituted β-amino acid via enantioselective H-atom transfer.

Scheme 16.24, various radicals added to **101** with excellent yield, which after ligand **49** and MgI_2 catalyzed enantioselective H-atom transfer provided α-substituted β-phthalimido esters **102** with modest to good enantioselectivity. Reactions with tertiary or cyclic radicals gave the best selectivity.

The asymmetric conjugate addition of diorganozincs to an activated nitroalkene, methyl 3-nitropropenoate **103a**, provided another efficient route to α-substituted β-amino acid derivatives. Timkus and Sewald have demonstrated this process with success via the use of a copper complex derived from BINOL-based P, N ligand **104** (Scheme 16.25*a*).[38] β-Nitroester **105** was obtained in 92% ee with only 0.5 mol % of copper triflate and 1 mol % of ligand **104**. A similar transformation was also reported by Lilitz et. al. where different dialkylzincs underwent selective conjugate addition to nitro acrylates **103** with excellent chemical yields and up to 85% ee in the presence of a Cu(I) catalyst (Scheme 16.25*b*).[39]



Scheme 16.25 Steroselective synthesis of α-substituted β-nitro esters by conjugate addition of diorganozic to nitroacrylates.

16.6 CONCLUSIONS

In this review we have presented conjugate amine addition strategies for the synthesis of β-amino acids in enantioenriched form. The formation of the C–N bond can be accomplished in good yields and high selectivity. The ready variation in the donor as well as the acceptor and availability of a large number of chiral Lewis acids make this method highly significant for the preparation of β-amino acids.

ACKNOWLEDGMENT

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CHAPTER 17

Biocatalytic Entry to Enantiomerically Pure β-Amino Acids

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17.1 INTRODUCTION

β-Amino acids are becoming extremely attractive as intermediates in organic, medicinal, and peptide chemistry. The synthesis of these amino acids, in their enantiomerically pure form, has been pursued by many in the field, resulting in the publication of several reviews.[1] Although there have been many attempts to synthesize these molecules by catalytic asymmetric methods, many are not convenient for application on a larger scale.

In contrast, biocatalytic methods designed for the resolution of these enantiomers are often easily scaled and environmentally benign. Since all of the enzymes from nature have evolved to promote transformations of naturally occurring compounds but not β-amino acids, one could appreciate that the resolution of β-amino acids or their derivatives, with these naturally occurring enzymes, is a very challenging task. In fact, it is rather amazing that these enzymes, with their associated selectivity, demonstrate even the slightest activity toward amino acids with such unique structural features.

This chapter is a critical review of the recent publications, since 1996, in the field of enzymatic resolution of various β-amino acids, since the prior studies in this area have already been comprehensively examined.[2] For the sake of convenience and organization, the β-amino acids have been categorized according to structures with

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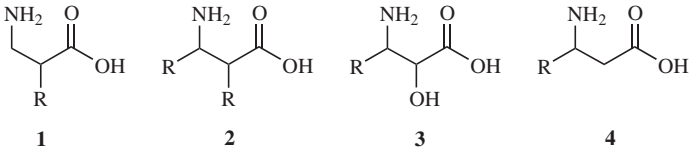
similar characteristics which are influenced by the position and nature of the substituents on the β-alanine skeleton (Scheme 17.1). This can be crucial in the determination of the appropriate biocatalytic method to resolve the enantiomers. The four general structures, which will be covered in this review, are depicted in Scheme 17.1.



Scheme 17.1

17.2 BIOCATALYTIC ENTRY TO ENANTIOMERICALLY PURE β-AMINO ACIDS

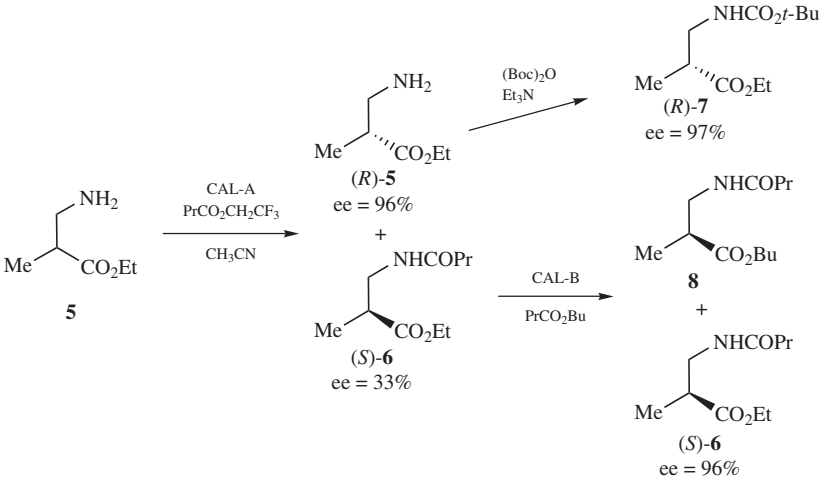
17.2.1 α-Substituted β-Amino Acids

A search of recent literature yielded only one example of the enzymatic resolution of α-substituted β-amino acids. Thus, Solymár et al. introduced a procedure to resolve the enantiomers of α-methyl-β-alanine ethyl esters via a lipase-catalyzed acylation–interesterification process.[3]

The ethyl ester of α-methyl-β-alanine **5** is readily available in racemic form; therefore, it was applied to study the kinetic resolution catalyzed by *Candida antarctica* lipases A and B (CAL-A and CAL-B). Based on previous experiments with CAL-A and CAL-B, butanoate esters were used as acylating reagents. Previous studies revealed that these lipases are known to prefer the butanoate esters to carboxylates with shorter chain lengths. The application of CAL-A for the catalysis of substrate **5** yielded the *N*-butanoylated product **7** as the only product with high enantiomeric excess (97% ee) in diisopropyl ether and 2,2,2-triflouroethylbutanoate as the acylating agent (Scheme 17.2). With the application of the enzyme CAL-B or other substrates, lower enantioselectivity was detected.

After screening a series solvents, acetonitrile was determined to be the most appropriate solvent because of the increased enantioselectivity observed. All attempts to enhance the enantioselectivity by adding water or hydrated salts to sustain constant water activity in the enzymatic reaction were unsuccessful. As expected, the acylation step proceeded with low enantioselectivity (33% ee), presumably due to the distance of the amino group from the chiral center. However, the unreacted (R)-enantiomer **5** revealed an enantiomeric excess of 96% but was isolated in a 30% yield.

It was also reported that the isolation of the (S) isomers of the racemic amidoester **6** could be accomplished by selective interesterification. On the basis of previous results from this group, the enzyme CAL-B was investigated for this process. The stereoselective outcome depended heavily on the size of the α-substituent.



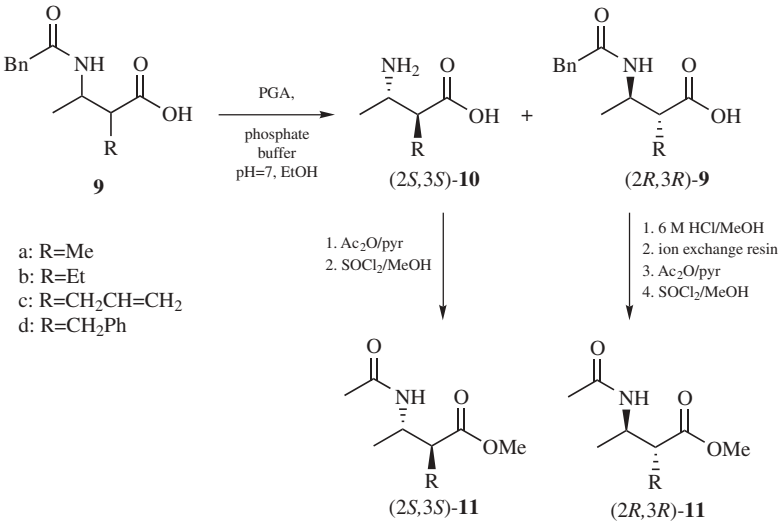
Scheme 17.2

Exploration of various substrates such as butanoates as well as butyl and methyl alcohols at different temperatures revealed the optimal conditions. These included the application of butyl butanoate at room temperature, which was determined according to the best combination of results in optical purities observed for the products and the rate of reaction. It should also be mentioned that, utilizing the opposite enantioselectivities of CAL-A and CAL-B, both enantiomers could be prepared cleanly.

17.2.2 α,β-Disubstituted β-Amino Acids

Notwithstanding the wide application of α,β-disubstituted β-amino acids, few studies have recently been published regarding their enzymatic resolution. Cardillo et al.[4] reported the efficient resolution of α,β-substituted β-amino acids by the hydrolysis of 2-alkyl-3-(phenylacetyl)-amino butanoic acids **9** with penicillin G acylase, PGA (Scheme 17.3). The butanoic acids **9** were easily prepared from the *N*-(phenylacetyl) methyl esters of the commercially available (+)-3-aminobutanoic acid. This procedure, introduced by Seebach and Esterman,[5] involves the treatment of the enolate generated from the (+)-3-aminobutanoic ester and lithium hexamethyldislane (LiHMDS) with alkyl halides. The PGA was selected for this procedure due to its high affinity for the phenylacetyl moiety[6] and previous applications on the industrial scale.[7]

The separation of enantiomers was achieved by the selective hydrolysis of butanoic acids **9** with immobilized PGA at temperatures of 30–35°C in a phosphate buffer of pH 7. The enantiomeric excess was measured after protecting the amino group with an acetate moiety and esterification of the acid to give (2S,3S)-isomer **11**, which was analyzed by gas chromatography (GC). The enantiomeric excess was



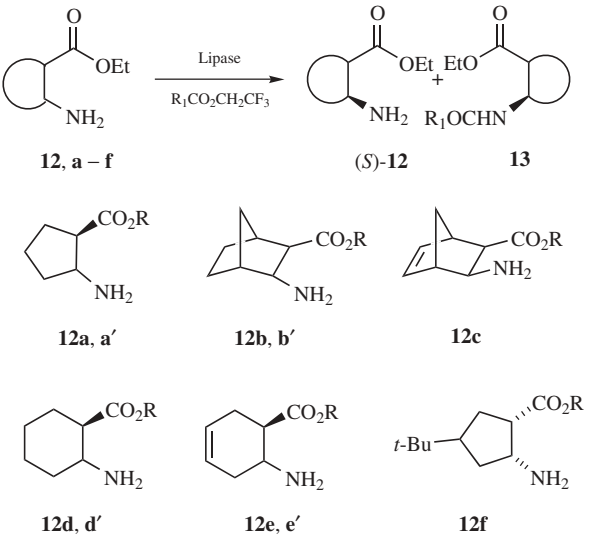
Scheme 17.3

reported to be higher than 94% and the conversion between 47 and 53% depending on the bulk of the substituent in the α-position.

After the separation of reacted amino acids **10**, the amino group of the amido acid **9** was deprotected and the amino acid was transformed to acetoamido-methyl ester **11**, which was characterized by GC. The observed enantiomeric excess was also very high in this case (>94%).

Kanerva's group investigated the enzymatic resolution of both diastereomers for four different alicyclic β-amino acids **12a–b′**, **12d–e′** as well as the cis isomers of amino acids **12c** and **12f** based on acylation of the amino group, bonded to the R stereogenic carbon in the β-position, with various 2,2,2-trifluoroethyl esters.[8] Lipase screening was performed in order to increase the asymmetric induction during the acylation step of the compounds (Scheme 17.4). A number of enzymes were catalytically active but displayed little selectivity. The most promising results were discovered by utilizing lipase PS from *Pseudomonas cepacia* and SP526 (from *C. antarctica*). As expected on the basis of previous results, the lipases directed acylation to the amino group, which resulted in (*R*)-**13**. To improve the selectivity, a series of experiments were conducted in a variety of solvents. However, the application of different solvents, polar and nonpolar, did not give rise to a general explanation for the solvent-dependent reactivity and enantioselectivity of the enzyme.

The selection of an acyl donor with the greatest positive influence on the reactivity was investigated for this enzymatic resolution. Commonly used acylating reagents (acid anhydrides or acetone oxime) cannot be employed for acylation due to competitive reaction rates which lead to racemic products. However, application of 2,2,2-trifluoroethyl carboxylates proved to be enantioselective in several cases. The hydrophobicity of the acyl donor seems to have an opposite effect on the two



Scheme 17.4

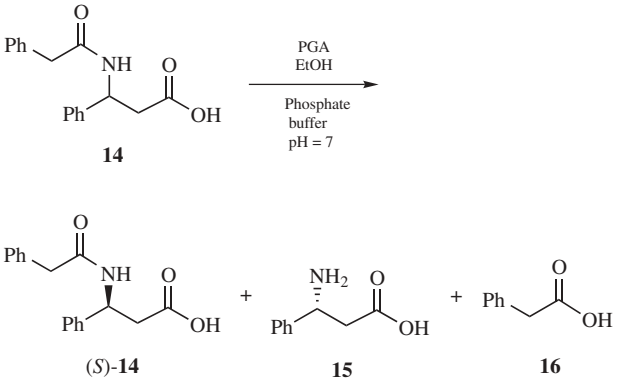
lipases PS and SP526. The reactivity and the enantioselectivity tend to decrease with increasing carbon chain length of the acyl donor when catalyzed by lipase PS; however, the same properties increased when lipase SP 526 was used.

These findings have proven useful for the separation of enantiomers of compounds such as **12**. Greater than 95% ee can be observed for many of the alicyclic β-amino esters by the selective acylation with lipases PS or SP 526 and 2,2,2-trifluoroethyl esters in diethyl ether with application of the proper acylating reagent.

17.2.3 β-Amino-α-Hydroxy Acids

β-Amino-α-hydroxy acids as well as large molecules that incorporate them are a distinct class of β-amino acids due to their biological activity as antitumor and anti–acquired immunodeficiency syndrome (AIDS) agents.[9] Taxol, which contains a β-amino-α-hydroxy acid moiety, has proven to be one of the most active agents in the chemotherapy of cancer cells.[10] However, modifications of the side chains generally decrease and, in some extreme cases, can destroy the activity of the molecule.[11]

Although there have been no recent direct applications of the enzymatic resolution of β-amino-α-hydroxy acids, Cardillo et al. have demonstrated[12] an approach to the synthesis of the methyl ester of (2*R*,3*S*)-*N*-benzoylphenylisoserine. The key step to this method (Scheme 17.5) was the application of PGA to resolve β-phenylisoserine **15** from the unreacted derivative **14** prior to the introduction of the alcohol moiety. This procedure was crucial because the stereochemical outcome of the addition of the hydroxy group is controlled by the previously formed chiral center to achieve the desired enantiomeric purity.

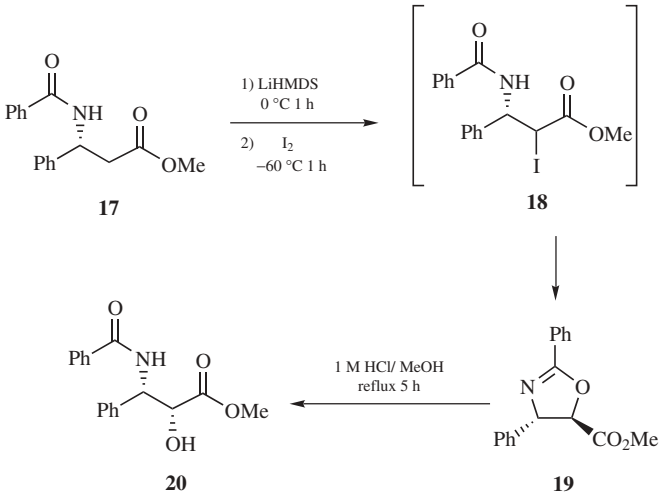


Scheme 17.5

The resolution of the *N*-(phenylacetyl)-3-amino-3-phenylpropanoic acid **14** was accomplished by the selective hydrolysis of the acetyl functionality by PGA in ethanol in the presence of a phosphate buffer adjusted to pH 7. Four hours was the optimal time for the selective deacylation to occur. After this time the unreacted (S)-enantiomer **14** was recovered from the reaction mixture in a 1 : 1 ratio with phenylacetic acid **16**. According to the authors, (3*R*)-3-amino-3-phenylpropanoic acid **15** was obtained enantiomerically pure but no enantioselectivity values were given. However, it was mentioned that the compounds were analyzed by high-performance liquid chromatography (HPLC).

The free amino acid was then transformed to the corresponding *N*-protected β-amino acid under the Schotten–Baumann reaction conditions followed by esterification with thionyl chloride in methanol (Scheme 17.6). The hydroxy group was introduced by the addition of iodine, at −60°C, to the lithium dianion formed from the *N*-protected β-amino ester **17** and LiHMDS in tetrahydrofuran (THF) at 0°C. This resulted in the formation of the corresponding oxazoline, which was isolated after the usual workup with 95% yield and a diastereomeric ratio of 98 : 2. Under acidic conditions the oxazoline was hydrolyzed to form (2*R*,3*S*)-*N*-benzoyl-phenylisoserine methyl ester in 85% yield (Scheme 17.7). The model proposed by Seebach and Prelog,[13] which predicts the addition of the I^+ to occur from the *si* face of the enolate, can rationalize the syn selectivity explaining the observed oxazoline product as well as the (2*R*,3*S*)-*N*-benzoylphenylisoserine formed after hydrolysis.

Scheme 17.6

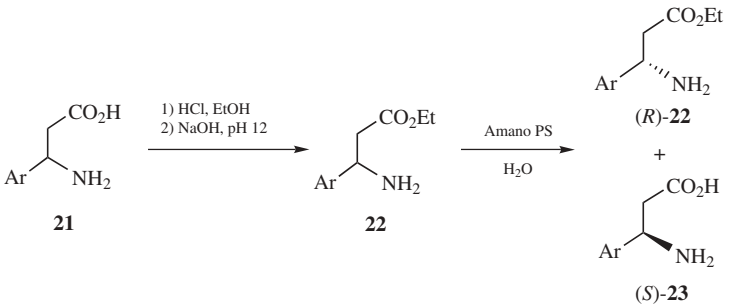


Scheme 17.7

17.2.4 β-Substituted β-Amino Acids

The resolution of β-substituted β-amino acids comprises most of the material that will be reviewed in this chapter. The activity in this area may be due to the increased probability of success for the process. Since most of the procedures described within the literature involve the transformation of the amino/amide group, it stands to reason that the stereochemical outcome would be enhanced due to the proximity of the chiral carbon to the amino group that is being transformed during the reaction.

Faulconbridge et al. reported the first enzymatic resolution of aromatic β-amino esters wherein the nitrogen atom was not protected.[14] The racemic esters of β-aryl-β-alanine **22** studied in this paper can be prepared by esterification of amino acid derivatives which are readily available from the Rodionow reaction of the corresponding aromatic aldehyde (Scheme 17.8).[15] The ester **22** was treated with



Scheme 17.8

TABLE 17.1 Results of Enzymatic Resolution of Aromatic β-Amino Esters

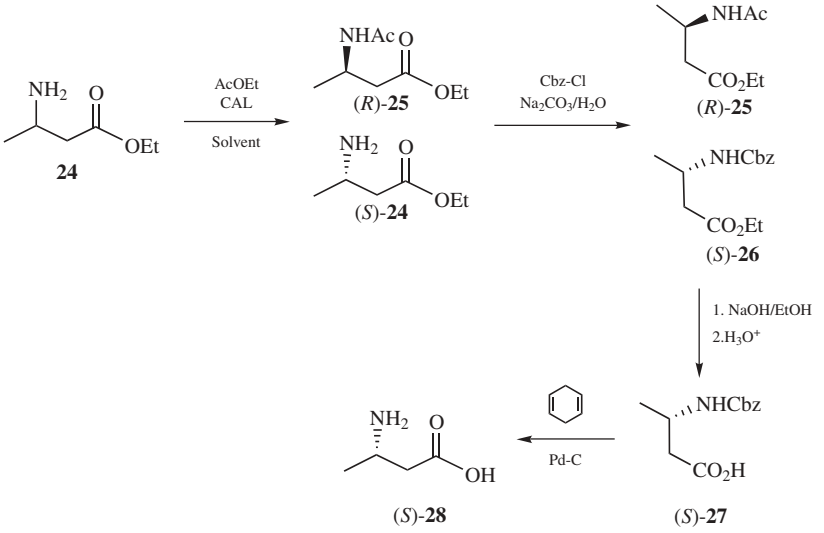
		(*R*)-**22**		(*S*)-**23**	
Entry	Ar	Yield,%	ee, %	Yield, %	ee, %
1	Ph	36	98	44	99
2	2-BrPh	41	96	43	99
3	4-BrPh	18	99	46	99
4	4-FPh	46	90	23	91
5	3-BrPh	42	74	44	77
6	1-Naphthyl	39	99	34	98

various commercially available enzymes to determine the activity and selectivity toward this series of compounds. The most promising results were achieved by the application of the lipase Amano PS from *Burkholderia cepacia* for resolution by selective hydrolysis of the ester function. The results of the collected data are summarized in Table 17.1. It was also determined that the selectivity is highly dependent on the pH value of the media. For instance, racemic phenylalanine ethyl ester **22** yielded the amino acid **23** with an optical purity of 73% ee at pH 7 while 99% ee was observed at pH 8.

Sánchhez and co-workers systematically studied the lipase-catalyzed enantiomeric resolution of ethyl 3-aminobutarate by the comparison of two different pathways, acetylation and aminolysis, to determine the most efficient method for resolution of the enantiomers.[16] The report began with an investigation into the acetylation of racemic β-amino ester **24** catalyzed by CAL in neat ethyl acetate as well as ethyl acetate diluted by 1,4-dioxane with varying reaction times (Scheme 17.9). The synthesis of amido esters allowed the selectivity of the reaction to be analyzed by GC. As one can see from Table 17.2, the acylation process yielded high enantioselectivity and conversion.

The mixture of compounds resulting from the catalytic reaction was treated with benzyloxycarbonylchloride to transform the unreacted β-amino ester (*S*)-**24** into the analogous Cbz derivative (*S*)-**26**. The resultant mixture of amido esters was separated by flash chromatography. The enantiomeric excess of the Cbz derivative was determined by HPLC. Prolonged reaction times allowed for higher conversion of the substrates without compromising the stereochemical outcome of the reaction (Table 17.2). Similar rates of reaction and enantioselectivities were achieved when the acetylation was performed in 1,4-dioxane or ethyl acetate as the solvent. However, less polar solvents such as hexane provided only 15% conversion after 4 days. Although the reaction was very slow, the enantiomeric purity of **25** remained very high (95% ee).

The group then focused on the acylation of benzylamine using the racemic ester **24** as the acyl donor with the same catalyst. Immediately following removal of

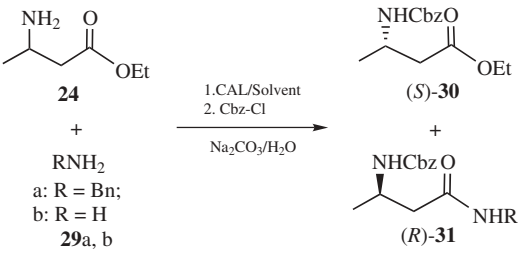


Scheme 17.9

TABLE 17.2 Acetylation of β-Amino Ester 24 Catalyzed by CAL

			Product **25**		Remaining Ester **24**	
Entry	Solvent	Time, h	Yield, %	ee, %	Yield,%	ee, %
1	1,4-Dioxane	8	38	95	49	75
2	AcOEt	6	35	95	52	62
3	AcOEt	12	47	88	45	99

the enzyme by filtration, the reaction mixture was treated with Cbz-Cl to facilitate the isolation as well as provide suitable derivatives for HPLC analysis (Scheme 17.10). Comparing the aminolysis pathway with the previously described acetylation procedure, the corresponding amide **31** was obtained with only



Scheme 17.10

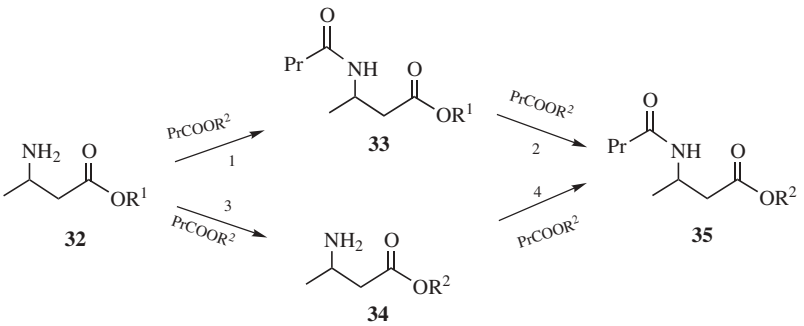
TABLE 17.3 Amidation of Ester 30 in Different Solvent Systems

				Product **31**		Remaining Ester **30**	
Entry	R	Solvent	Time (h)	Yield, %	ee, %	Yield,%	ee, %
1	Bn	1,4-Dioxane	3	22	77	33	55
2	Bn	Toluene	8	15	66	34	93
3	H	1,4-Dioxane	8	33	36	28	71
4	Bn	Toluene	13	40	69	42	62
5	H	TBA	8	27	75	38	98
6	H	1,4-Dioxane	8	3	84	38	87

moderate enantioselectivities in all the solvent systems explored (Table 17.3). However, at 50% conversion, the remaining (*S*)-**30** was obtained with high enantioselectivity (93%) in toluene.

Gedey et al.[17] contributed a procedure useful for the enzymatic resolution of β-amino-esters employing the enzyme CAL-B. In the first example they investigated the application of this lipase on a variety of β-substituted β-amino esters with neat butyl butanoate, 2,2,2-trifluoroethyl butanoate in diisopropyl ether, as well as neat butanol.

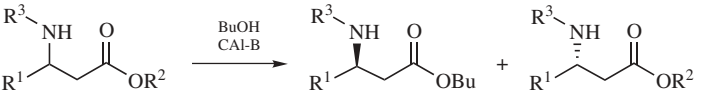
First the reactions of aminobutarate **32** (Scheme 17.11) with 2,2,2-trifluoroethyl chloroacetate catalyzed by lipases from *C. antarctica, P. cepacia*, and *Pseudomononas fluorescens* were screened. Each lipase demonstrated certain regioselectivity and stereoselectivity trends toward the amino and ester functionalities of the substrate **32**.[17] CAL-B revealed better enantioselectivity of the unreacted enantiomer (*S*)-**32** as well as the butanamide of butyl (*R*)-3-aminobutyrate **33**, but the interesterification product, butyl 3-aminobutyrate **34**, was also formed.



Scheme 17.11

The structural effects of a series of achiral esters with the general structure $PrCO_2R^2$ were investigated in terms of enantioselectivity as well as reactivity toward the substrate under the same conditions. It was found that the rate of the catalyzed reaction was proportional to the steric bulk of the substituents. It was also observed that more hydrophilic or chloro-substituted ethyl carboxylates favor high enantioselectivity. Of all of the investigated compounds, the most promising derivatives for further studies were the butyl and 2,2,2-trifluoroethyl butyrates, although there is concern with the chemoselectivity of the reaction. Although the reaction of compound **32** with acyl donors, such as the previously mentioned butanoates, could yield the *N*-acylated or cross-esterification products, CAL-B demonstrated selectivity for the latter. However, the size of the R^1 group and the nature of an achiral acyl donor strongly affect this chemoselectivity. For the CAL-B-catalyzed reactions in the presence of a butyl group ($R^2 = Bu$), predominance of interesterefication became clearer as the acylation products **33** and **35** were not detected in the course of reaction but the product **34** was isolated with a relatively high enantioselectivity. When 2,2,2-trifluoroethyl butanoate ($R^2 = CH_2CF_3$) was employed as an acyl donor, enhanced selectivity toward products **34** was observed.

The same research group also investigated the structural effects on the chemo- and enantioselectivity of CAL-B-catalyzed resolutions of β-amino esters.[18] With the information provided by previous investigations, it was expected that CAL-B would be selective for the interesterification pathway rather than the acylation. The structural features of various amino esters as well as esterification/acylating reagents were studied to aid in the understanding of the chemo- and enantioselectivity of the lipase. This was accomplished by subjecting several substituted β-amino esters as well as *N*-butanoylated dimethyl aspartate to CAL-B-catalyzed reactions with neat butyl butanoate ($R^2 = Bu$) and with 2,2,2-trifluoroethyl butanoate ($R^2 = CH_2CF_3$) in diisopropyl ether (Scheme 17.12).



36 **37** **38**

R^1 = Me, Et, *i*-Pr, Ph, CO_2Me

R^2 = Et, Me

R^3 = H, PrCO

Scheme 17.12

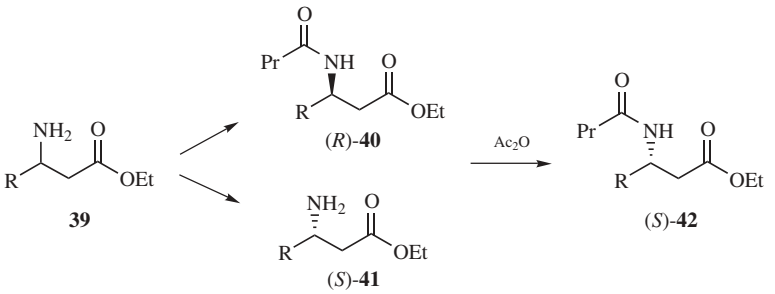
With the increasing size of the substituent in the β-position of **36**, the acylation step became less favorable and enhanced chemoselectivity toward interesterefication was observed. This outcome was the most pronounced with butyl butanoate as the acyl donor, as only a trace of the acylated products was detected when the

conversion was 90%. With increasing conversion a noticeable drop in enantioselectivity was detected; at 25% conversion it was found to be >99%, while it was only 92% at 47.5% conversion. The authors suggest the reverse interesterefication as a competitive pathway, which could explain the drop in enantioselectivity.

This report also yields information as to the effect of the acyl donor on the selectivity of the reaction. It was found that the reactions with the 2,2,2-trifluoroethyl butanoate were fairly chemoselective, forming the interesterification product predominantly. However, the butyl butanoate derivatives were much more selective. This effect could be attributed to the difference in reactivity of the acylating reagent.

With these significant results concerning the application of CAL-B, Gedey et al.[18] focused their attention on CAL-A, which was employed to elucidate the effect of substrate structure on the enantioselectivity in the acylation of **39** with neat butyl butanoate as well as 2,2,2-trifluoroethyl butanoate in diisopropyl ether.

This series of experiments demonstrated that the enzyme has straightforward stereochemical demands, which were observed for the CAL-A-catalyzed acylation by the necessity of similar steric arrangements of the appropriate groups (Scheme 17.13).[19] It was also noted that the observed enantioselectivities could also be correlated to structural features introduced by the acyl donor. Results of trial series are presented in Table 17.4.



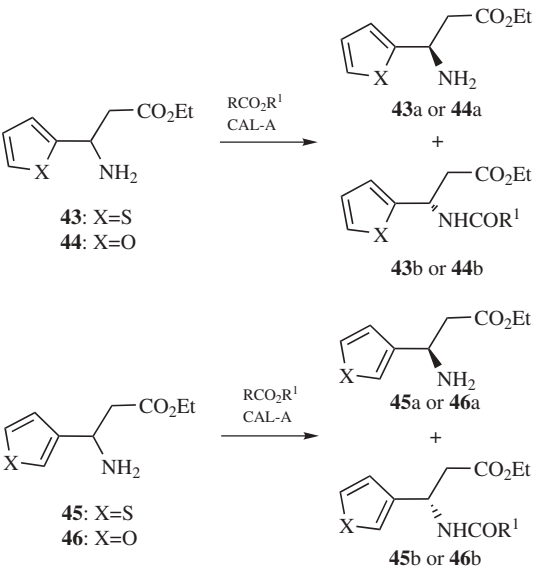
Scheme 17.13

TABLE 17.4 Enantioselectivities for Preparation Esters (*R*)-40 and (*S*)-42

		$PrCO_2Bu$		$PrCO_2CH_2CF_3$	
Entry	R	Conversion, %	*E*	Conversion %	*E*
1	Me	51	32	50	6
2	Et	50	256	52	168
3	*n*-Pr	50	>100	55	72
4	*i*-Pr	50	115	49	106
5	$CHEt_2$	33	2	52	38
6	Cyclohexyl	23	9	53	>100
7	Ph	52	29	52	75

The application of butyl butyrates as acyl donors to the β-substituted β-alanine derivatives in the presence of the enzyme CAL-A seems to work well as long as the β-substituent is an alkyl group. With these results in hand, application of this procedure on the multigram scale was successfully investigated. Racemic ethyl 3-aminobutyrate **41** (R = Me) was resolved on the multigram scale with the application of the enzyme CAL-A in the presence of butyl butyrate for 2 h.

To extend the overall generality of the CAL-A-catalyzed resolution of β-amino acids, this enzyme was investigated under modified conditions (Scheme 17.14). The immobilization of CAL-A on Celite in the presence of sucrose showed significant impact on the reactivity as well as the enantioselectivity of the catalyst. The increased reactivity was explained by the ability of the sucrose to sustain a high level of water in anhydrous solvents, which can stabilize the highly hydrophilic enzyme.



Scheme 17.14

In the previous examples it was demonstrated that CAL-A catalyzed the *N*-acylation of β-amino esters selectively whereas other lipases tended to induce competition between *N*-acylation and transesterification. This observed chemoselectivity is controlled by the structure of the amino ester.[20]

From the data obtained in this series of experiments it can be determined that the rate is heavily dependent on multiple factors, such as the solvent, substrate structures (compare from Table 17.5 entries 1 and 7, 2 and 8, 3 and 9, or 13 and 14), and acylating reagents (entries 5 and 11 vs. 6 and 12). The rate of reactions with

TABLE 17.5 Acylation of 43–46 by CAL-A with Achiral Esters at Room Temperature

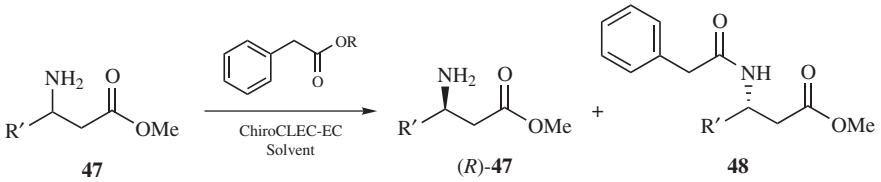
Entry	Substrate	RCO_2R^1	Solvent	Time, h	Conversion, %	ee_a,%	ee_b,%	E
1	**43**	$PrCO_2CH_2CF_3$	BuOMe	0.33	48	89	98	380
2	**43**	$PrCO_2CH_2CF_3$	Pr_2O	1.5	50	99	97	380
3	**43**	$PrCO_2CH_2CF_3$	MeCN	1	50	95	95	130
4	**43**	$PrCO_2Et$	$PrCO_2Et$	3	50	96	97	305
5	**43**	$PrCO_2Bu$	$PrCO_2Bu$	0.5	45	82	99	580
6	**43**	$MeCO_2Et$	$MeCO_2Et$	60	49	88	90	60
7	**44**	$PrCO_2CH_2CF_3$	BuOMe	0.67	40	62	94	60
8	**44**	$PrCO_2CH_2CF_3$	Pr_2O	1.3	50	96	96	210
9	**44**	$PrCO_2CH_2CF_3$	MeCN	1.3	52	99	89	90
10	**44**	$PrCO_2Et$	$PrCO_2Et$	3	48	90	96	150
11	**44**	$PrCO_2Bu$	$PrCO_2Bu$	1	49	94	97	220
12	**44**	$MeCO_2Et$	$MeCO_2Et$	66	51	97	92	100
13	**45**	$PrCO_2Et$	$PrCO_2Et$	11	50	93	94	110
14	**46**	$PrCO_2Et$	$PrCO_2Et$	11	51	>99	96	470

ethyl butanoate were found to be slower but quite comparable to those observed with the fluorinated reagents while conserving high enantioselectivities (entries 4 and 10).

Keeping in mind that these reactions are equilibrium processes, one might assume that with the accumulation of products the reverse process could lower the enantiomeric excess of the products. However, the authors reported that enantiomeric excess remains unaltered after reaching 50% conversion. It should also be noted that the authors suggest that heteroatoms in thiophyl and furyl rings interact with the amino acid residues of the enzyme, which would explain the enhanced enantioselectivity and reactivity of the substrates.

These results from Gedey et al. clearly establish that the application of CAL-A-catalyzed acylation is excellent for the kinetic resolution of racemic β-amino esters. High enantioselectivities and operationally convenient conditions make these methods useful for small-scale separation. However, this process is currently limited by the cost and availability of the enzyme (more than $200 per 100 mg).

In another biocatalytic protocol developed by Roche et al.,[21] the resolution of racemic amino esters **47** was achieved by selective acylation catalyzed by penicillin G acylase (ChiroCLEC-EC).[21] Racemic β-amino esters **47** were directly acylated to their *N*-benzoyl derivatives **48** with different phenyl acetyl donors (Scheme 17.15). The key feature of this resolution procedure is the simplicity of the one-pot separation involving a biphasic reaction mixture. During the investigation of the three acyl donors it was observed that a catalytic amount of water is critical to the outcome of the reaction. The water is necessary to trigger the catalytic activity of the enzyme, which drastically accelerates the rate of acylation. This was shown by the reaction of 3-amino-3-(3,4-dimethoxyphenyl)propionate with the appropriate phenylacetate, which did not yield any of the acylated products in anhydrous



R = H, CH_2CF_3, Me;
R′ = Me, Ph, 1-propene,
p-MeOPh, 3,4-MeOPh

Scheme 17.15

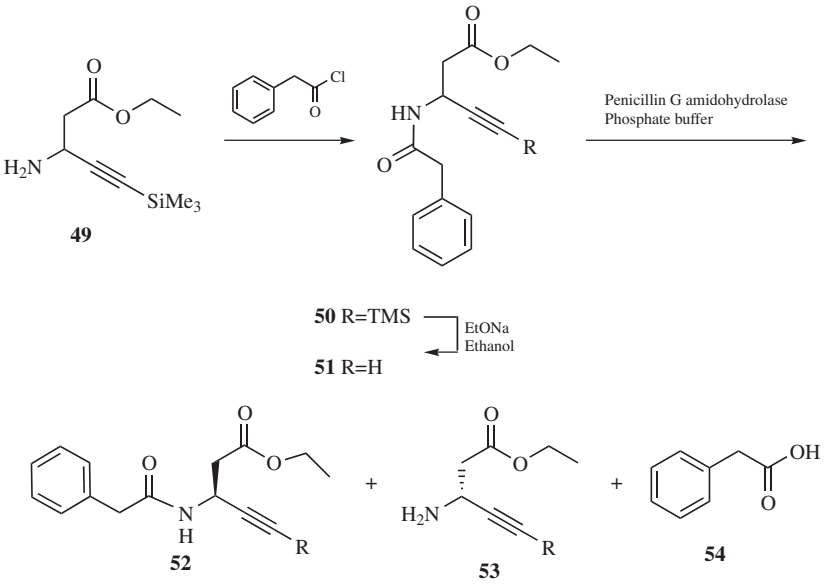
solvents (Dioxane, CH_3CN, $PhCH_2CO_2Me$, and EtOAc) within 6 days. However, a system of EtOAc with 1–2% water provided nice results with enantiomeric purities of >95% as well as high chemical yields.

This selective acylation procedure, with trace amounts of water in the organic solvent, was applied for several substituted β-amino esters. It is assumed that the enzymatic catalysis takes place in the trace water layer due to the large kinetic dependence on the hydrophobic nature of the substrate. It was noted that the reverse hydrolysis of the phenylacetate to phenylacetic acid was faster than the catalyzed acylation in several cases where the R-group was benzylic or allylic. It was found that the competing hydrolysis could be overcome by the application of less polar solvents such as toluene. Employing the new solvent systems lowered the rate of saponification of the phenylacetate and the desired enantiomer was separated with high enantioselectivity (>95%). Only the amino ester, with an allylic substituent, showed disappointingly low enantiomeric excesses under the modified conditions.

Topgi et al. reported a study of penicillin acylase–catalyzed resolutions. However, in contrast to the previous application, the enzyme was used to selectively remove the acyl group of one enantiomer.[22] This methodology was applied to synthesize the enantiomers of ethyl 3-amino-5-(trimethylsilyl)-4-pentynoate **53** in optically pure form (Scheme 17.16).

The catalytic activity of the enzyme, PGA significantly depends on pH. For instance, a pH range of 7–8.5 is necessary for deacylation reactions to occur, but acylation becomes predominate at a slightly acidic pH (5–6). The starting materials for this procedure were synthesized by reacting the racemic amino ester **49** with phenylacetylchloride and triethylamine in heptane or ethyl acetate. The acylated amino ester **51** was then subjected to treatment with penicillin G aminohydrolase in a basic phosphate buffer (pH 7.4). This procedure yielded the (*S*)-amide **52** with 96% isolated yield; unfortunately the enantiopurity remained unreported.

Since the authors' target xemilofiban, an anti–platelet aggregation agent,[23] does not contain the trimethylsilyl group, it was removed prior to the enzymatic deacylation by sodium ethoxide in ethanol. The resulting racemic amide **51** was subjected to the enzyme-catalyzed deacylation and, as expected, the reaction yielded the unprotected (R)-enantiomer. The difference in physical properties, namely solubility, of the amine **53** and amide **52** allowed for their easy separation



49 **50** R=TMS **51** R=H **52** **53** **54**

Scheme 17.16

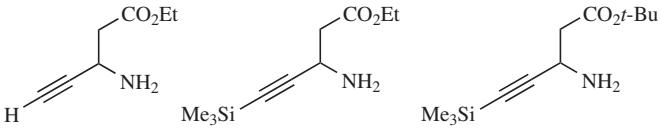
by simple filtration. After completion of the room temperature reaction, the amide (*R*)-**52** was isolated in excellent yield and enantiomeric excess (>96%) by filtration of the reaction mixture.

The advantage of deacylation versus the acylation procedure is the synthesis of the free amino esters, which in this case have greatly diverse physical properties, therefore allowing their facile separation. These reaction conditions are convenient and provide impressive chemical and stereochemical outcomes.

After screening several commercially available enzymes, penicillin G amidohydrolase from *Escherichia coli* resulted in the most convenient resolution of ethyl 3-amino-5-(trimethylsilyl)-4-pentynoate.[24] This enzyme showed activity toward phenylacetylation of the previously mentioned starting materials. Investigations into the reactivity of several penicillin acylases as well as the rational selection of the substrate amino esters were reported. This includes optimization of the process by testing several reaction conditions at varying pH, number of times the catalyst could be effectively recycled, and concentration and with different substituents on the amino esters for the biocatalytic resolution.

An investigation into the influence of pH on the reaction revealed that phenylacetylation had the highest rate when the reaction medium had a pH of 5.7 and there was no dependence on the concentration of the substrates. This optimum pH value may be explained by accumulation of the protonated amine at lower pH and ionization of phenylacetic acid as well as an increase in the reverse reaction (optimum pH for hydrolysis is 7–9) by raising the pH.[25]

The pK_a's of amines **55**–**57** (Scheme 17.17) were determined to be 6.8–6.9, 6.9, and 6.4–6.5, respectively. The low pK_a values of these derivatives are very



55 **56** **57**

Scheme 17.17

important for biocatalyzed acylation to occur at a pH of 6 or less. The highest probability for the successful resolution would be of the amino ester **56** due to the drastic difference in the rates of the two enantiomers while the rates of the enantiomeric resolution of compound **55** differed by only a factor of 4–5. It was also found that, due to the low solubility of amines **56** and **57** in water, the rate of acylation was drastically slower than with the unprotected derivative. However, due to the previously mentioned rate data, observations and adjustments were made on the basis of amine **56** during the majority of the optimization reactions.

The rate dependence of the bioconversion on the concentration of phenylacetic acid was also determined, since minimizing its concentration would affect the cost of the procedure. At low amine concentration, it appeared that increasing concentrations of phenylacetic acid could severely inhibit the acylation. However, at higher concentrations of amine **55**, the inhibition was not as great.

An analysis of the activity of the enzyme, after being recycled, was necessary in order to consider the financial feasibility of this procedure at the industrial scale. The bioactivity of the enzyme did not decrease after the first cycle, but after three cycles it had significantly diminished. An extrapolation of these data to 11 cycles predicts a loss of activity of 50%. However, application of this procedure on the large scale, up to 70 L, has revealed that 25 cycles is plausible.

17.3 CONCLUSION

The separation of enantiomers by application of naturally occurring enzymes is one of the more attractive areas in modern organic chemistry, as it leads to optically active molecules by replenishable sources. Although transformations of β-amino acids was not the purpose for which these naturally occurring catalysts evolved, they have exemplified high specificity in reactivity toward slight structural differences among substrates as well as individual enantiomers.

Each method reviewed in this chapter possesses its own advantages and limitations. In some cases, the enzymatic approach is the method of choice to prepare enantiomers of the corresponding β-amino acids. However, the major disadvantage of the biocatalytic procedures is the limit of 50% theoretical yield for the resolution process. With this in mind, the economical efficiency must be taken into account. Therefore, the starting materials must be inexpensive and easily prepared, and the separation must be simple and operationally convenient, while the biocatalytic step must retain a high enantioselectivity.

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CHAPTER 18

Stereoselective Synthesis of β-Amino Acids via Radical Reactions

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18.1 INTRODUCTION

The β-amino acids[1] have aroused considerable attention due to their having important biological properties in drugs and natural products. Although much less abundant than their α-analogs, β-amino acids are also present in nature. They are found, for instance, in the anticancer agent taxol, macrocyclic peptides, antibiotic β-lactams, and cispentacin. Furthermore, they are useful tools in the synthesis of modified peptides with increased activity and in vivo stability. For the above-mentioned reason, numerous methods for the synthesis of β-amino acids have been developed. In this chapter we review the synthesis of β-amino acids and the related β-lactams using a radical reaction which has been used as a crucial construction method. Among the three chemical reaction species (i.e., cations, anions, and radicals), radicals have recently drawn much attention of synthetic chemists due to their high stereo- and regioselectivity in radical reactions and their potential utility in the synthesis of biologically active acyclic and cyclic compounds.[2]

The stereoselective synthesis of acyclic 2,3-disubstituted β-amino acids via radical reaction can be classified into three types based on the method of asymmetric induction. The type 1 radical reaction proceeds with 1,2-asymmetric induction to give the β-amino acids derivatives.[3–8] The type 2 reaction consists of hydrogen atom transfer followed by 1,3-asymmetric induction.[9] In the type 3 method, the substituents at 2- and 3-positions in β-amino acids induce diastereoselectivity via the radical cyclization reaction.[10–12]

Cyclic β-amino acids have been synthesized via radical addition–cyclization reaction.[13–15]

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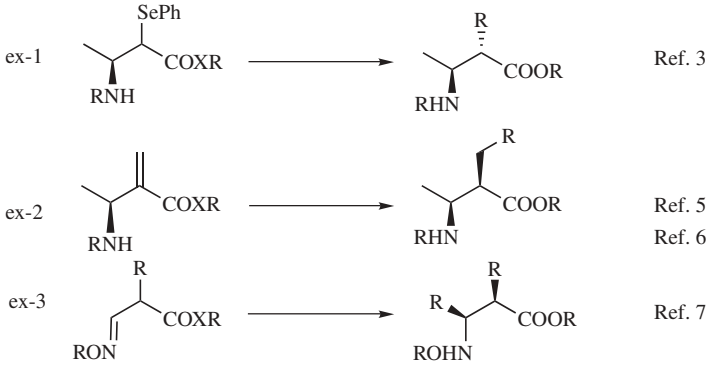
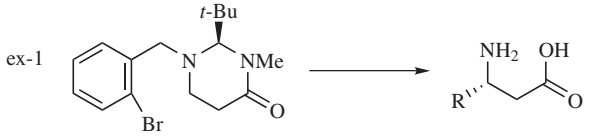
Since β-amino acids are chemically isosteres of β-lactams and thus can be obtained from β-lactams by hydrolysis, we also review the representative examples of β-lactam synthesis via the radical cyclization reaction (Scheme 18.1).[16–27]

Synthesis of Acyclic β-Amino Acids

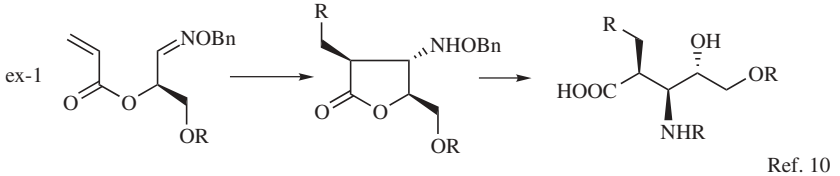
(1) 1,2-Asymmetric Induction (Type 1)



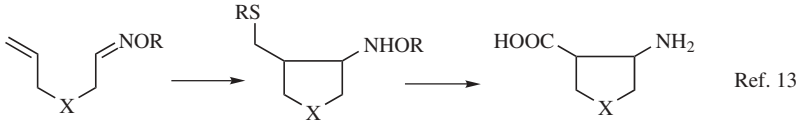
(2) 1,3-Asymmetric Induction Including Hydrogen Atom Transfer (Type 2)



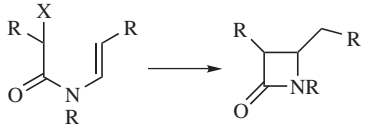
(3) 1,2- and 1,3-Asymmetric Inductions (Type 3)



Synthesis of Cyclic β-Amino Acids



Synthesis of β-Lactams



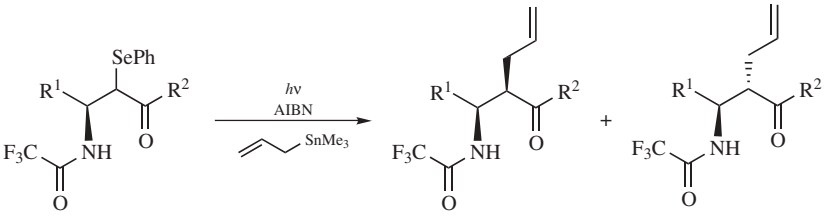
Scheme 18.1

18.2 SYNTHESIS OF ACYCLIC β-AMINO ACIDS

18.2.1 1,2-Asymmetric Induction

Hanessian et al.[3,4] have reported examples of remarkably high stereoselectivity in the 1,2-induction in free-radical *C*-allylation of α-acyl radicals derived from a series of *N*-substituted acyclic amino acid derivatives. Treatment of the readily available α-selenophenyl esters or amides **1** with allyl tributylstannane in the presence of 2,2′-azobisisobutyronitrile (AIBN) under the irradiation conditions led to a quasi-exclusive formation of the *anti*-*C*-allyl derivatives **3** (series A) regardless of the nature of the β-alkyl (aryl) substituent. Changing the β-substituent to a carbomethoxy group resulted in a complete reversal of selectivity, giving the syn-*C*-allylated product **2** while maintaining high stereoselectivity (series B) (Scheme 18.2) (Table 18.1).

The quasi-exclusive formation of anti products in series A (1,2-induction) can be interpreted on the basis of the prevalence of ground-state and transition-state conformations in which H-bonding plays a dominant role in favoring a pseudo



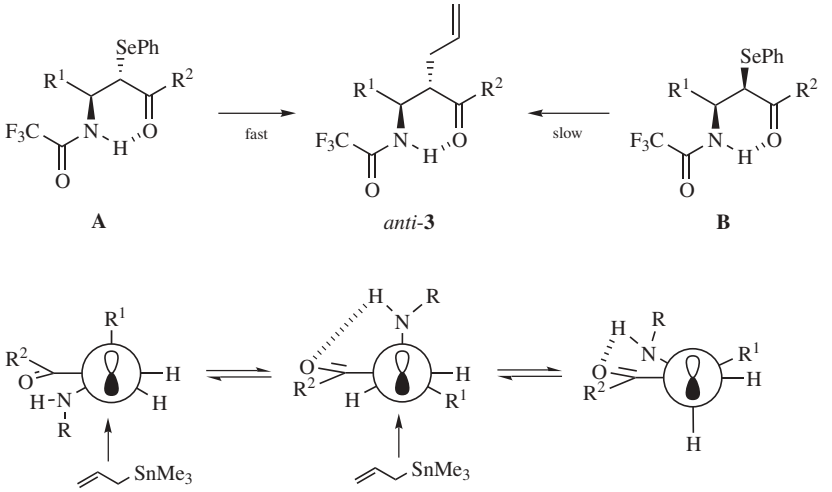
1 *syn*-**2** *anti*-**3**

Scheme 18.2

TABLE 18.1 Free-Radical *C*-Allylation of α-Selenophenyl Esters or Amides

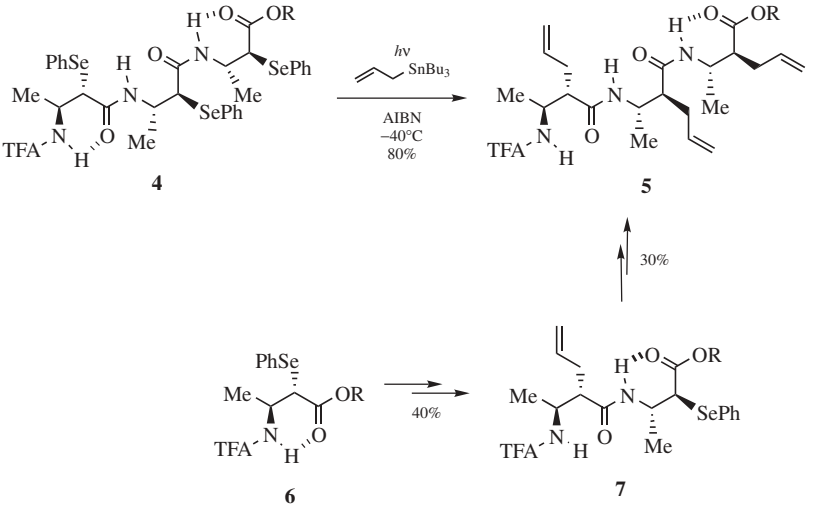
Entry	R^1	R^2	*anti*-**3**/*syn*-**2**	Yield (%)
		Series A		
1	Me	OMe, NMe_2	>98 : 2	90
2	*i*-Pr	OMe	>98 : 2	79
3	Ph	OMe, NMe_2	>98 : 2	76
		Series B		
4	COOMe	OMe	4 : 96	74
5	COO*t*-Bu	OMe	5 : 95	71

six-membered ring. Interestingly, the (2S)-anti isomer **A** (Scheme 18.3), with a distinctive Fourier transform infrared (FTIR) H-bonding band at 3293 cm^{-1}, reacted faster than the (2R)-syn isomer **B** (FTIR 3410 cm^{-1}).



Scheme 18.3

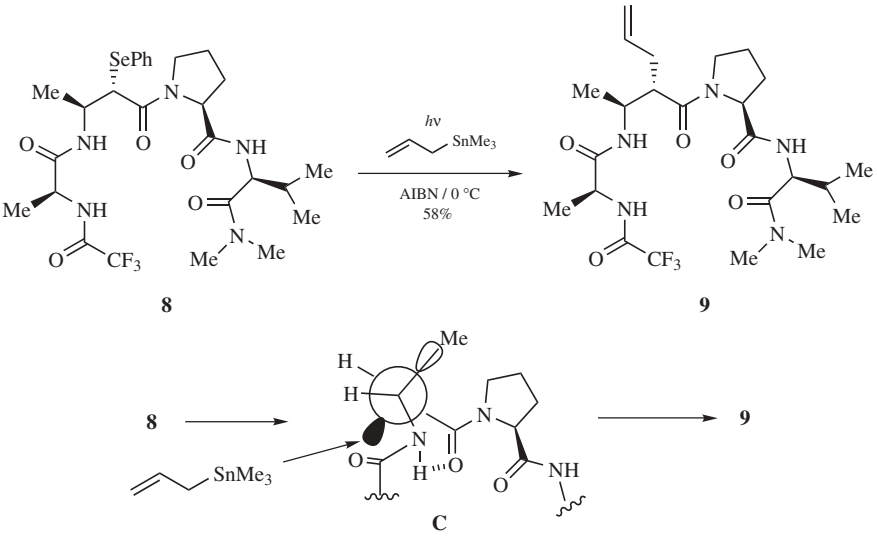
Hanessian et al.[3,4] demonstrated the versatility of the methodology in iterative and one-step multiple *C*-allylation protocols leading to the tripeptide congener **5** (Scheme 18.4). Thus, *C*-allylation of the (2*S*)-tri-α-phenylseleno peptide derivative



Scheme 18.4

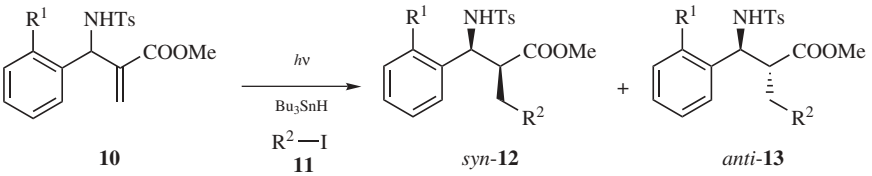
4 gave a major product **5**. Alternatively, *C*-allylation of **6**, amide formation, and iteration of the process on the α-phenylseleno dipeptide ester **7** also gave **5**. They have shown that H bonding can be a strong stereocontrolling element in the free-radical *C*-allylation of a variety of acyclic amino acid derivatives.

Furthermore, Hanessian et al. applied this method to the allylation of tetrapeptide **8**. The free-radical allylation took place with a greater than 95 : 5 ratio of stereoselectivity as in related β-amino acid amides. The successful stereocontrolled α-allylation under mild free-radical conditions within peptidic motifs is most likely due to the approach of the allyl group from the less hindered side of a conformationally biased and H-bonded α-amino radical **C**, as illustrated in Scheme 18.5.



Scheme 18.5

Kündig et al.[5] reported that radical addition to acrylates **10** having an α-aminomethyl group gave β-amino acid derivatives **12** with moderate to good diastereoselectivity (Table 18.2) (Scheme 18.6). The acrylates **10** were submitted to the carbon radical addition sequence which was carried out at ambient temperature under continuous irradiation and with slow addition of Bu_3SnH. Reaction of acrylate **10a** with alkyl iodide **11a** gave product **12a** in 97% yield and with a



Scheme 18.6

TABLE 18.2 Radical Conjugate Addition of Alkyl Iodides

Entry	Substrate	R^1	R^2I	Product	*syn*-**12**/*anti*-**13**	Yield (%)
1	**10a**	H	$Me_2CHCH_2CH_2I$ **11a**	**a**	9.1 : 1	97
2	**10b**	OMe	$Me_2CHCH_2CH_2I$ **11a**	**b**	5.1 : 1	90
3	**10b**	OMe	Me_3CI **11b**	**c**	1.1 : 1	89
4	**10c**	Me	$Me_2CHCH_2CH_2I$ **11a**	**d**	12 : 1	84
5	**10d**	Cl	$Me_2CHCH_2CH_2I$ **11a**	**e**	8.9 : 1	98
6	**10e**	F	$Me_2CHCH_2CH_2I$ **11a**	**f**	7.5 : 1	89

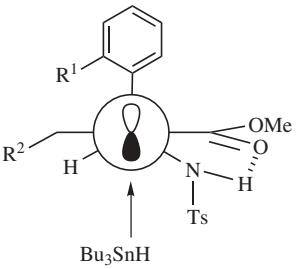


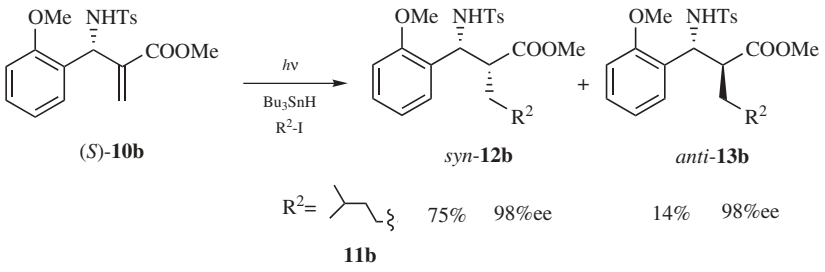
Figure 18.1 Proposed H-bonded radical intermediate.

9 : 1 ratio of the syn/anti diastereomers. Diastereoselectivity in reactions with **11a** is highest for **10c** ($R^1 = Me$) (12 : 1) and lowest for **10b** ($R^1 = OMe$) (5 : 1).

The stereochemical outcome of the reactions is expected from an α-chiral radical which is conformationally restricted by intramolecular hydrogen bonding, as shown in the model of the transition-state structure (Fig. 18.1).

Turning to chiral nonracemic acrylates, the radical addition reaction was carried out with enantiomerically pure (*S*)-**10b**. The reaction with iodide **11b** and Bu_3SnH gave the two diastereomeric β-amino acid derivatives, *syn*-**12b** and *anti*-**13b**, in the ratio of 5.4 : 1 and in 89% yield (Scheme 18.7).

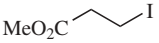
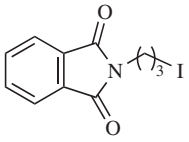
Huck et al.[6] also described an efficient and general two-step synthesis of a wide range of α-substituted β-amino esters from commercially available alkyl halides. The alkyl radical addition products were converted into β-urethane *N*-carboxyanhydrides

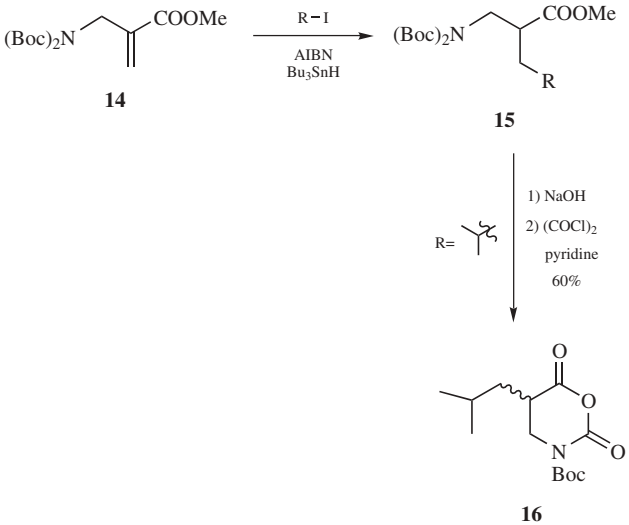


Scheme 18.7

(β-UNCAs). These molecules are of strong interest as their α-UNCA analogs can be easily and cleanly incorporated into biologically active targets. Furthermore, Huck et al.'s rapid synthesis of a wide variety of α-substituted β-UNCAs may be of use within the medicinal and combinatorial chemistry areas. The reaction of **14** with AIBN, alkyl iodide, and Bu_3SnH proceeded in 1,4-radical addition manner to give **15**, which was subjected to hydrolysis in basic conditions (NaOH) to afford carboxylic acid. Finally, cyclization of the acid into its β-UNCA derivatives **16** was achieved by treatment with $(COCl)_2$ in 65% yield (Table 18.3) (Scheme 18.8).

TABLE 18.3 Radical Addition of Alkyl Iodides

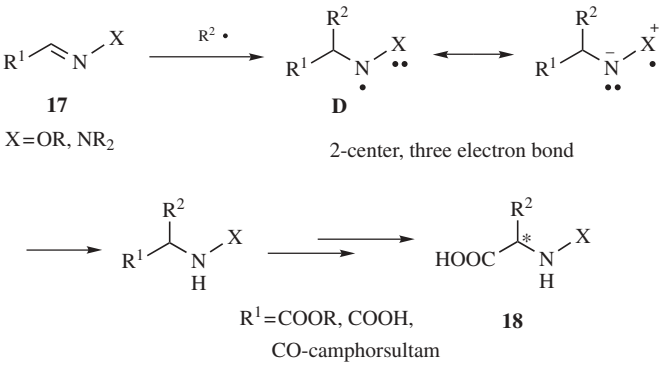
Entry	RI	Yield (%)
1		75
2		74
3		80
4		70



Scheme 18.8

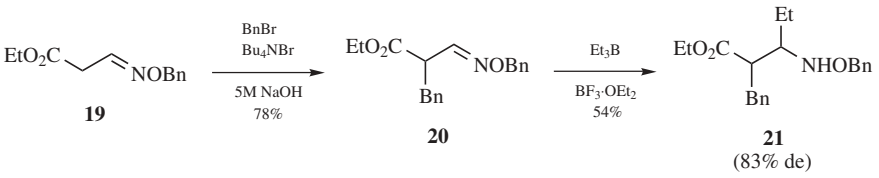
Miyabe et al.[7,8] introduced general methodology for the synthesis of enantiomerically pure β-amino acids. This group has already reported studies on the radical addition to oxime ethers and hydrazones, which were successfully used for the novel asymmetric synthesis of α-amino acid **18**.

Among the different types of radical acceptors containing a carbon–nitrogen double bond, the oxime ethers and hydrazones **17** are well known to be excellent radical acceptors because of the extra stabilization (three-electron bond) of the intermediate aminyl radical **D** provided by the lone pair on the adjacent oxygen or nitrogen atom (Scheme 18.9). The adducts having either ester or carboxylic acid as the R^1-group were converted into α-amino acids.[28]



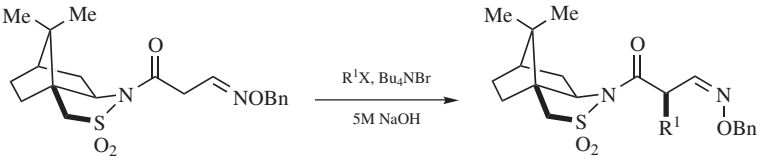
Scheme 18.9

Alkylation of oxime ether **19** with benzyl bromide in the presence of tetrabutylammonium bromide as a phase transfer catalyst gave benzylated oxime ether **20**. In the presence of $BF_3 \cdot OEt_2$, the ethyl radical addition reaction of **20** with triethylborane proceeded smoothly to give ethylated product **21** with 83% de (Scheme 18.10).



Scheme 18.10

The above result was then applied to asymmetric synthesis of β-amino acids as follows. The auxiliary of choice was Opplozer's camphorsultam. Methylation of sultam derivative **22** was carried out using MeI and tetrabutylammonium bromide as a phase transfer catalyst. The desired methylated oxime ether **23a** was obtained in 80% yield and 95% ee after recrystallization. The phase transfer–catalyzed alkylation of sultam compound **22** using different alkylating reagents R^1–X afforded (R,Z)-alkylated products **23** with high diastereoselectivity (Scheme 18.11).



22 (*R,Z*)-**23a–d**
95% de

a : R^1 = Me
b : R^1 = Bn
c : R^1 = 4-NO_2-benzyl
d : R^1 = Propargyl

Scheme 18.11

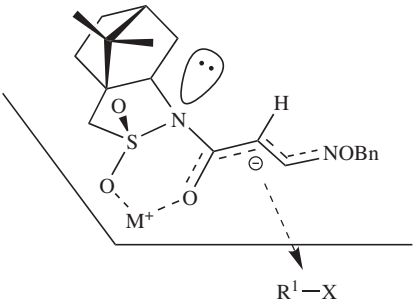
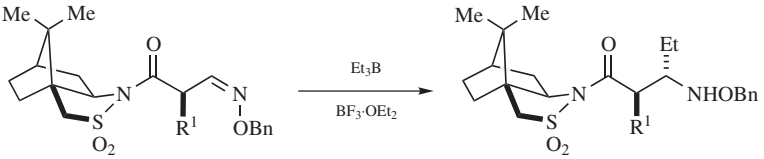


Figure 18.2 Transition-state model for alkylation of **22**.

As suggested by the studies on the camphorsultam derivative, the stereochemical feature of this alkylation reaction can be rationalized in terms of the electronic effect in the chelated (*Z*)-enolate anion of the conformationally restricted oxime ether (Fig. 18.2).

In the presence of $BF_3 \cdot Et_2O$, ethyl radical addition to the oxime ether **23a** proceeded smoothly to give the α,β-dialkyl-β-amino acid derivative **24aA** in 70% yield. Similarly, in the case of the ethyl radical addition reaction to other alkylated oxime ethers (*R,Z*)-**23b–d**, high diastereoselectivity was observed. The high diastereoselectivity and chemical yield were still maintained in the reaction at 20°C (Scheme 18.12, Table 18.4).



(*R,Z*)-**23a–d** **24aA–dA**

a : R^1 = Me, **b** : R^1 = Bn, **c** : R^1 = 4-NO_2-benzyl, **d** : R^1 = Propargyl

Scheme 18.12

TABLE 18.4 Ethyl Radical Addition to Oxime Ethers

Entry	Substrate	Solvent	T (°C)	Product	Yield (%)	Selectivity
1	(*R*,*Z*)-**23a**	Toluene	20	**24aA**	70	>95% de
2	(*R*,*Z*)-**23b**	CH_2Cl_2	−78	**24bA**	95	>95% de
3	(*R*,*Z*)-**23b**	CH_2Cl_2	20	**24bA**	99	>95% de
4	(*R*,*Z*)-**23b**	Toluene	20	**24bA**	99	>95% de
5	(*R*,*Z*)-**23c**	CH_2Cl_2	−78	**24cA**	66	>95% de
6	(*R*,*Z*)-**23c**	Toluene	−78	**24cA**	72	>95% de
7	(*R*,*Z*)-**23c**	Toluene	20	**24cA**	60	>95% de
8	(*R*,*Z*)-**23d**	CH_2Cl_2	−78	**24dA**	43	>95% de
9	(*R*,*Z*)-**23d**	Toluene	−78	**24dA**	31	>95% de

In the radical addition to unsubstituted oxime ether **23** ($R^1 = H$), the ethylated product **24** ($R^1 = H$) was obtained with low diastereoselectivity (<5% de), probably because the approaching ethyl radical was too far away from the chiral sultam part. This result suggests that 1,2-asymmetric induction is responsible for diastereocontrol in the radical reaction **23a–d**. In the case of **23a–d**, the conformer **E** minimizing stable conformation was also supported by the crystal structure resulting from X-ray analysis of **23b**. Thus, ethyl radical addition took place predominantly from the less hindered π-face of oxime ethers activated by BF_3, in which the bulky alkyl group (R^1) shields the opposite face (Fig. 18.3).

The present procedure was successfully extended to the different radical precursors (Scheme 18.13, Table 18.5). The isopropyl radical addition proceeded smoothly in the absence of tin hydride to give a good yield of isopropylated product **24bB** with a high level of diastereoselectivity. Other secondary alkyl radicals also worked well under similar reaction conditions, allowing facile incorporation of a variety of structures into the oxime ether.

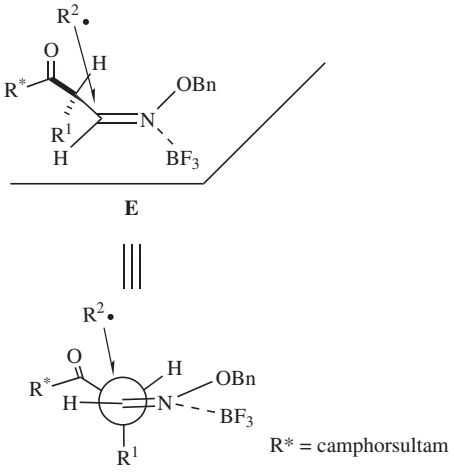
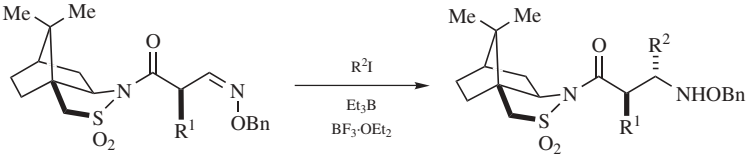


Figure 18.3 1,2-Asymmetric induction.



(*R*,*Z*)-**23b,c**

b : R^1 = Bn
c : R^1 = 4-NO_2-benzyl,

24bB–cF

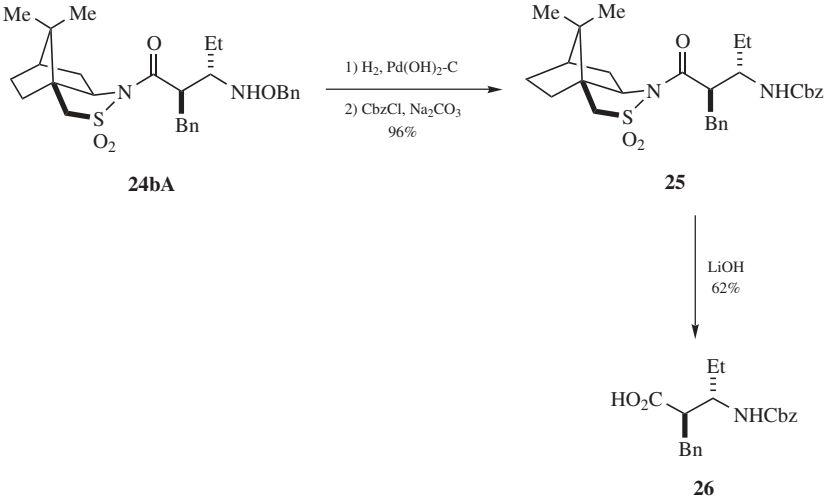
B : R^2 = Pr^i
C : R^2 = *c*-Hexyl
D : R^2 = *c*-Pentyl
E : R^2 = Bu^s
F : R^2 = Bu^t

Scheme 18.13

TABLE 18.5 Alkyl Radical Addition to Oxime Ethers

Entry	Substrate	R^2	Product	Yield (%)	Selectivity
1	(*R*,*Z*)-**23b**	*i*-Pr	**24bB**	70	>95% de
2	(*R*,*Z*)-**23b**	*c*-Hexyl	**24bC**	57	>95% de
3	(*R*,*Z*)-**23b**	*c*-Pentyl	**24bD**	59	>95% de
4	(*R*,*Z*)-**23b**	*s*-Bu	**24bE**	50	>95% de
5	(*R*,*Z*)-**23b**	*i*-Bu	**24bF**	20	>95% de
6	(*R*,*Z*)-**23c**	*i*-Pr	**24cB**	40	>95% de

Hydrogenolysis of the benzyloxy group of **24bA** in the presence of $Pd(OH)_2$–C and subsequent protection of the resulting amine with benzyloxycarbonyl chloride gave **25** in 96% yield from **24bA**. The removal of the sultam auxiliary by standard hydrolysis afforded the enantiomerically pure α,β-dialkyl-β-amino acid **26** in 62% yield (Scheme 18.14).



24bA

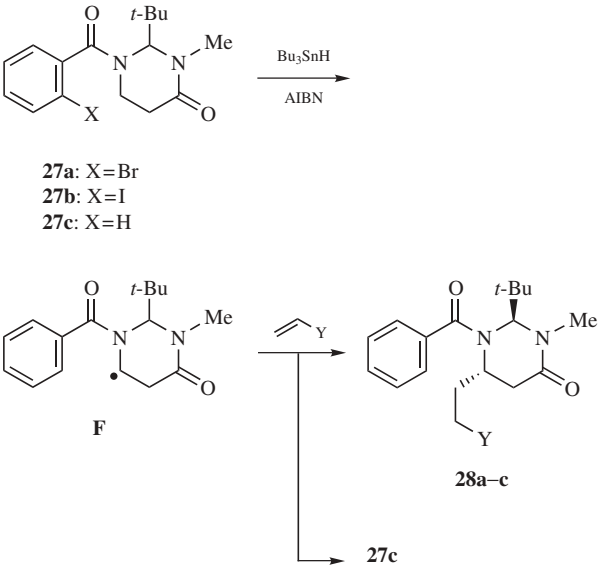
25

26

Scheme 18.14

18.2.2 1,3-Asymmetric Induction Including Hydrogen Atom Transfer

Beaulieu et al.[9] reported on the highly (>95 : 5) diastereoselective transformation of racemic and enantiomerically pure *N*-(*o*-bromo- and iodo-benzoyl)-2-*tert*-butylperhydropyrimidinones **27a,b** with electron-deficient alkenes into substituted products **28a–c**. This aryl to α-amidoyl 1,5-radical translocation, tailored for the first time for 1,3-asymmetric induction, offers a new general route for the synthesis of unusually functionallized, optically active β-substituted β-amino acids such as **29a,b** which are of considerable current interest as bioactive natural and unnatural entities and as precursors for β-lactams (Scheme 18.15, Table 18.6).



Scheme 18.15

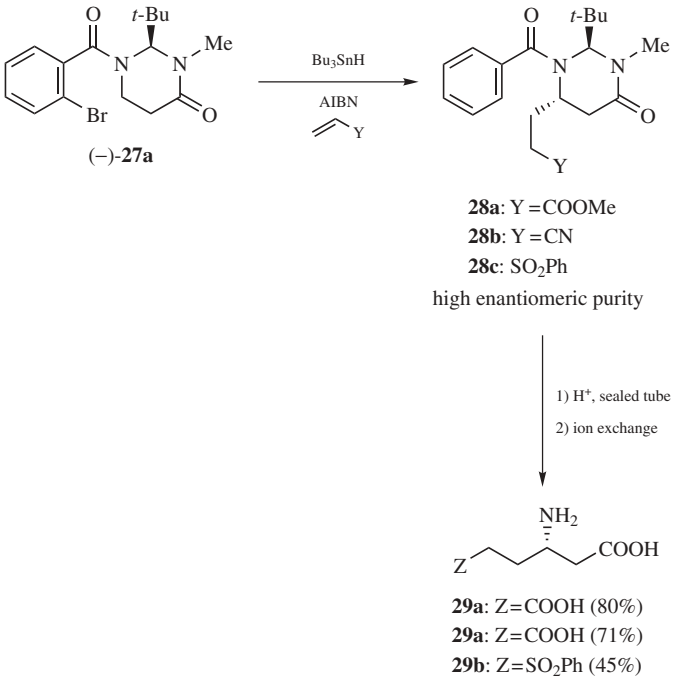
TABLE 18.6 α-Amidoyl Functionalization of Pyrimidinones

Entry	Substrate	X	Y	Conditions[a]	Product	Yield (%)
1	**27a**	Br	COOMe	A	**28a**	53
2	**27a**	Br	COOMe	B	**28a**	62
3	**27b**	I	COOMe	B	**28a**	63
4	**27a**	Br	CN	B	**28b**	64
5	**27b**	I	CN	B	**28b**	42
6	**27a**	Br	SO_2Ph	B	**28c**	40
7	**27b**	I	SO_2Ph	B	**28c**	27

[a]Condition A: Bu_3SnH (2 eq.)/AIBN (cat)/Alkene (5 eq.)/benzene/reflux (standard conditions). Condition B: Bu_3SnCl (0.1 eq.)/$NaBH_3CN$ (2 eq.)/AIBN (cat)/Alkene (5 eq.)/*t*-BuOH/reflux.

Prior to the radical reaction, Beaulieu et al. analyzed X-ray crystallographic data of enantiomerically pure substrate (−)-**27a** that showed the heterocyclic ring in a sofalike conformation with a quasi-axial *tert*-butyl group, similar to that described for the debromo analog and related derivatives, and that *tert*-butyl group strongly shields the β-face of the molecule. Then Beaulieu et al. investigated 1,3-asymmetric radical induction. Efficacy of the 1,5-hydrogen atom transfer was proved by the preliminary experiment on the deuterated pyrimidinone in which the ratio is in good agreement with corresponding rotamer populations as determined by variable-temperature nuclear magnetic resonance (NMR).

Under the standard tin hydride conditions in the presence of methyl acrylate, bromoperhydropyrimidinone **27a** cleanly furnished a mixture of addition product **28a** with >90% de and reduced material **27c** (Scheme 18.16). By applying the catalytic tin method, the yield of the addition product **28a** was improved. Trapping the α-amidoyl radical **F** derived from the iodo compound **27b** with these alkenes led to a predominant amount of **28**.

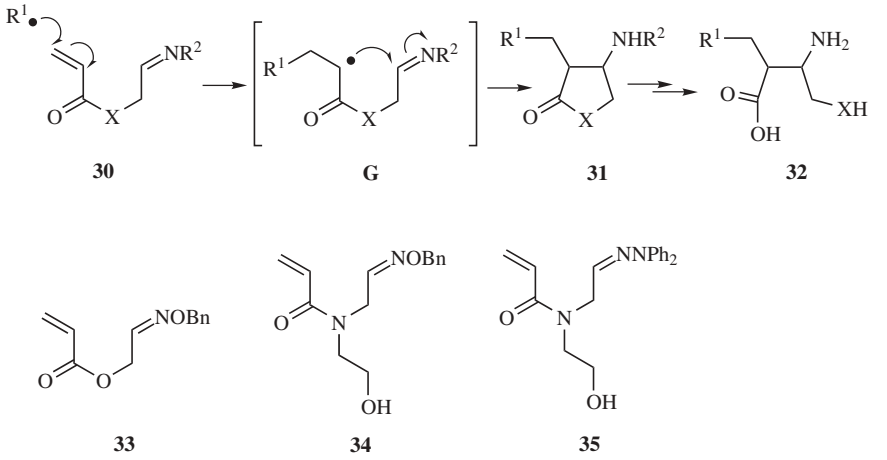


Scheme 18.16

Optically active (−)-**27a** gave substituted products **28a–c** in acceptable yields and high enantiomeric purity which were treated under acid-catalyzed conditions followed by acidic ion exchange resin to afford 3-aminoadipic acids **29a**. Beaulieu et al.[9] have demonstrated the generality and application to the synthesis of β-substituted β-amino acids.

18.2.3 1,2- and 1,3-Asymmetric Inductions

The Mannich reaction is an important method for the preparation of β-amino carbonyl compounds. Recently, Miyabe et al.[10–12] have found a new Mannich-type reaction based on free-radical chemistry which has been successfully applied to the asymmetric synthesis of β-amino acid. The alkyl radical would attack the terminal alkenyl group in the substrates **30** to provide the α-carbonylalkyl radical species **G** which is expected to give the cyclic compounds **31** as a result of 5-exo-trig cyclization of **G**. Subsequent cleavage of the lactone ring would furnish the desired 2,3-disubstituted β-amino acids **32** (Scheme 18.17).

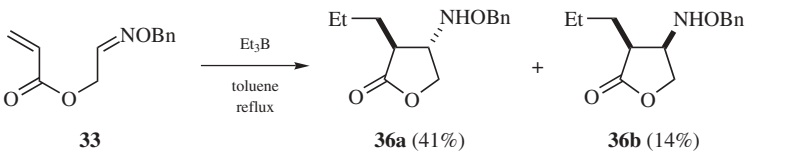


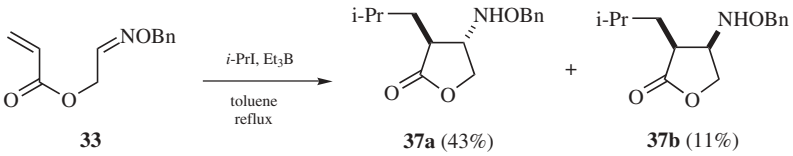
Scheme 18.17

As a preliminary study, Miyabe et al. examined the radical addition–cyclization reaction of substrates **33–35** having two different radical acceptors such as acrylate and aldimine moieties.

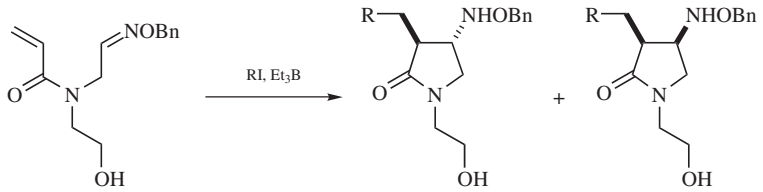
Treatment of an E/Z-mixture of **33** with 1 M Et_3B in hexane in boiling toluene gave a 3 : 1 mixture of two cyclized products **36a** and **36b** in favor of trans product **36a**. Similarly, treatment of oxime ether **33** with isopropyl iodide and 1 M Et_3B in hexane in boiling toluene gave a 4 : 1 mixture of two isopropylated products *trans*-**37a** and *cis*-**37b** in 54% combined yield. A favorable experimental feature of this reaction is that the reaction proceeds smoothly even in the absence of toxic tin hydride or heavy metals via a route involving an iodine atom transfer process (Scheme 18.18).

Oxime ether **34** having 2-hydroxyethylated amide moiety, which would exist in the preferable conformer for intramolecular cyclization, has shown good reactivity (Scheme 18.19, Table 18.7). It is important to note that the tandem reaction of **34** proceeded even in aqueous media (entry 6). Miyabe et al.[10,11] reported the related radical addition–cyclization reaction of hydrazones **35**.





Scheme 18.18



A: R = Et
B: R = *i*-Pr
C: R = *c*-Hexyl
D: R = *c*-Pentyl
E: R = *s*-Bu

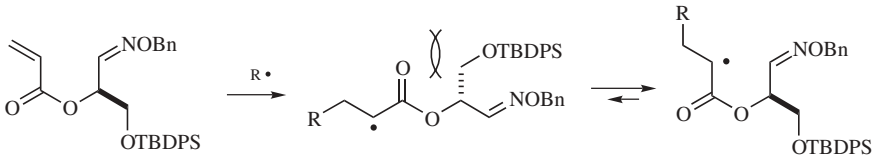
Scheme 18.19

TABLE 18.7 Tandem Radical Addition–Cyclization of Oxime Ethers

Entry	RI	Solvent	T (°C)	Product	Yield (%)
1	None	Toluene	reflux	**38aA** : **38bA** = 4 : 1	69
2	*i*-PrI	Toluene	80	**38aB** : **38bB** = 3 : 1	67
3	*c*-Hexyl I	Toluene	80	**38aC** : **38bC** = 3 : 1	58
4	*c*-Pentyl I	Toluene	80	**38aD** : **38bD** = 3 : 1	55
5	*s*-BuI	Toluene	80	**38aE** : **38bE** = 4 : 1	71
6	*i*-PrI	H_2O	80	**38aA** : **38bA** = 3 : 1	63

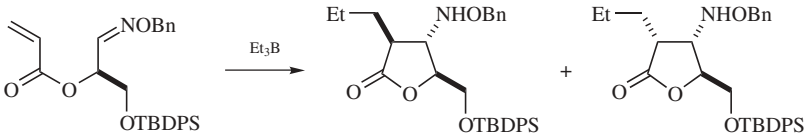
For the asymmetric synthesis of various types of γ-butyrolactones and β-amino acid derivatives, Miyabe et al.[10,11] investigated the reaction of chiral oxime ether **39** having the bulky substituent (Scheme 18.20).

Expecting that the presence of a bulky substituent of chiral oxime ether **39** would be important not only for stereoselectivity but also for efficiency in cyclization, Miyabe et al. initially studied the reaction of oxime ether **39** with an



39

Scheme 18.20



39 **40aA** **40bA**

Scheme 18.21

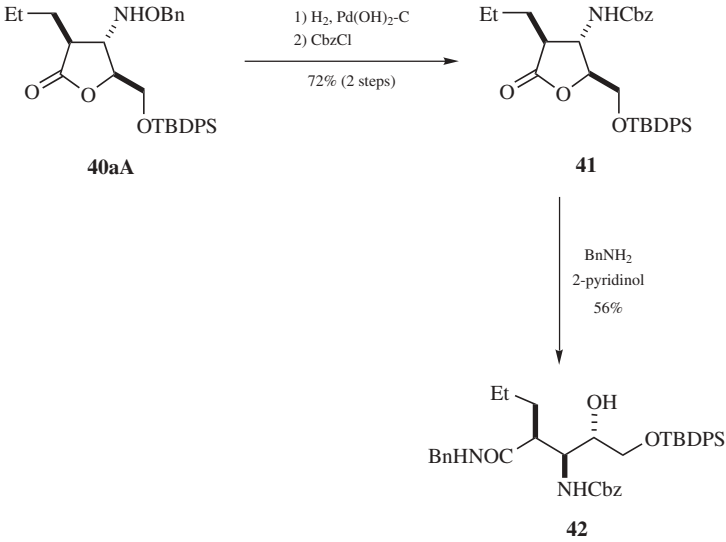
TABLE 18.8 Tandem Ethyl Radical Addition–Cyclization of Oxime Ethers

Entry	Solvent	*T* (°C)	Yield (%)	Selectivity, **40aA** : **40bA**
1	Toluene	Reflux	70	8 : 1
2	Benzene	Reflux	64	12 : 1
3	Toluene	20	53	18 : 1
4	CH_2Cl_2	20	53	10 : 1
5	H_2O-MeOH	Reflux	55	9 : 1

ethyl radical by using triethylborane (Scheme 18.21, Table 18.8). Interestingly, the tandem reaction of **39** proceeded even in aqueous media to afford **40aA** in 55% yield (entry 5).

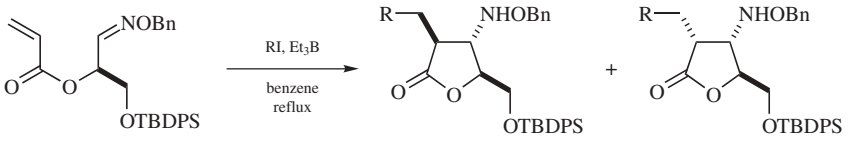
As shown in Scheme 18.22, the γ-butyrolactone **40aA** was converted to a β-amino acid derivative **42**. Hydrogenolysis of the benzyloxyamino group of **40aA** in the presence of $Pd(OH)_2$–C, protection as the *N*-Cbz derivative **41** of the resulting amine, then treatment of **41** with benzylamine in the presence of 2-pyridinol gave the desired β-amino acid derivative **42** in 56% yield.

For the asymmetric synthesis of various types of chiral γ-butyrolactones and the related β-amino acids, Miyabe et al. also investigated the reaction using different radical precursors under iodine atom transfer reaction conditions and obtained various types of alkylated γ-butyrolactones (Scheme 18.23). Under iodine atom transfer reaction conditions as environmentally benign conditions, the tandem reaction of **39** also proceeded in aqueous media to afford **40aB–40aD** (Scheme 18.24). Diastereoselective tandem radical addition–cyclization of chiral oxime ether was successfully applied to a solid-state reaction, which provides a useful



40aA **41** **42**

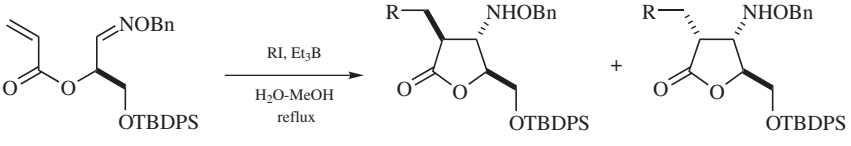
Scheme 18.22



39 **40a** **40b**

R = *i*-Pr, 68% (**40aB** : **40bB** = 12 :1)
R = *c*-Hexyl, 64% (**40aC** : **40bC** = 12 :1)
R = *c*-Pentyl, 70% (**40aD** : **40bD** = 12 :1)

Scheme 18.23



39 **40a** **40b**

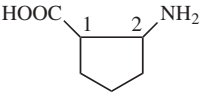
R = *i*-Pr, 80% (**40aB** : **40bB** = 7 :1)
R = *c*-Hexyl, 56% (**40aC** : **40bC** = 8 :1)
R = *c*-Pentyl, 47% (**40aD** : **40bD** = 11 :1)

Scheme 18.24

method for the construction of a chemical library of amino γ-butyrolactones and the related β-amino acid derivatives.

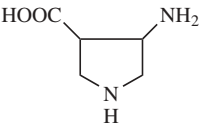
18.3 SYNTHESIS OF CYCLIC β-AMINO ACIDS

β-Peptide **41**, called β-17 by Gellman's group,[29b,c] is active against four species of bacteria, including those that are vancomycin resistant and methicillin resistant. β-17 is composed of the β-amino acids, *trans*-2-aminocyclopentanecarboxylic acid **42** and *trans*-4-amino-3-pyrrolidinecarboxylic acid **43**. Miyata et al.[13–15] have recently explored a new efficient carbon–carbon bond-forming reaction based on the sulfanyl radical addition–cyclization of oxime ether and hydrazones connected with alkenes and the successful application of the reaction to synthesis of cyclic β-amino acids such as 2-aminocyclopentanecarboxylic acid **42** and 4-amino-3-pyrrolidinecarboxylic acid **43**, both of which are crucial components of β-17 (Scheme 18.25).

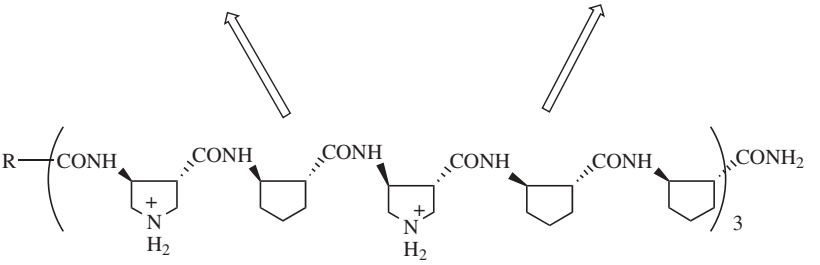


2-aminocyclopentanecarboxylic acid **42**

(1*R*,2*S*): (−)-Cispentacin



4-amino-3-pyrrolidinecarboxylic acid **43**

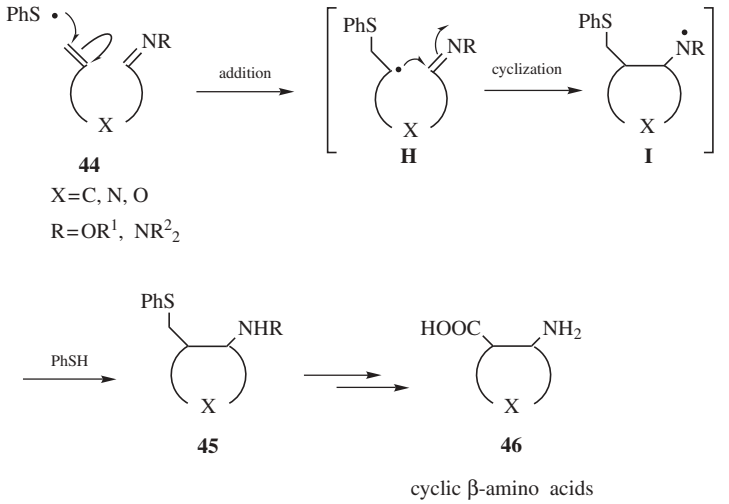


β-17 **41**

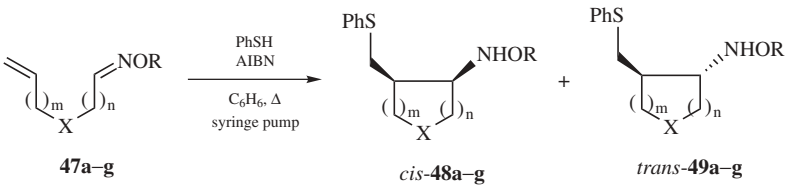
Scheme 18.25

Miyata's approach is shown in Scheme 18.26. The sulfanyl radical would attack the terminal alkenyl group in the substrates **44** to provide the alkyl radical species **H**, which is expected to give **I** as a result of 5-exo-trig cyclization of **H**. Subsequent conversion of the phenylsulfanylmethyl group into the carboxyl group would furnish the desired β-amino acids **46** (Scheme 18.26).

As shown in Scheme 18.27 and Table 18.9, the sulfanyl radical addition–cyclization of **47a** proceeded smoothly to give a 4.0 : 1 mixture of the *cis*- and *trans*-cyclopentylamines **48a** and **49a** in good yield but with modest cis/trans



Scheme 18.26



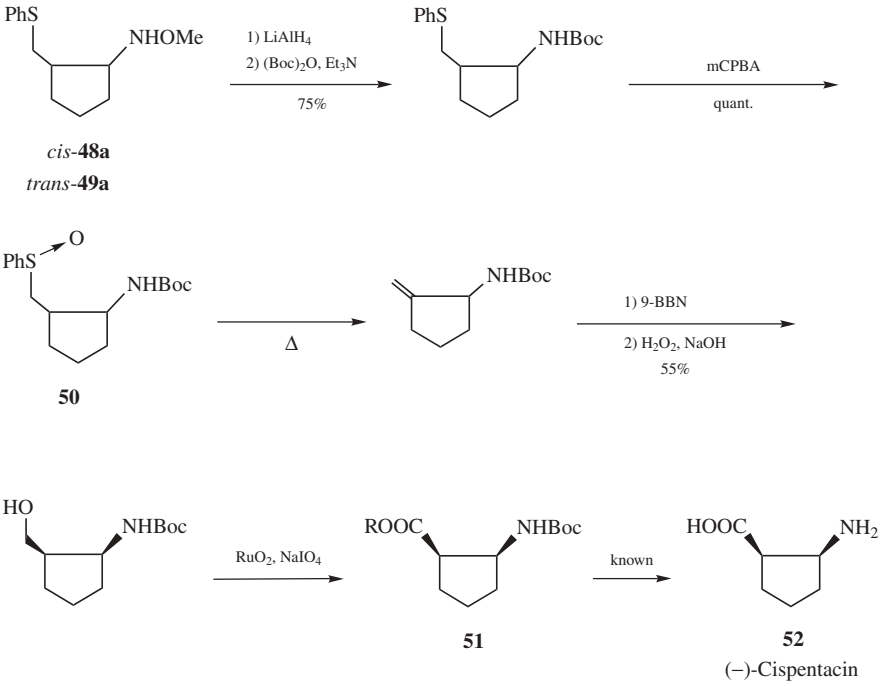
Scheme 18.27

TABLE 18.9 Sulfanyl Radical Addition–Cyclization of Oxime Ethers

Entry	Substrate	X	R	*m*	*n*	PhSH (eq.)	AIBN (eq.)	Yield (%)	Ratio, *cis*-**48** : *trans*-**49**
1	**47a**	$C(COOEt)_2$	Me	1	1	1	0.5	76	4.0 : 1
2	**47b**	CH_2	Me	1	1	1	0.5	49	3.3 : 1
3	**47c**	NTs	Me	1	1	1	0.5	88	2.0 : 1
4	**47d**	NBoc	Me	1	1	1	0.5	62	3.0 : 1
5	**47e**	O	Bn	1	1	1	0.5	72	3.0 : 1
6	**47f**	NTs	Me	1	2	1	0.5	14	1.2 : 1
7	**47f**	NTs	Me	1	2	3	1.5	41	1.6 : 1
8	**47g**	NTs	Me	2	1	1	0.5	34	1 : 2.0
9	**47g**	NTs	Me	2	1	3	1.5	47	1 : 2.0

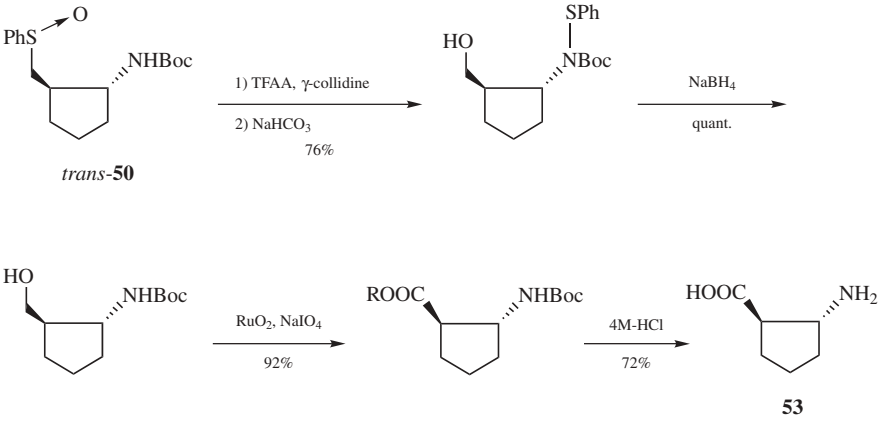
selectivity (entry 1). Under the same reaction conditions, sulfanyl radical addition–cyclization of the simple substrate **47b** gave a mixture of the desired **48b** and **49b** in 49% combined yield (entry 2). Sulfanyl radical addition–cyclization of the oxime ethers **47c** and **47d**, having the nitrogen atoms (X = NTs, NBoc) as the X-group, proceeded smoothly to give the cyclized products **48c** and **49c** and **48d** and **49d** in 88 and 62% yields, respectively (entries 3 and 4). Similarly, **47e**, having the oxygen atom as the X-group, gave almost the same result, leading to the formation of a 3.0 : 1.0 mixture of *cis*-**48e** and *trans*-**49e** in good yield (entry 5). The newly found readical addition–cyclization was successfully extended to the formation of a six-membered product (entries 6–9). The sulfanyl radical addition–cyclization to the hydrazones was also investigated.[13,14]

Conversion of the cyclopentylamines **48a** and **49a** to β-amino acids such as *cis*-2-aminocyclopentanecarboxylic acids (cispentacin) **52** and its trans isomer **53** was



Scheme 18.28

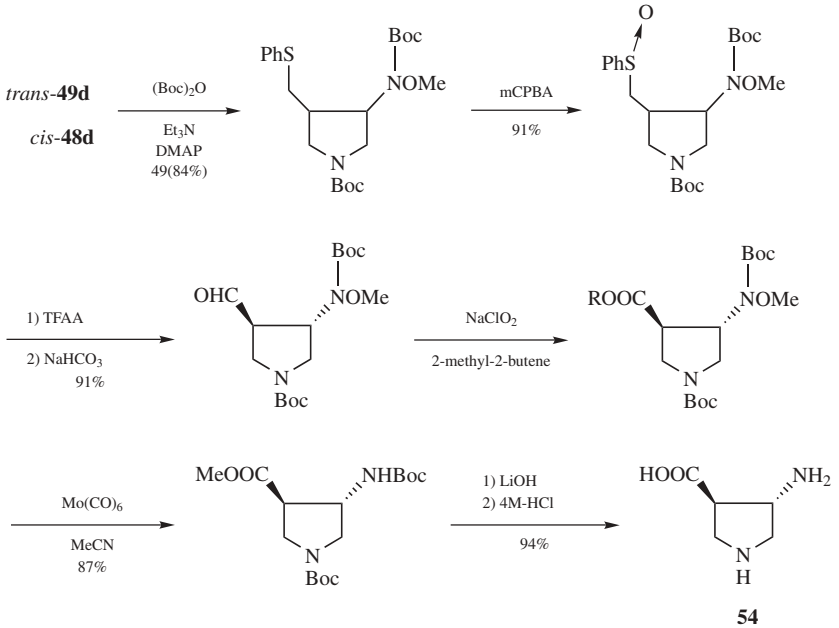
readily achieved via conventional reaction sequences, as shown in Schemes 18.28 and 18.29. Cispentacin is an antifungal antibiotic isolated from the culture broth of a *Bacillus cereus* strain. Racemic (±)-**51** had previously been transformed into (−)-cispentacin (**52**) via the optical resolution.



Scheme 18.29

trans-Sulfoxide **50** was also converted into *trans*-2-aminocyclocyclopentanecarboxylic acid **53**, which is a constituent amino acid of β-peptide β-17.

Heterocyclic β-amino acids such as *trans*-4-aminopyrrolidine-3-carboxylic acid **54** were also synthesized via almost the same procedures (Scheme 18.30).



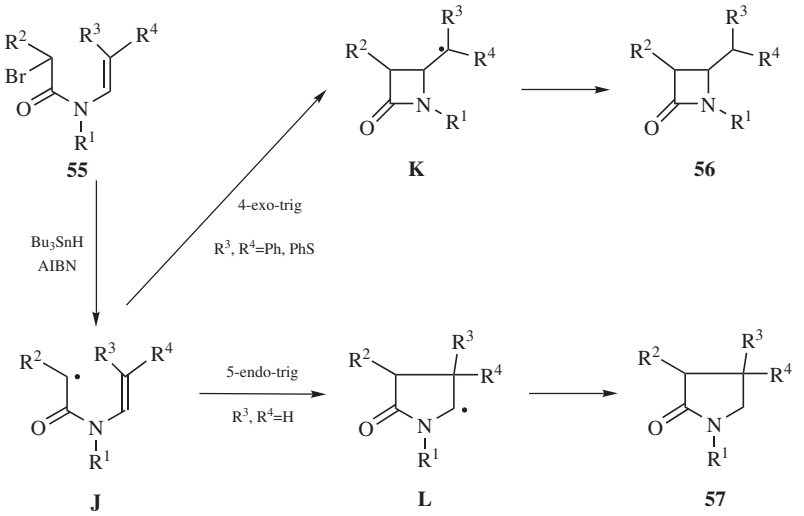
DMAP: dimethylaminopyridine
TFAA: trifluoroacetic anhydride

Scheme 18.30

18.4 SYNTHESIS OF β-LACTAMS

Since β-amino acids are chemically isosteres of β-lactams and thus could be obtained from β-lactams by hydrolysis, in this section we also review representative examples of the preparation of β-lactams using radical cyclization.

Ishibashi et al.[16–21] and Fremont et al.[22] found that *N*-alkenylacetamides **55** gave β-lactam **56** by 4-exo radical cyclization in competition with 5-endo cyclization (Scheme 18.31, Table 18.10).



Scheme 18.31

The radical reaction of **55a,b** with Bu_3SnH in the presence of AIBN gave β-lactam **56a,b** in low yield (entries 1 and 2). The reaction of **55c,d**, having two phenylthio groups, proceeded smoothly to give β-lactam **56c,d** in moderate yield (entries 3 and 4). The enamide **55e**, with both a phenylthio and a phenyl group, also gave β-lactam **56e** (entry 5). Similarly, when the two phenyl groups were present at the terminus of the *N*-vinylic bond, β-lactams **56f,g** were obtained in good yield (entries 6 and 7).

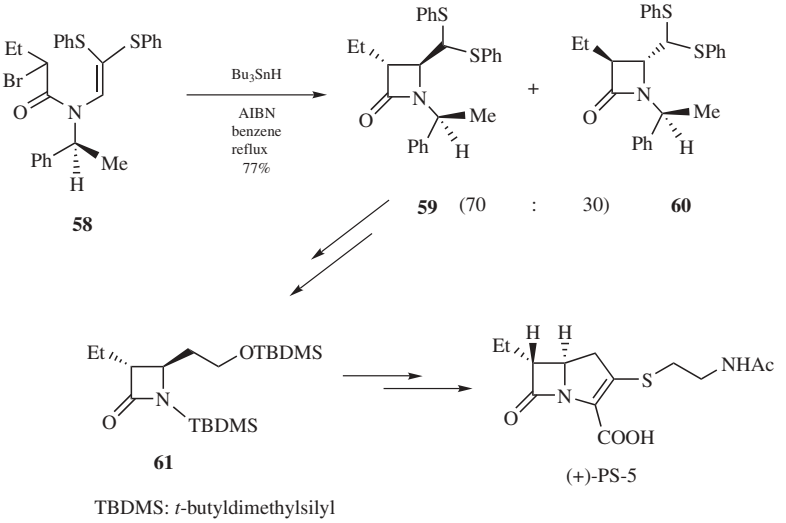
TABLE 18.10 Radical Cyclization of *N*-Alkenyl Acetamides

Entry	Substrate	R^1	R^2	R^3	R^4	Yield (%)
1	**55a**	PMB	H	SPh	H	22
2	**55b**	PMB	Et	SPh	H	45
3	**55c**	PMB	H	SPh	SPh	46
4	**55d**	PMB	Et	SPh	SPh	58
5	**55e**	PMB	Et	SPh	Ph	58
6	**55f**	Me	Et	Ph	Ph	40
7	**55g**	C_6H_{11}	Et	Ph	Ph	70

PMB: *p*-methoxybenzyl.

The *N*-vinylic carbamoylmethyl radicals **J**, generated from the corresponding α-halo amide **55**, cyclize generally in a 5-endo-trig manner, yielding γ-lactams **57** through the intermediates **L**. On the other hand, the introduction of radical stabilizing groups such as phenylthio or phenyl at the terminus of the vinyl group leads to the formation of β-lactams **56** (Scheme 18.31). These results suggest that the high stability of the radical intermediates **K** plays a crucial role in the switch of regioselectivity from the 5-endo-trig mode to the 4-exo-trig mode in the ring closure of **J**.

Ishibashi et al.[16,18] applied this method to the asymmetric synthesis of key intermediates for carbapenem antibiotics PS-5 and thienamycin. They examined the cyclization of enamide **58** bearing an (*S*)-1-phenylethyl group as a chiral inductor on the nitrogen atom. The enamide **58**, upon treatment with Bu_3SnH–AIBN in boiling benzene, gave a mixture of **59** and **60** in a ratio of 70 : 30 and 77% combined yield. The β-lactam **59** was converted into **61**, which is a key intermediate for the synthesis of (+)-PS-5 (Scheme 18.32). In a similar manner, the



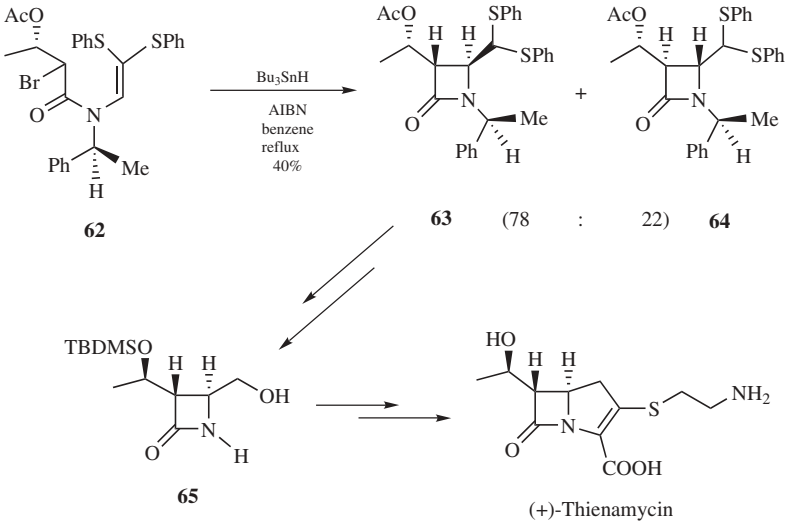
TBDMS: *t*-butyldimethylsilyl

Scheme 18.32

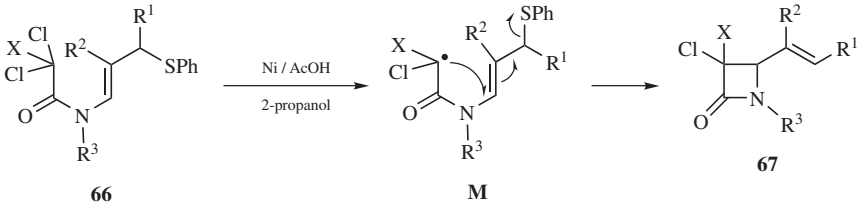
enamide **62** was converted into the chiral intermediate **65** for the synthesis of (+)-thienamycin (Scheme 18.33).

Quiclet-Sire et al.[23] reported that *N*-ethenyl trichloroacetamides **66** undergo a radical cyclization to give β-lactams **67** and in some case γ-lactams when exposed to nickel powder and acetic acid in refluxing 2-propanol. The method involves the use of nickel powder/acetic acids as a mild method for generating radicals with sufficient life time to undergo difficult cyclizations, which is a quite promising result on the utility of this new process for the synthesis of β-lactams (Scheme 18.34).

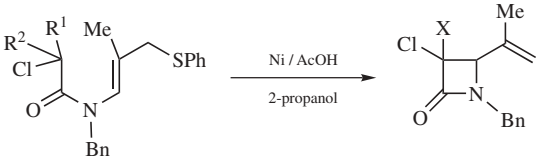
Thus compound **68a**, prepared from methacrolein, thiophenol, and benzylamine, gave **69a** in an unoptimized yield of 50% upon exposure to nickel powder and acetic acid in refluxing 2-propanol. In a similar manner, enamide **68c** derived from perillaldehyde afforded β-lactam **69c** in 65% as a mixture of two diastereomers along with a smaller amount (20%) of the monoreduced enamide (Scheme 18.35 and 18.36).



Scheme 18.33



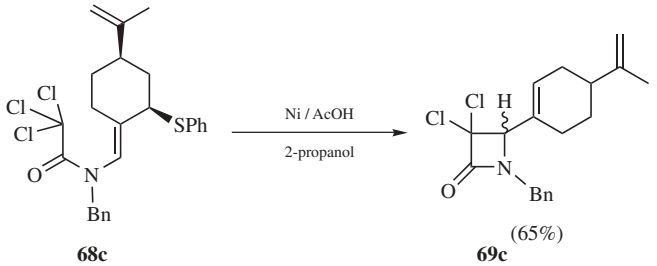
Scheme 18.34



68a: $R^1=R^2=Cl$
68b: $R^1=Me$; $R^2=Cl$

69a: X=Cl (50%)
69b: X=Me (60%)

Scheme 18.35

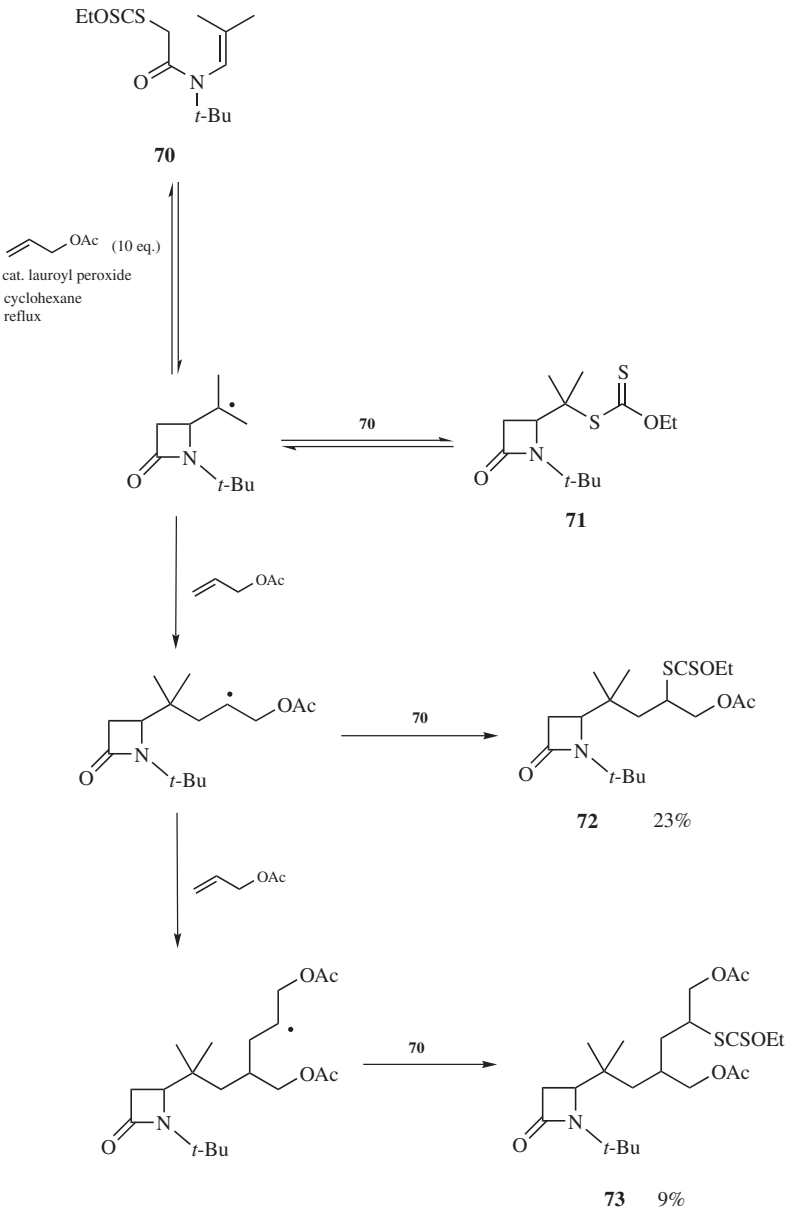


68c

(65%)
69c

Scheme 18.36

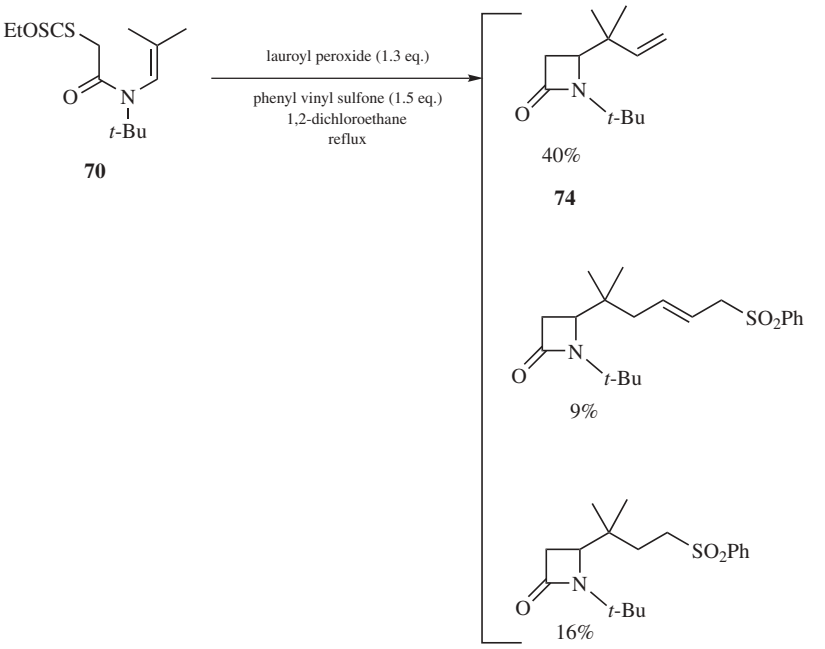
Two years later, Boiteau et al.[24] developed another synthetic method for β-lactams via radical cyclization of xanthates, which are known to be synthetically convenient sources of a variety of radicals. They found that appropriately substituted xanthate derivatives **70** of *N*-ethenyl acetamides undergo radical cyclization to afford β-lactams with an unexpected hydrogen atom transfer process (Scheme 18.37).



Scheme 18.37

When xanthate **70** was subjected to the usual radical-generating conditions (refluxing cyclohexane, catalytic lauroyl peroxide), no cyclized product **71** was obtained. However, in the presence of excess allyl acetate as the external olefin, the cyclization–addition product **72** (23%) along with lesser amounts of double addition derivative **73** (9%) were obtained, with 27% of the starting xanthate **70** being recovered.

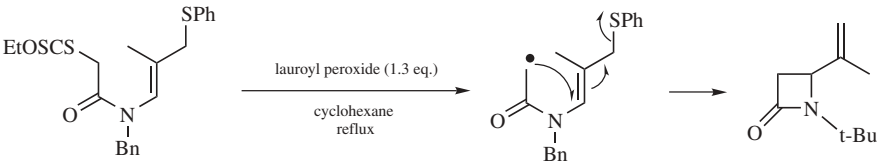
From a synthetic standpoint, using 1,2-dichloroethane as the solvent because of its greater solubility, the yield of **74** rose to 40% (Scheme 18.38).



Scheme 18.38

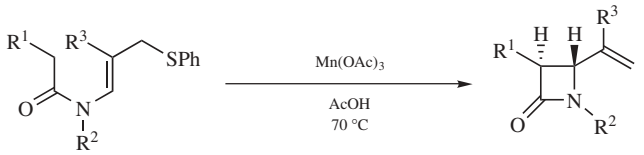
Boiteau et al. also developed the cyclization of compound **75** with the concomitant expulsion of a phenylthiyl radical. The yield of β-lactam **76** is 48% and a stoichiometric amount of lauroyl peroxide is needed since phenylthiyl radicals are capable of propagating the chain (Scheme 18.39).

Attenni et al.[25] carried out the synthesis of β-lactam vinylated at C-4 from *N*-(3-phenylthio-1-alkenyl)amides via the route involving Mn(III)-promoted 4-exo-trig radical cyclization followed by β-fragmentation loss of phenylthiyl radical. The fragmentation of β-phenylthio radical intermediates involved in these reactions strongly controlled both the regiochemical (i.e., 4-exo vs. 5-endo-trig) and stereochemical outcome (formation of the only *trans*-azetidinones) of the cyclization (Scheme 18.40).



75 76

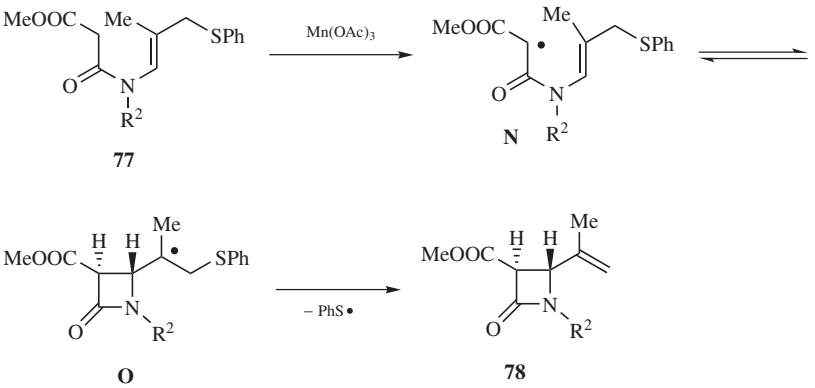
Scheme 18.39



77 78

Scheme 18.40

When enamides **77** bearing an activating group R^1 in the α-position of the acyl group were reacted with 1 eq. of Mn(III) acetate dihydrate in glacial acetic acid at 70°C, the expected β-lactams **78** vinylated in C-4 were obtained in modest to good yields. The reaction path seemed to be that shown in Scheme 18.41 for enamides



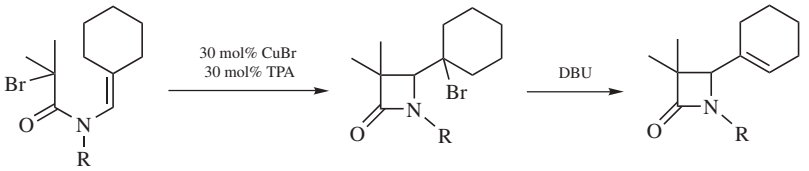
Scheme 18.41

77, that is, the Mn(III)-promoted generation of α-carbamoylalkyl radicals **N** followed by their 4-exo-trig cyclization to **O** which underwent a β-fragmentation to give products **78** and phenylthiyl radicals. Attenni et al. also investigated systematically the substituent effects of the R^1-, R^2-, and R^3-groups (Table 18.11).

Clark et al.[26] reported that tripyridylamine Cu(I) halide complex mediates the atom transfer radical cyclization of bromo-enamides **79** to give β-lactams **80** exclusively with no formation of γ-lactams (Scheme 18.42).

TABLE 18.11 Radical Cyclization of Enamides

Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**77a**	COOMe	Bn	Me	**78a**	43
2	**77b**	COOMe	Cyclohexyl	Me	**78b**	45
3	**77c**	COOMe	*t*-Bu	Me	—	—
4	**77d**	COOMe	CH(Me)Ph	Me	**78d**	54
5	**77e**	COOMe	Bn	H	—	—
6	**77f**	COOMe	Bn	Ph	**78f**	58
7	**77g**	$COO(CH_2)_3Me$	Bn	Me	**78g**	47
8	**77h**	$COOCH_2CHMe_2$	Bn	Me	**78h**	41
9	**77i**	$COOC_6H_{11}$	Bn	Me	**78i**	36

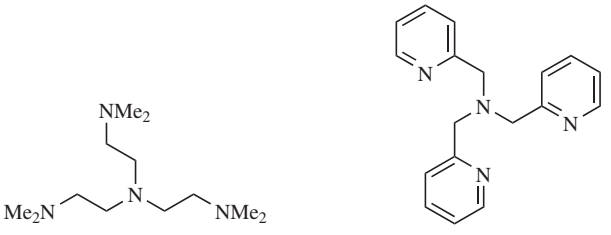


79 **80** **81**

Scheme 18.42

Clark et al. found that the tetradentate ligands **82** and **83** are the most active in simple 5-exo radical cyclizations, allowing the reactions to be carried out under milder conditions (room temperature or below) than existing copper-dipyridine (Fig. 18.4).

Reaction of the bromo-enamides **79a–e** with 30 mol % CuBr and 30 mol % TPA **83** in CH_2Cl_2 at room temperature for 1 h followed by work-up by passing through a silica plug furnished the bromo 4-exo atom transfer products **80a–e** in high yields with no 5-endo-cyclized product. The synthetic utility of the process is expanded by manipulation of the *tertiary* bromides **80** to the corresponding alkenes **81** (Table 18.12).



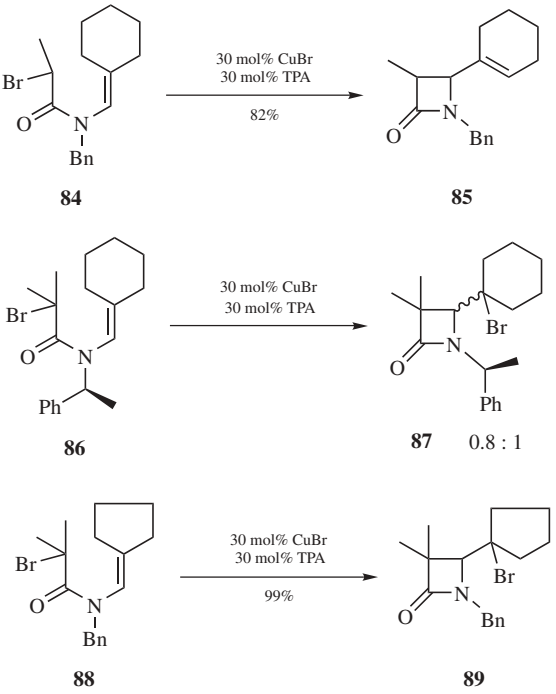
82 **83**

Figure 18.4 Tetradentate ligands.

TABLE 18.12 Cyclization and Elimination Reactions

Entry	Substrate	R	Yield **80** (%)	Yield **81** (%)
1	**79a**	Bn	96	94
2	**79b**	PMB	98	92
3	**79c**	*t*-Bu	0	—
4	**79d**	*i*-Bu	98	—
5	**79e**	*o*-BrBn	98	98

Heating **84** at a higher temperature in refluxing toluene for 24 h gave a 2.8 : 1 mixture of diastereomers **85** in 82% yields, and other substrates **86** and **88** worked well to give the corresponding β-lactams **87** and **89** (Scheme 18.43).



84 **85**

86 **87** 0.8 : 1

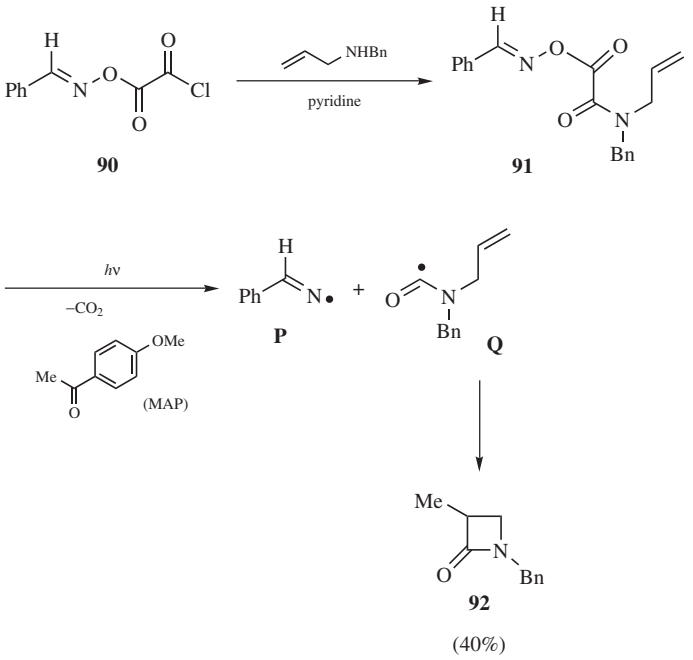
88 **89**

Scheme 18.43

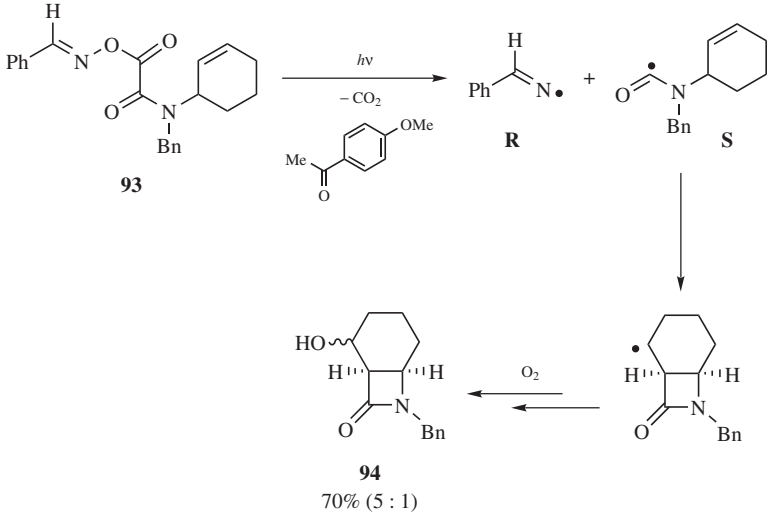
Scanlan and Walton[27] found that photosensitized decomposition of oxime oxalate amides is a useful new route to carbamoyl radicals that may cyclize to afford β-lactams.

As a mild, clean free-radical precursor, Scanlan and Walton picked up oxime oxalate amides **91** which were prepared from *O*-(chlorooxalyl)oxime **90** by the

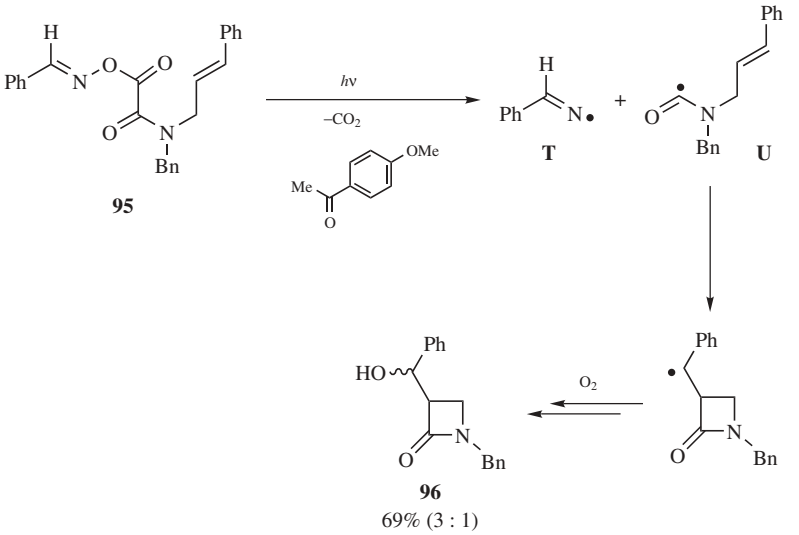
treatment with 1 eq. of a primary or secondary amine in the presence of pyridine at 0°C. Dilute solution in toluene with a threefold excess of *p*-methoxyacetophenone (MAP) was found to afford β-lactam **92** (Scheme 18.44).



Scheme 18.44



Scheme 18.45



Scheme 18.46

Ring closures of the aminoacyl radicals **S**, **U** derived from the cyclohexenyl- and phenyl-substituted materials **93**, **95** afforded the bicyclic β-lactams **94** and **96**, respectively.

An interesting feature was that both **94** and **96** were obtained as hydroxyl derivatives, the former as a 5 : 1 mixture of anti and syn isomers and the latter as a pair of diastereomers (3 : 1). Thus photosensitized decompositions of oxime amide oxalates provide an efficient and general route to aminoacyl radical, which finally gives good yield of β-lactams (Schemes 18.45 and 18.46).

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CHAPTER 19

Recent Advances in Synthesis of α-Hydroxy-β-amino Acids and Their Use in SAR Studies of Taxane Anticancer Agents

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19.1 INTRODUCTION

The significance of β-amino acids has been recognized with regard to the design and development of potential therapeutic drugs and the studies of enzymatic reaction mechanisms as well as the unique properties of β-*peptides*.[1,2] It has been shown that peptides bearing β-amino acid residues possess higher stability against enzymatic hydrolysis than normal peptides and β-peptides form unique secondary structures as compared to those made of α-amino acids.[3] Among various types in the β-amino acid family, α-hydroxy-β-amino acids (isoserines) are arguably the most important members because many of them act as potent enzyme inhibitors and also serve as crucial building blocks for the compounds of biological and medicinal importance.[2,4] A unique example for the importance of α-hydroxy-β-amino acid components in chemotherapeutic drugs is found in a highly potent anticancer agent, paclitaxel (Taxol), and its congeners.

Paclitaxel, a highly functionalized, naturally occurring taxane diterpenoid bearing a (2*R*,3*S*)-*N*-benzoylphenylisoserine residue at the C-13 position, is currently considered one of the most important drugs in cancer chemotherapy.[5,6] Paclitaxel was approved by the Food and Drug Administration (FDA) for treatment of advanced ovarian cancer (1992), metastatic breast cancer (1994), acquired immunodeficiency (AIDS)–related Kaposi's sarcoma (1997), and non-small-cell

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lung cancer (1999). A semisynthetic analog of paclitaxel, docetaxel (Taxotère),[7] was also approved by the FDA for treatment of advanced breast cancer and non-small-cell lung cancer. These two taxane anticancer drugs are currently undergoing phase II and III clinical trials worldwide for a variety of other cancers as well as for combination therapy with other agents. Paclitaxel and docetaxel have been shown to have a unique mechanism of action acting as spindle poisons, causing cell division cycle arrest at the G2/M stage, which eventually leads to the apoptosis of cancer cells.[8,9]

Paclitaxel was originally isolated from the bark of the Pacific yew tree (*Taxus brevifolia*), a nonrenewable resource, through a cumbersome and low-yielding extraction process. Accordingly, the long-term use of this drug could not be secured once the supply of yew trees had become depleted. Fortunately, 10-deacetylbaccatin III (DAB), a diterpenoid comprising the complex tetracyclic core of paclitaxel, can be isolated in good quantity from the leaves of the European yew (*Taxus baccata*).[10] The isolation of DAB from a renewable resource opened the possibility of using semisynthetic methods to secure the long-term supply of paclitaxel. Accordingly, the semisynthesis of paclitaxel via the coupling of a phenylisoserine moiety with DAB has been extensively studied, including the asymmetric synthesis of *N*-benzoylphenylisoserine and its synthons (Figure 19.1).[7,11–15] These synthetic studies led to the development of a highly efficient commercial process for the manufacturing of paclitaxel by semisynthesis which has secured the supply of this extremely important anticancer drug. The semisynthetic approaches to paclitaxel have also resulted in the discovery and development of a highly potent paclitaxel analog, docetaxel, which has now become an equally important anticancer drug as paclitaxel (Figure 19.1).[7] In addition, these studies opened an avenue for the development of new-generation taxoids (i.e., Taxol-like compounds) that may have higher potency and better pharmacological properties than the parent two drugs through structure–activity relationship (SAR) studies.[11,14–17]

The SAR studies have revealed that the (2*R*,3*S*)-*N*-acyl-3-phenylisoserine moieties of paclitaxel and docetaxel are extremely important for their cytotoxicity and antitumor activity; for example, the loss of this β-amino acid moiety results in >1000-fold reduction in their potency and the deletion of any substituent or introduction of other stereochemistry also substantially lowers their potency by

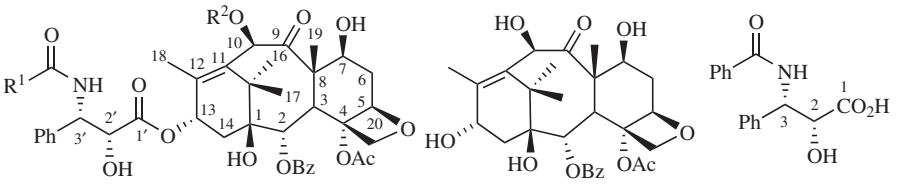


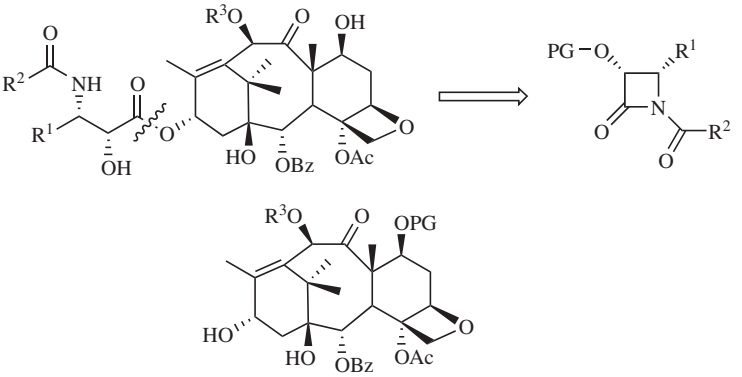
Figure 19.1

several to >500 times.[14,18] We discovered that the introduction of nonaromatic isoserine residues to the C-13 position of taxoids brought about a series of highly potent taxoids, especially against drug-resistant cancer cells, and have developed the "second-generation" taxoids. This chapter describes the recent advances in the synthesis of enantiopure α-hydroxy-β-amino acids (isoserines) and their use in the medicinal chemistry and chemical biology of taxane anticancer agents, primarily as an account of our research program.

19.2 SYNTHESIS OF ENANTIOPURE α-HYDROXY-β-AMINO ACID COMPONENTS OF TAXANE ANTICANCER AGENTS BY β-LACTAM SYNTHON METHOD

19.2.1 β-Lactam Synthon Method

The semisynthesis of paclitaxel, docetaxel, and their analogs via the coupling of a phenylisoserine moiety with DAB has been extensively studied by many laboratories, as mentioned above.[7,11–15] Among these coupling methods, the Ojima–Holton β-lactam coupling method has been proven to be the most efficient and versatile method.[19–23] Our strategy has been to apply the β-*lactam synthon method* (β-LSM)[24–26] for the asymmetric synthesis of a (2′*R*,3′*S*)-*N*-benzoyl-3-phenylisoserine moiety in high yield with excellent enantiopurity through ring-opening coupling of (3*R*,4*S*)-*N*-benzoyl-β-lactam with an appropriately modified DAB (Scheme 19.1).



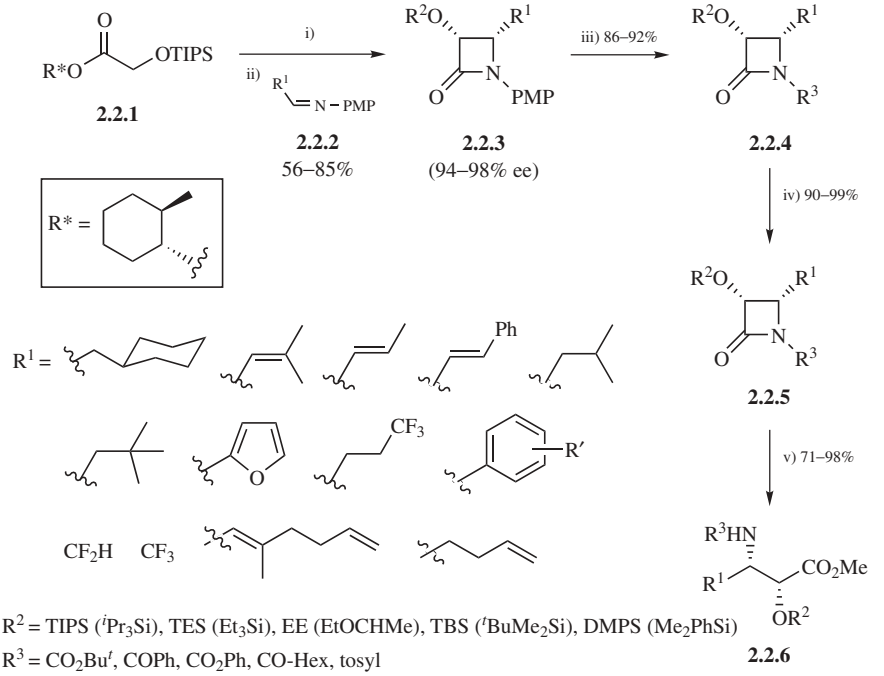
Scheme 19.1

Our studies on the development and applications of the β-LSM have been well reviewed.[4,11,15,24–27] In addition to its industrial application to the synthesis of paclitaxel, the Ojima–Holton protocol has opened an extremely efficient and practical route to a diverse array of new taxoids, which paved the way for extensive SAR studies of taxoid anticancer agents. The most important issue for the β-LSM to be successfully applied to such taxoid syntheses is to secure the supply of

enantiopure β-lactams with the correct absolute configuration and proper substituents. Accordingly, we employed the following two methods: (i) asymmetric ester–imine cyclocondensation and (ii) the Staudinger reaction followed by enzymatic optical resolution, which will be described next.

19.2.2 Synthesis of Enantiopure β-Lactams via Asymmetric Enolate–Imine Cyclocondensation

Asymmetric enolate–imine cyclocondensation process using (−)-trans-2-phenyl-1-cyclohexanol as the chiral auxiliary provides *N,O*-diprotected (3*R*,4*S*)-3-hydroxy-β-lactams with extremely high enantiopurity in high yields (Scheme 19.2).[19,28]



(i) LDA (LiNPr$^i_2$), THF (tetrahydrofuran), –84 °C; (ii) LiHMDS (LiN(SiMe$_3$)$_2$), THF, –84 °C-RT;
(iii) CAN, –10 °C; (iv) (^{t}Boc)$_2$O, BzCl, or HexCOCl, Et$_3$N/DMAP;
(v) MeOH, Et$_3$N, DMAP, RT

Scheme 19.2

A chiral lithium ester enolate is generated in situ from a silyloxyacetate **2.2.1** and reacts with an *N*-(*p*-methoxyphenyl)aldimine (*N*-PMP-aldimine) **2.2.2** to afford the corresponding chiral β-lactam **2.2.3**.[19,28] The silicon *O*-protecting group is typically triisopropylsilyl (TIPS), but *t*-butyldimethylsilyl (TBS) gives excellent enantioselectivity as well.[19,29] Deprotection of the *p*-methoxyphenyl *N*-protecting group with cerium ammonium nitrate (CAN) gives the corresponding NH-free

3-TIPSO-β-lactam **2.2.4** ($R^3 = H$). The subsequent acylation (alkoxycarbonylation, carbamoylation, or sulfonylation) of the NH-free β-lactam with acyl chlorides, chloroformates, carbamoyl chlorides, or sulfonyl chlorides affords a variety of enantiopure 4-substituted 1-acyl-(carbalkoxy, carbamoyl or sulfonyl)-3-TIPSO-β–lactams **2.2.5**. *N*-TMS-benzaldimine (TMS = trimethylsilyl) can be used for the asymmetric synthesis of (3*R*,4*S*)-3-TIPSO-4-phenylazetidin-2-one (**2.2.4a**; $R^3 = H$) with >96% ee in 90% yield; that is, the reaction directly affords the NH-free β-lactam without the CAN deprotection step.[19,30]

The resulting 1-acyl-(carbalkoxy, carbamoyl or sulfonyl)-3-TIPSO-β-lactams **2.2.5** are highly activated for nucleophilic attack at the N^1–C^2(O) bond. For example, methanolysis of β-lactams **2.2.5** under very mild conditions (NEt_3 and a catalytic amount of 4-*N,N*-dimethylaminopyridine (DMAP) at room temperature) gives *O*-TIPS-protected α-hydroxy-β-amino acid methyl esters **2.2.6** in high to quantitative yields.[28,31–33] This excellent reactivity is crucial for the efficient coupling with the highly hindered C-13 α-hydroxyl group of the 7,10-diprotected baccatins in the taxoid syntheses.

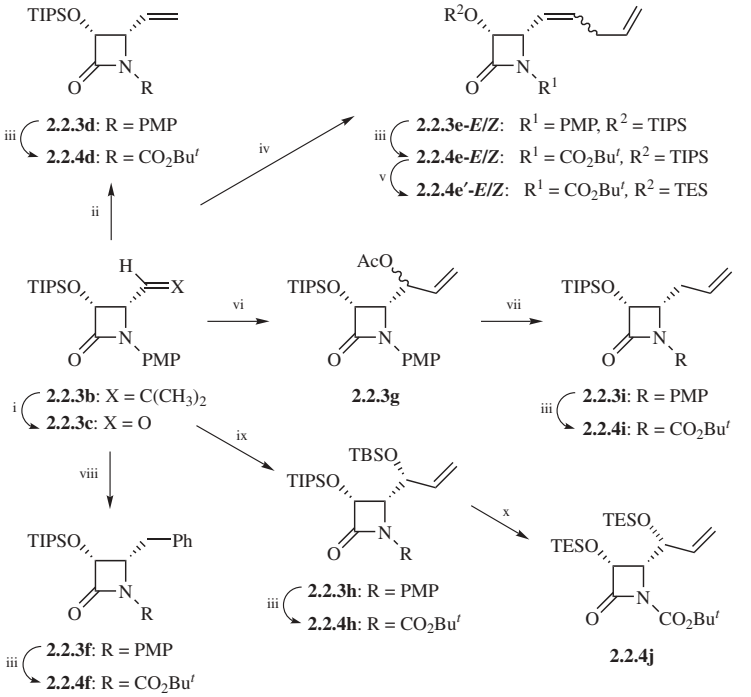
It is worth mentioning that (3*R*,4*S*)-1-PMP-3-TIPSO-4-formylazetidin-2-one (**2.2.3c**), obtained by the ozonolysis of the corresponding 4-(2-methylbut-2-enyl)-azetidin-2-one (**2.2.3b**), serves as a very useful key intermediate for the syntheses of various enantiopure β-lactams through C-4 modifications. Examples are illustrated in Scheme 19.3.[34,35]

19.2.3 Synthesis of Enantiopure β-Lactams through Asymmetric Staudinger Reaction followed by Enzymatic Optical Resolution

The ketene–imine cycloaddition reaction, known as the Staudinger reaction,[36] is one of the most convenient approaches to the diastereoselective synthesis of β-lactams from readily available imines and ketenes, generated in situ from acid chlorides in the presence of a base.[27,37,38]

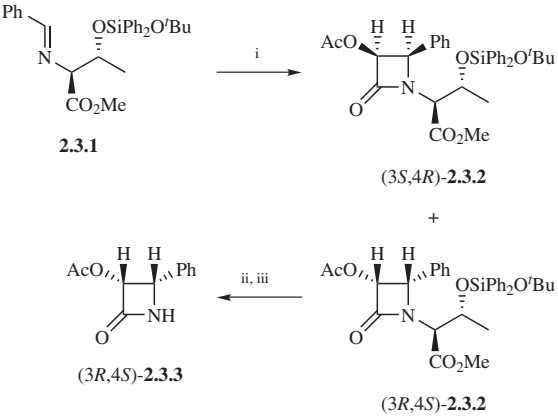
The exclusive or major product of the Staudinger reaction is normally cis-β-lactams formed via an orbital-controlled conrotatory process of the zwitterionic key intermediate in the second step of the two-step reaction.[26] Various chiral groups could be attached to either the ketene or the imine component to control the diastereoselectivity in this cycloaddition process.[39] For example, for the asymmetric synthesis of 3-amino-β-lactams, the *Evans–Sjögren ketene* generated from 4-phenyloxazolidinylacetyl chloride and triethylamine has been widely used.[19,37,40] However, few successful examples of the introduction of chiral auxiliaries to hydroxyacetate has been reported to date, probably due to the difficulty in controlling the flexibility of the resulting ether linkage to the chiral auxiliaries.[41] Thus, the introduction of chiral auxiliaries is limited to the imine component, specifically at the imine nitrogen.

As Scheme 19.4 shows, the reaction of chiral benzaldimine **2.3.1**, derived from L-serine, with acetoxyketene gives the desirable β-lactam, (3*R*,4*S*)-**2.3.2**, accompanied by a small amount of the other diastereomer, (3*S*,4*R*)-**2.3.2** (up to 1 : 11.5 ratio).[42,43] (Scheme 19.4). The major product (3*R*,4*S*)-**2.3.2** is isolated and then



(i) O_3/Me_2S, quant.; (ii) $Ph_3P{=}CH_2$, 90%; (iii) (a) CAN, −10 °C, (b) (^{t}Boc)$_2$O, Et_3N/DMAP, 82–96%; (iv) $Ph_3P{=}CHCH_2CH{=}CH_2$, 93%; (v) HF/Py; TES-Cl, Et_3N/DMAP; *Z*, 88%; *E*, 77% (2 steps); (vi) $CH_2{=}CHMgBr$; then Ac_2O; 98% (2 steps), *R*/*S* = 11/1); (vii) $Pd_2(dba)_3CHCl_3$, HCO_2NH_4, PBu_3, dioxane, 65%; (viii) PhMgBr, then Ac_2O; Pd/C, H_2 (100 psi); 50% (3 steps); (ix) $CH_2{=}CHMgBr$; TBSCl, Et_3N; 82% (2 steps); (x) HF/Py; TESCl, Et_3N/DMAP, 90% (2 steps)

Scheme 19.3



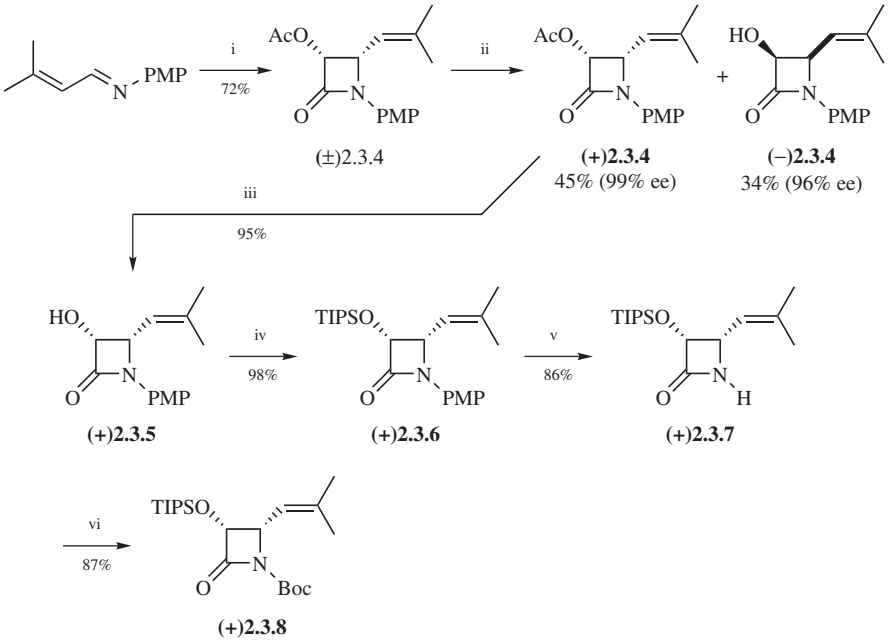
(i) $AcOCH_2COCl$, Et_3N, CH_2Cl_2, −40 °C to RT, 4 h;
(ii) Bu_4NF, MsCl, Et_3N; (iii) O_3 and $NaHCO_3$

Scheme 19.4

transformed to (3*R*,4*S*)-3-acetoxy-4-phenylazetidin-2-one, (3*R*,4*S*)-**2.3.3**. After *N*-benzoylation, the resulting *N*-benzoyl-β-lactam serves as the C-13 isoserine precursor of paclitaxel.[42]

Enzymatic kinetic optical resolution provides another route to enantiopure 3-hydroxy-β-lactams from the corresponding racemic β-lactams.[44–47] Although at least half of the racemic β-lactam cannot be converted to the desired enantiomer in this process, the starting materials are very inexpensive and the ketene–imine cycloaddition process is general and convenient. Thus, the enzymatic resolution process is economically attractive even though the ''atom economy'' is not high. Also, the other diastereomers, (3*S*,4*R*)-β-lactams, can be used as versatile synthetic building blocks and may not be wasted.

Among various hydrolytic enzymes examined, Amano lipases and pig liver acetone powder (PLAP) have been found to provide the best results in the kinetic optical resolution of 3-acetoxy-4-phenyl-β-lactams, yielding the β-lactam products with high enantiopurity.[46,47] We successfully applied the PS-Amano lipase to the kinetic resolution of racemic cis-1-PMP-3-acetoxy-4-(2-methylbut-2-enyl)azetidin-2-one [(±)-**2.3.4**], as illustrated in Scheme 19.5.[33,48,49] The PS-Amano lipase preferentially hydrolyzes the acetate moiety at the C-3 position of (±)-**2.3.4**. Therefore, (3*R*,4*S*)-β-lactam (+)-**2.3.4** is obtained with extremely high enantiopurity



(i) $AcOCH_2COCl$, Et_3N, CH_2Cl_2, −78 °C to RT, overmight; (ii) Amano PS-30, MeCN/ buffer (1/1 v/v), 55 °C, pH = 7.5; (iii) 1M KOH, THF, 0 °C, 1H; (iv) TIPSCl, Et_3N, DMAP, CH_2Cl_2; (v) CAN, $MeCN/H_2O$, −10 °C, 2 h; (vi) Boc_2O, Et_3N DMAP, CH_2Cl_2

Scheme 19.5

(>99% ee) when the reaction is stopped over 50% conversion.[33,48] Routine transformations of (+)-**2.3.4** afford (3*R*,4*S*)-1-*t*-Boc-3-TIPSO-4-(2-methylbut-2-enyl)azetidin-2-one [(+)**2.3.8**] (Scheme 19.5), which is readily used for the ring-opening coupling with baccatins to give the corresponding second-generation taxoids. Similar applications of the enzymatic kinetic optical resolution to fluorine-containing β-lactams are discussed in Section 19.3.3.

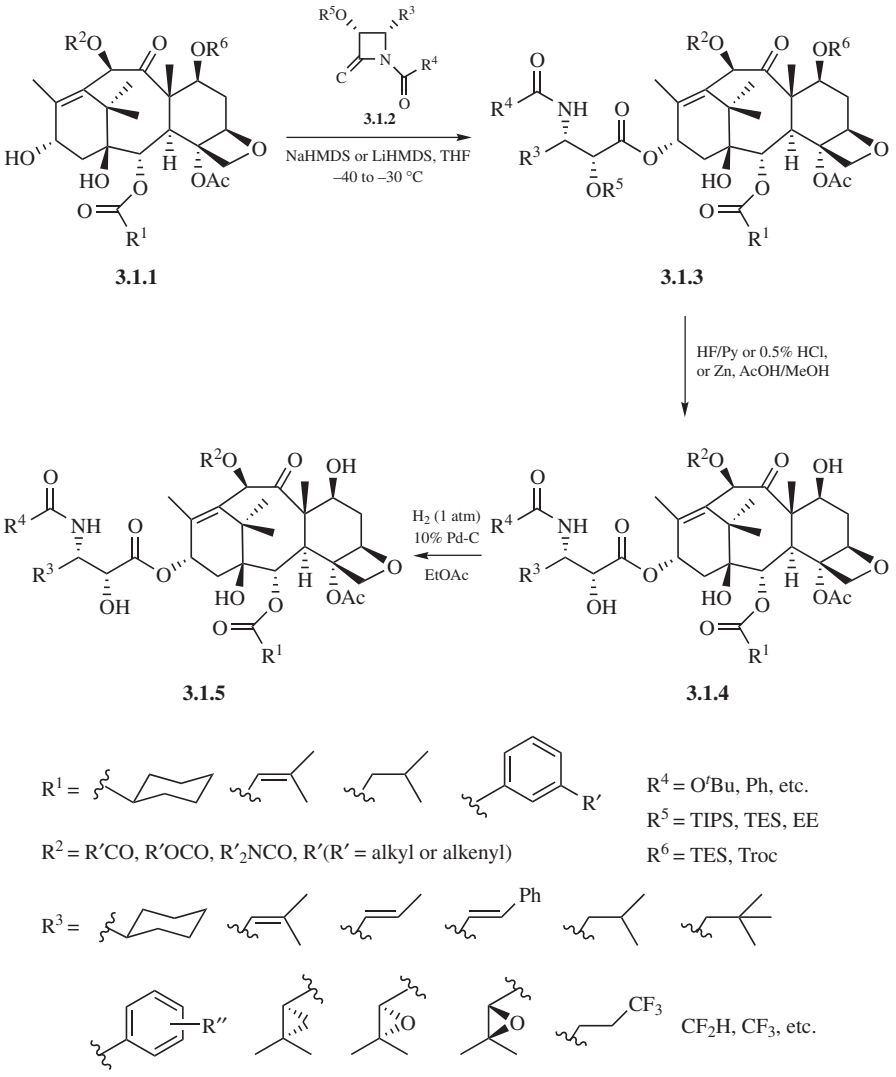
19.3 NEW C-13 α-HYDROXY-β-AMINO ACID RESIDUES AND THEIR SIGNIFICANCE IN SECOND-GENERATION TAXOIDS

Since the β-LSM provided an efficient and practical route to a diverse array of novel taxoids bearing various α-hydroxy-β-amino acid residues at the C-13 position, the SAR studies of this highly promising class of anticancer agents were greatly facilitated. A series of new and highly potent taxoids, termed the *second-generation taxoids*, have emerged out of these extensive SAR studies.[50–54] The second-generation taxoids exhibit excellent cytotoxicity against different types of human cancer cell lines, especially drug-resistant cancer cell lines expressing multidrug resistance (MDR) phenotypes. The potency of many of the second-generation taxoids is one order of magnitude higher than paclitaxel against drug-sensitive cancer cell lines and two to three orders of magnitude higher than paclitaxel and docetaxel against drug-resistant cancer cell lines. Some of these taxoids exhibited excellent in vivo antitumor activity in preclinical studies, and one of them has advanced to the phase III human clinical trials.

19.3.1 3-Alkyl- and 3-Alkenylisoserines at the C-13 Position

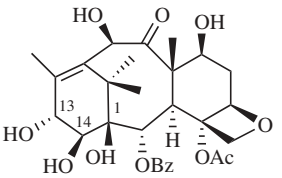
In the SAR studies the following key observations have been made for achieving high potency[51,54]: (i) A *tert*-butoxycarbonyl group at the N-3′ position is so far optimal, (ii) replacement of the phenyl group at the C-3′ position by an alkyl or alkenyl group with three or four carbons exhibits substantial effects on the increase in cytotoxicity against drug-sensitive and drug-resistant human cancer cell lines, and (iii) substitution of the hydroxyl group at the C-10 position with a proper acyl group, such as propanoyl, cyclopropanoyl, *N,N*-dimethylcarbamoyl, and methoxycarbonyl groups, in combination with the introduction of an alkyl or an alkenyl group at the C-3′ position exerts remarkable effects on the cytotoxicity against the drug-resistant human cancer cell lines expressing MDR phenotypes. Besides these crucial findings, it has also been found that a proper meta substitution of the benzoyl group at the C-2 position further enhances the potency of the second-generation taxoids.[55]

Synthesis of the second-generation taxoids is illustrated in Scheme 19.6. The ring-opening couplings of (3*R*,4*S*)-*N*-acyl-β-lactams **3.1.2** with 10- and/or 2-modified baccatins **3.1.1** give the corresponding 7,2′-diprotected taxoids **3.1.3**, which are deprotected to afford taxoids **3.1.4**. Hydrogenation of the alkenyl group at the C-3′ position of taxoids **3.1.4** on Pd–C gives the corresponding 3′-alkyl taxoids **3.1.5**.

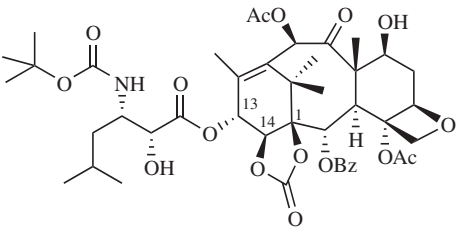


Scheme 19.6

The second-generation taxoids derived from 14β-OH-10-deacetylbaccatin III (14-OH-DAB),[56] another taxane diterpene isolated from the Himalayan yew tree (*Taxus wallichiana zucc.*), have also been developed.[50,52] One of these taxoids, SB-T-101131 (IDN-5109, BAY59-8862, Ortataxel), which is found to have high oral activity, exhibited highly potent cytotoxicity and antitumor activity against human cancer cell lines and tumor xenografts, expressing MDR, and an excellent pharmacological profile in preclinical studies.[50,57–61] This taxoid is currently undergoing phase II and III human clinical trials sponsored by Bayer (Fig. 19.2).



14β-OH-10-deacetylbaccatin III



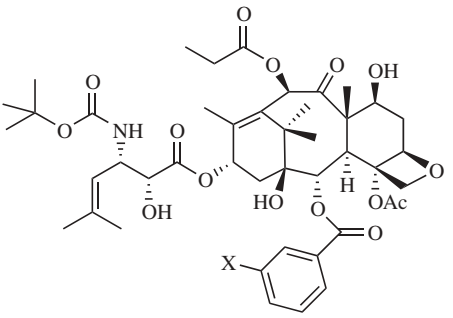
SB-T-1011131 (IDN5109, BAY59-8862, Ortataxel)

Figure 19.2

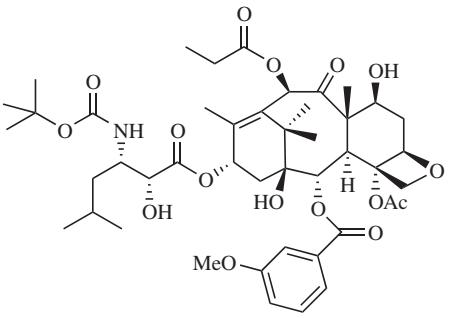
Further SAR studies have revealed that a modification of the benzoate group at the C-2 position also has significant positive effects on the activity of the second-generation taxoids, especially against drug-resistant cancer cell lines.[50,55] It was reported that the modification at the meta position of the 2-benzoate of paclitaxel (including CN, N_3, MeO, and Cl, especially N_3) led to substantially improved cytotoxicity against a P-388 cell line.[62–64] By incorporating this finding, a series of highly active ''advanced'' second-generation taxoids with modifications at the C-3′, C-10, and C-2 positions has been developed.[55] Some of these compounds possess two to three orders of magnitude higher potency against the drug-resistant cancer cell lines LCC6-MDR and MCF7-MDR as compared to paclitaxel and docetaxel. Three of them, SB-T-110303, 121303, and 121304, exhibited the same activities against drug-sensitive and drug-resistant cell lines and virtually overcome the MDR completely, making them highly promising anticancer agents (Fig. 19.3).

19.3.2 Novel α-Hydroxy-β-amino Acids Bearing Cyclopropane and Oxirane Moieties and Their Incorporation to Taxoids

Novel α-hydroxy-β-amino acids bearing a cyclopropane or an epoxide moiety possess unique steric and electronic properties and serve as useful building blocks



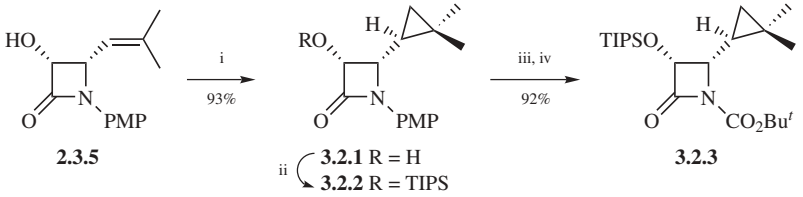
SB-T-121303 (X = OMe)
SB-T-121304 (X = N_3)



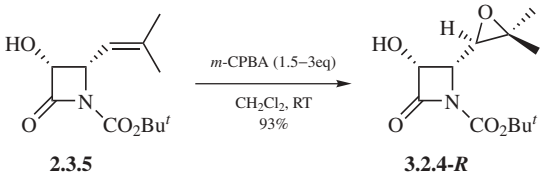
SB-T-110303

Figure 19.3

for peptides, peptidomimetics, protease inhibitors, and taxoid antitumor agents. We have developed efficient asymmetric synthesis routes to β-lactams bearing a cyclopropane or an epoxide moiety at the C-4 position, which are synthons of novel methanonorstatine and oxanorstatine.[53] Syntheses of these novel β-lactams are illustrated in Scheme 19.7. Cyclopropanation of (3*R*,4*S*)-3-OH-4-(2-methylbut-2-enyl)-β-lactam **2.3.5** under the Simmons–Smith conditions gave 4-((*S*)-2,2-dimethylcyclopropyl)-β-lactam **3.2.1** as the single product in 93% yield. Protection of the 3-OH group with TIPS and removal of the *N*-PMP group followed by *N*-*t*-Boc acylation afforded β-lactam **3.2.3** in 92% yield for three steps. The reaction of β-lactam **2.3.5** with *m*-chloroperbenzoic acid (*m*-CPBA) afforded 4-((*R*)-2-methyl-1,2-epoxypropyl)-β-lactam **3.2.4-*R*** as the sole product in high yield. In sharp contrast with this, the same reaction with 3-TIPSO-(2-methylbut-2-enyl)-β-lactam **2.3.8** resulted in the formation of a 1 : 1 mixture of two diastereomeric 4-(2-methyl-1,2-epoxypropyl)-β-lactams, **3.2.4-*R*** and **3.2.4-*S***, which were easily separated by flash column chromatography on silica gel. These β-lactams were further converted to the novel *N*-*t*-Boc-methanonorstatine and oxanorstatine methyl esters through facile methanolysis.[53]

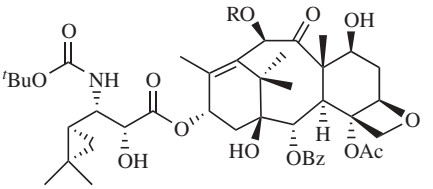


i) Et_2Zn, CH_2I_2, $(ClCH_2)_2$; ii) TIPSCl, Et_3N/DMAP; iii) CAN, –10 °C;
iv) $(Boc)_2O$, Et_3N, DMAP

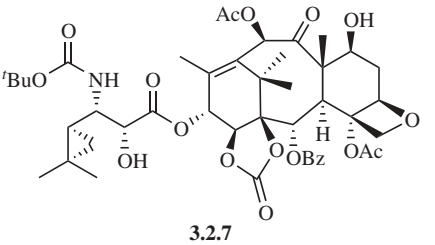


Scheme 19.7

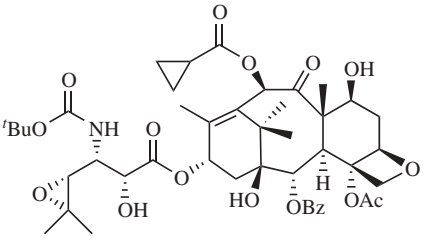
Novel taxoids bearing methanonorstatine and oxanorstatine residues at the C-13 position (Fig. 19.4) were synthesized through a β-lactam ring-opening coupling method in the same manner as that described above (see Scheme 19.6).[15,53] Taxoids **3.2.5**, **3.2.6**, and **3.2.7** exhibited excellent cytotoxicity, especially against drug-resistant LCC6-MDR human breast cancer cell lines (two orders of magnitude higher potency than paclitaxel).[15,53] Taxoid **3.2.8-*R*** is also highly active while the other isomer **3.2.8-*S*** showed one to two orders of magnitude lower activity as compared to paclitaxel against several drug-sensitive human cancer cell lines.[53] This observation clearly indicates that the cytotoxicity of taxoids is highly sensitive to the structure of the substituent at the C-3′ position of the C-13 isoserine moiety.



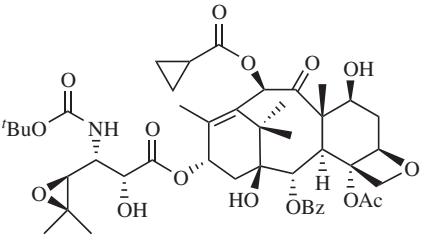
3.2.5 R = Ac
3.2.6 R = cyclopropanecarbonyl



3.2.7



3.2.8-*R*



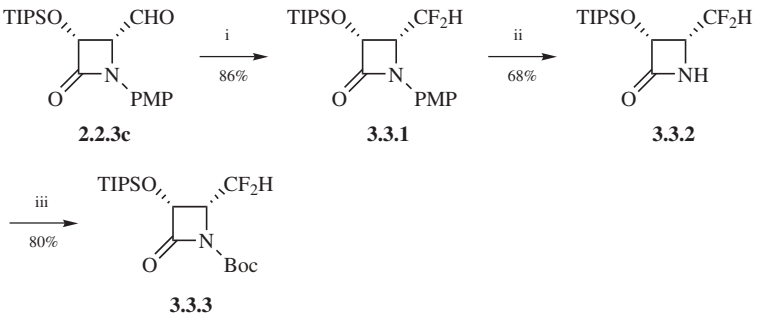
3.2.8-*S*

Figure 19.4

19.3.3 CF_3- and CF_2H-Containing Isoserines and Their Use in Fluoro-Taxoids

The introduction of fluorine(s), difluoromethyl, or trifluoromethyl group to modulate the properties of bioactive molecules very often results in substantially improved pharmacological properties because of increased membrane permeability, enhanced hydrophobic binding, stability against metabolic oxidation, and so on.[65,66] Syntheses and applications of fluorine-containing paclitaxel and taxoids have been reviewed.[67–69] The syntheses of fluoro-taxoids containing CF_3-isoserine residue at the C-13 position by means of efficient enantiomer-selective ring-opening coupling of a racemic 1-*t*-Boc-4-CF_3-β-lactam with baccatins have also been reported.[70,71] Accordingly, in this section, newer approaches to the efficient syntheses of enantiopure 4-R_f-β-lactams ($R_f = CF_2H$ or CF_3) and their use in the SAR study of R_f-containing second-generation taxoids are described. As Scheme 19.8 shows, (3*R*,4*S*)-1-*t*-Boc-4-CF_2H-β-lactam **3.3.3** was readily obtained from (3*R*,4*S*)-1-PMP-3-TIPSO-4-formyl-β-lactam **2.2.3c** (see Scheme 19.3) through diethylaminosulfur trifluoride (DAST) reaction, deprotection, and *t*-Boc acylation in good overall yield.[72] No epimerization was observed at the DAST reaction step.

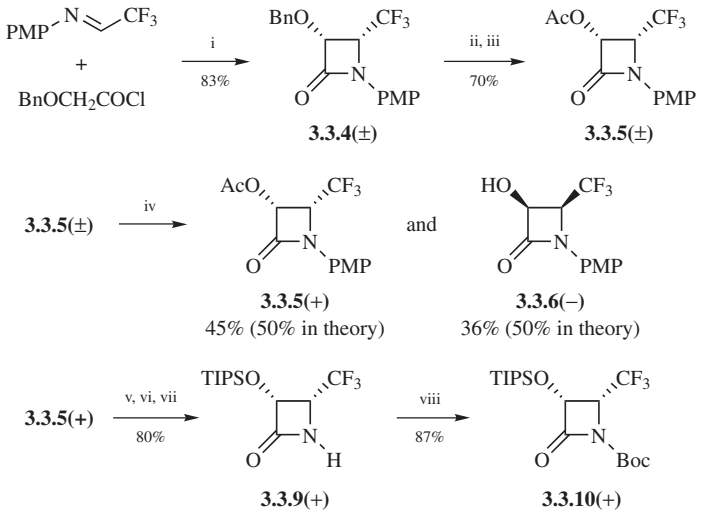
(3*R*,4*S*)-1-*t*-Boc-4-CF_3-β-lactam **3.3.10**(+) was synthesized through the enzymatic optical resolution of racemic 1-PMP-3-AcO-4-CF_3-β-lactam **3.3.5**(±), which had been obtained from the ketene–imine cycloaddition of benzyloxyketene with *N*-PMP-trifluoroacetaldimine followed by debenzylation and acetylation (Scheme 19.9).[33]



2.2.3c **3.3.1** **3.3.2** **3.3.3**

(i) DAST, CH_2Cl_2; (ii) CAN, H_2O/CH_3CN, –15 °C; (iii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, RT

Scheme 19.8

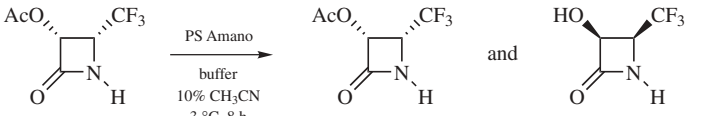


(i) Et_3N, CH_2Cl_2, 45 °C; (ii) H_2, Pd/C, MeOH, 45 °C; (iii) Ac_2O, DMAP, Py, CH_2Cl_2; (iv) PS-Amano, buffer 10% CH_3CN, 3 °C, 12 h; (v) KOH, THF, –5 °C; (vi) TIPSCl, TEA, CH_2Cl_2; (vii) CAN, $MeCN/H_2O$, –10 °C; (viii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, RT.

Scheme 19.9

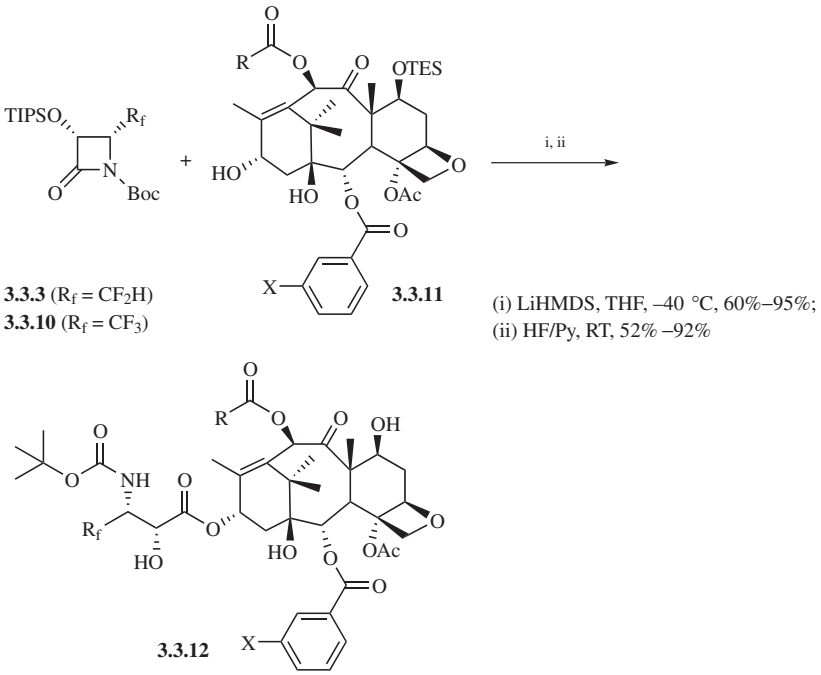
The enzymatic optical resolution of 3-AcO-β-lactam **3.3.5**(±) was carried out with the PS-Amano lipase at 3°C in a buffer (pH 7)/10% acetonitrile to give (3*R*,4*R*)-3-AcO-β-lactam **3.3.5**(+) with >99% ee in excellent yield (45% isolated yield out 50% in theory) accompanied by (3*S*,4*S*)-3-OH-β-lactam **3.3.9**(−) (36% out of 50% in theory).[33] More recently, we have found that the same enzymatic optical resolution proceeds even faster and cleaner when racemic NH-free 3-AcO-4-CF_3-β-lactam **3.3.7**(±) was used (Scheme 19.10).[33]

A library of 3′-R_f-taxoids **3.3.12** was synthesized through the ring-opening coupling of modified baccatins with 4-CF_2H-β-lactam **3.3.3** and 4-CF_3-β-lactam



3.3.7(±) **3.3.7**(+) 45% (50% in theory) **3.3.8**(–) 44% (50% in theory)

Scheme 19.10



3.3.3 ($R_f = CF_2H$)
3.3.10 ($R_f = CF_3$)

3.3.11

(i) LiHMDS, THF, –40 °C, 60%–95%;
(ii) HF/Py, RT, 52% –92%

3.3.12

R = Me, Et, MeO, NMe_2, $^tBuCH_2$, etc.
$R_f = CF_2H$, CF_3
X = MeO, F, Cl, N_3

Scheme 19.11

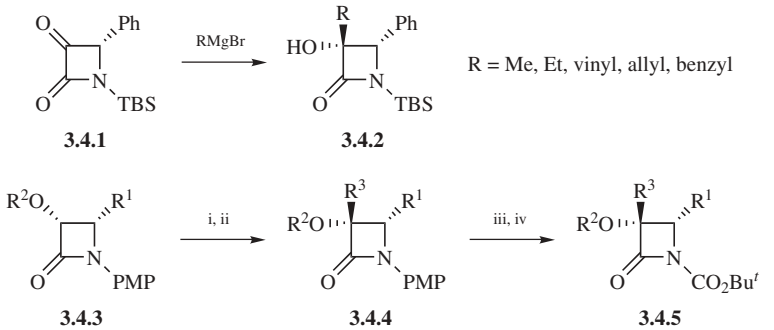
3.3.10 under the standard conditions (Scheme 19.11) and their cytotoxicity assayed against human breast cancer cell lines.[33,72]

All 3′-R_f-taxoids assayed possess excellent cytotoxicity against drug-sensitive and drug-resistant human breast cancer cell lines, but the following three 3′-R_f-taxoids deserve special attention: SB-T-12842-4 (**3.3.12**, $R_f = CF_2H$, R = Et, X = Cl) and SB-T-128221-3 (**3.3.12**, $R_f = CF_3$, R = Et, $X = N_3$) possess more than two orders of magnitude higher cytotoxicity than paclitaxel against the drug-resistant cell lines, MCF7-MDR and LCC6-MDR, and several times higher potency than paclitaxel against the drug-sensitive cell lines, MCF7 and LCC6-WT.[33] The third taxoid, SB-T-12843 (**3.3.12**, $R_f = CF_2H$, R = *t*-$BuCH_2CO$, X = H),

possesses exceptional activity in inducing apoptosis, especially in the MDR expressing CEM-VBLr leukemia and MCF7-MDR cancer cells wherein paclitaxel and docetaxel do not show any appreciable activity.[72]

19.3.4 α-Alkyl-α-hydroxy-β-amino Acids and Their Use as Conformationally Constrained C-13 Isoserine Moiety

Introduction of rigidity to the biologically active molecules often increases their potency through favorable entropy effects. Along this line, the syntheses of enantiopure α-alkyl-α-hydroxy-β-amino acids by mean of the β-LSM and their applications to novel 2-alkylisoserines, peptides, and taxoids have been studied.[73,74] As Scheme 19.12 shows, the diastereoselective addition of Grignard reagents to (*S*)-4-phenylazetidine-2,3-dione **3.4.1** afforded (3*R*,4*S*)-3-(substituted)-4-phenyl-β-lactam **3.4.2** exclusively.[75] The highly stereoselective alkylation of (3*R*,4*S*)-3-siloxy-β-lactam **3.4.3** also gave (3*R*,4*S*)-3-alkyl-β-lactam **3.4.4** as the sole product.[74]



3.4.1 **3.4.2** **3.4.3** **3.4.4** **3.4.5**

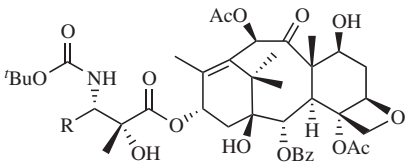
R^1 = isobutenyl, isobutyl, cyclohexylmethyl, phenyl; R^2 = $PhMe_2Si$, TES;
R^3 = methyl, allyl

(i) LDA, THF, –40 °C; (ii) MeI or allyl bromide, –78 °C ~ –10 °C; (iii) CAN, –10 °C;
(iv) $(^tBoc)_2O$, Et_3N, DMAP

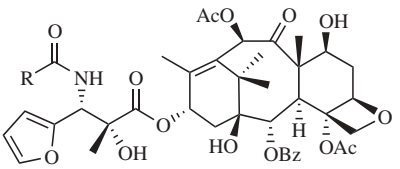
Scheme 19.12

The corresponding taxoids bearing 2-methylisoserine moiety at the C-13 position (2′-methyl-taxoids) **3.4.6** were synthesized in good yields through ring-opening coupling of (3*R*,4*S*)-3-methyl-β-lactams with 7-TES-baccatin III (**3.1.1**: R^1 = Ph, R^2 = Ac, R^6 = TES : TES = triethylsilyl) under the standard conditions and their cytotoxicity assayed (Fig. 19.5).[73,74] More recently, several more 2′-methyl taxoids derived from DAB (**3.4.7**) and 14-OH-DAB (**3.4.8**) were synthesized and their potency evaluated (Fig. 19.5).[76] All of these 2′-methyl-taxoids exhibited moderately enhanced activity compared to the parent taxoids.

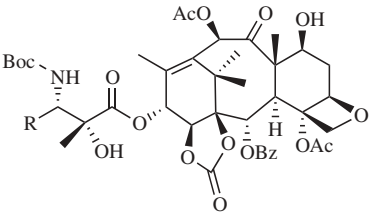
Cyclic isoserine analogs have also been used to introduce rigidity to taxoids. Conformationally constrained analogs of paclitaxel and docetaxel were synthesized by introducing a tether between the C-2′ carbon and the ortho position of the C-3′



3.4.6 (R = Ph, Me_2CH=CH)



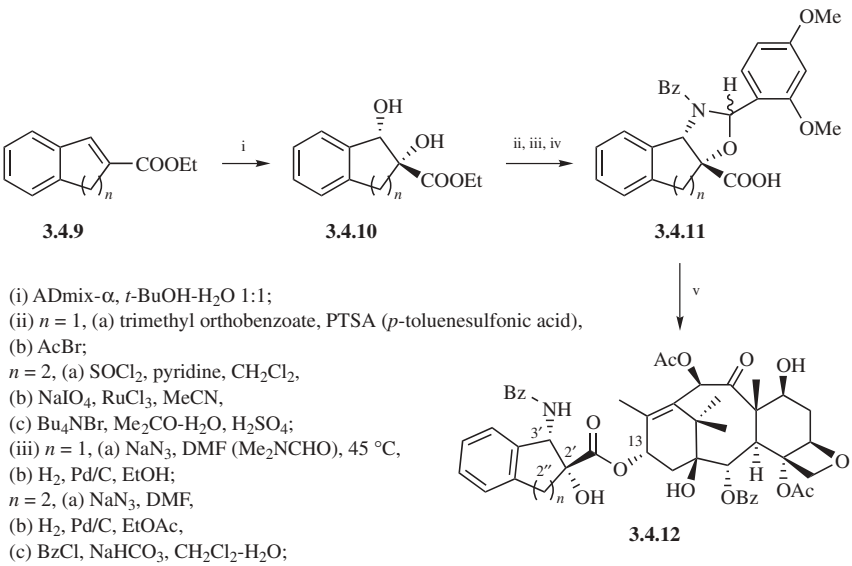
3.4.7 (R = Ph, *t*-BuO)



3.4.8 (R = 2-furyl, Ph, CF_3)

Figure 19.5

phenyl group.[77,78] Two approaches were used for the synthesis. One approach is applying the asymmetric dihydroxylation (AD) to cyclic cinnamate **3.4.9**, giving the corresponding diol **3.4.10** with excellent enantioselectivity. The diol **3.4.10** was subsequently converted to amino acid precursors **3.4.11**, which was further coupled with 7-TES-baccatin III to afford paclitaxel analog **3.4.12** (Scheme 19.13). Alternatively, the aminohydroxylation of **3.4.9** yielded racemic amino alcohol **3.4.13**,

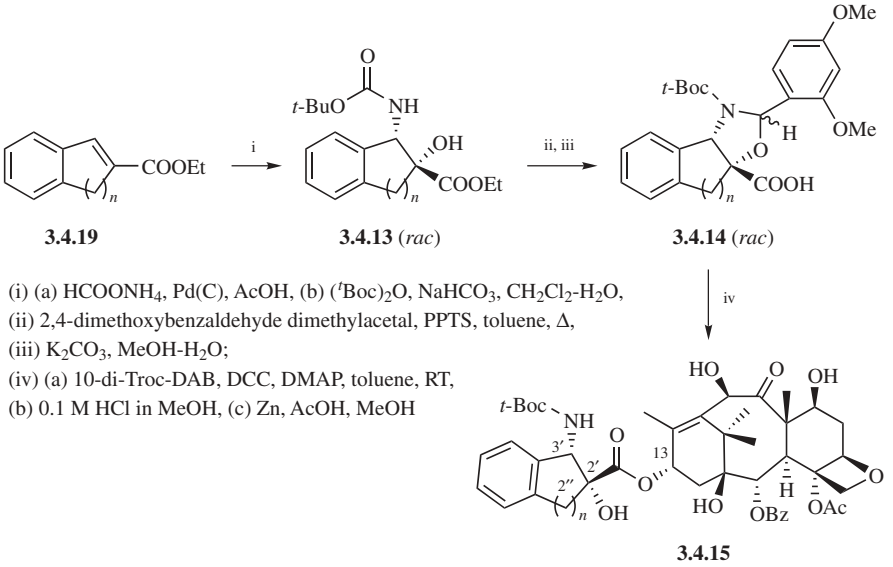


3.4.9 **3.4.10** **3.4.11** **3.4.12**

(i) ADmix-α, *t*-BuOH-H_2O 1:1;
(ii) *n* = 1, (a) trimethyl orthobenzoate, PTSA (*p*-toluenesulfonic acid),
(b) AcBr;
n = 2, (a) $SOCl_2$, pyridine, CH_2Cl_2,
(b) $NaIO_4$, $RuCl_3$, MeCN,
(c) Bu_4NBr, Me_2CO-H_2O, H_2SO_4;
(iii) *n* = 1, (a) NaN_3, DMF (Me_2NCHO), 45 °C,
(b) H_2, Pd/C, EtOH;
n = 2, (a) NaN_3, DMF,
(b) H_2, Pd/C, EtOAc,
(c) BzCl, $NaHCO_3$, CH_2Cl_2-H_2O;
(iv) 2,4-dimethoxybenzaldehyde dimethylacetal, PPTS (pyridinium *p*-toluenesulfonate), toluene, Δ;
(v) (a) 7- TES-baccatin III, DCC, DMAP, toluene, RT,
(b) 0.1 M HCl in MeOH

Scheme 19.13

which was converted to 2,4-dimethoxybenzyloxazoline **3.4.14**. Efficient kinetic resolution was observed in the dicyclohexylcarbodiimide (DCC) coupling with 7,10-di-Troc-DAB to afford the diastereomerically pure docetaxel analog **3.4.15** with 2′*R*,3′*S* configuration (Scheme 19.14). The SAR of these conformationally constrained taxoids provided useful information about the preferable conformation of the isoserine moiety to secure strong cytotoxicity.[78]



3.4.19 **3.4.13** (*rac*) **3.4.14** (*rac*)

(i) (a) $HCOONH_4$, Pd(C), AcOH, (b) $(^tBoc)_2O$, $NaHCO_3$, CH_2Cl_2-H_2O,
(ii) 2,4-dimethoxybenzaldehyde dimethylacetal, PPTS, toluene, Δ,
(iii) K_2CO_3, MeOH-H_2O;
(iv) (a) 10-di-Troc-DAB, DCC, DMAP, toluene, RT,
(b) 0.1 M HCl in MeOH, (c) Zn, AcOH, MeOH

3.4.15

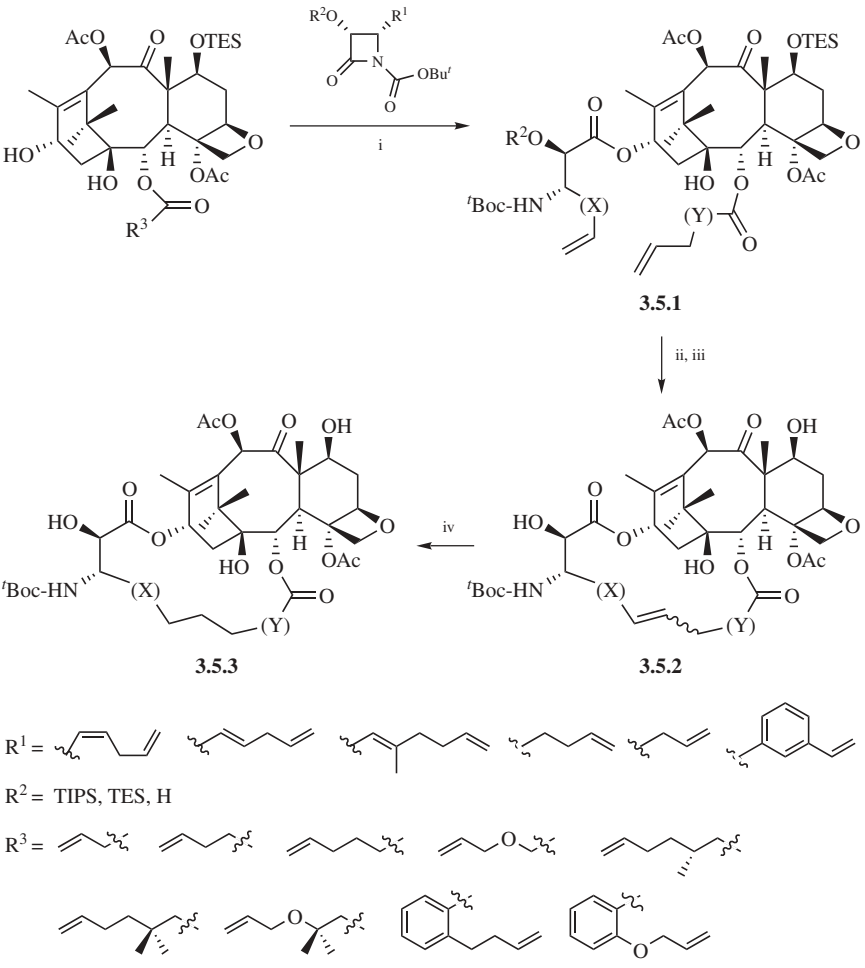
Scheme 19.14

19.3.5 Functionalized α-Hydroxy-β-amino Acids and Their Use for the Synthesis of Macrocyclic Taxoids

Recently, a series of novel macrocyclic taxoids has been designed and synthesized based on a common pharmacophore hypothesis[79] for several microtubule-stabilizing naturally occurring anticancer agents, that is, paclitaxel, epothilones, eleutherobin, and discodermolide.[34,80] Paclitaxel–epothilone hybrid constructs, featuring a 16–18-membered macrocycle linking the C-2 benzoate and the C-3′ group of the molecule, and docetaxel–epothilone hybrid constructs, bearing a 19-membered macrocycle that connects the C-2 benzoate and the C3′-N moiety, were synthesized.[34,80]

As Scheme 19.15 illustrates, the syntheses of hybrid constructs **3.5.2** and **3.5.3** were accomplished using the highly efficient Ru-catalyzed ring-closing metathesis (RCM) of the open-chain precursors, taxoids **3.5.1**, which were obtained by using the β-LSM from the corresponding β-lactams and baccatins in the key step.[34] The C2-C3′N-linked hybrid constructs were synthesized in a similar manner.[80]

Macrocyclic taxoids, mimicking the proposed β-tubulin-binding structure of paclitaxel,[81] have also been designed and synthesized.[82,83] These syntheses

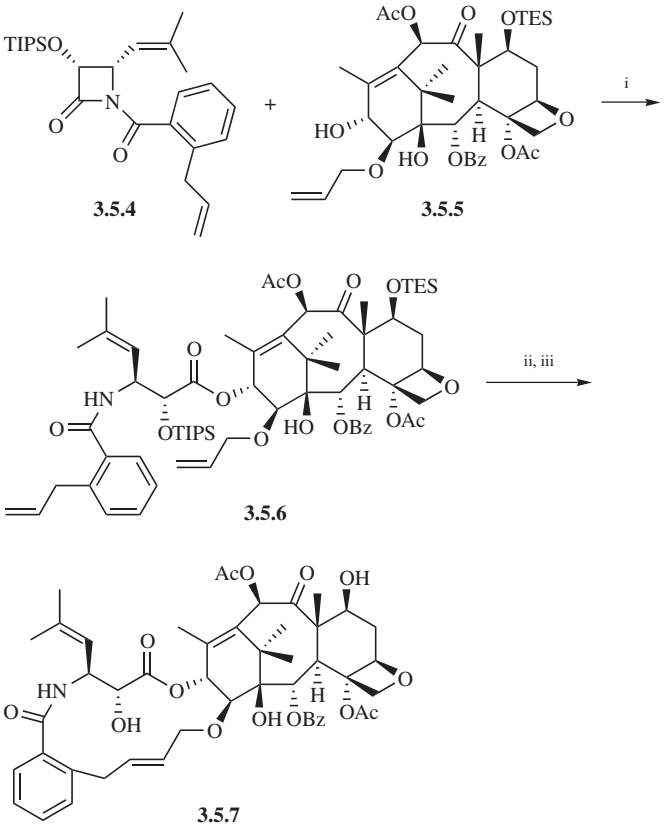


(i) LiHMDS, –40 °C, 70–90%; (ii) $(Cy_3P)_2Cl_2Ru(=CHPh)$ (20–60 mol%), 35–96%; (iii) HF/Py, 60–90%; (iv) H_2/Pd-C, 90–100%

Scheme 19.15

used the β-LSM and the RCM in the key steps as well. Two examples are shown in Schemes 19.16 and 19.17.[83]

Besides RCM, the intramolecular Heck reaction has been used in the macrocyclization step as well.[84,85] As Scheme 19.18 illustrates, a functionalized isoserine moiety was introduced to 2-(3-vinylbenzoyl)taxoid **3.5.9** by the β-LSM, and the subsequent Pd-catalyzed Heck macrocyclization and deprotection gave 19-membered macrocyclic taxoid **3.5.2** in good yield. This taxoid **3.5.2** and its



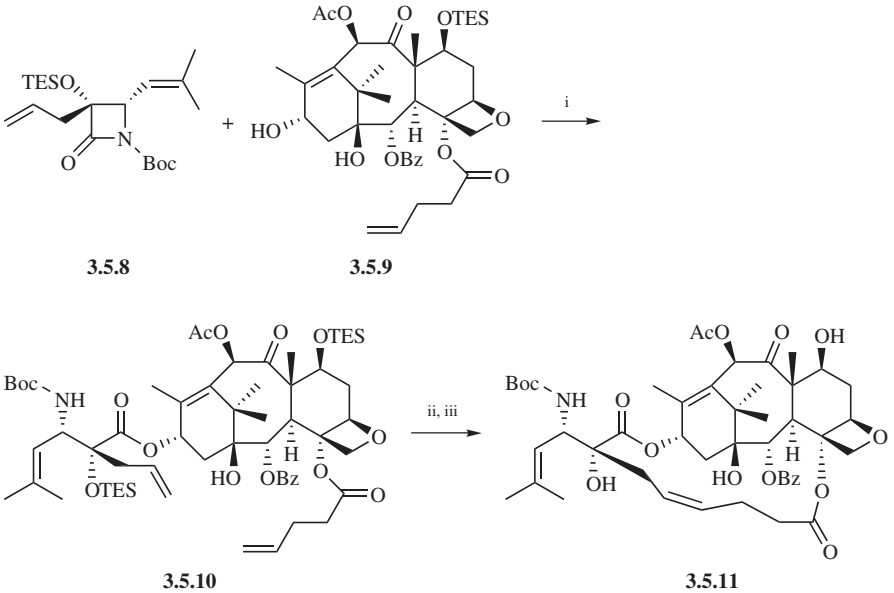
(i) NaHMDS, THF, −30 °C, 81%; (ii) $(Cy_3P)_2Cl_2Ru(=CHPh)$ (20 mol%), CH_2Cl_2, 80%; (iii) HF/Py/CH_3CN, 83%

Scheme 19.16

saturated conterpart **3.5.3** were found to possess unexpectedly good cytotoxicity against LCC6 human breast cancer cell line.

19.4 TAXOIDS WITH PHOTOAFFINITY-LABELED α-HYDROXY-β-AMINO ACID RESIDUES

Several photoaffinity-labeled paclitaxel analogs have been developed to probe the paclitaxel binding domains of microtubules and P-glycoprotein that is a transmembrane protein overexpressed in MDR cancer cells.[86–94] It was reported that [^{3}H]-3′-(4-azidobenzamido)paclitaxel photolabeled the N-terminal 31 amino acid sequence of β-tubulin,[87] and [^{3}H]-2-(4-azidobenzoyl)paclitaxel bound to the 217–233 amino acid sequence of β-tubulin.[88] To identify the paclitaxel binding sites on β-tubulin as



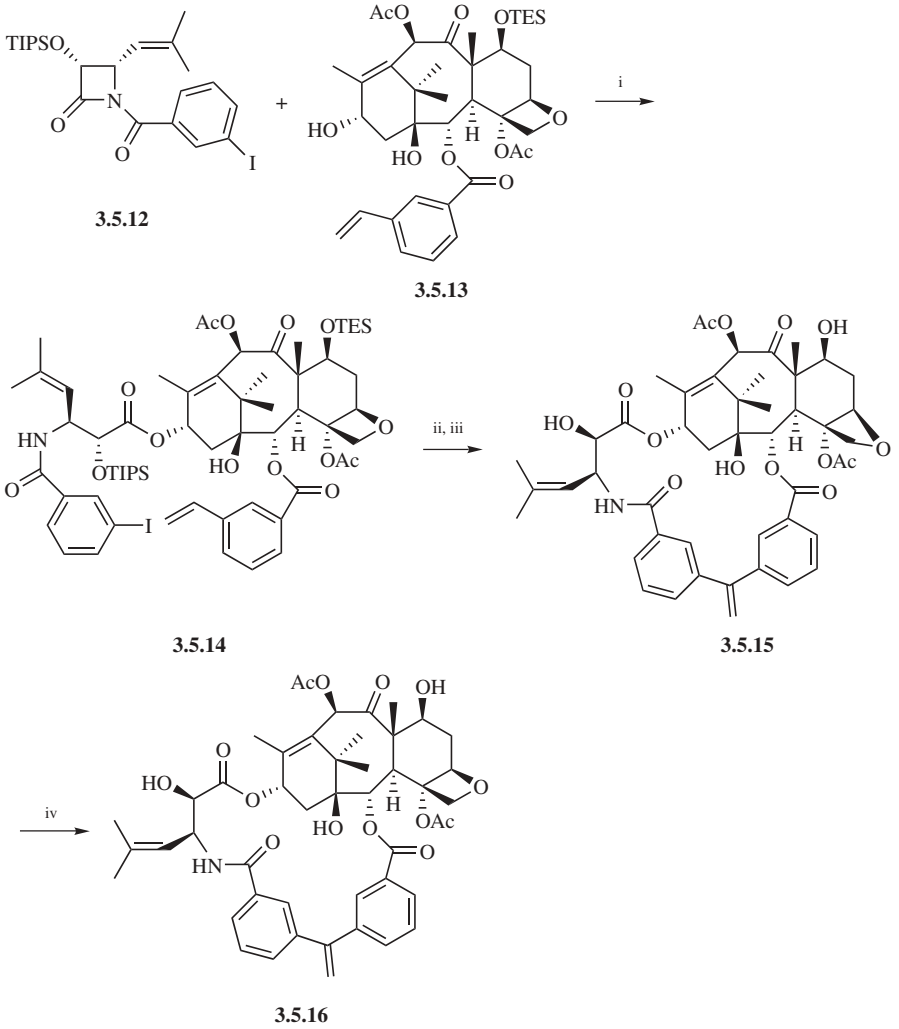
(i) NaHMDS, THF, −30 °C 60%; (ii) $(Cy_3P)_2Cl_2Ru(=CHPh)$ (20 mol%), CH_2Cl_2, 70%; (iii) HF/Py/CH_3CN, 60%

Scheme 19.17

well as P-glycoprotein more accurately, three new photoaffinity analogs of paclitaxel, [^{3}H]-3′N-BzDC-paclitaxel ([^{3}H]-SB-T-5101), [^{3}H]-7-BzDC-paclitaxel ([^{3}H]-SB-T-5111), and [^{3}H]-10-BzDC-paclitaxel ([^{3}H]-SB-T-5121) [BzDC = (4-benzoyl)dihydrocinnamoyl], bearing a benzophenone moiety as the photoreactive probe at the C-3′N, C-7, and C-10 positions, respectively, have been developed.[90–92] Synthesis of [^{3}H]-SB-T-5101 (**4.4b**) is shown in Scheme 19.19. Ring-opening coupling of 7-TES-baccatin III with *N*-Cbz-β-lactam **4.1** followed by hydrogenolysis gave 3′-NH-free taxoid **4.2** in good yield. Taxoid **4.2** was subsequently reacted with an activated BzDC ester **4.3b** followed by deprotection to afford **4.4b**.

The photoaffinity labeling of microtubules with [^{3}H]-SB-T-5111 successfully identified the single amino acid residue (Arg 282) in the β-tubulin subunit, which is a remarkable achievement,[92] but the details are beyond the scope of this chapter. [^{3}H]-SB-T-5101 (**4.4b**) and [^{3}H]-SB-T-5111 have also been successfully used for mapping P-glycoprotein.

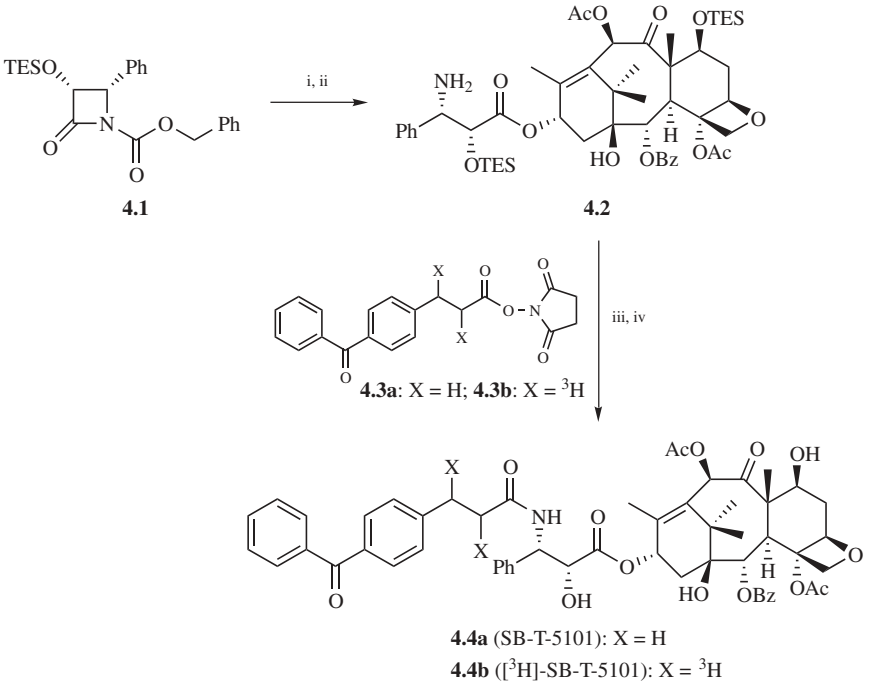
Recently, a novel nonradioactive bifunctional photoaffinity probe (BPP) taxoid **4.5** was reported.[95] Taxoid **4.5** carries a unique phenylisoserine moiety including 3-nitro-5-(trifluoromethyldiazirinyl)phenoxyacetyl group at the C-3′N position as photoreactive probe and a biotin tag at the C-7 position for affinity chromatography (Fig. 19.6).



(i) LiHMDS, THF, −30 °C, 81%; (ii) $Pd(PPh_3)_4$, Et_3N, CH_3CN, 80%; (iii) HF/Py/CH_3CN, 74%; (iv) H_2/Pd-C, 83%

Scheme 19.18

N-[C(^{3}H)$_3$]-*N*-(4-azidophenyl)ureidodocetaxel (**4.6**) was also synthesized and used for the mapping of microtubules (Fig. 19.6).[93,94] The photoaffinity labeling study revealed that **4.6** photolabeled the peptide sequence 281–304 on α-tubulin and two partial peptide sequences in the 217–229 region of β-tubulin. This result has identified, for the first time, a peptide sequence on α-tubulin that binds to a paclitaxel analog.[93,94]



(i) 7-TES-baccatin III, THF, NaHMDS, −30 to 0 °C, 90%;
(ii) H_2, 5% Pd-C, MeOH, RT, 5 h, 77%;
(iii) Et_3N, DMAP, CH_2Cl_2, RT, 6d, dark;
(iv) 0.5% HCl, EtOH, 5 °C, 2d, 62% (for 2 steps for **4.4a**)

Scheme 19.19

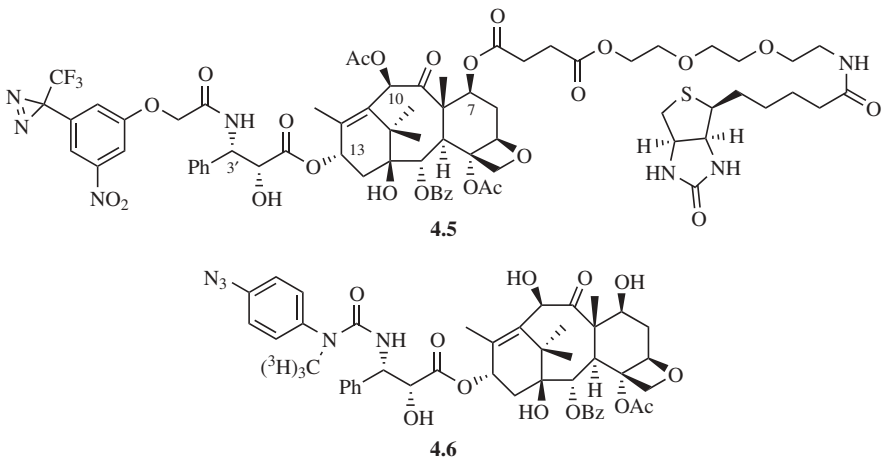


Figure 19.6

19.5 TAXOIDS WITH FLUORINE- AND ISOTOPE-LABELED α-HYDROXY-β-AMINO ACID RESIDUES FOR NMR STUDIES

Nuclear magnetic resonance (NMR) spectroscopy serves as an unparalleled tool for the study of structural and dynamic aspects of biologically active molecules. The NMR analysis in conjunction with molecular modeling can provide insights into possible bioactive conformations as well as the binding structure of a drug in its target protein. Accordingly, extensive studies on the conformational analysis of paclitaxel and taxoids by solution NMR analysis as well as the determination of the tubulin-bound paclitaxel and docetaxel by solid-state NMR analysis have been performed.[67,96–100]

To conduct such NMR analyses, paclitaxel and docetaxel analogs with appropriate labeling became necessary. Accordingly, several paclitaxel and docetaxel analogs bearing fluorine-labeled and/or isotope-labeled isoserine moieties at the C-13 position have been synthesized from the corresponding labeled β-lactams and baccatins by means of the β-LSM.[67,96,97] Three such analogs are shown in Figure 19.7 as examples.

Difluoro-paclitaxel **5.1** was used for investigating the solution structures and dynamic behavior of paclitaxel by means of variable-temperature ^{19}F NMR and ^{1}H–^{19}F heteronuclear nuclear Overhauser effect (NOE) measurements.[97] Difluorodocetaxel **5.2** was used in the solid-state NMR study on the microtubule-bound structure of docetaxel by means of magnetization exchange via RFDR (radio

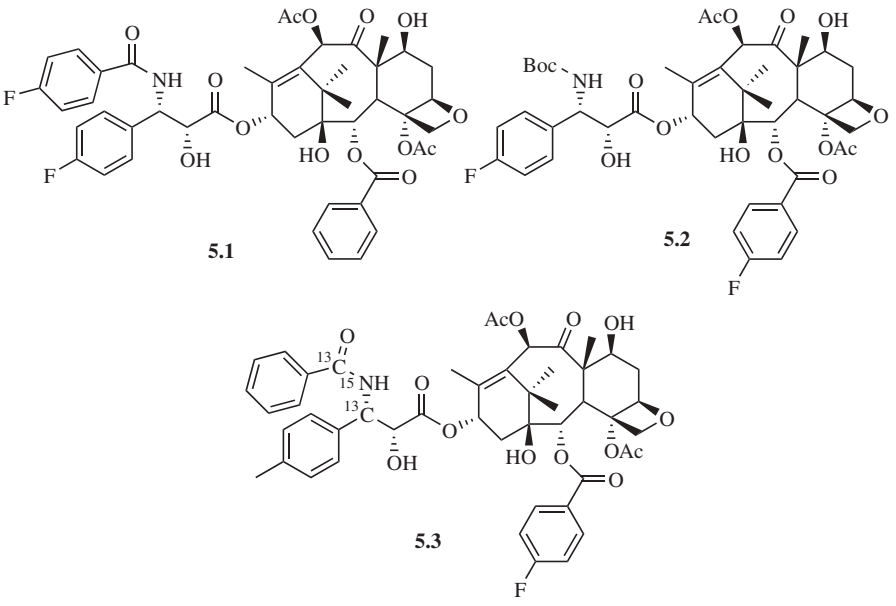
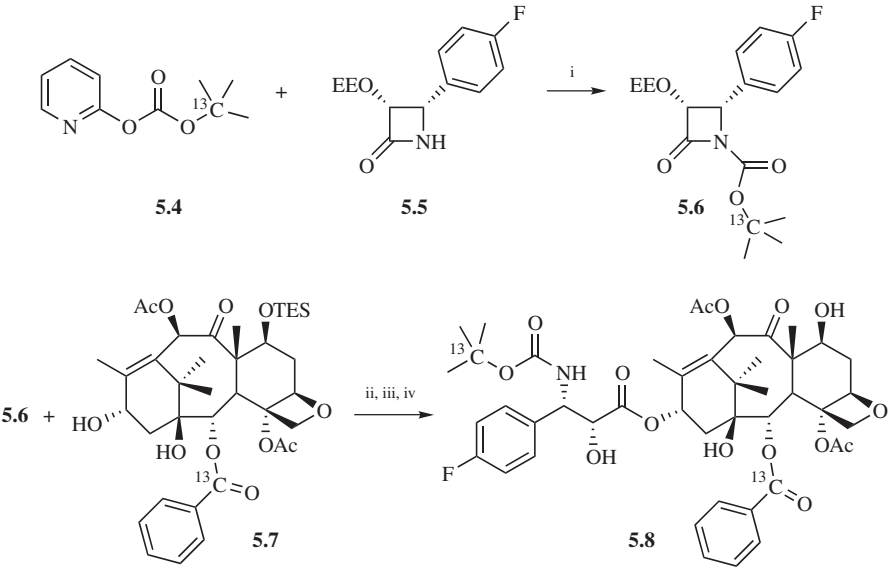


Figure 19.7

frequency driven recoupling).[67] Fluoro-paclitaxel **5.3**, bearing doubly ^{13}C-labeled as well as ^{15}N-labeled *N*-benzoylphenylisoserine moiety, was employed for the same solid-state NMR study, but by means of magnetization exchange via REDOR (rotational echo double resonance).[96]

For the synthesis of taxoids bearing a ^{13}C-labeled *t*-Boc group at the C3′-N position, a new and efficient method has been developed which includes the use of an unsymmetrical carbonate, that is, {^{13}C}-*t*-butyl pyridin-2-yl carbonate (**5.4**).[101] Carbonate **5.4** is readily prepared by reacting bis(pyridin-2-yl) carbonate with {^{13}C}-*t*-butanol, which is obtained from 2-{^{13}C}-acetone and MeMgBr. For example, the *t*-Boc acylation of β-lactam **5.5** gave {^{13}C}-*t*-Boc-β-lactam **5.6**, which was coupled with 2-{^{13}C}-benzoyl-7-TES-baccatin (**5.7**) to afford doubly ^{13}C-labeled fluoro-docetaxel **5.8** in good yield (Scheme 19.20).



(i) DMAP, DCM; (ii) LiHMDS, THF, –40 °C to –20 °C; (iii) HCl 0.1 N; (iv) HF/Py/CH_3CN

Scheme 19.20

19.6 SUMMARY

This chapter has described the recent advances in the synthesis of a variety of α-hydroxy-β-amino acids (i.e., isoserines) by means of the β-LSM and their applications to SAR studies as well as chemical biology of taxoid anticancer agents. The SAR studies have clearly demonstrated the critical importance of the α-hydroxy-β-amino acid moiety at the C-13 position. The discovery and development of the second-generation taxoids that possess superior cytotoxicity to paclitaxel and docetaxel, especially against drug-resistant human cancer cell lines, and excellent

antitumor activity against tumor cancer xenografts in mice are noteworthy. These highly potent second-generation taxoids include not only those derived from DAB and its congeners but also those derived from novel 14-OH-DAB and fluorine-containing taxoids. It is worthy of note that one of the second-generation taxoids (Ortataxel) has advanced to the phase II and III clinical trials. Numerous novel α-hydroxy-β-amino acids and their β-lactam synthons have been synthesized for the construction of conformationally constrained and macrocyclic taxoids. A variety of C-13 α-hydroxy-β-amino acid residues have been developed for photoaffinity labeling studies with photoreactive and in most cases radiolabeled taxoids and for the solution of solid-state NMR studies on the bioactive conformations and dynamics of taxoids with and without the target protein. Consequently, it is fair to state that significant progress has been made in the synthetic chemistry, medicinal chemistry, and chemical biology of α-hydroxy-β-amino acids in conjunction with taxoid anticancer agents in the last decade and more to come in the next decade.

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CHAPTER 20

Synthesis of β-Amino Acids and Their Derivatives from β-Lactams: Update

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20.1 INTRODUCTION

The chemical basis for both the biological activity and inhibition of β-lactam antibiotics is directly related to the reactivity of the four-membered β-lactam ring and, in particular, to the susceptibility of the carbonyl group toward nucleophilic attack. Upon the action of certain proteins and enzymes, the β-lactam ring is opened in vivo, leading to either irreversible blocking of some key site of an ''infectious'' protein (antibiotic action, allergenic response) or inactivation by β-lactamases through hydrolysis (inhibition).[1] It might be predicted that, if such a ring opening could be extended to other β-lactams and could be carried out in a controlled manner by ''chemical'' methods, some interesting building blocks, that is, β-amino acids and derivatives thereof would be accessible (Fig. 20.1).

In the past two decades, a better understanding of the mechanistic aspects of the bioactivity[1,2] and inhibition[1,3] of β-lactams has seen complementary advances in the chemical exploitation of β-lactams as synthetic intermediates[4]. The accessibility of enantiopure β-lactams is obviously a prerequisite which is already fulfilled to some extent.[5] This review focuses on the chemical preparation of β-amino acids and their derivatives from β-lactams and covers the most salient examples from the literature, including some pertinent general experimental procedures, since publication of the first edition of this book in 1996.[6]

In the area of chemical methods for the opening of β-lactams by *O*-, *N*-, and *C*-nucleophiles, the use of *N*-acyl β-lactams, that is, *N*-*tert*-butoxycarbonyl (*N*-Boc) β-lactams, has been revealed to be of major importance. The *N*-acyl group serves

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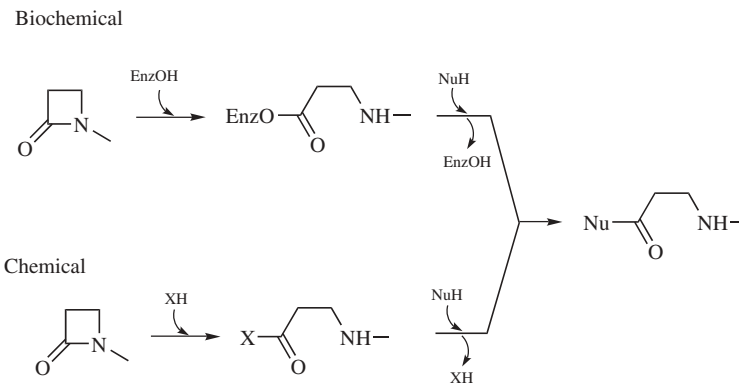


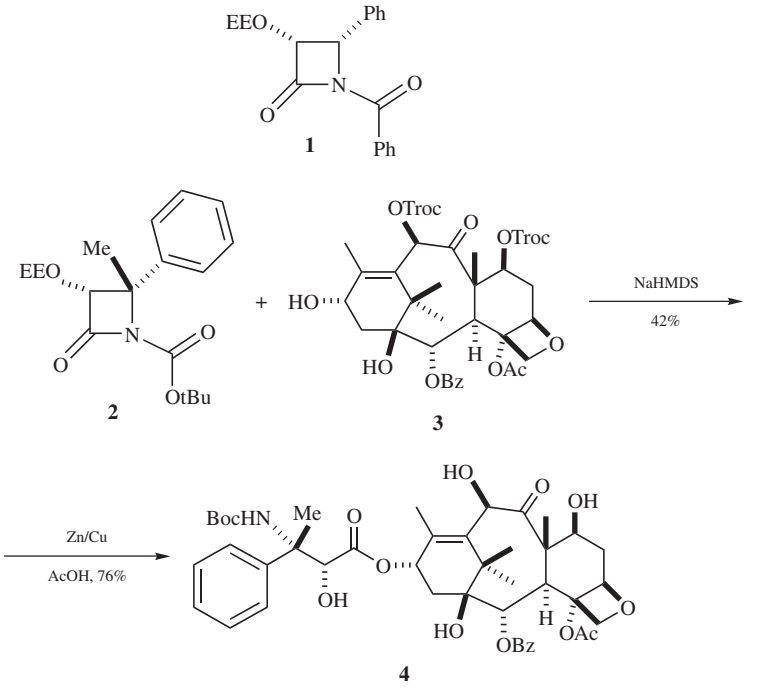
Figure 20.1 β-Lactam ring opening through cleavage of the N_1–C_2 bond leading to β-amino acid units.

to enhance the β-lactam carbonyl reactivity toward nucleophilic attack and also to protect the amino function in the β-amino acid derivative that results from the ring opening.

20.2 β-LACTAM RING OPENING BY OXYGEN NUCLEOPHILES: β-AMINO ESTERS AND RELATED PRODUCTS

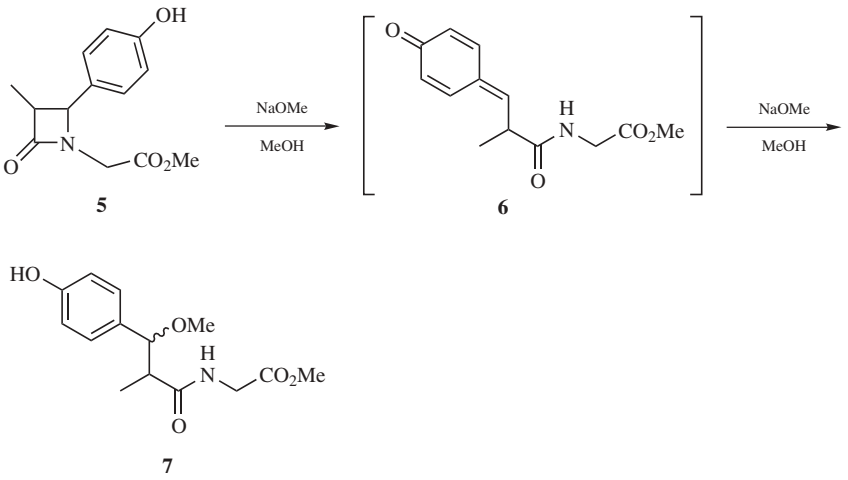
Metal alkoxides react with *N*-acyl β-lactams to afford β-amino acid esters. Acylation of alcohols with β-lactams is suitable not only for simple alcohols such as methanol but also for more complex alcohols. For example, the technique has been extensively applied in the preparation of the broad-spectrum anticancer drug Taxol (paclitaxel)[7] and its analogs through the coupling reaction of *N*-acyl β-lactams such as **1** with the protected sodium salt of baccatin and its analogs.[8] In the search for structurally modified taxoteres with improved properties, modifications at the phenyl isoserine side chain have been studied leading to the synthesis of a variety of enantiopure β-lactams suitable for further coupling reactions. A recent challenging example (Scheme 20.1) involves the opening of the sterically hindered β-lactam **2**, which bears a quaternary stereocenter.[9] Treatment of desacetylbaccatin III derivative **3** with sodium hexamethyldisilazide and β-lactam **2** and subsequent triple deprotection with zinc–copper afforded the target β-amino acid ester **4** in 32% overall yield.

The inherent basic character of alkoxylate salts, however, can be a problem when β-lactams with base-sensitive peripheral substituents are to be used. In addition, a specific limitation applies in the use of sodium methoxide or potassium *tert*-butoxide salts in combination with 4-(4′-hydroxyphenyl) β-lactams. In these instances, an anomalous β-lactam ring opening through the N_1–C_4 bond occurs (Scheme 20.2).[10]



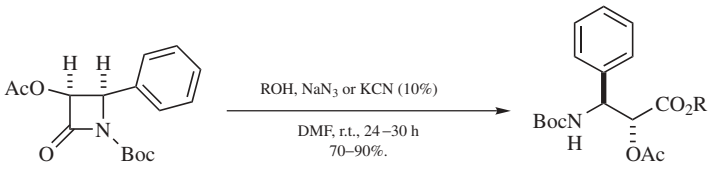
EE: ethoxyethyl; Troc: 2,2,2-trichloroethoxycarbonyl; NaHMDS: sodium hexamethyldisilazide

Scheme 20.1



Scheme 20.2

To avoid the strongly basic alcoholate salts, acylation of free alcohols with *N*-acyl β-lactams has been pursued. In general, however, the reactions are too slow to be practical, although several additives, specifically NaN_3, KCN, and some tertiary amines, have been found to be useful accelerants. In the mid-1990s it was discovered that the ring opening of *N*-Boc β-lactams with free alcohols in the presence of NaN_3 or KCN takes place under almost neutral conditions and compares favorably with the use of alkoxylate salts in some instances. For example, alcoholysis of **8** to give **9** (Scheme 20.3) in the absence of these additives is



8 **9**

R: CH_3 R: $C_6H_5CH_2CH_2$
R: $C_6H_5CH_2$ R: $(C_6H_5)_2CH$
R: 4-$NO_2C_6H_4CH_2$ R: *c*-C_6H_{11}

DMF: dimethylformanide

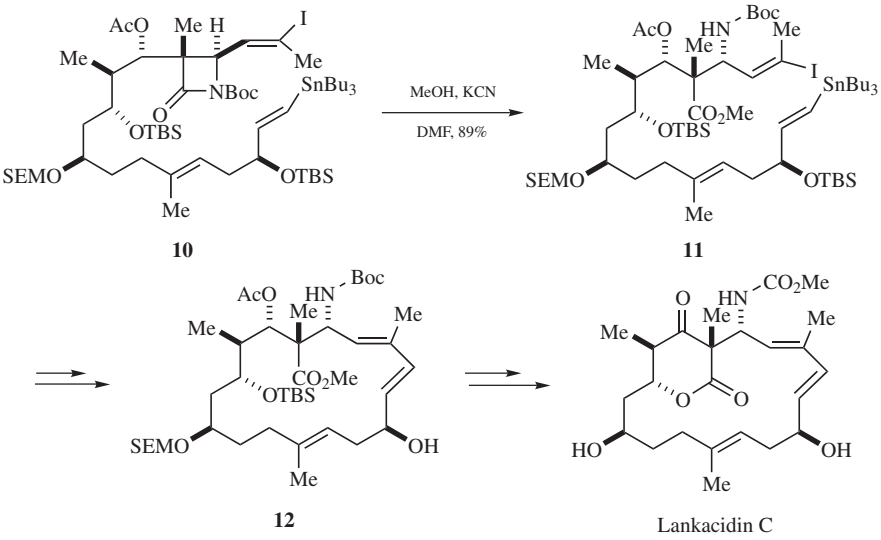
Scheme 20.3

exceedingly slow whereas in the presence of 10 mol % of NaN_3 or KCN the coupling proceeds smoothly to give β-amino esters **9** in good to excellent yields. Interestingly, under these conditions the acetoxy group remains intact while it is cleaved under the basic conditions of NaOMe or NaOEt.[11]

Implementation of this methodology in the synthesis of advanced macrocyclic precursors of the lankacidin antitumor antibiotics, which possess a carbocyclic structure, has recently been reported by Chen et al.[12] A key step in the route (Scheme 20.4) is the ring opening of the β-lactam nucleus in **10** by methanol, assisted by KCN, to give the corresponding β-amino ester intermediate **11**. The latter, upon cyclization and protecting group manipulation, produces **12**, which upon further elaboration affords lankacidin C.

Taking advantage of the same concept in an intramolecular variant, Romo et al. have documented[13] the synthesis of (−)-panteamine A (Fig. 20.2) in which a β-lactam-based macrocyclization is the crucial step to construct the β-amino macrolactone **13**.

Among the different reaction conditions investigated for the intramolecular coupling of the secondary alcohol and the β-lactam unit in **14** (Scheme 20.5), the use of KCN or Et_4NCN as additives produces the best results. Further elaboration of **15** leads to the immunosuppressive agent (−)-panteamine A.

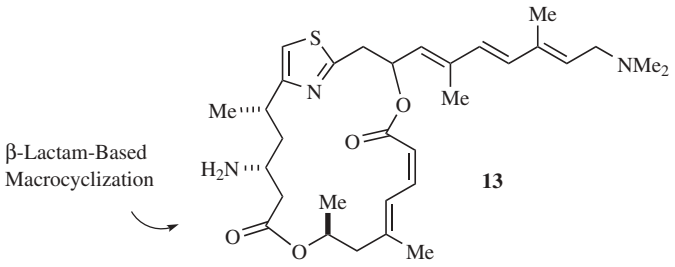


10 **11** **12**

Lankacidin C

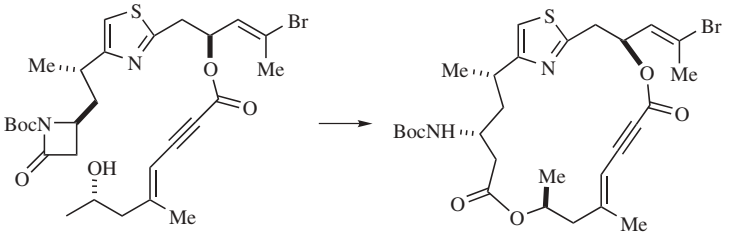
SEM: 2-(trimethylsilyl)ethoxymethyl

Scheme 20.4



13

Figure 20.2



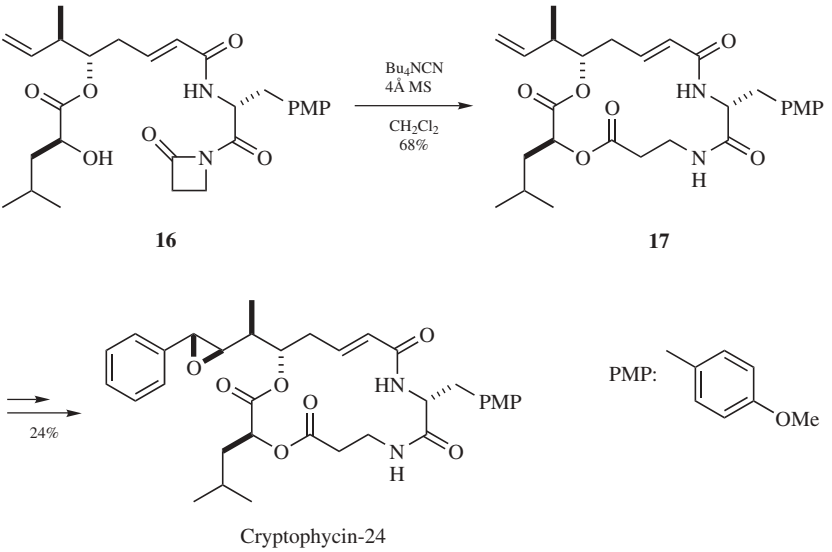
14 **15**

Conditions	Temp. °C	Yield %
1.1 eq. NaHMDS, THF, 45min	–40	37
1.1 eq. LiHMDS, THF, 2.5h	–40	11
1.1 eq. NaH, THF, 1h	–10	42
0.5–0.6M KCN, DMF, 1–2h	25	52–72
9.0 eq. Et_4NCN, CH_2Cl_2, 4–9h	25	59–68

Scheme 20.5

Typical Procedure[13] A solution of Et_4NCN (684.7 mg, 4.38 mmol) in 23 mL of CH_2Cl_2 was stirred over freshly activated (flame dried under high vacuum), powdered 4-Å molecular sieves for 1 h. To this solution was added alcohol **14** (288.9 mg, 0.47 mmol) as a solution at 0°C which had been stirred for 1 h over sieves. The solution was stirred for 9.5 h at ambient temperature and then filtered through Celite and concentrated in vacuo. The crude residue was purified by chromatography on SiO_2 eluting with hexanes–Et_2O (4 : 1 to 3 : 2) and gave macrocycle **15** as a clear, colorless oil in yields in the range 59–68%.

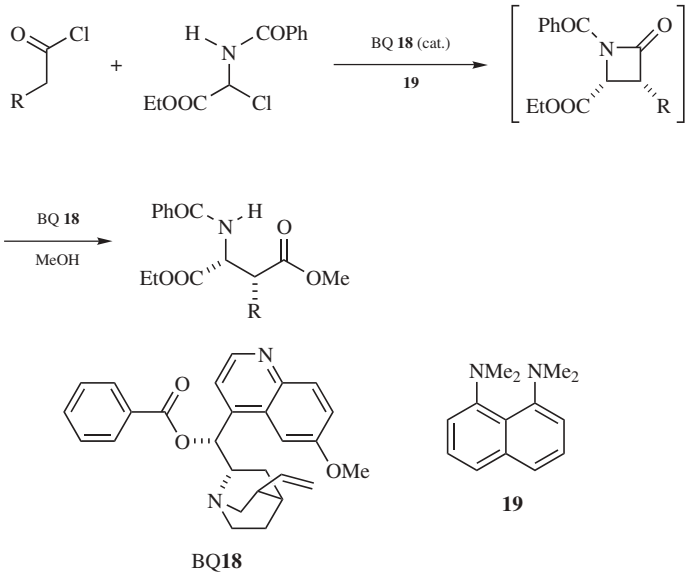
A related example of β-lactams as acylating agents for macrolactonization has been reported by Eggen et al., who used it as an approach to the antimicotic agent cryptophycin-24.[14] Again, macrolactonization of compound **16** to obtain **17** is promoted by a cyanide salt (Scheme 20.6).



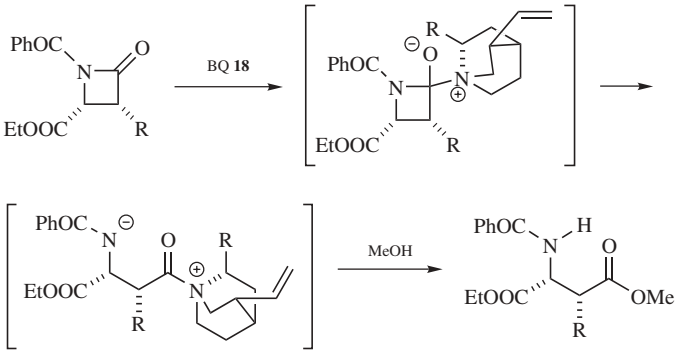
Scheme 20.6

Apart from azide and cyanide, tertiary amines have also been shown to promote the opening of *N*-acyl β-lactams by alcohols. Methanolysis of *N*-Boc β-lactams to afford the corresponding β-amino methyl esters can be carried out at room temperature in the presence of triethylamine and 4-*N*,*N*-dimethylaminopyridine (DMAP).[15] An impressive one-pot access to β-amino acid esters from acid chlorides and α-chloroamines has recently been described via a chiral amine–catalyzed alcoholysis of the corresponding intermediate β-lactam adducts (Scheme 20.7).[16] Besides catalyst BQ **18**, stoichiometric quantities of proton sponge **19** as base were required for the dehydrohalogenation steps that occur before β-lactam ring formation.

The crucial role played by benzoylquinine **18** during β-lactam ring opening could be assessed by studying this process separately. Using previously isolated β-lactams, it was found that BQ **18** greatly enhanced the rate of opening of the



Scheme 20.7



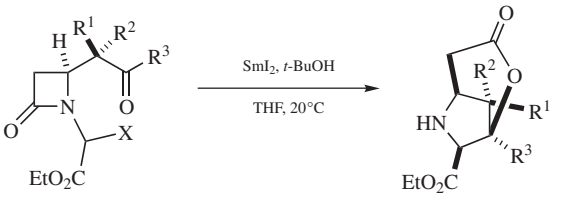
Scheme 20.8

β-lactams, even at elevated temperatures (Scheme 20.8). It was also found that a metal triflate salt (10 mol %) further accelerated the alcoholysis reaction of *N*-acyl β-lactams.[17] The metal center appears to serve as an activator of the β-lactam carbonyl, thus mimicking the way class B β-lactamases work during hydrolysis of β-lactam antibiotics.

General Procedure for β-Substituted Aspartic Acids[17] A 25-mL round-bottom flask equipped with a stir bar was loaded under nitrogen with the respective α-chloroamine (0.26 mmol), proton sponge **19** (83 mg, 0.39 mmol), and the benzoylquinine catalyst **18** (6 mg, 0.013 mmol). Toluene (1 mL) was added to the mixture and stirred for 1 h. The solution was diluted with toluene (7 mL) and cooled

to −78°C in a dry ice/acetone bath. Phenylacetyl chloride (20 mg, 0.13 mmol) in toluene (1 mL) was added to the reaction dropwise. The reaction was allowed to slowly warm to room temperature overnight. Exccess methanol (6 mL) was added, and the solution was refluxed. The reaction was monitored by thin-layer chromatography (TLC) and stopped when all of the β-lactam had reacted (≈4 h). The solvent was removed in vacuo, and the residue was taken up in chloroform (10 mL) and washed with 1 M HCl (3 × 10 mL). The organic layer was dried with $MgSO_4$ and filtered through Celite. The filtrate was concentrated and the residue was submitted to flash column chromatography.

Activation of the β-lactam nitrogen by acylation is not always required. For example, intramolecular ring opening in 4-(2′-oxoalkyl) β-lactams of type **20** can occur through an SmI_2-mediated radical process (Scheme 20.9), leading to some bi- and tricyclic lactones such as **21**.[18]



20, X: BzO, (2-Pyr)-S **21**

Scheme 20.9

20.3 β-LACTAM RING OPENING BY NITROGEN NUCLEOPHILES: β-AMINO AMIDES AND β-AMINO ACID–DERIVED PEPTIDES

Ring opening of β-lactams by amines and α-amino acid esters generates β-amino amides and β-amino acid–derived peptides (Fig. 20.3).

In some instances, these couplings can proceed in the absence of any additive, but often two- or threefold excesses of the amino compound may be required for efficient reaction.[19] Both NaN_3 and KCN can facilitate these couplings.[20,21]

Typical Procedure[20,21] To a solution of the corresponding *N*-Boc β-lactam (2 mmol) in DMF (4 mL) at ambient temperature were added successively sodium azide (13 mg, 0.2 mmol) and the α-amino ester (2.6 mmol). The mixture was stirred at the same temperature for 24 h and then diluted with Et_2O (15 mL) and washed

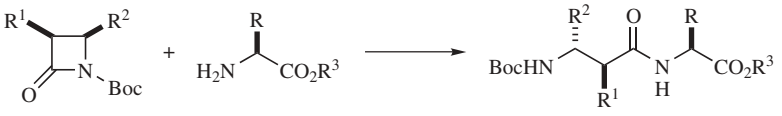
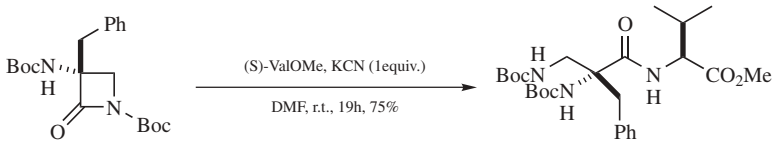


Figure 20.3

with HCl 1 M (3 × 10 mL), $NaHCO_3$ (10 mL), and brine (3 × 10 mL). The resulting solution was dried over $MgSO_4$ and filtered and the solvent removed in vacuo. The solid products could be purified by crystallization from Et_2O–hexane mixtures.

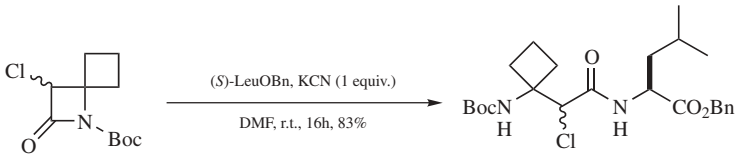
For the opening of difficult substrates such as α-amino α-branched β-lactams with α-amino esters,[21] KCN usually works better. For example, treating β-lactam **22** with (*S*)-ValOMe in the presence of NaN_3 (Scheme 20.10) does not produce the corresponding dipeptide product, while the reaction in the presence of KCN leads to dipeptide **23** in 75% isolated yield.



22 **23**

Scheme 20.10

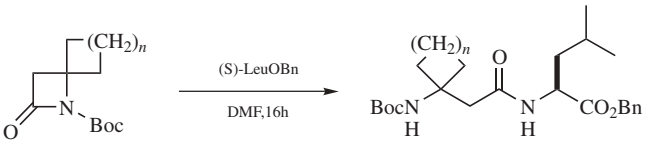
The coupling of spiranic β-lactams bearing a quaternary carbon atom at the β-position constitutes another example of the ability of KCN to promote β-lactam ring opening. For example, 3-chloro β-lactam **24** (Scheme 20.11), upon treatment with (*S*)-LeuOBn in DMF as solvent, affords detectable formation of dipeptide **25** (15%) in the absence of any promoter. When the same coupling is carried out under identical conditions but with the assistance of 1 eq. of KCN the yield rises to 83%.[22]



24 **25**

Scheme 20.11

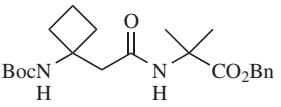
An even more dramatic influence of KCN is observed during the opening of α-unsubstituted spiranic β-lactams. These substrates possess two unfavorable characteristics which hinder nucleophilic attack: One is steric and the other is the lack of a heteroatom at C_α, which enhances carbonyl electrophilicity. No coupling reaction from **26** is observed to any appreciable extent under the reaction conditions noted above. However, the coupling takes place efficiently in DMF at 40°C in the presence of stoichiometric amounts of KCN to produce **27** in good yields (Scheme 20.12). Under these conditions, even the bulky AibOBn efficiently couples with **26a** to afford dipeptide **28** in 70% yield.



26 **27**

a $n=1$ 90%
b $n=2$ 80%
c $n=3$ 86%

Conditions	T, °C	Yield, %
1 equiv. NaN_3	r.t.	–
1 equiv. KCN	r.t.	–
1 equiv. KCN	40–60	80–90



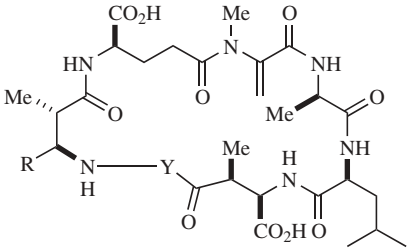
28, 70%

Scheme 20.12

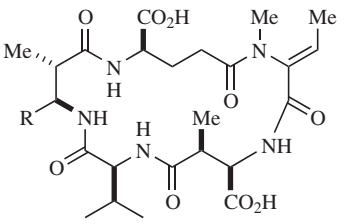
Ring opening of *N*-Boc β-lactams by using amino esters as nucleophiles under KCN- or NaN_3-promoted conditions has been successfully employed by several authors. For instance, Cundy and co-workers have used this strategy en route to ADDA ((2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4(*E*), 6(*E*)-dienoic acid) conjugates,[23] residues that are found in the cyclic peptides microcystin LA **29**, microcystin LR **30**, and nodularin R **31** (Fig. 20.4).

In particular, the ADDA-containing fragment **33** can be prepared by coupling **32** with glycine methyl ester (Scheme 20.13).

Coupling of α,α-disubstituted *N*-Boc β-lactams with α-amino esters is also effective in the presence of KCN to afford α,β-dipeptides of type **35** (Scheme 20.14).[24] In one exceptional case, glycine methyl ester reacted with the spiro β-lactams **34** in good yield without any additive.



Y: Ala, Microcystin LA **29**
Y: Arg, Microcystin LR **30**



Nodularin R **31**

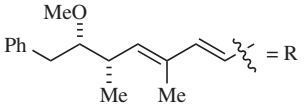
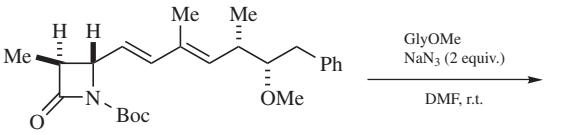


Figure 20.4



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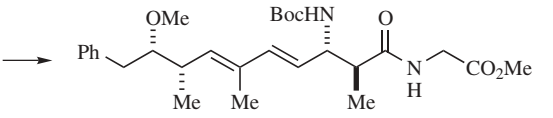

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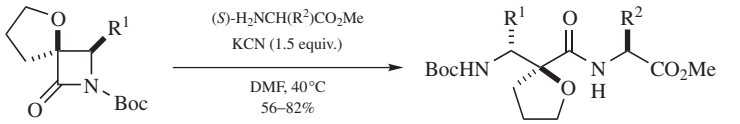
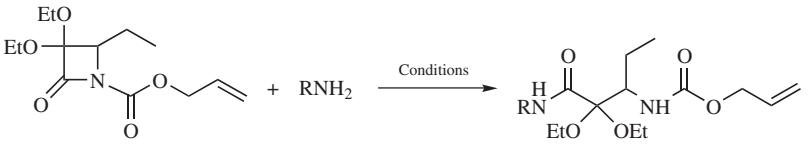
Scheme 20.13



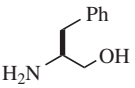
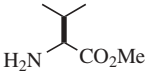
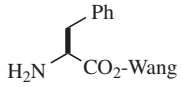
34 **35**

Scheme 20.14

Based on the same conceptual approach, Khim and Nuss have suceeded in applying the method to the preparation of α-keto amide acetals **37** from **36** (Scheme 20.15). The best results were again attained, particularly with hindered nucleophiles, by performing the ring opening in the presence of KCN.[25]



rac-**36** *rac*-**37**

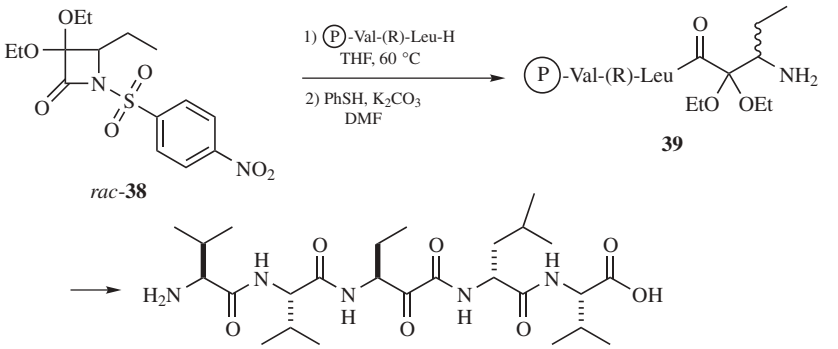
RNH_2	Conditions*	Yield
	KCN, DMF, r.t., 4h	87
	KCN, DMF, 70°C	68
	KCN, NMP, 90°C	61

* No coupling observed in the absence of KCN

NMP: 1-methyl-2-pyrrolidinone

Scheme 20.15

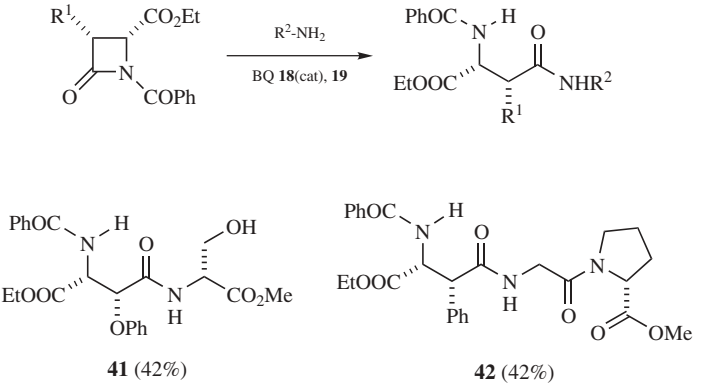
The same authors have shown that activation of the β-lactam ring toward nucleophilic opening can be achieved by sulfonylation at the ring nitrogen. For example (Scheme 20.16), the ring opening of *N*-sulfonyl β-lactam **38** with a dipeptide affords α-keto amide precursor **39**. Subsequent elaboration of **39** and final hydrolysis of the ketal moiety afford poststatin **40**, a naturally occurring pentapeptide which shows inhibitory activity against prolyl endopeptidase.



Scheme 20.16

For the β-lactam opening reactions promoted by CN^-- or N_3^--containing additives, acyl azide (or acyl cyanide) species have been postulated as intermediates.

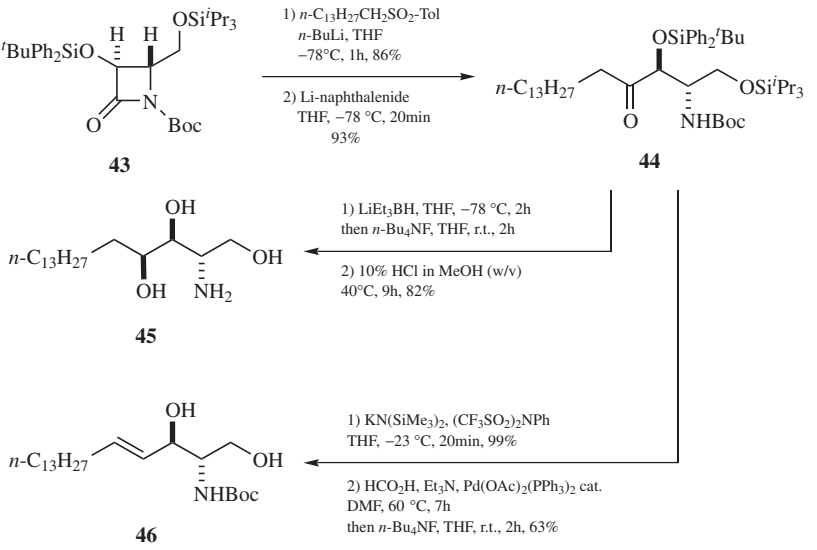
Tertiary amines have also been reported to catalyze the ring opening of *N*-acyl β-lactams by nucleophiles such as simple amines, α-amino esters, or dipeptides, giving rise to simple amides or peptide products such as **41** and **42** (Scheme 20.17).[16,17]



Scheme 20.17

20.4 β-LACTAM RING OPENING BY CARBON NUCLEOPHILES: β-AMINO KETONES AND RELATED PRODUCTS

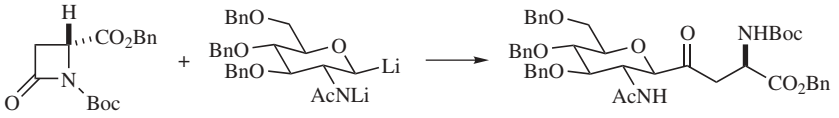
Carbanions have also been used as nucleophiles for the ring opening of *N*-Boc β-lactams.[26] A recent example of this methodology is the opening of β-lactam **43** (Scheme 20.18), with a lithiated sulfone to give compound **44** after desulfonation. This compound was then converted into L-lyxo-phytosphingosine **45** or, alternatively, it could be employed to prepare D-erythro-sphingosine **46**, a potent inhibitory agent against protein kinase C.[27]



Scheme 20.18

Typical Procedure[26b] The aryl- or alkylmagnesium bromide (3.0 M in Et_2O) (0.43 mL, 1.3 mmol) was added to a solution of β-lactam (1 mmol) in tetrahydrofuran (THF) (3 mL) at −78°C. The reaction mixture was stirred at −40°C (acetonitrile–CO_2 bath) for 1 h. A saturated solution of NH_4Cl (5 mL) was then poured into the mixture, which was later extracted with methylene chloride (2 × 10 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. Purification of the crude product was effected by column chromatography on silica gel with hexanes–ethyl acetate (10 : 1 to 5 : 1) as eluent to give the corresponding β-amino ketone as an oil or white solid, which can be recrystallized from hexane.

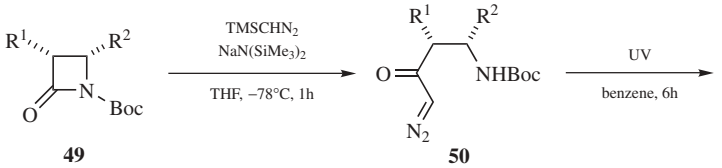
Three further recent examples delineate the utility of β-lactams in synthesis. In an approach to *C*-linked glycosyl amino acids (Scheme 20.19), addition of the lithium dianion **47** to the corresponding *N*-Boc β-lactam provided the β-amino ketone **48**.[28]



47 **48**

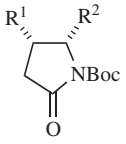
Scheme 20.19

The sodium anion of trimethylsilyl diazomethane has been used to open *N*-acylated β-lactams **49** (Scheme 20.20). The resulting intermediate α-diazoketones **50** afford the corresponding γ-lactams **51** after photolytic Wolff rearrangement.[29]



49 **50**

R^1: ^{i}Pr R^2: $PhCH_2CH_2$ 65%
R^1: BnO R^2: 4-MeO-C_6H_4 61%

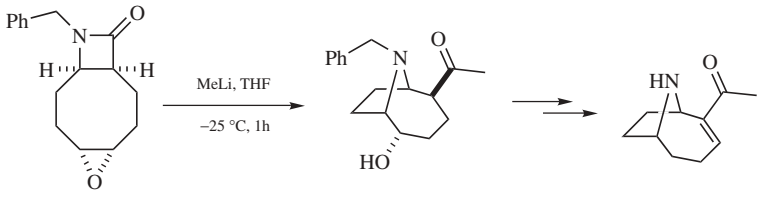


51

R^1: ^{i}Pr R^2: $PhCH_2CH_2$ 75%
R^1: BnO R^2: 4-MeO-C_6H_4 62%

Scheme 20.20

Nonactivated racemic *N*-benzyl β-lactam **52** was opened selectively by methyllithium to yield, after intramolecular oxirane opening, the methyl ketone **53** (Scheme 20.21). This compound could be transformed through several steps into

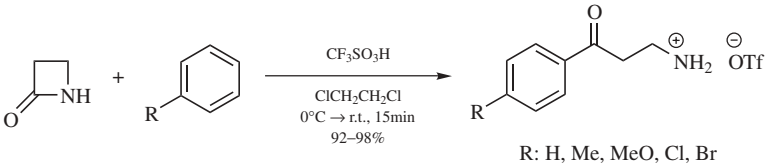


rac-**52** **53** **54**
rac-Anatoxin-a

Scheme 20.21

the nicotinic acetylcholine receptor agonist anatoxin-a **54**.[30] Simple hydrolysis of nonacylated β-lactams has also been employed for the preparation of some racemic and enantiopure precursors of anatoxin-a.[31]

The capacity of β-lactams as agents for acylating carbon nucleophiles has also been demonstrated in acidic reaction media. Simple (N–H) azetidin-2-ones are protonated under strongly acidic conditions, that is, triflic acid, producing excellent reagents for achieving Friedel–Crafts-type acylation of aromatic compounds leading to the corresponding β-amino ketone products (Scheme 20.22).[32] Several Lewis acids have been surveyed as alternatives to triflic acid but were unsuccessful. The Friedel–Crafts reaction can be satisfactorily applied to other aromatics such as naphthalene and pyrrol derivatives.



Scheme 20.22

Typical procedure[32] Azetidin-2-one (50 mg, 0.7 mmol) was dissolved in 1,2-dichloroethane (3 mL) and benzene (1.5 mL) and cooled to 0°C. Trifluoromethanesulfonic acid (0.065 mL, 0.7 mmol) was then added dropwise to the stirring solution at 0°C. The mixture was warmed to room temperature and stirred for an additional 10 min. The reaction was quenched with saturated $NaHCO_3$, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield crude product, 206 mg (98%), sufficiently pure by nuclear magnetic resonance (NMR).

20.5 LARGE-RING HETEROCYCLES FROM β-LACTAMS

Cycloexpansion of the four-membered β-lactam ring to either medium- or large-ring heterocycles can be achieved through N_1–C_2 bond cleavage by intramolecular nucleophilic attack from a suitable peripheral substituent. Some medium rings have been already discussed, and others, like pyrrolidines, pyrrolizidines, piperidines, morpholines, and so on, have been reviewed elsewhere.[6,33] Some more recent cases from the literature have been chosen here for illustration (Fig. 20.5).

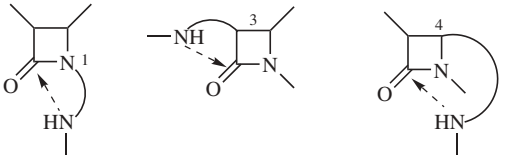
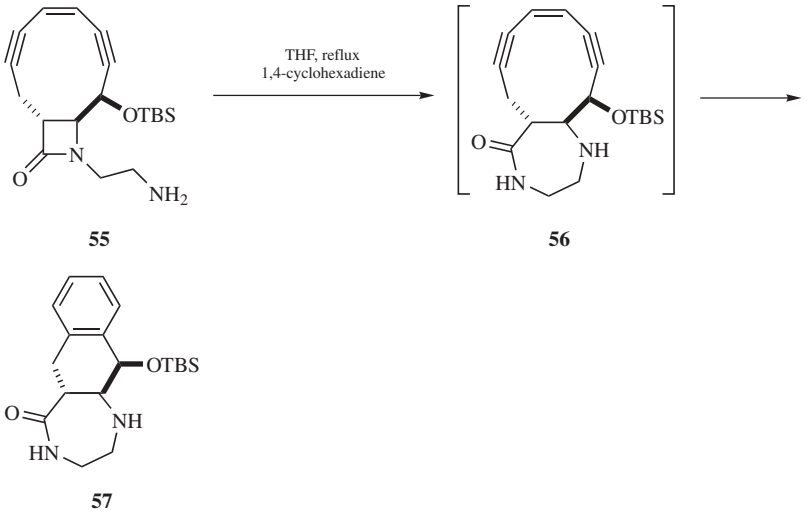


Figure 20.5 Intramolecular transamidation in β-lactams leading to medium- and large-sized *N*-containing heterocycles.

Intramolecular transamidation in β-lactam enediynes can induce concomitant Bergman-type cycloaromatization. For instance, amine **55**, which can be stored as its hydrochloride salt in the freezer, reacts in THF at reflux in the presence of cyclohexadiene as a hydrogen donor to produce only trace amounts of the expanded lactam **56** along with aromatic compound **57** as the major compound (Scheme 20.23).[34]



Scheme 20.23

β-Amino acid fragments containing large heterocycles are sometimes found in alkaloids, and approaches to the synthesis of these compounds using β-lactams as key intermediates have long been known since the pioneering contributions of Wasserman[35] an later by Hesse.[36] In Figure 20.6, some of the heterocyclic compounds synthesized through β-lactam intermediacy are represented.[37]

20.6 CONCLUDING REMARKS AND PROSPECTS

The interest in β-lactams, formerly unidirectional and marked by the preeminence of β-lactam antibiotics, is now broadening due in part to their synthetic value as intermediates for β-amino acid–containing structures. Emulating the enzymatic cleavage of the β-lactam ring by β-lactamases, several strategies for the selective ring opening of β-lactams have been developed. Most often *N*- and *O*-nucleophiles, but also *C*-nucleophiles, can be acylated by the proper β-lactam system to access a wide variety of β-amino esters, amides, and ketones (and derivatives thereof) under fairly smooth and functional group-tolerant reaction conditions. With the recent advent of catalytic methods for both the β-lactam ring formation and its further cleavage, the route has gained even more interest. It is clear that the potential of β-lactams as synthons for the construction of more complex products containing

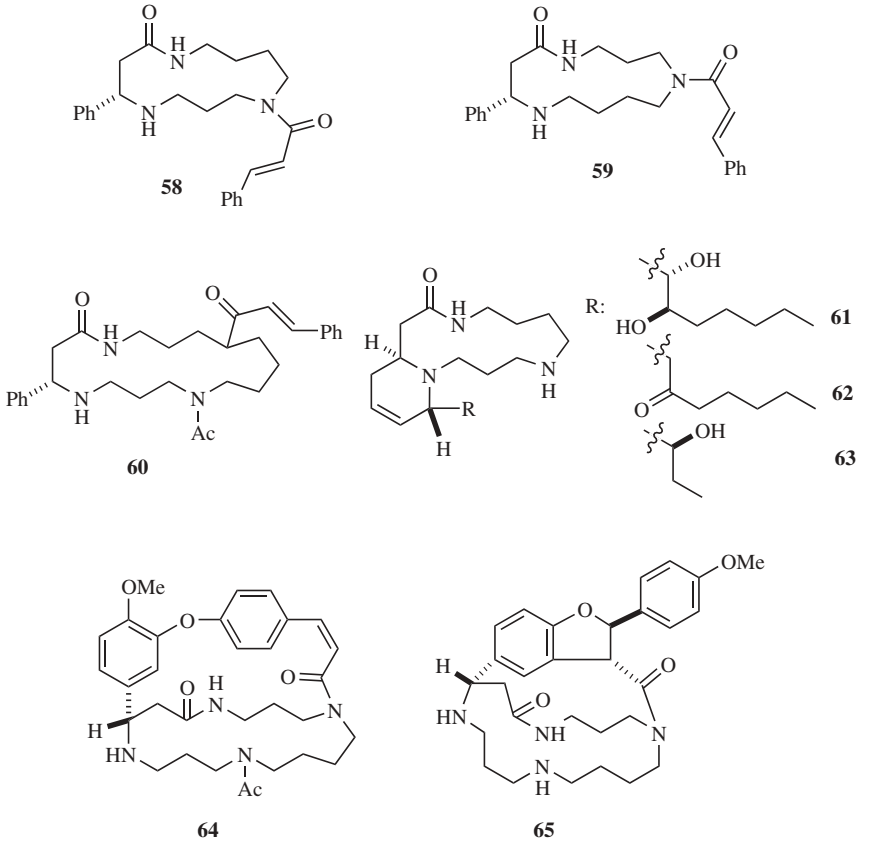


Figure 20.6

the β-amino carbonyl framework has not yet been fully explored and new advances and applications can be predicted for the area in the near future.

ACKNOWLEDGMENTS

We thank the following institutions for financial support of our β-lactam program: Ministerio de Educación y Ciencia (Spanish Government), Eusko Jaurlaritza (Basque Government), and Euskal Herriko Unibertsitatea-Universidad del País Vasco (University of the Basque Country). All collaborators cited within the references are also acknowledged.

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CHAPTER 21

Multiple-Component Condensation Methods for Preparation of Combinatorial Libraries of β-Amino Carbonyl Derivatives

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21.1 INTRODUCTION

The preproteomic/genomic paradigm for drug discovery involves the iterative screening of potential drug candidates against biological targets followed by the sequential optimization of lead compounds through systematic modifications to a core structure. In the postproteomic environment, high-throughput biological assays and the ability to evaluate large numbers of compounds in parallel place a severe strain on this serial approach. A complementary strategy and recognized solution to the synthetic limitations of the iterative strategy is the use of multiple-component condensations (MCCs) to provide the requisite small-molecule diversity more efficiently.[1] Many unique structures can be prepared rapidly when three or more reactants are combined in a single step to afford new compounds possessing the combined features of the building blocks but sharing in a molecular scaffold characterized by a core set of atoms common to the condensation reaction. One of many examples of a three-component condensation (3CC), the Biginelli reaction, brings together ureas, aldehydes, and β-ketoesters to afford functionalized pyrimidinones as the core structure, which includes a bis-β-amino ester group (Fig. 21.1).[2] The combinatorial nature of these types of reactions allows for the preparation of numerous compounds from a relatively few building blocks. In this regard, the MCC strategy can be a valuable tool for the preparation of libraries of compounds based

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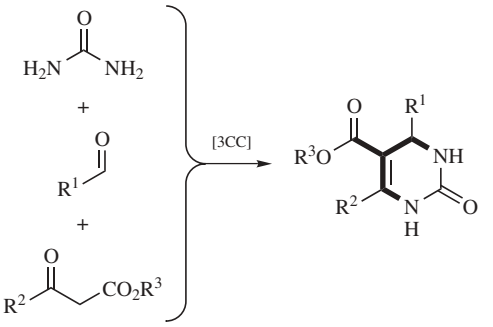
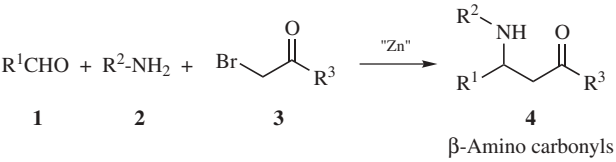


Figure 21.1 The 3CC Biginelli reaction; the bis-β-aminoester group is highlighted.

on a common core structure whose diversity will be proportional to the number and uniqueness of the inputs.

At a minimum, a MCC reaction requires three components to combine in a single chemical operation to afford products with features of all the inputs. Further, what is required is not that all the ingredients be added at the same time—there are cases where sequential addition is required for optimal results—but only that the overall reaction take place in the same vessel. Thus, the use an MCC protocol will entail certain advantages in compound library generation. For example, because of the requirement that each condensation be a single reaction, each compound in a library of such compounds can be generated in a separate reaction vessel, in other words one compound per reaction vessel; potentially this can lead to substantial savings in time and resources required to generate and assay a particular compound library. Based on the reaction inputs, the experimentalist can know, with certainty, the product of each reaction. Armstrong and co-workers have defined a library synthesis using an MCC protocol as a multiple-component condensation array synthesis (MCCAS) in which the array consists of a group of discrete, spatially addressed compounds whose identities are defined by the building blocks employed at each location.[1a]

Consider an experiment in which a 3CC Reformatsky reaction is used to conduct a MCCAS (Scheme 21.1). As with all MCCASs, the number of inputs will define the dimensionality of such an array. For example, assuming no component is held



Scheme 21.1

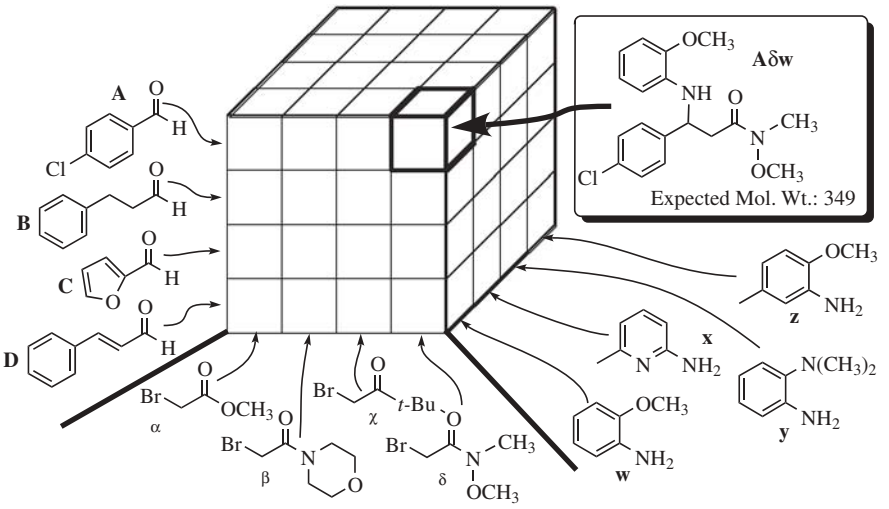


Figure 21.2 Chemical inputs for a three-dimensional three-component array and example positional decoding for product structure *A* δ*w*.

constant and that an equal number of components are used in each dimension, a hypothetic 3CC affords a three-dimensional array which can be most easily visualized as a cube (Fig. 21.2). Thus, 64 discrete compounds, based on the β-amino carbonyl core structure, can be prepared in an array in which four aldehydes, four α-bromo-carbonyls, and four anilines are employed. Because the array is spatially addressed, that is, the inputs at any specific location in the cube are known, it is possible to unequivocally assign the structure of the expected products, in the example case, *A* **δ** *w*.

The MCC will likely prove to be an important tool in the organic chemist's tool chest for the preparation of compound libraries based on a common core structure for two reasons. First, the products are prepared in a single step leading to a considerable savings in time, resources, and synthetic effort on the part of the chemist; second, because of the independent variability of the inputs, considerable molecular diversity is accessible in the products and will be directly proportional to the number of components available.

As a reaction class, the MCC has a long pedigree, beginning with Strecker's synthesis of α-amino acids in 1850.[3] Other examples include the Hantzsch[4] and the already mentioned Biginelli[2] reactions, both dating from the nineteenth century, and the Mannich[5] reaction, a relatively new addition that dates from the early twentieth century. Given the long history behind MCC reactions, it seems surprising that only recently have researchers begun to focus on the subject. Whether this is due to the advent of combinatorial chemical methods or the increased interest in "diversity-oriented synthesis"[6] does not matter, the train has left the station and will only pick up steam. In the past decade or so, MCC methods to prepare β-amino

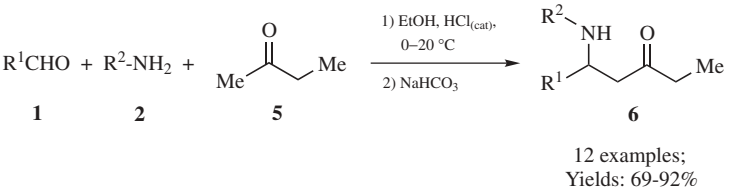
carbonyl compounds have begun to appear with increasing frequency; it is the intent of this chapter to review those methods.

21.2 MANNICH REACTION

The Mannich reaction is one of the most important 3CC reactions in organic synthesis.[7] In its classic form, the Mannich reaction is an aminoalkylation of aldehydes which brings together three components: (1) a nonenolizable aldehyde, classically formaldehyde; (2) ammonia, a primary or secondary amine; and (3) an acidic CH-bonding partner. The products of this MCC are β-aminoketones (Mannich bases). Historically the Mannich reaction suffered from some severe side reactions. Due in part to the advent of new protocols that have greatly improved the process, the products of this 3CC are now obtained generally in good to excellent yields.

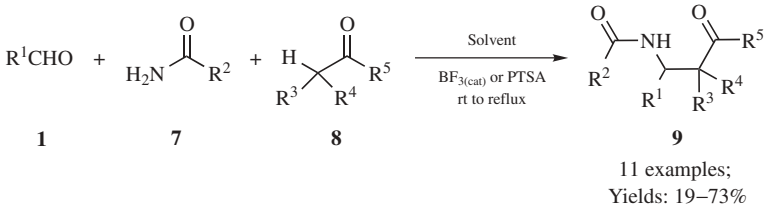
21.2.1 Lewis and Brønsted Acid–Catalyzed 3CC Mannich-Type Reactions

In 1991, Lin and co-workers published the first general 3CC Mannich reaction between aryl aldehydes, aniline derivatives, and butanone catalyzed by HCl in ethanol (Scheme 21.2).[8] Problems associated with deamination to afford the enone were avoided by keeping the temperature between 0 and 20°C; if the reaction temperature was raised significantly above this level, no β-aminoketone products were observed. In contrast to previous observations, the reaction was completely regioselective for the methyl group; this was attributed to steric hindrance from the aromatic aldehyde.



Scheme 21.2

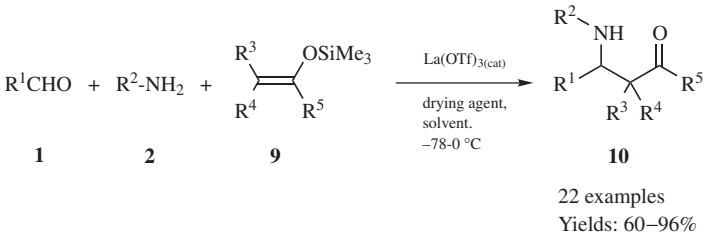
A few years later, ten Hoeve and Wynberg reported a 3CC amidoalkylation of ketones catalyzed by either BF_3 or *p*-toluenesulfonic acid (PTSA) to afford directly β-aminoketones protected as the amide or urethane (Scheme 21.3).[9] The reaction was restricted to aromatic aldehydes, but both amides and urethanes were found to be effective amine sources, with the latter slightly more reactive than the former. Not surprisingly, the use of amides and urethanes completely suppressed deamination, despite the relatively high reaction temperatures required. When diastereomeric mixtures were obtained, the resulting diastereomers could be separated



Scheme 21.3

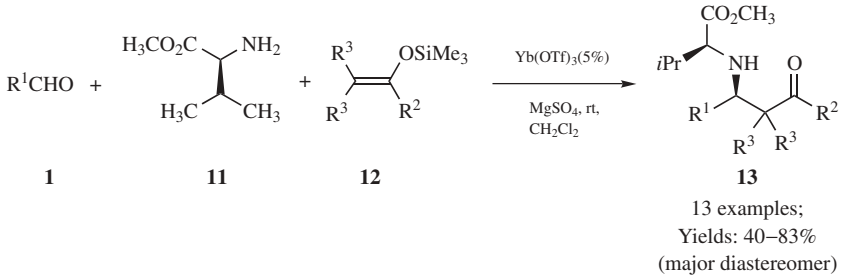
usually by crystallization, but the relative stereochemistry of the major isomer was not reported. In two cases (−)-menthylcarbamate was employed as chiral auxiliary enhanced urethane; however, the resulting 10% ee after deprotection was not synthetically useful.

In 1995 Kobayashi and co-workers published a ground-breaking paper[10] in which they demonstrate that the triflates of yitterbium and scandium catalyze effectively the 3CC of aldehydes, amines, and silyl enolates derived from esters, thioesters, and ketones to afford β-amino carbonyl derivatives in good to excellent yields (Scheme 21.4). The success of both aryl and alkyl aldehydes and amines in these reactions greatly expanded this Mannich methodology. Not surprisingly the use of either E- or Z-enolates lead to high levels of diastereoselectivity, anti products in the case of E-enolates and syn products in the case of Z-enolates. Interestingly, the β-lactam products could be accessed directly if $Hg(OCOCF_3)_2$ was added to the reaction vessel.



Scheme 21.4

Inspired by Kobayashi's work, Cozzi et al. reported a similar yitterbium triflate–catalyzed 3CC system that combined chiral amines (as chiral auxiliary) with aldehydes and silylketene acetals (Scheme 21.5).[11] The methyl ester of (*S*)-valine was found to afford the best diastereoselectivity and, in general, aryl aldehydes were more selective than their alkyl counterparts. The absolute configuration at the β-position was determined to be R, the result of *si* face approach by the nucleophile. Further, both aryl and alkyl aldehydes afforded an identical (**13**) result. This was rationalized though a transition state model in which the imine is chelated to the ytterbium (Fig. 21.3).



Scheme 21.5

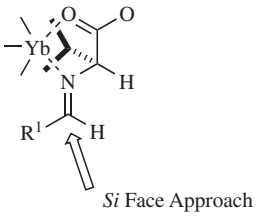
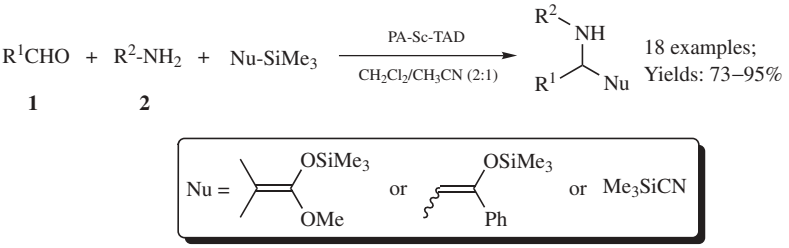


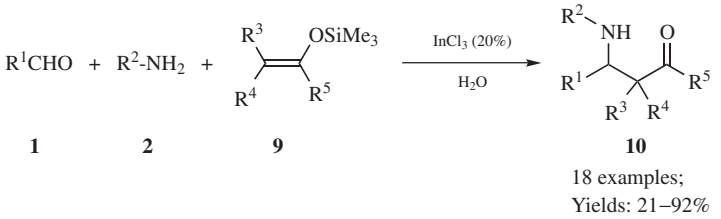
Figure 21.3 The *si* face approach of the enolate.

During this time, Kobayashi and co-workers extended their Lewis acid–catalyzed 3CC reaction of aldehydes (both aryl and aliphatic), aromatic amines, and silyl enolates though the use of a polymer-supported scandium catalyst (Scheme 21.6).[12] These reactions proved to be highly effective in several ways; first, as is typical of many 3CC reaction systems, the starting material molar ratios were nearly 1:1:1; second they afforded the β-amino carbonyl products in excellent



Scheme 21.6

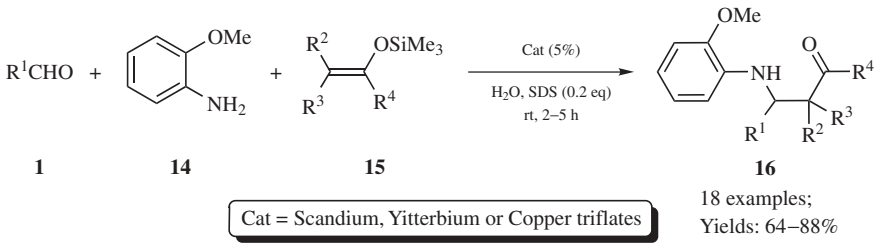
yields; and, third, perhaps most significant, the catalyst was easily isolated and proved to be reusable. Unfortunately the diastereoselectivities for the β-amino ketone cases were modest, typically about 2:1 (the relative stereochemistry obtained was not reported). Interestingly, if silyl ketene acetals were used as nucleophiles, the drying agent $MgSO_4$ was required to obtain the desired β-amino esters, presumably due to the in situ formation of water causing the decomposition of the silyl ketene acetal.



Scheme 21.7

In contrast to this, Loh and co-workers reported a nearly identical 3CC reaction catalyzed by $InCl_3$ in water (Scheme 21.7).[13] While these reactions afforded the β-amino ester products when the silyl ketene acetal 1-methoxy-2-methyl-1-trimethylsiloxypropene was used, they tended to be more effective when silyl enol ethers were used to afford β-amino ketones. In general, these reactions appear to be restricted to nonenolizable aldehydes. The syn diastereomer was the major isomer observed, but selectivity was modest, typically about 2:1. Despite the fact that the aldehyde and imine were in equilibrium and reaction times of 24 h were routine, aldol products were not normally observed unless a significant excess of aldehyde was employed. The authors conclude that $InCl_3$ catalyzes the Mannich reaction of imines preferentially over the aldol reaction of aldehydes.

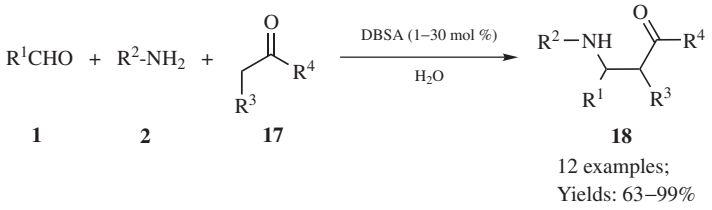
Extending their Lewis acid–catalyzed Mannich reactions to an aqueous medium, Kobayashi and co-workers reported a 3CC reaction system in an aqueous/surfactant mixture in which sodium docecyl sulfate (SDS) was used to generate a micelle environment (Scheme 21.8).[14] Both enolizable and nonenolizable aldehydes were



Scheme 21.8

shown to be reactive and in all cases 2-methoxyaniline was used. Three types of silyl enolates were all shown to work well, the ketone-derived silyl enol ethers, thioesters, and ester-derived ketene acetals. Side-reaction adducts such as aldol or deamination products were not observed. In the two cases where diastereoselectivity was possible, the major isomer is the syn diastereomer (3.0 and 2.7:1, respectively).

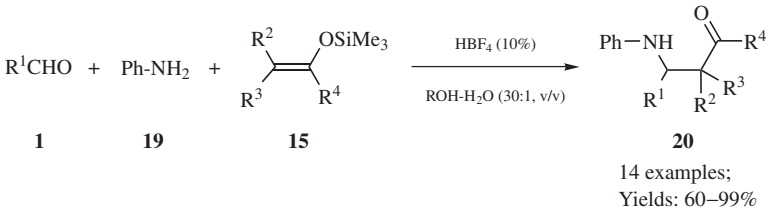
In a further expansion of their work with colloidal reaction systems, Manabe and Kobayashi reported a 3CC Mannich reaction in water catalyzed by the Brønsted acid–surfactant–combined catalyst dodecylbenzenesulfonic acid (DBSA,



Scheme 21.9

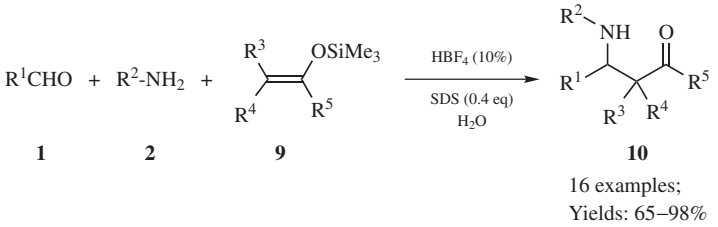
Scheme 21.9).[15] The reaction combined an aldehyde, both enolizable and nonenolizable, an aniline derivative, and an enolizable ketone to afford the β-amino ketone products. To avoid self-condensation problems, however, enolizable aldehydes were added slowly to the reaction mixture, improving greatly the overall yield. As with previous Lewis acid–catalyzed 3CC aqueous systems, the diastereoselectivity is modest at best (the relative stereochemistry obtained was not reported). As was observed by Lin and co-workers,[8] the regioselectivity observed for butanone favored aminoalkylation of the methyl position. For ketones with two enolizable α-positions, an excess of 5 eq. of the ketone was required to avoid polyaminoalkylation.

In an examination of Mannich reactions in aqueous media, Akiyama and co-workers reported a successful 3CC reaction catalyzed by HBF_4.[16a] Initially they reported an effective 3CC reaction in an alcohol–water environment (Scheme 21.10) between nonenolizable aldehydes, aniline, and silyl enolates that afforded the respective β-amino carbonyl products in good to excellent yields. Diastereoselectivity observed in a single case was 2 :1 in favor of the syn isomer.



Scheme 21.10

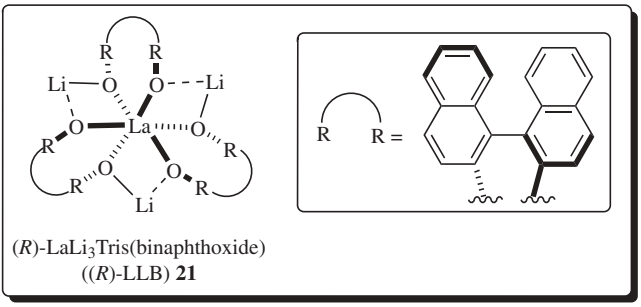
In a follow-on report, Akiyama et al. extended their HBF_4-catalyzed 3CC into a micellar system derived from the surfactant SDS and water (Scheme 21.11).[16b] Alternative detergents were tested and the neutral surfactant Triton X100 was found to support the reaction but required a longer reaction time. On the other hand, the cationic surfactant cetyl trimethylammonium bromide did not support the reaction. The scope of this 3CC reaction was expanded to include enolizable aldehydes. In both the alcohol and micellar systems, the silyl enol ethers were more robust, requiring an excess of only 1.5 eq. To achieve similar yields with silyl ketene acetals required 3 eq. of the enolate. Overall, the yields of the micellar system

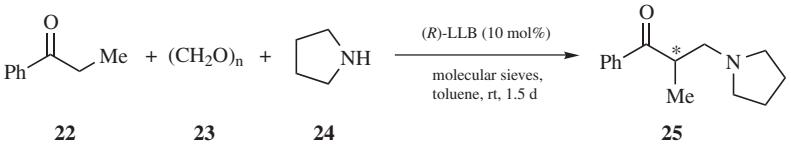


Scheme 21.11

were superior to similar reactions run in the alcohol-based environment. Diastereoselectivity (one case) in the surfactant system improved by a factor of 2 over the alcohol-based system, although, interestingly, the relative selectivity switched for this reaction run in SDS and the anti isomer became the major stereoisomer.

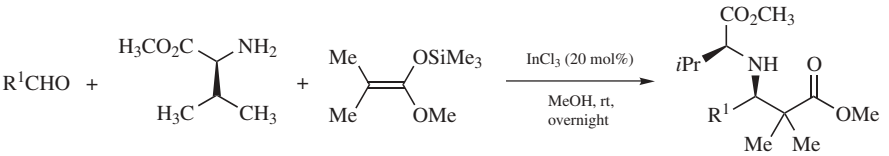
In a seminal paper in 1999, Shibasaki and co-workers published the first direct enantioselective, catalyzed 3CC Mannich reaction using unmodified ketones.[17] The $LaLi_3$tris(binapthoxide) complex (**21**) developed earlier for a direct asymmetric aldol reaction[18] proved to also catalyze a 3CC Mannich reaction. Only one example was reported, the reaction between propiophenone (**22**), paraformaldehyde (**23**), and pyrrolidine (**24**) to afford the β-amino ketone **25** (Scheme 21.12). Unfortunately, the catalyst proved to be water intolerant; thus the best results in terms of yield and enantioselectvitiy were obtained when 3-Å molecular sieves were included. While a 64% ee was encouraging, the yields were generally low, with 16% representing the highest observed.





Scheme 21.12

Following the work of Cozzi and co-workers,[11] Loh and Chen adapted their $InCl_3$-catalyzed 3CC system to incorporate chiral amines (as chiral auxiliary) in reaction with aldehydes (both alkyl and aryl) and silylketene acetals (Scheme 21.13).[19] In results similar to those observed in the yitterbium-catalyzed system of Cozzi et al.,[11] the methyl ester of (*S*)-valine (**11**) was found to afford the best



1 **11** **26** **27**

7 examples;
Yields: 40–80%
de: up to 98%
(major diastereomer
shown)

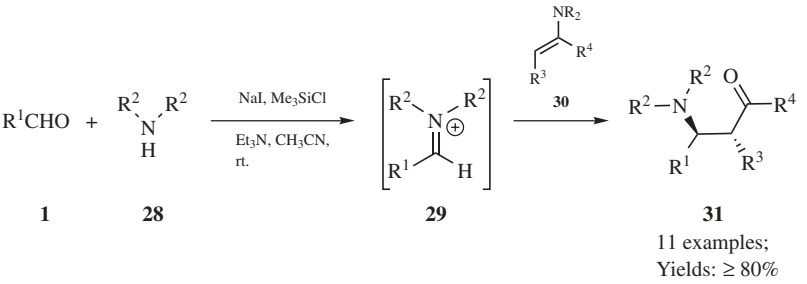
Scheme 21.13

diastereoselectivity and, in general, aryl aldehydes were more selective than alkyl aldehydes. The resulting absolute configuration at the β-position was determined to be R the result of *si* face approach of the nucleophile, rationalized though a transition-state model in which the imine is chelated to the indium (Fig. 21.3). The reactions proceeded smoothly in methanol, affording the β-amino ester products in good yields, with moderate to excellent diastereoselectives. Interestingly, in contrast to reaction in water,[13] attempts to prepare β-amino ketones using silyl enol ethers proved to be unsuccessful. Significantly, Loh and Chen[19] demonstrate that the catalyst $InCl_3$ can be recovered with no loss of activity.

21.2.2 Noncatalyzed 3CC Mannich-Type Reactions

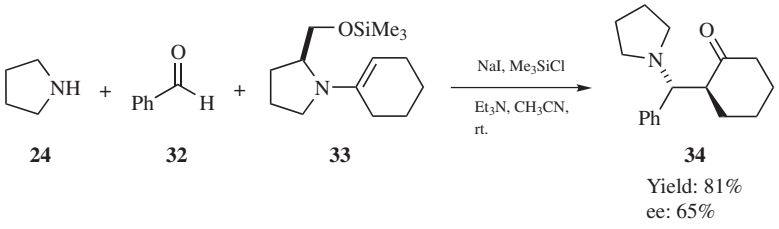
Despite the great strides which have been made in the area of Lewis and Brønsted acid catalysis of 3CC Mannich reactions, such as the development of mild reaction systems that circumvent the need for drastic reaction conditions,[7c] some noteworthy problems remain, chief among them is a significant lack of stereo- and, to a lesser extent, regioselectivity. The development of mild reaction systems with sufficiently reactive components in order to avoid some of the concerns over reaction conditions remains an important goal, and judicious choice of those reagents might also address the significant problems with stereo- and regioselectivity.

To begin addressing the above concerns, Arend and Risch proposed the use of preformed iminium salts as the electrophilic component and enamines[20a] or imines[20b] as the nucleophilic components. The success of this bimolecular process and the lack of commercially available iminium salts prompted them to develop a mild method for the in situ generation of iminium salts and thus introduce a novel



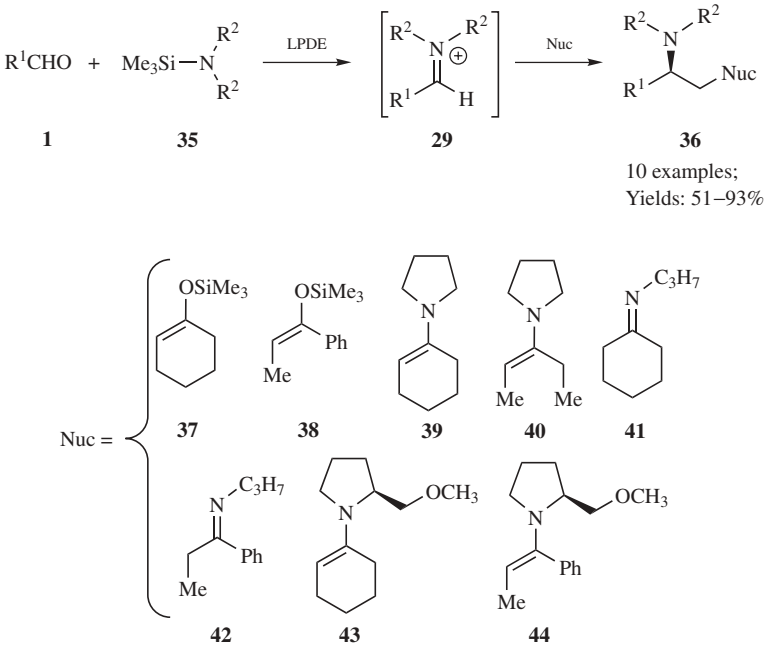
Scheme 21.14

3CC Mannich-type reaction (Scheme 21.14).[21] In this reaction the sequence of addition is important; the reaction of aldehydes with secondary amines mediated by $NaI/Me_3SiCl/NEt_3$ provides the iminium salt (**28**) in situ. To this mixture the preformed *E*-enamine was added affording the desired β-amino ketone. The reaction occurs with complete diastereocontrol affording only the anti isomer, consistent with earlier observations in which E-enolates afford the anti isomers exclusively.[10] Overall, the reactions occur in good to excellent yields, but unfortunately it appears to be limited to nonenolizable aldehydes. In the bimolecular reaction, regioselectivity was for the less substituted C_α atom and, based on one example, this trend also appears to be the case in the 3CC reaction. In another example, the chiral enamine **33** was used (Scheme 21.15) affording ketone **34** in an 81% yield with a 65% ee.



Scheme 21.15

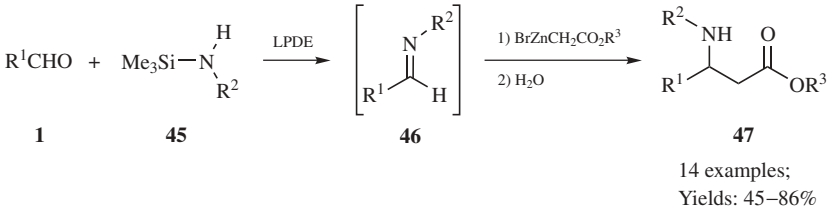
Following the work of Arend and Risch,[20] Zarghi and co-workers reported a related 3CC Mannich-type reaction in which iminium salts are prepared by reacting aldehydes with (trimethylsilyl)dialkyl amines in 5 M $LiClO_4$–ether (LPDE) solution (Scheme 21.16).[22] The resulting iminium salts can then be trapped in situ by a wide variety of nucleophiles to afford the desired β-amino ketones in good to excellent yields. These reactions are highly diastereoselective, affording the anti isomer, in most cases, as the sole isomer. An improvement here was that enolizable aldehydes were also reactive, but they afforded lower yields and showed no stereoselectivity. Experiments with the chiral enamines **43** and **44** were encouraging, affording chiral β-amino ketone products in enantiomeric excess of up



Scheme 21.16

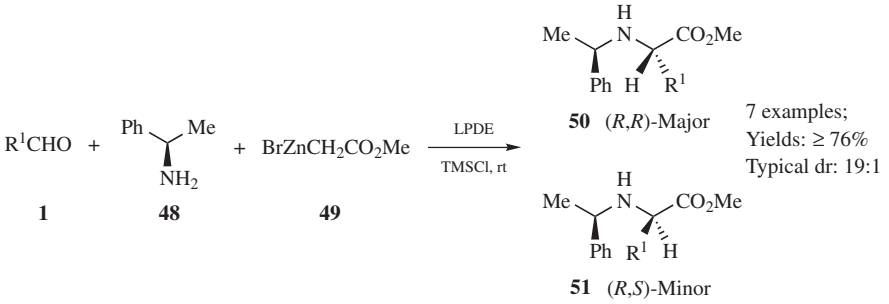
to 86%, but the chemical yields tended to be low (≈15–20%). Unfortunately, attempts to increase the yields resulted in greatly decreased enantioselectivity.

Extending their work with LPDE-mediated 3CC reactions, Saidi et al. reported that LPDE also promoted the formation of substituted imines (**46**) by the reaction of *N-alkyl-(*trimethylsilyl) amines (**45**) with various alkyl and aryl aldehydes.[23] The resulting imines were then trapped by reaction with a bromoalkylzinc ester (a Reformatsky reagent) that had been prepared separately to afford the β-amino ester products in good yields (Scheme 21.17).



Scheme 21.17

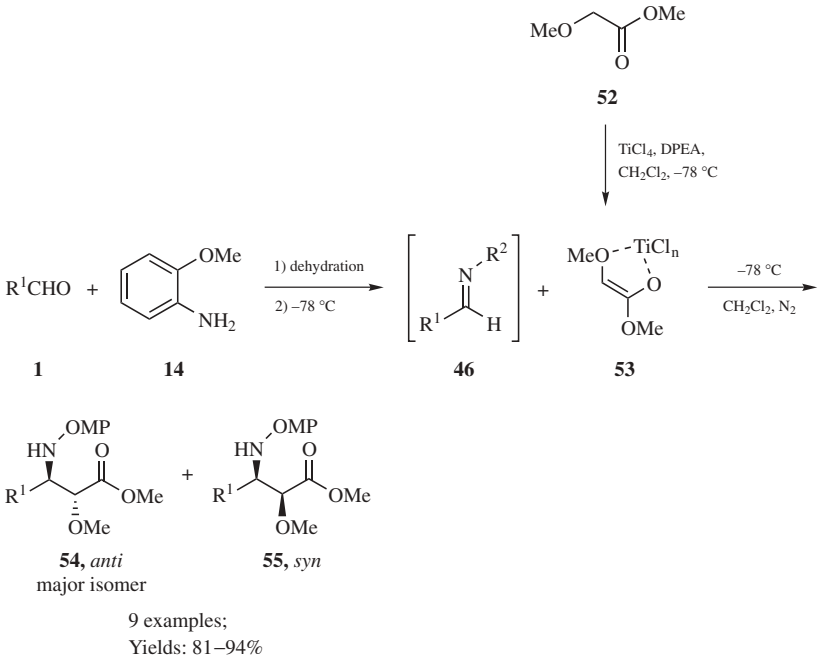
In a further expansion of the LPDE methodology, Saidi and Azizi developed an asymmetric 3CC using (*R*)-1-phenylethylamine (**48**) as a chiral auxiliary.[24] This 3CC reaction, which combined an aryl aldehyde, chiral auxiliary **48**, and Reformatsky reagent, achieved good to excellent diastereoselectivity (82–95% de)



Scheme 21.18

with generally high yields (Scheme 21.18). A significant advance was the discovery that the need for a preformed silylamine could be circumvented by the simple expedient of reacting the aldehyde with a primary amine in the presence of trimethylsilyl chloride (TMSCl) in the LPDE followed by addition of the Reformatsky reagent. The need to use $LiClO_4$ in high concentrations in a very volatile solvent, however, may pose a problem on scale-up, making these processes potentially unattractive in an industrial setting.

Our own contribution in this area has been to develop a diastereoselective 3CC reaction which affords predominately the anti-isomer of α-oxy-β-amino esters (Scheme 21.19).[25] During the course of the reaction, imines (**46**) generated by



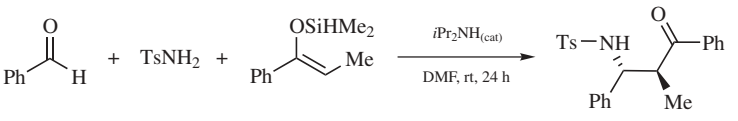
Scheme 21.19

reaction of aldehydes with 2-methoxyaniline (**14**) in the presence of a dehydrating agent are trapped in situ by the addition of a chlorotitanium enolate of methyl methoxyacetate (**52**). While we found that both enolizable and nonenolizable aldehydes were equally reactive in terms of chemical yield, the latter tended to deliver a higher level of diastereoselection (≈65% de vs. ≥90% de, respectively). As had been observed earlier,[26] the diastereoselectivity of the reaction was sensitive to the presence of an ortho substituent on the aniline, with a substituent other than hydrogen showing improved diastereoselectivity. Interestingly, which dehydrating agent was used depended on the type of aldehyde; 4-Å molecular sieves worked well for nonenolizable aldehydes but failed for the enolizable aldehydes. On the other hand, we found that the use of 1 eq. of dimethylzinc as dehydrating agent worked exceptionally well for the enolizable aldehydes, affording the desired β-amino esters in good yields, but failed for the nonenolizable aldehydes.

21.2.3 Organo-Catalyzed 3CC Mannich-Type Reactions

In the past 3 years, important strides in developing enantioselective 3CC Mannich-type reactions have been made through the use of organo-catalysis, most notably through the use of the amino acid proline.

Recently, Miura et al. reported a novel, highly distereoselective, secondary amine–catalyzed Mannich reaction in which dimethylsilyl enolates (**57**) were activated by diisopropylamine and water and added cleanly to *N*-tosylimines to afford β-amino ketones, predominantly as the anti isomer (typical ≈98% de).[27] Miura et al. then extended this reaction to a 3CC strategy in which the in situ imine formation furnishes the requisite water (Scheme 21.20), affording the β-amino ketone (**58**) in 79% yield and 70% de. Unfortunately, they provided only one MCC example, so it is difficult at this point to determine the scope of this promising 3CC process.

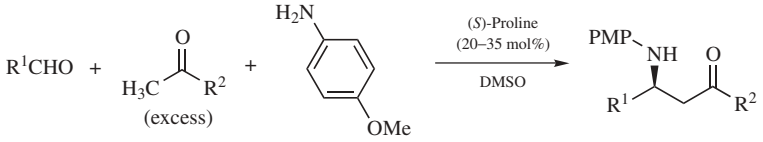


32 **56** **57** **58**

79%
anti:syn = 85:15

Scheme 21.20

In a series of landmark papers, the research groups of List[28] and Notz[29] reported independently an asymmetric, proline-catalyzed 3CC Mannich reaction between aldehydes, aniline derivatives, and ketones that furnishes β-amino ketone products in up to 99% ee and >90% de (Scheme 21.21). Several secondary amines were tested as potential catalysts and *S*-proline was found to be the most effective. In most cases, the ketone was used in excess; for example, in the case of acetone, it was both the solvent and the nucleophile. In the case of hydroxyacetone (**70**), however, List et al.[28b] found that as little as 1.3 eq. was sufficient for



1 **59** **60** **61**

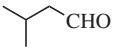
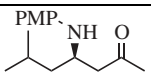
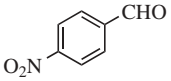
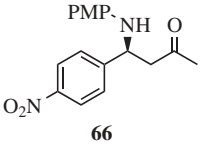
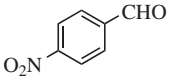
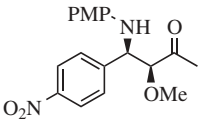
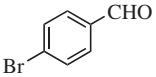
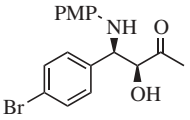
20 examples;
Yields: 35–95 %

Scheme 21.21

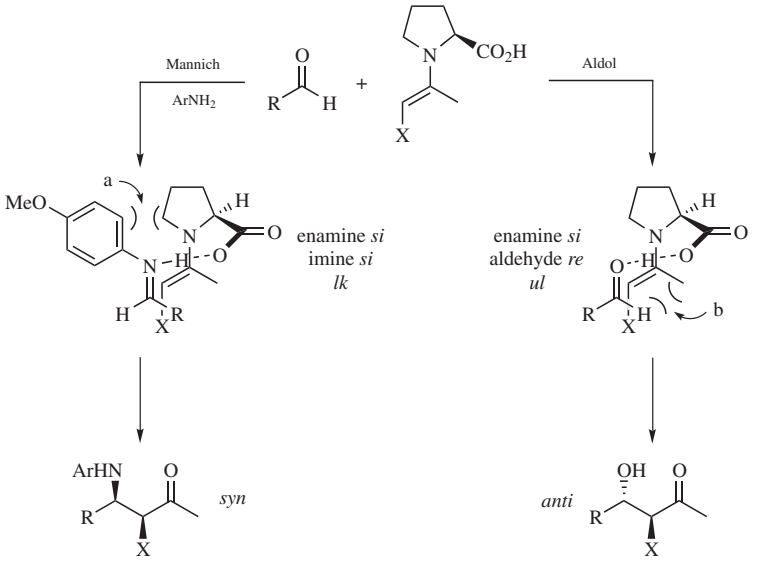
obtaining the product in excellent enantioselectivity and very good chemical yield in 4 h.[28b]

As is evident from the four examples presented in Table 21.1, the reaction displays significant regioselectivity. In these typical cases the more substituted α-position affords the major product, in contrast to previous 3CC Mannich reactions. These reactions also display significant chemoselectivity since essentially no aldol products were formed.

TABLE 21.1 Representative Examples of Proline-Catalyzed 3CC Mannich Reaction

Ketone	Aldehyde	Product	Yield %	de %	ee %
 **62**	 **63**	 **64**	90	—	93
62	 **65**	 **66**	50	—	94
 **67**	 **68**	 **69**	93	90	98
 **70**	 **71**	 **72**	90	88	98

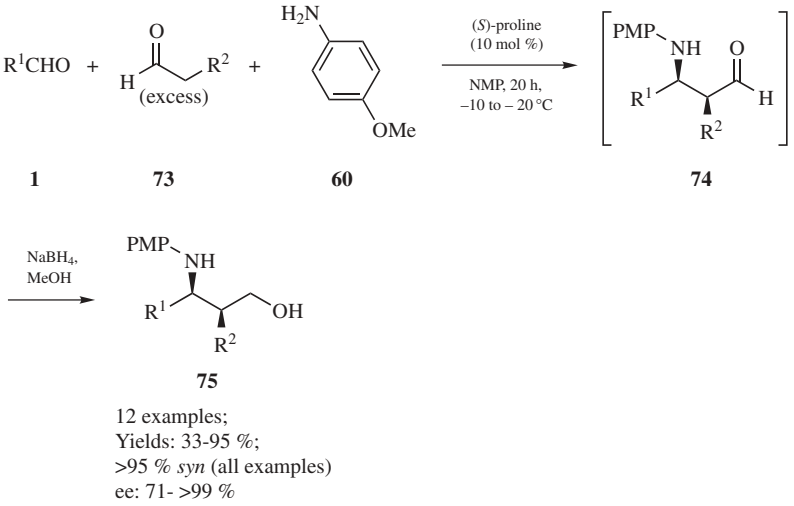
Note: In all cases *p*-methoxyaniline (PMP) was used.



Scheme 21.22 Opposite enatiofacial selectivities and topicities in aldol and Mannich transition states. [Reprinted with permission from, *J. Am. Chem. Soc.*, **124**, 827 (2002). Copyright 2002 by the American Chemical Society.]

To rationalize the observed relative and absolute stereoselection, List and coworkers[28b] assumed an E-configuration for both the imine and proline enamine and a *si* enamine enantiofaciality (assuming the X is highest priority, Scheme 21.22). To account for the syn selectivity observed in the Mannich reaction, the *si* face of the imine must be approached by the *si* face of the enamine in like topicity (lk), thus allowing for both the directing and stabilizing effect of protonation of the *E*-imine's loan pair of electrons by the proline acid group. Consideration of an approach on the imine re face, while possible, would lead to unfavorable steric interactions (Scheme 21.22, arrow a). On the other hand, in the aldol reaction, while *si* enamine enantiofaciality is still the rule, steric interactions between the aldehyde and the enamine carbon group dominate (Scheme 21.22, arrow b), leading to an enamine *si* face aldehyde *re* face unlike topicity (ul) that would result in anti selectivity.

Hayashi et al.[30] recently expanded the scope of proline-catalyzed enantioselective 3CC Mannich reactions by developing a reaction that combines two different aldehydes and *p*-methoxyaniline (**60**) to afford β-amino aldehydes (**74**) isolated as the β-amino alcohols (**75**, Scheme 21.23). The best results were achieved in the polar aprotic solvents *N*,*N*-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidinone (NMP) at low temperatures where side reactions such as aldol condensation are suppressed. Consistent with the ketone Mannich reactions of List et al.[28] and Notz et al.,[29] the syn isomer was selectively generated, presumably through a similar transition-state model. In general, the enantioselectivities were excellent. Not surprisingly, for the mixed Mannich reactions, the order of addition was very important. The acceptor aldehyde was mixed with the aniline first to prepare an



Scheme 21.23

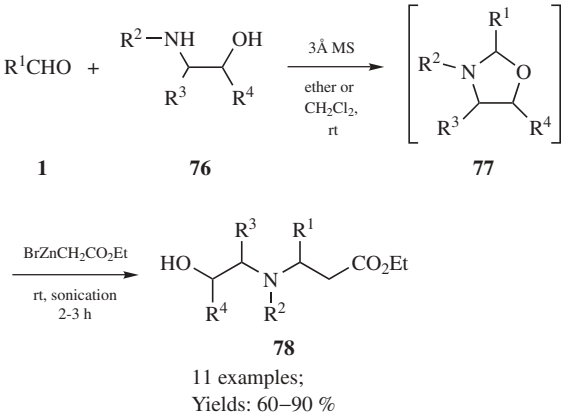
imine in situ. The resulting imine was then trapped by the enamine formed through condensation of the donor aldehyde and proline. When self-condensation was desired, all three components were simply mixed together.

21.3 OTHER MULTIPLE-COMPONENT REACTIONS

While the Mannich and Mannich-type reactions are the most common 3CC methods for the preparation of β-amino carbonyl compounds (or ''Mannich bases''), alternative multiple-component reactions (MCRs) that afford this useful class of compounds have been reported. These alternative approaches include reactions that employ, as Mannich acceptors, compounds other than imines, transition metal–catalyzed MCC reactions, isocyanide-based MCRs, and Baylis–Hillman MCRs.

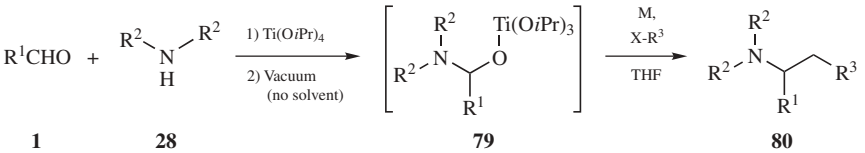
21.3.1 Reactions with Imine Alternatives

In 1994 Nishiyama et al. reported a 3CC reaction that afforded derivatives of ethyl 3-(2-hydroxyalkyl)-aminoalkanotes (**78**) by the coupling of 1,3-oxazolidines (**77**) prepared by the reaction of 2-aminoethanol derivatives with an aldehyde in the presence of 3-Å molecular sieves (MS) and trapped in situ with a Reformatsky reagent derived from ethyl bromoacetate (Scheme 21.24).[31] Oxazolidines derived from either alkyl or aryl aldehydes were equally efficacious and in all cases reacted smoothly with the Reformatsky reagent under very mild conditions to afford the desired β-amino esters in good to very good yields. Interestingly, the reactions could be carried out in either diethyl ether or CH_2Cl_2, with the later affording the best yields.



Scheme 21.24

Mosset and co-workers reported a novel 3CC reaction in which an aldehyde (alkyl or aryl) was condensed with a secondary amine (**28**) in the presence of Ti(IV) isopropoxide generating the intermediate titanium complex **79,** which was not isolated but in turn reacted with allyl bromide, isopropyl bromoacetate, or iodoacetonitrile in the presence of either zinc or indium (Scheme 21.25).[32] This process can approach β-amino acids from three directions: (1) as homo allyl amines, (2) as the β-amino esters, and (3) as the β-amino nitriles. Overall yields tended to be moderate with aryl aldehydes and indium generally performing better.



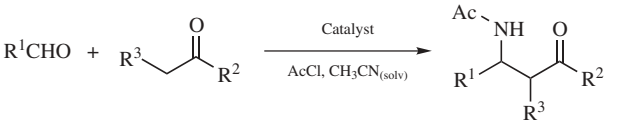
	R^3	X	Yields	
	Allyl	Br	58–83%	8 Examples
M = In or Zn	CH_2CO_2iPr	Br	19–82%	8 Examples
	CH_2CN	I	48–63%	4 Examples

Scheme 21.25

21.3.2 Transition Metal–Catalyzed MCR

Starting in 1994, Bhatia and co-workers published a series of papers in which they reported a novel Co(II)-catalyzed three-component reaction (3CR) that combines aldehydes (both aryl and enolizable), ketones or ketoesters, and acetonitrile (also

the solvent) in the presence of acetyl chloride to directly afford the acetamide-protected β-aminoketones and esters in generally good yields (Scheme 21.26).[33] Overall, aryl aldehydes tended to be more effective than enolizable aldehydes, affording higher yields and requiring shorter reaction times. They also found these reactions to be selective for the anti diastereomer (50% de).



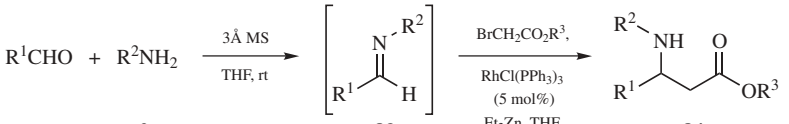
1 **81** **82**

Ref.	Catalyst	Base	Yield (%) **82**	# Examples	Typical de %
34	$CoCl_2$	DABCO	26–78	26	50
36		3-HQD	51–68	9	≥ 90

Scheme 21.26

In work on other Co(II)-catalyzed 3CR, Das and Iqbal developed a solid-phase system by immobilizing Co(II) acetate in a polyaniline matrix.[34] Prabhakran and Iqbal then demonstrated that the resulting heterogeneous catalyst effectively promotes their previously reported 3CR (Scheme 21.26).[35] In general, they found that chemical yields with polymer-supported catalyst were improved by 10–20% and that the major isomer was also in the anti configuration. Significant improvement in the resulting diastereoselectivity was observed, however, going from 50% de in the homogeneous reaction to ≥90% de in the heterogeneous case. The use of a heterogeneous catalyst also greatly simplified the work-up by allowing the isolation of β-amino carbonyl products in high purity without the need for a final chromatography. Unfortunately, the heterogeneous catalyst was not reusable.

Recently, Honda and co-workers developed a 3CC version of their rhodium-catalyzed Reformatsky-type reaction,[36] which affords β-amino esters in 45–85% yields (Scheme 21.27).[37] In this reaction a Reformatsky reagent is generated in situ from esters of bromoacetate and diethylzinc in the presence of Wilkinson's catalyst and then reacted with an imine (**83**), also generated in situ. Imine combinations were not restricted and could be derived from any combination of either enolizable



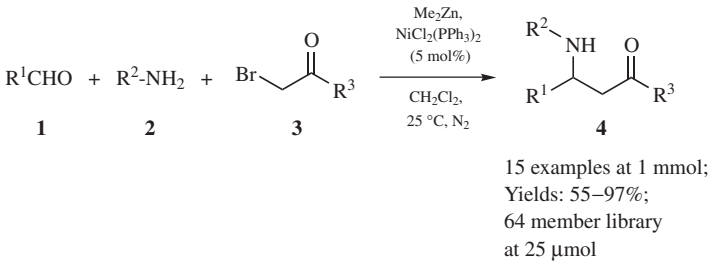
1 **2** **83** **84**

12 examples;
Yields: 45–85%

Scheme 21.27

and nonenolizable aldehydes with either aryl or aliphatic primary amines. In an asymmetric extension of this 3CC reaction, Honda employed the benzyl ether of (*R*)-phenylglycinol as a chiral auxiliary and amine source to afford the desired β-amino esters in good yields. Interestingly, while they observed only one diastereomer on deprotection of the amine, the chiral products were obtained in only 59–85% ee. The absolute configuration of several products was assigned unambiguously as R by polarimetry.

Independent of Honda and co-workers, we developed a 3CC metal-catalyzed Reformatsky-type reaction that employs an inexpensive Ni(II) catalyst to combine aldehydes (of all types), primary aromatic amines, and α-bromocarbonyl compounds, thus affording the desired β-amino carbonyl products in generally excellent yields (typical yields were ≥90%; Scheme 21.28).[38] Not surprisingly, the order of addition proved to be crucial; an imine was prepared in situ by condensation of the aldehyde with the amine in the presence of excess dimethylzinc, which played the dual role of dehydrating agent and then, later, the zinc source. The α-bromocarbonyl and Ni(II) catalyst were then added to complete the reaction. This 3CC reaction proved to be efficient, requiring starting component molar ratios of only 1:1.02:1.05 (aldehydes–amines–bromocarbonyls) to achieve nearly 100% conversion within 1–3 h.

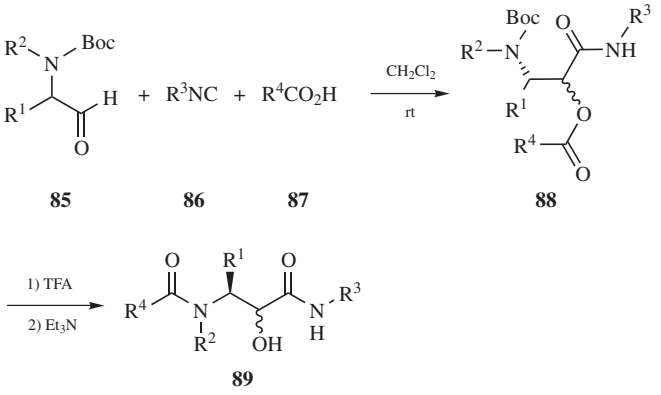


Scheme 21.28

The high efficiency of our Ni-catalyzed 3CC Reformatsky reaction afforded an ideal opportunity for the parallel synthesis of a combinatorial library of compounds based on the β-amino carbonyl core structure (Scheme 21.28). A 96-well microtiter plate proved to be an excellent reaction vessel for the preparation of a small library consisting of 64 members (four aldehydes, five 4-α-bromocarbonyls, five 4-anilines) distributed such that one product was formed per well (Fig. 21.2). A liquid chromatography mass spectroscopy ultraviolet (LCMS-UV) analysis of the array synthesis conducted on a 25-μmol scale indicated that in every case the major, if not only, product was the predicted β-aminocarbonyl compound.

21.3.3 Other Name MCR

21.3.3.1 Passerini Reaction An isocyanide-based 3CC, the older Passerini[39] reaction, has received less attention than the more well-known 4CC Ugi[40] reaction.



85 **86** **87** **88**

89

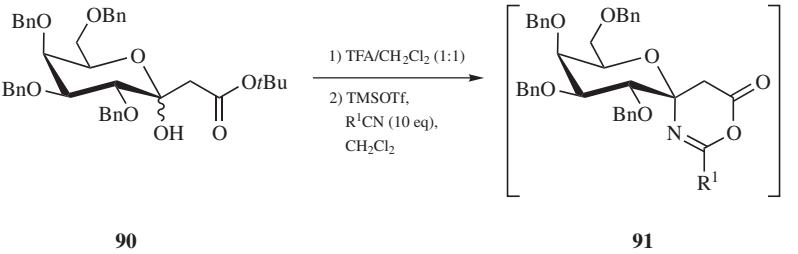
20 examples;
Yields: 59–95 %
dr - 2:1 in all cases
TFA = trifluoroacetic acid

Scheme 21.29

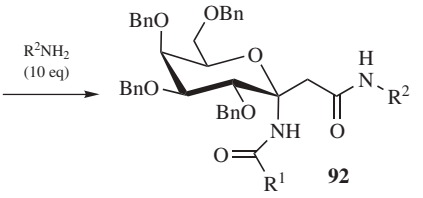
Nonetheless Banfi and co-workers have recently employed the Passerini reaction to prepare a test library of 20 β-acylamido-α-hydroxy-amides (**89**).[41] In this process (Scheme 21.29) they combined *N*-Boc-α-aminoaldehydes, isocyanides, and carboxylic acids to afford the Boc-protected β-amino-α-oxy-amides (**88**) in 59–95% yields. Upon deprotection, these products rearrange spontaneously to the β-acylamido-α-hydroxy-amides **89** in equally good yields. The reaction proved to be diastereoselective, typically affording the major isomer in a 2:1 ratio; however, the relative configuration of the major isomer was not reported.

21.3.3.2 Ritter Reaction As part of a program to employ carbohydrates in combinatorial processes, Schweizer and co-workers developed a method for preparing unnatural glyco-β-peptides (**92**) via a one-pot intramolecular Ritter[42] reaction (Scheme 21.30).[43] Deprotection of the ketose **90** followed by treatment with Trimethylsilyl-trifluoromethane sulfonate (TMSOTf) and a nitrile formed the cyclic imino anhydride **91**, which was then treated with a primary alkyl amine in situ to afford the β-peptide sugar diamides **92** as a single diastereomer in good yields. Through the use of the amino acid derivative glycine methyl ester as the amine component, the potential for further combinatorial elaboration was clearly established.

21.3.3.3 Baylis–Hillman Reaction Beginning in 2001, Balan and Adolfsson[44] published a series of reports on their work developing an enantioselective 3CC aza-version of the Baylis–Hillman[45] reaction system (Scheme 21.31). In an initial report, Balan and Adolfsson presented a 3CC aza-Baylis–Hillman reaction that combined an aryl aldehyde (alkyl aldehydes were found to completely unreactive), a sulfonamide derivative (**94**), and an acrylate derivative (**93**) in the presence of either amine catalyst DABCO (**97**) or 3-HQD (**98**) and the Lewis acid catalyst



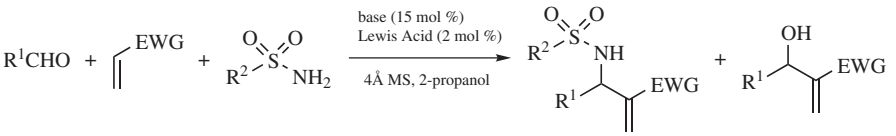
90 **91**



92

6 examples;
Yields: 60–71%

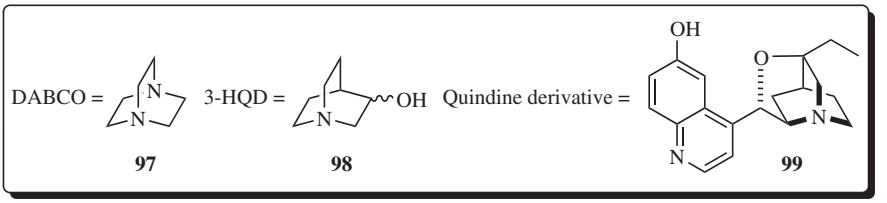
Scheme 21.30



1 **93** **94** **95** **96**

Ref.	Lewis Acid	Base	Yield (%) **95**	**96**	ee (%)	# Examples
47a	$La(TOf)_3$	DABCO	27-87	5-13	-	15
47a	$La(TOf)_3$	3-HQD	21-90	0-26	-	15
47b	$Ti(iOPr)_4$	3-HQD	12-94	0-22[a]	-	12
47c	$Ti(iOPr)_4$	Quindine Derivative	12-95	1	52-74	9

[a] Of the 12 examples only three afforded alcohol adducts.



97 **98** **99**

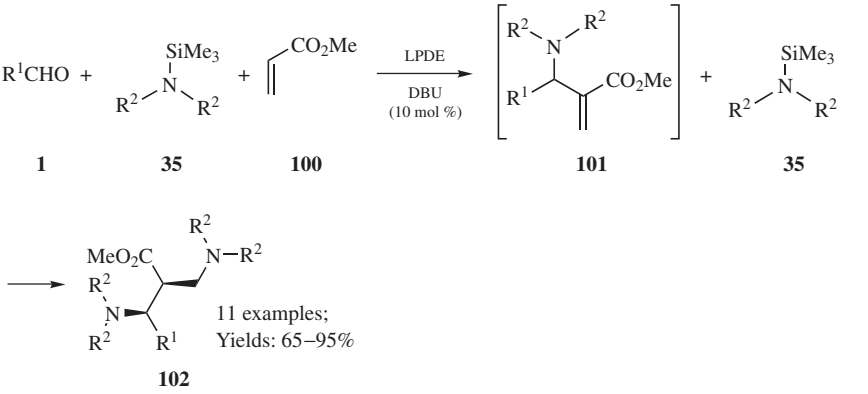
Scheme 21.31

$La(OTf)_3$ to afford the α-methylene-β-sulfonylamido carbonyl compounds (**95**).[44a] These reactions proceeded generally in reasonable yields; however, as is typical for Baylis–Hillman reactions, they suffered from the relatively long reactions times of 24–72 h. Disappointingly, the formation of the competitive alcohol adduct **96** proved to be unpredictable for this reaction system.

Subsequent work by Balan and Adolfsson yielded significant improvement. They demonstrated that the amine catalyst 3-HQD (**98**) in combination with the Lewis acid $Ti(i\text{-}OPr)_4$, reduced reaction times to $\leq$24 h while generally increasing selectivity for the α-methylene-β-sulfonylamido carbonyl product **95**.[44b]

Extending their work further, Balan and Adolfsson very recently reported an enantioselective varient.[44c] By combining the accelerating effect of $Ti(i\text{-}OPr)_4$, with the Hatakeyama[46] cinchona alkaloid **99** as a chiral base catalyst, they were able to achieve excellent chemical yields with moderate to good enantioselectivity. These reactions also displayed excellent chemoselectivity—essentially no alcohol adduct **96** was observed; unfortunately, overall reaction times also increased to 48 h.

In an extension of their work in LPDE solutions, Azizi and Saisi developed a highly efficient 3CC aza-Baylis–Hillman protocol (Scheme 21.32).[47] They found



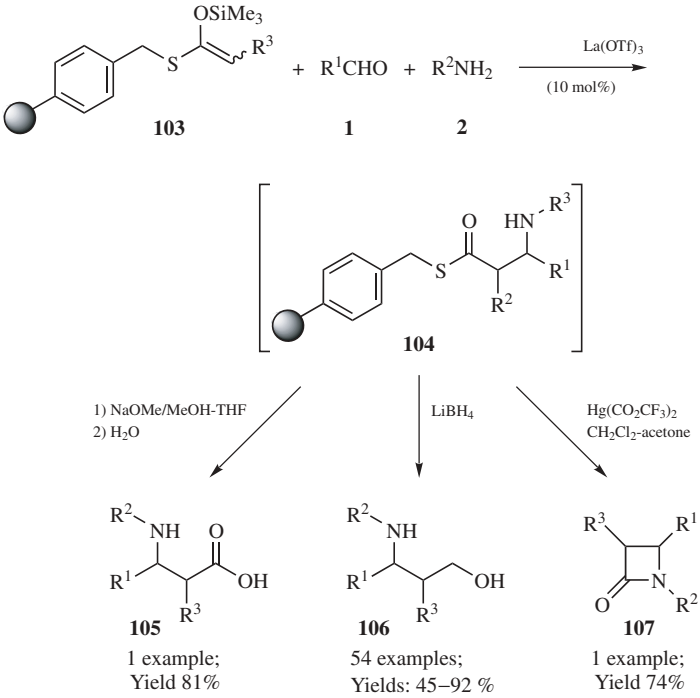
Scheme 21.32

that the iminium salts prepared by reacting aldehydes with (trimethylsilyl)dialkyl amines **35** in LPDE solution were exceptionally reactive toward methyl acrylate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the α-methylene-β-aminoesters **101**, which were not isolated, but reacted with a second equivalent of **35** to provide the isolated bis-β-aminoesters **102** in 65–95% yields. These MCC reactions were also highly diastereoselective, affording only the syn isomer. A significant improvement was the substantially shorter reaction times (5 h) needed for these Baylis–Hillman reactions, likely due to the high solvent polarity. Importantly, this reaction system was shown to be sensitive to the $LiClO_4$ concentration, with lower concentrations resulting in alternative and rearranged products, presumably due to the decrease in solvent polarity. Interestingly, no data were provided on reaction times for the low perchlorate reaction systems.

21.4 SOLID-PHASE MCC METHODS

Solid-phase organic synthesis (SPOS) offers several potential advantages for the preparation of small-molecule libraries; however, very few MCC-SPOS approaches to β-amino carbonyl compounds have been reported.

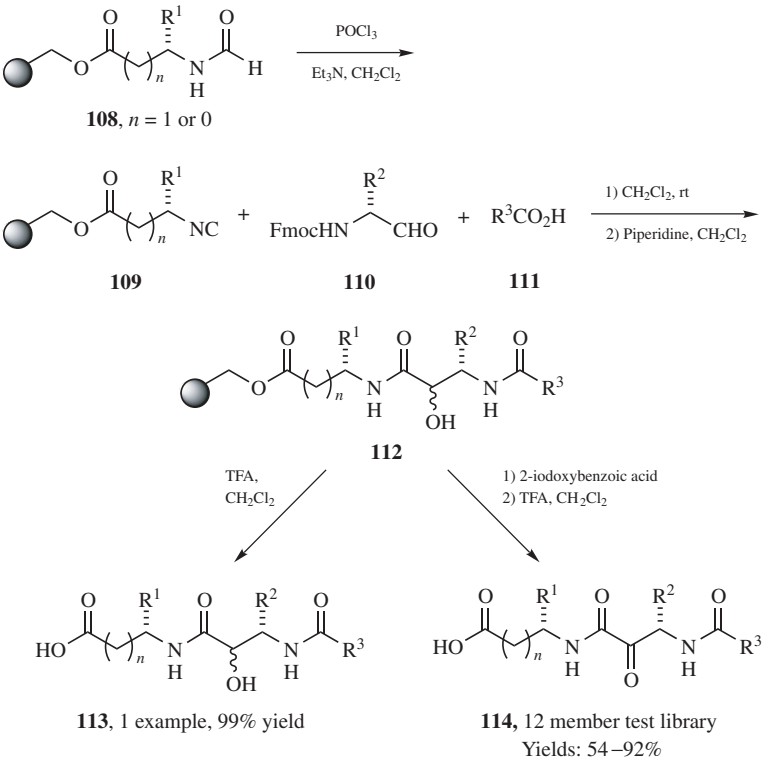
In an extension of their solution-phase Lewis acid–catalyzed 3CC silyl ketene acetal Mannich reactions,[10,12,14] Kobayashi and co-workers adapted this system to a solid-phase reaction strategy (Scheme 21.33).[48] The key development was the



Scheme 21.33

preparation of a silyl enol ether immobilized on a chloromethyl copoly(styrene–1% divinylbenzene) resin through a thioester linkage (PSSEE, **103**).[48a] The reactivity of the heterogeneous PSSEE system was found to be identical to the homogeneous system. Condensation with aldehydes and aniline derivatives in the presence of the catalyst $Sc(OTf)_3$ afforded the polymer-bound β-amino thioesters **104** which were then liberated from polymer and isolated as either the β-amino alcohols (**106**), esters (**105**), or lactams (**107**). Moderate diastereoselectivities were observed ($\leq$3:1), but assignment of the relative configuration was not reported. Kobayashi et al. subsequently applied this 3CC protocol in a parallel synthesis to successfully prepare a 48-member library in generally very good yields.[48b]

In an expansion of their recently published 3CC Passerini reaction,[41] Basso and co-workers smoothly transferred this technology to a solid-phase organic synthesis



Scheme 21.34

strategy using the solid support Lantern (Scheme 21.34).[49] They chose to append the isocyanide moiety to the solid support as the *N*-formylamino acid **108**, which was then dehydrated to afford the isocyano **109**. The resulting isocyano species was then reacted with an Fmoc-protected α-aminoaldehyde (**110**) and a carboxylic acid (**111**) to afford the Fmoc-protected β-amino-α-oxy-amide (not pictured) in the 3CC protocol. Upon deprotection with piperidine, these compounds rearrange to afford the polymer-supported β-acylamido-α-hydroxy-amides **112** and are then either liberated directly or can be oxidized to the corresponding β-acylamido-α-oxy-amides **114** and then released from the solid support. A test library generating 12 of the ketoamides (**114**) was then prepared successfully. Of particular note, the progress of these reactions could be followed using photoacoustic IR spectroscopy (FTIR-PAS), monitoring the appearance and then disappearance of the isocyano group (2150 cm^{-1}).

21.5 CONCLUSIONS

In this review I have attempted to present the current state of MCC/MCR systems for the preparation of β-amino carbonyl compounds and also highlight excellent

directions for future investigations. If a major goal for combinatorial synthesis is the preparation of large numbers of diverse compounds, with relative synthetic ease, then the MCR presents the chemist with a largely underexploited field. As an important class of pharmacophores, the β-amino carbonyl core structure is particularly amenable to preparation by MCC. To date, the Mannich reaction constitutes the vast majority of the MCC approaches to β-amino carbonyl compounds. Notwithstanding the success thus far enjoyed, there remain several important needs. First, since the majority of the MCCs/MCRs are in a single area, there is a clear need for the discovery of new MCRs for the preparation of this class of compounds. The second and perhaps most important area in need of development involves issues regarding stereocontrol. Despite the recent successes in catalytic enantioselection through the use of organo-catalysts,[28,29,30] most MCRs reported thus far suffer from low or absent stereoselection, particularly in an absolute sense. While considerable work has been done in the area of Lewis acid–catalyzed MCC reactions, and despite the pioneering work by Shibasaki and coworkers,[17] comparatively little attention has been focused on developing enantioselective Lewis acid catalysts for those same MCC reactions. The development of a broadly applicable and robust enantioselective catalyst may represent a considerable challenge since MCRs by their very nature present an extensive palette in terms of component diversity. Ideally, such a catalyst would also be inexpensive or easily recovered and reused without loss of activity.

If work in this field continues to accelerate at its current pace, the next few years are likely to see great strides in the development of new and more powerful MCRs which can be used for the stereoselective preparation of β-amino carbonyl compound libraries.

(S)-Proline-Catalyzed Mannich Reaction: Synthesis of (R)-4-(4-Methoxy-phenylamino)-6-methyl-heptan-2-one (64) as Representative Experiment[*] A suspension of (*S*)-proline (40 mg, 0.35 mmol), *p*-anisidine (135 mg. 1.1 mmol), and isovaleraldehyde (1.0 mmol) in 10 mL of acetone was stirred at room temperature for 18 h. The mixture was filtered to recover the proline (∼ 35 mg). Concentration of the filtrate followed by silica gel column chromatography (15% ethyl acetate–hexanes) gave Mannich product **6** as a clear oil (224 mg, 0.9 mmol, 90%). HRMS (MALDI): calculated for MNa^+ 272.1626, found 272.1630. IR: 2954, 1708, 1513, 1240. t_r (R) = 6.5 min, t_r (S) = 7.3 min, ee = 93% (Chiralcel AS, λ = 315 nm, 10% *i*-PrOH–hexanes). Proton nuclear magnetic resonance (^{1}H NMR) (300 MHz, $CDCl_3$): δ(0.90 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 1.33 (m, 1H), 1.47 (m, 1H), 1.75 (m, 1H), 2.12 (s, 3H), 2.54 (dd, J = 6.6, 16.7 Hz, 1H), 2.66 (dd, J = 5.3, 16.7 Hz, 1H), 3.73 (s, 3H), 3.81 (m, 1H), 6.58 (m, 2H), 6.76 (m, 2H), ^{13}C NMR (300 MHz, $CDCl_3$): δ 22.2, 22.9, 24.9, 31.0, 44.6, 48.0, 48.9, 55.7, 114.8, 114.9, 141.3, 152.0, 208.4.

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Multiple-Component Condensation Array Synthesis: Nickel-Catalyzed Multicomponent Array[*] The array was run using a standard 96-well plate in a glovebox under an inert atmosphere of N_2. Vials containing solutions of the aldehydes (0.5 M), anilines (0.52 M), and α-bromo compounds (0.52 M) in 1,2-dichloroethane were transferred into the glovebox. Using a stepping pipette, a 50-μL aliquot of the aldehyde (25 μmol) and then a 50-μL aliquot of the aniline (26 μmol) were combined in the appropriate wells of the plate. The wells were then covered to minimize evaporation. After 30 min, a 45-μL aliquot of a solution of $Zn(CH_3)_2$ (2 M in toluene) was added to the aldehyde and aniline mixtures with an eight-tip pipettor and again the wells were covered. After 15 min, a 50-μL aliquot of the α-bromo compound solutions (26 μmol) was added to the wells using the stepping pipettor. The Ni catalyst $[NiCl_2(PPh_3)_2]$ was freshly dissolved in CH_2Cl_2 (0.025 M) and 50 μL of the solution (1.25 μmol) was added to each well using an eight-tip pipettor. The wells were then covered. After 1.5 h, 10-μL aliquots were taken from six random wells for thin-layer chromatography (TLC) analysis; all indicated complete consumption of the starting aldehyde. The 96-well plate was then taken from the glovebox, and using an eight-tip pipettor, the reactions were quenched by passing them through a plug (1 cm) of neutral alumina which had been covered with a thin layer of activated charcoal. Vacuum was applied to pull the reaction mixtures through the alumina, which was subsequently rinsed with acetonitrile (600 μL per well). Aliquots of the resulting product solutions could then be diluted further for LCMS-UV analysis.

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CHAPTER 22

Using Constrained β-Amino Acid Residues to Control β-Peptide Shape and Function

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22.1 INTRODUCTION: β-PEPTIDES IN THE FOLDAMER CONTEXT

Exciting discoveries in the field of β-peptides have provided new impetus in recent years for the development of synthetic routes to β-amino acids. While individual β-amino acids and closely related compounds, most notably the β-lactams, have long held a prominent position in medicinal chemistry (and have been extensively reviewed[1]), the study of discrete β-amino acid oligomers has been very limited until the past few years. Such oligomers are interesting because they allow one to test basic assumptions about the forces responsible for molecular folding in natural systems such as proteins and because of potential biomedical applications.

As we acquire a deeper understanding of folding in proteins and nucleic acids, it is reasonable to attempt to generalize these insights to a wider array of systems.[2–4] Such generalization should allow us both to check the universality of what has been learned and to access novel structures and functions that may be otherwise unattainable. For example, proteins and nucleic acids can be problematic as therapeutics because they are easily degraded by enzymes. However, the incorporation of even isolated β-amino acids into α-peptides appears to protect against peptide degradation.[5]

Oligomers that adopt specific conformations have been dubbed ''foldamers.''[2,6] A recent comprehensive review discusses both the theoretical determinants of folding and the various classes of foldamers that have been synthesized and studied.[7] To date, β-peptides have seen the most thorough structural characterization among known foldamers. There are interesting parallels and contrasts between the folding

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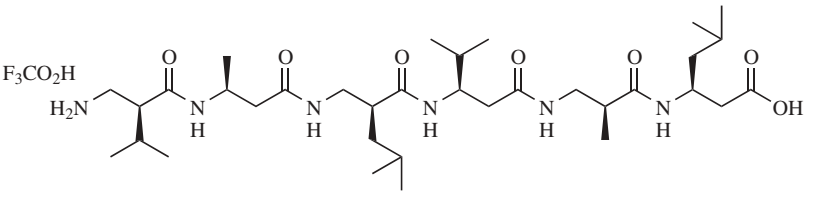
behavior of α- and β-peptides. All three of the regular secondary structures observed in α-peptides—helix, sheet, and reverse turn[8]—are seen also in β-peptides.[9–11] With proper choice of residues, however, secondary-structure stability can be significantly higher among β-peptides than among α-peptides. For example, a helical secondary structure in α-peptides often requires 15–20 residues, but in β-peptides helix formation is observed with as few as six[12,13] or even four[9] residues.

Work in our laboratory has focused on the use of conformationally constrained residues (e.g., α,β-cyclized or *syn*-α,β-disubstituted residues) to induce specific, predictable conformations in the resulting β-peptides. This chapter will concentrate on the synthesis of constrained β-amino acids and properties of β-peptides containing such residues. Our goal is to provide a chemist's perspective on the synthesis of conformationally constrained monomers, with sufficient background to situate the reader within the larger field of β-amino acid synthesis.

For a β-peptide to adopt a particular secondary structure, each constituent residue must be able to adopt the required torsional angles (ϕ, θ, ψ, and ω, according to the convention of Banerjee and Balaram[14]; Fig. 22.1) characteristic of that structure. In addition, there must be no undesired conformation of greater stability for the entire β-peptide. While the former, positive condition is local in nature (i.e., ruling out certain residues at each position in the β-peptide sequence), the latter, negative condition is global and can be met by including one or more "forcing" residues that will destabilize alternative conformations for the β-peptide. A prime example of the need for such "forcing" residues is given by Seebach et al.,[15] who constructed β-peptide **1** entirely of residues permissive for the 14-helical conformation only to discover that it adopts an alternative helical conformation, the remarkable 12/10-helix.

β-Amino acid nomenclature is summarized in Figure 22.2.[15] A single side chain can be attached to the β-amino acid backbone in any of four isomeric ways, giving so-called β^2- or β^3-residues (numeral superscripts indicate the point of side-chain attachment) of either (*R*)- or (*S*)-configuration. It should be noted that residues



1

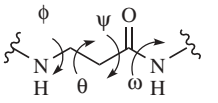


Figure 22.1 Torsion angles in a β-peptide, defined according to convention of Banerjee and Balaram.[14]

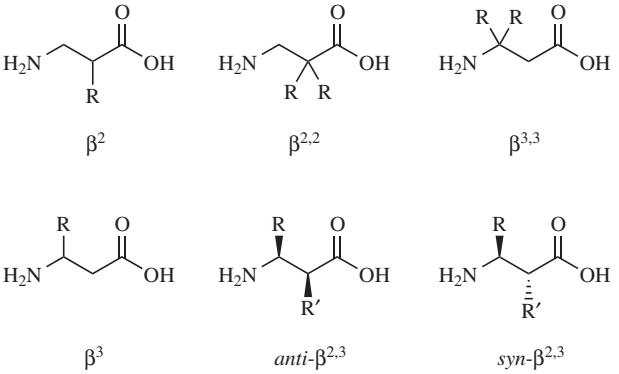


Figure 22.2 Nomenclature convention for mono- and disubstituted β-amino acids.

with analogous chirality can have opposite configurations [e.g., (*R*)-β³HSer and (*S*)-β³HLeu are both synthesized by one-carbon homologation of (L)-(*S*)-α-amino acids]; absent a comprehensive nomenclature system of the (D)/(L)-type, caution is required in the stereochemical nomenclature of β-amino acids. For disubstituted β-amino acids bearing one substituent on the α-carbon and one on the β-carbon (''β²,³-amino acids''), an aldol *syn/anti* convention is used to differentiate between diastereomeric structures, according to precedent.[16]

While appropriately selected monosubstituted residues permit the adoption of a regular pattern of torsional angles, the selective stabilization of one particular pattern over another (conformational ''forcing'') often requires disubstituted residues. We sought to dictate β-peptide conformation using residues in which the θ-torsion is constrained. Because the θ-bond connects two sp^3-hybridized carbons, its torsional minima are the *trans* (or *anti*-periplanar) and two *gauche* (or *syn*-clinal) conformations. Seebach et al.'s conformational analysis[15] provides a useful framework for relating substitution patterns to residue conformational preferences. The unsubstituted β-amino acid, β-alanine (hereafter referred to as β-homoglycine or βHGly), is flexible. Alkyl monosubstitution induces a mild conformational preference for one of the gauche conformations. In anti-disubstituted β-amino acids, this preference is strengthened, and it may be further strengthened by constraining the two substituents into a six-membered ring. In syn-disubstituted β-amino acids, both gauche conformers are destabilized relative to the extended trans conformation. Finally, the θ-torsion can be forced to adopt a skewed syn-clinal angle, where the torsion angle is wider or narrower than canonical gauche, by constraining anti substituents into a five-membered ring[20] or syn substituents into a four-membered ring,[18] respectively (Fig. 22.3).

Conformationally constrained residues, especially residues that strongly favor a particular θ-torsion value, may be used to induce formation of a particular helical or sheet secondary structure. Potential β-peptide helices, some of which are indicated in Figure 22.4*a*, can be defined by the size of their backbone hydrogen-bonded

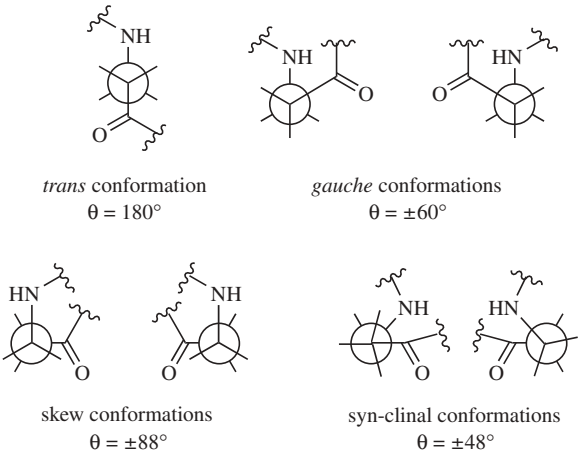


Figure 22.3 Conformations for θ-torsion.[16–19]

rings. [An analogy can be drawn to regular α-peptide helices, which, with the exception of polyproline helices, are characterized by hydrogen-bonded networks forming a set of overlapping backbone hydrogen-bonded rings. The α-helix, for example, has 13-membered ring hydrogen bonds from C=O of residue *i* to NH of residue $i + 4$ (Fig. 22.4*b*).] A conversion table between the nomenclature used

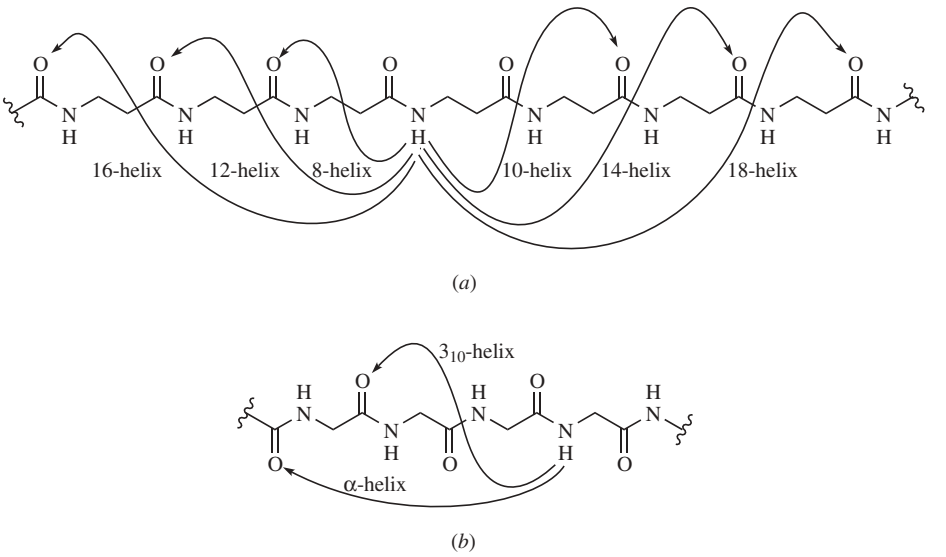
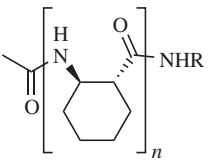


Figure 22.4 (*a*) Helical hydrogen-bonding patterns for β-peptides; (*b*) helical hydrogen-bonding patterns for α-peptides.[2]

here and other systems has recently been published.[16] The nearest-neighbor 6- and 8-helices were shown to be disfavored in a βHGly-based model system.[21] Of the possible regular helical conformations, the 14-helix,[6] the 12-helix,[22] the 10-helix,[18] and the 8-helix[23] have been demonstrated in synthetic β-peptides. A 12/10-helix, in which hydrogen-bonded ring sizes alternate as residues are added, has also been reported.[15,24] Extended sheet secondary structure[10] and reverse turns[11,25,26] have also been developed.

Computational studies have laid the groundwork for the use of constrained (cyclic as well as anti- or syn-disubstituted) residues to program β-peptides to adopt specific secondary structure. Ab initio calculations on monosubstituted β-amino acids[27] suggested multiple possible conformations. Similarly, ab initio studies of $(\beta\text{HGly})_n$ $(n = 1, \cdots, 9)$[28] and molecular dynamics simulations of oligomers of monosubstituted β-amino acids[29] suggested a competition among various helical structures. Molecular dynamics simulations of $(\beta\text{HGly})_{10}$ indicated that the 10-, 12-, 14-, 16-, 18-, and even 20-helical conformations represented local potential energy minima in conformational space.[6,30] On the other hand, ab initio calculations on cyclic model compound **2** ($n = 1$, R = H), accounting for solvent effects, indicated that the lowest energy conformation in polar solvent was the basic repeating unit of the 14-helix.[31] This study indicated also that the second lowest energy conformation for cyclic model compound **3** ($n = 1$, R = H) is the basic unit of the 12-helical structure, which was estimated to be favored in systems allowing formation of at least four 12-helix interresidue hydrogen bonds.[31] Simulations of homodecamers of three, four, five, and six-membered ring residues, in both *cis* and *trans* diastereomeric series, were performed to determine compatibility of each residue with various potential helix structures.[6] Follow-on molecular dynamics simulations of model systems **2** and **3** ($n = 10$, R = Me) predicted the 14- and 12-helical structures later observed by crystallography and nuclear magnetic resonance (NMR).[32] We will refer to residues constrained by the inclusion of C-2 and C-3 in an *n*-membered ring as "*n*-constrained" residues. Simulations based upon a different type of cyclic constraint led to the development of a β-peptide reverse-turn unit.[11]



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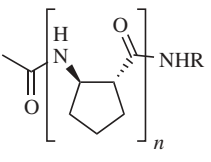


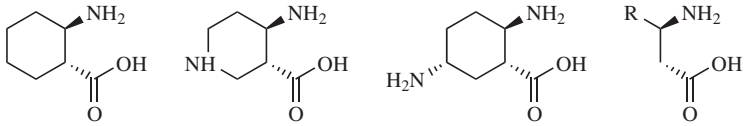
3

22.2 MONOMER SYNTHESIS

22.2.1 6-Constrained Residues

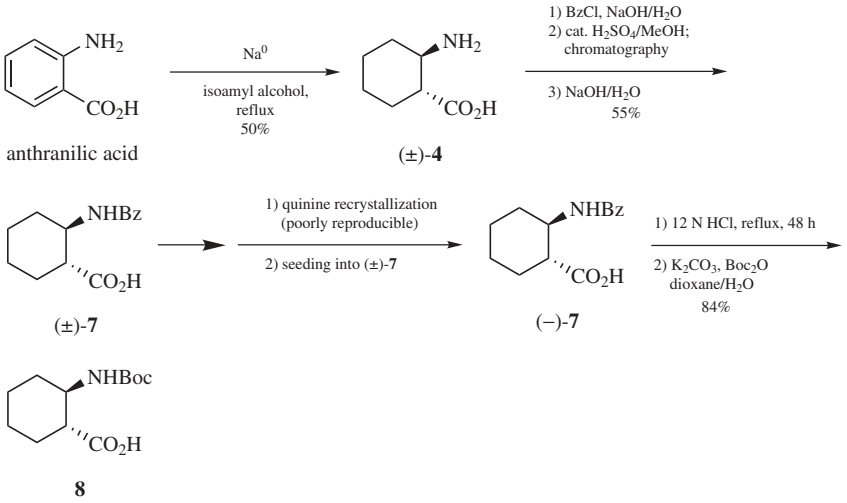
Monomers used by our group in the synthesis of 14-helical β-peptides include *trans*-2-aminocyclohexanecarboxylic acid (ACHC, **4**), *trans*-aminopiperidinecarboxylic

acid (APiC, **5**), the all-equatorial diastereomer of 2,5-diaminocyclohexanecarboxylic acid (DCHC, **6**), and β^3-homoamino acids (β^3HXaa). The synthesis of β^3HXaa by homologation of α-amino acids is very powerful and has been reviewed,[33] and a comprehensive review of the synthesis of conformationally constrained β-amino acids would be beyond our scope. However, we will briefly discuss relevant enantioselective routes to protected ACHC, APiC, and DCHC residues.



ACHC **4** APiC **5** DCHC **6** β^3HXaa

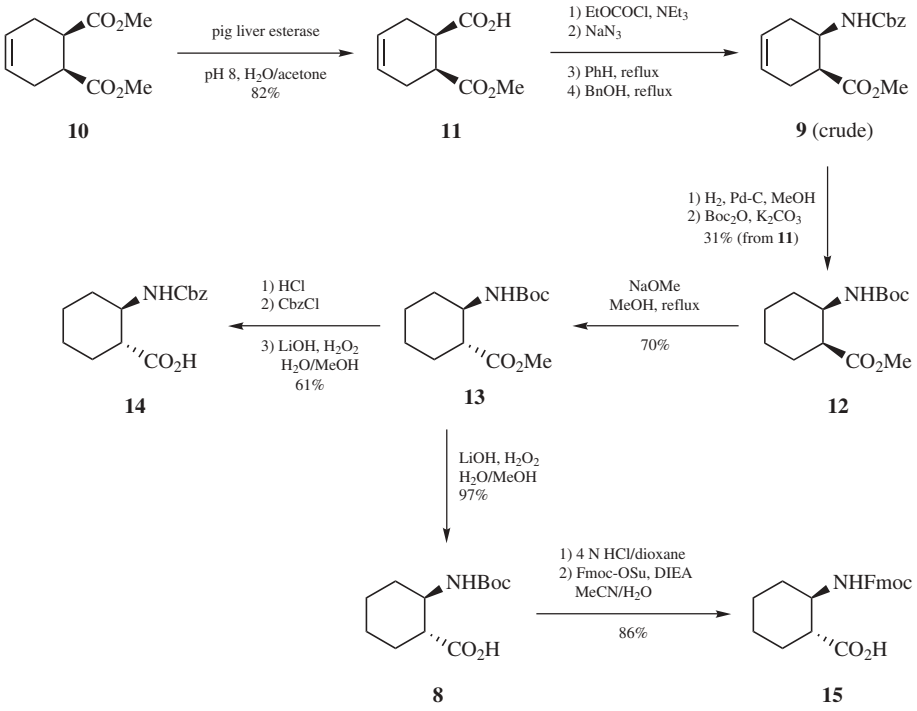
At the start of our group's work with ACHC and its oligomers, existing enantioselective preparations were scarce. In a change of a literature procedure (Scheme 22.1), Appella et al.[6,9] modified benzoylated racemic **4**, prepared from anthranilic



Scheme 22.1 First-generation synthesis of protected ACHC monomer.[9]

acid by Prout's procedure,[34] to give racemic **7**. Nohira's modified resolution, in which seed crystals obtained by the fractional crystallization of (±)-**7** with quinine were used to seed hydroxypropylamine solutions of racemic **7**, was capricious. Repeated seedings eventually gave enantiopure (−)-**7**, which was converted to (−)-**8**.

An enzymatic resolution developed by Kobayashi et al.[35] inspired the development of a second-generation ACHC synthesis (Scheme 22.2) by Appella et al.[36] In

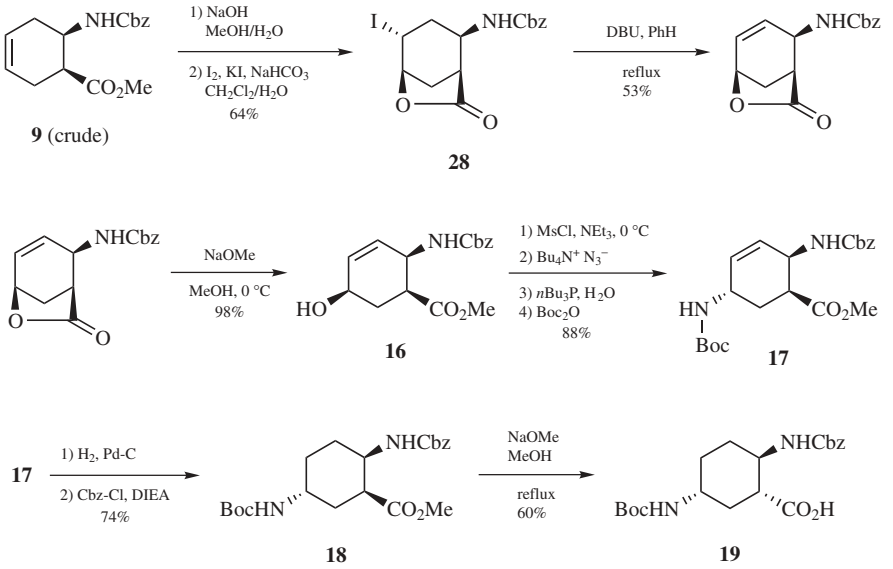


Scheme 22.2 Second-generation synthesis of protected ACHC monomer.[36,37]

this route, Kobayashi's enzymatic resolution/Curtius rearrangement sequence yielded **9** from **10** via **11**, but the product was contaminated with benzyl alcohol. Hydrogenation of the double bond concurrent with a protecting group switch gave **12**, which was then epimerized (as precedented by Kobayashi et al. for **9** itself) to **13**. Further protecting group manipulations yielded Cbz-protected ACHC **14**. Raguse et al. later adapted this route to give Boc- and Fmoc-protected ACHC monomers **8** and **15**, respectively.[37]

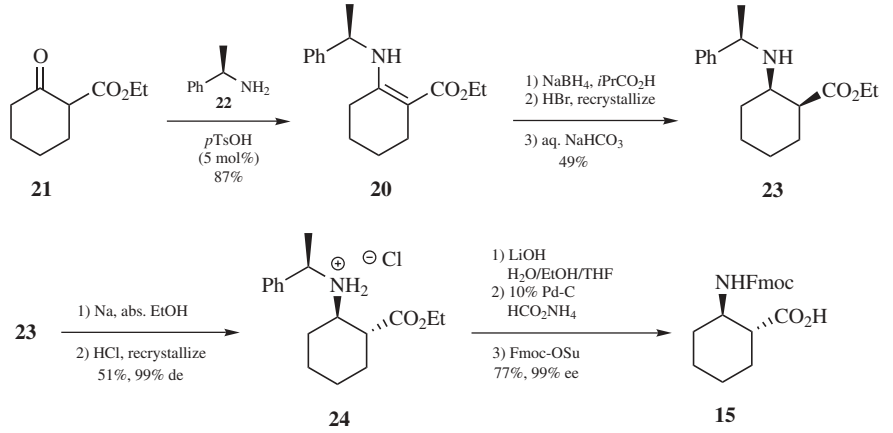
Other 6-constrained β-amino acids are useful to permit the display of a variety of functional groups on the 14-helical scaffold and to increase the aqueous solubility of β-peptides.[38,39] A protected derivative of (*R,R,R*)-DCHC was synthesized (Scheme 22.3) from intermediate **9** in the second-generation route to ACHC.[36] A precedented sequence of iodolactonization followed by elimination of iodide and saponification gave alcohol **16**.[35] The alcohol was then mesylated, and the mesylate was displaced with azide. The azide group was reduced and protected to give **17**. Protecting group manipulations gave *cis*-DCHC derivative **18**, which was epimerized to **19**.

Although the second-generation route to ACHC overcame the capricious nature of the resolution of **7**, the enzymatic resolution made only the (*R,R*)-enantiomer of **15** available. This enantiomer is incompatible, with respect to 14-helix formation,



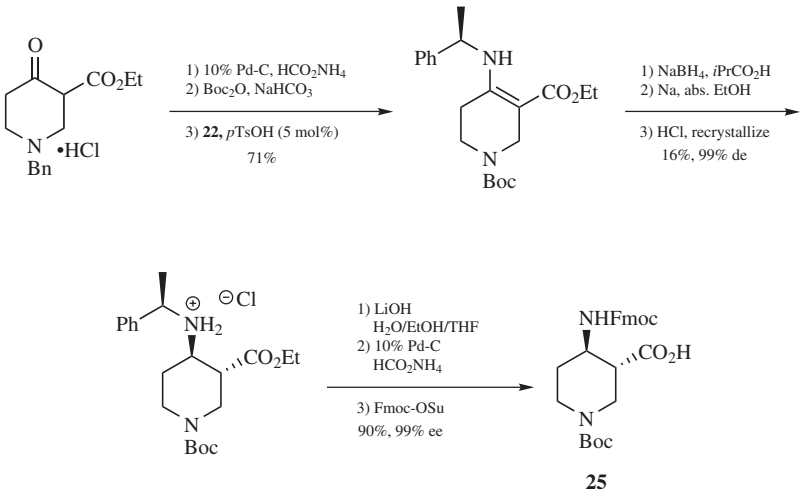
Scheme 22.3 Synthesis of protected DCHC monomer.[35,36] Structure **28** is referenced later in the text.

with β^3-amino acids prepared by homologation from (L)-(*S*)-α-amino acids. In response to this problem, Schinnerl et al. developed a third-generation route (Scheme 22.4) to ACHC,[39] based on work by Xu et al. on the synthesis of *cis*-ACHC[40] and precedented by work on racemic *trans*-ACHC.[41] Enamine **20**, formed from keto ester **21** and chiral amine **22**, was reduced with sodium borohydride to give **23**, which was purified from its three diastereomers by crystallization as the HBr salt. The free base **23** was regenerated and epimerized to give **24**, which was



Scheme 22.4 Third-generation synthesis of protected ACHC monomer.[39]

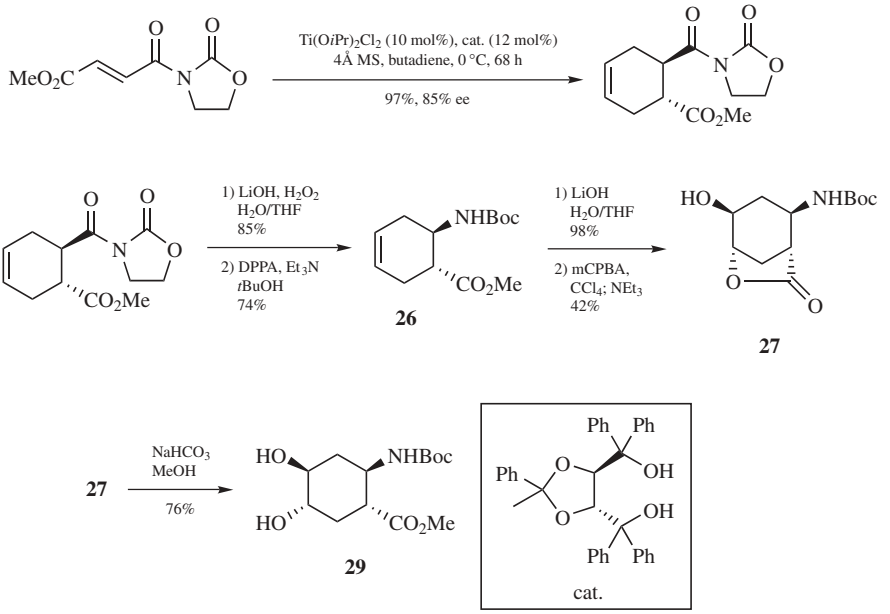
crystallized as the HCl salt. Protecting group interconversion with removal of the chiral auxiliary gave **15**. Because both enantiomers of **22** are commercially available, this synthesis leads to either ACHC enantiomer in >99% *ee*. Concurrent with the development of this third-generation route to ACHC, an analogous strategy was applied to the synthesis of APiC derivative **25** (Scheme 22.5).[39]



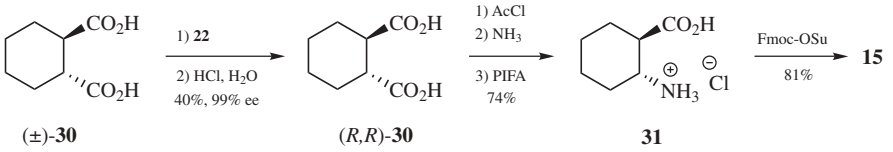
Scheme 22.5 Synthesis of protected APiC monomer.[39]

Wipf and Wang synthesized a dihydroxylated derivative of ACHC via a catalytic enantioselective Diels–Alder reaction (Scheme 22.6). Functional group interchange yielded **26**, which resembles intermediate **9** in our group's second-generation ACHC synthesis. Ester **26** was saponified to **27**, which resembles intermediate **28** in the DCHC synthesis (Scheme 22.3). Saponification of the lactone gave published product **29**. We have incorporated this residue, with appropriate protection, into 14-helical β-peptides (M. Schinnerl and T. L. Raguse, unpublished observations).

Other groups have also developed routes to ACHC and other 6-constrained β-amino acids. As part of their work on thrombin inhibitors, Harmat et al.[42] prepared all four diastereomers of ACHC by Curtius rearrangement of the corresponding chiral diacid mono methyl esters; however, the reference given for synthesis of the mono esters discussed only the cis diastereomers.[43] Berkessel et al. developed an elegant route to either enantiomer of ACHC (Scheme 22.7).[44] Cocrystallization of **30** with amine (*R*)-**22** gave (*R,R*)-**30**, which was converted to **31** in a three-step, one-pot procedure involving dehydration, opening of the anhydride with ammonia, and Hofmann rearrangement mediated by the hypervalent iodine reagent bis-(trifluoroacetoxy)iodobenzene. Protection with Fmoc-OSu yielded **15**. Kanerva

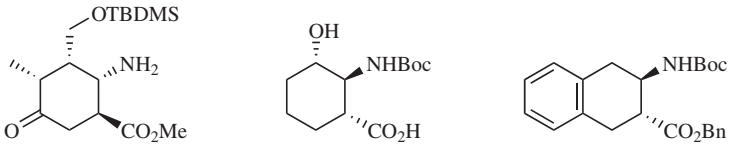


Scheme 22.6 Wipf and Wang's synthesis of a dihydroxy-ACHC derivative.

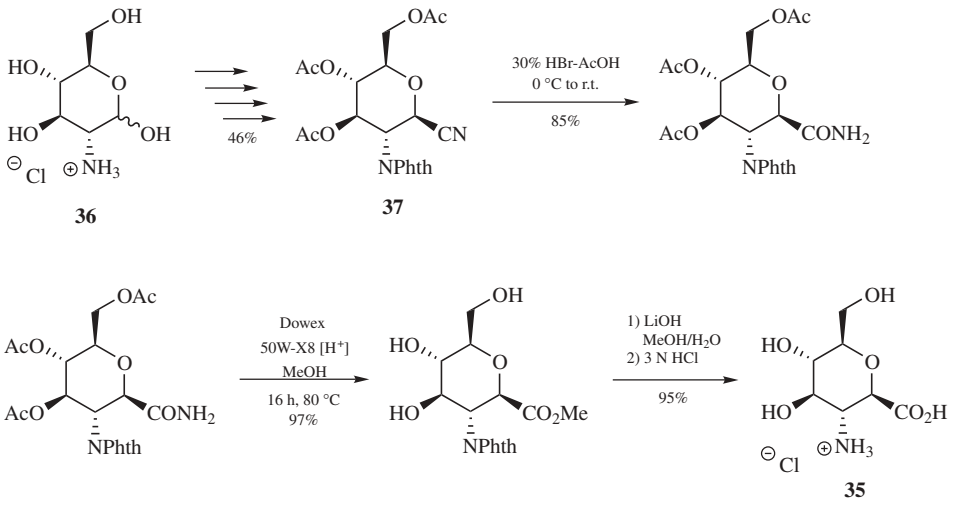


Scheme 22.7 Berkessel et al.'s route to protected ACHC monomer.[44]

et al. used lipase catalysis to resolve ACHC derivatives.[45] Bolm et al.[46] and Chen et al.[47] demonstrated that cinchona alkaloids mediate desymmetrization of succinic anhydride derivatives, providing an alternative point of access to intermediates such as **11** in enantiomerically enriched form.

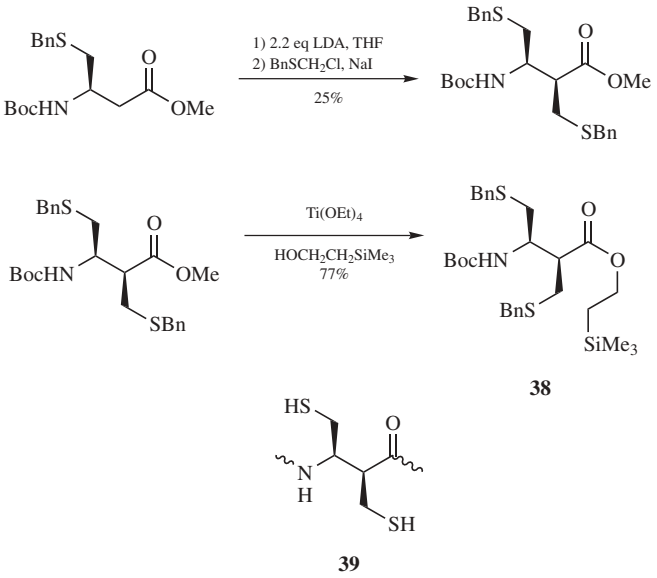


Several other syntheses of ACHC derivatives deserve mention here. Barluenga et al. have synthesized densely functionalized ACHC derivative **32** via Diels–Alder chemistry with a chiral auxiliary.[48] The 3-hydroxy derivative **33** was a by-product of Bunnage et al.'s synthesis of the putative structure of (−)-oryzoxymycin.[49] Bicyclic ACHC derivative **34** was synthesized by Kawahata and Goodman[50]; chirality was introduced with an asymmetric epoxidation. Other β-amino acids with a six-ring α,β-backbone cyclization include **35**. Suhara et al. homologated amino sugar **36**, via known intermediate **37**, to **35** in seven steps (Scheme 22.8).[51] Graf von Roedern et al. have also synthesized a derivative of **35**.[52]



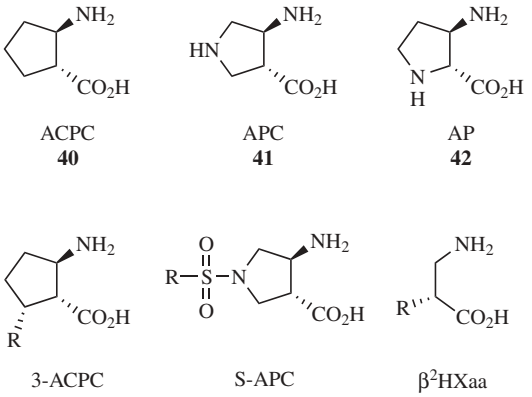
Scheme 22.8 Synthesis of monomer **35** as reported by Suhara et al.[51]

Seebach et al. have demonstrated that acyclic anti-disubstituted $\beta^{2,3}$-amino acids (as opposed to cyclic anti-disubstituted $\beta^{2,3}$-amino acids such as ACHC) are compatible with 14-helical structure.[53] Their procedure for diastereoselective synthesis of these amino acids relies on dilithiation of β^3-homoamino acid derivatives obtained by Arndt–Eistert homologation of α-amino acid derivatives, quenching with an alkylating agent, and subsequent separation of the diastereomeric products. One example of this procedure, of special interest will be mentioned here. Working from a β^3-HCys derivative, Seebach et al. generated precursor **38** via a three-step sequence. The silyl ethyl ester protecting group was removed with TBAF/THF immediately prior to coupling. Under oxidizing conditions, the fully deprotected **39** residue, dubbed $\beta^{2,3}$-HCCy, formed a six-membered 1,2-dithiane ring (Scheme 22.9).[54]



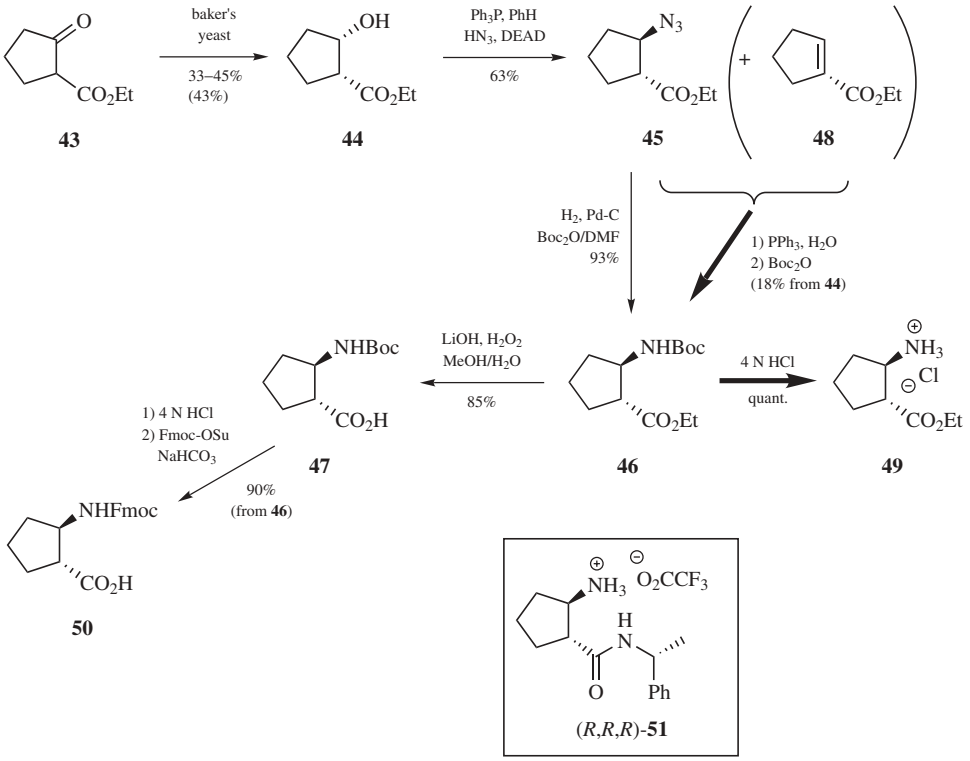
Scheme 22.9 Route of Seebach et al. to a 1,2-dithiane monomer precursor.[54]

22.2.2 5-Constrained Residues



Monomers employed by our group in the synthesis of 12-helical β-peptides have included *trans*-2-aminocyclopentanecarboxylic acid (ACPC) **40** and 3-substituted derivatives (3-ACPC), *trans*-3-aminopyrrolidine-4-carboxylic acid (APC) **41** and sulfonylated derivatives (S-APC), and *trans*-3-aminoproline (AP) **42**. Because our work with 12-helical β-peptides has come to involve the use of β^2-residues, our preferred route to β^2-residues is discussed in a subsequent section.

When our group first became interested in 5-constrained β-amino acids, the most practical available synthesis of the protected ACPC monomer was that developed

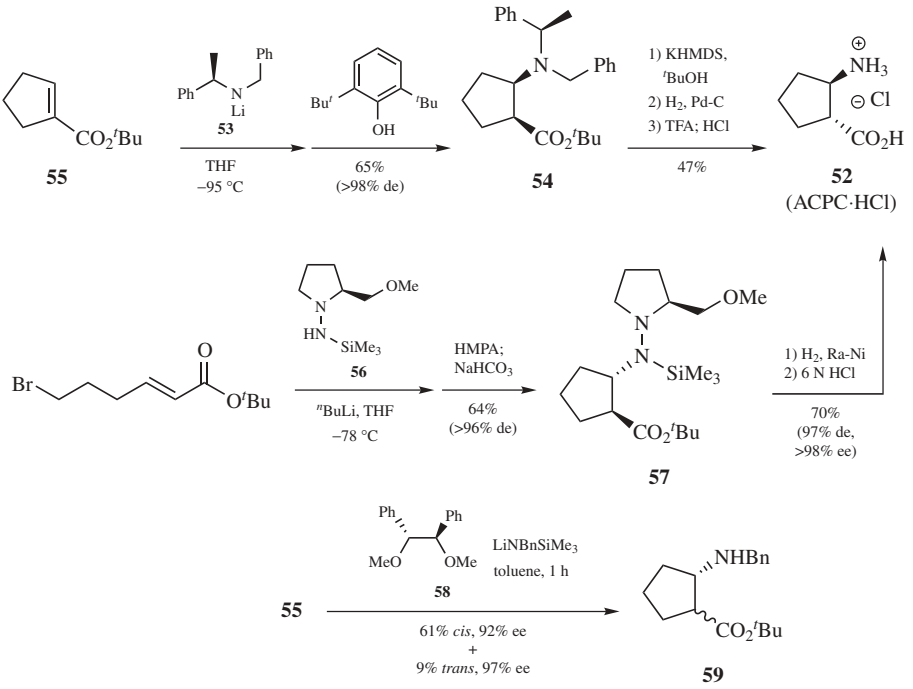


Scheme 22.10 First-generation synthesis of protected ACPC monomer,[55,56] with modifications by Appella et al. (bold reaction arrows, yields in parentheses)[57] and additions by LePlae et al.[58] Also shown: resolved intermediate **51** from Yamazaki et al.'s synthesis of ACPC monomer.[59]

by Herradón and Seebach[55] and Tilley et al.[56] (Scheme 22.10). The baker's yeast–mediated reduction of **43** to **44** was developed by the Seebach group[55]; the Mitsunobu displacement of *ent*-**44** (a side product from an enantioselective BINAP reduction) to *ent*-**45**, reduction and protection to *ent*-**46**, and hydrolysis to *ent*-**47** were reported by Tilley et al.[56] Appella et al., however, found that significant amounts of elimination product **48** contaminated **45**.[57] Staudinger reduction of the crude mixture followed by Boc protection gave isolable protected monomer **46**. Appella et al. followed the Tilley et al. conditions for hydrolysis to **47** and also generated **49** for use in solution-phase couplings. LePlae et al. later extended this route to give **50** for solid-phase applications.[58] The enantioselective yeast reduction allows access only to the (*R*,*R*)-ACPC monomer. This route is also complicated by large reaction volumes, tedious filtration and extraction, and difficult chromatographic separations.

Alternatives to this route already existed at the time of the work by Appella et al. For example, Yamazaki et al. resolved racemic **47** by amidation with (*R*)-amine **22**,

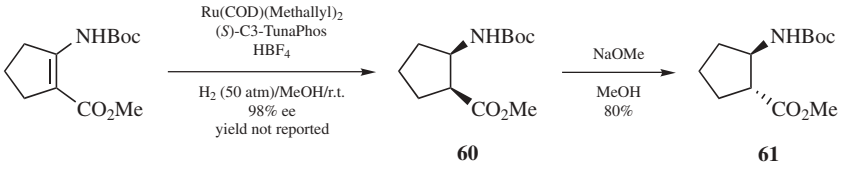
deprotection of the amine, and chromatographic separation of diastereomers (*R*,*R*,*R*)- and (*R*,*S*,*S*)-**51**.[59] Meanwhile, other groups were using chiral ammonia equivalents in Michael addition–based routes to ACPC·HCl (**52,** Scheme 22.11).



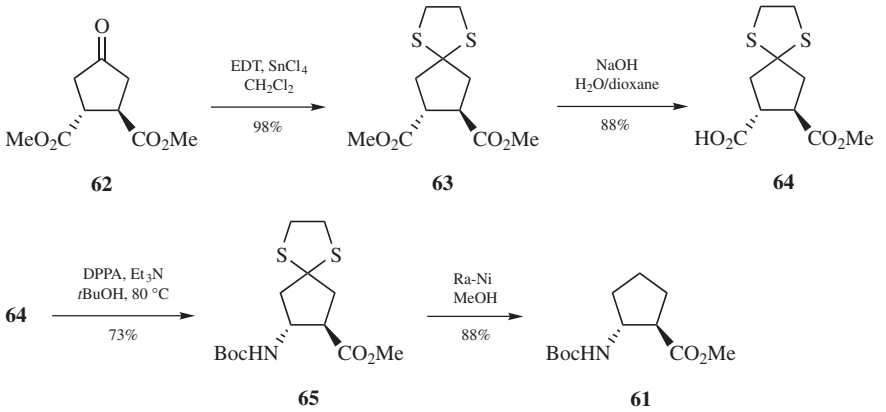
Scheme 22.11 Chiral ammonia equivalent routes to ACPC.[60–62]

Davies et al. used sterically hindered lithium amide reagent **53** to generate cis amino ester **54** from unsaturated ester **55**.[60] Epimerization α to the ester group and deprotection gave ACPC·HCl. Enders and Wiedemann used TMS-SAMP (**56**) as a chiral ammonia reagent (for 31 h at −78°C) in a tandem Michael addition–cyclization strategy, giving trans product **57**, which was deprotected to ACPC·HCl.[61] More recently, Doi et al. showed that **58** catalyzed asymmetric Michael addition of lithium *N*-benzyltrimethylsilylamide to **55**, giving cis/trans mixture **59**.[62] Related cis compound **60**, obtained by ruthenium-catalyzed hydrogenation of a β-(acetamido)acrylate, was converted to methyl ester **61** by epimerization of the α-carbon under basic conditions (Scheme 22.12).[63]

A later route (Scheme 22.13), developed by Nöteberg et al., took an alternative approach.[64] Ketone **62**, reported to be available in either enantiomeric series, was converted to thioketal **63**, and then one of the equivalent esters was hydrolyzed to give **64**, which was subjected to Curtius conditions. Amino ester **65** was desulfurized to give methyl ester **61**.

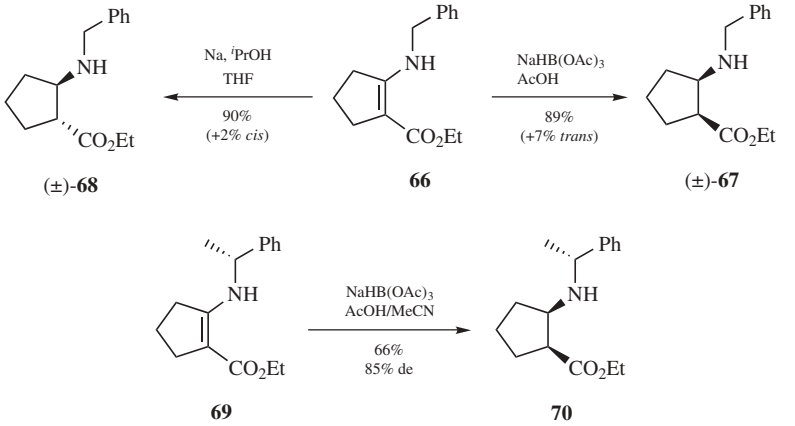


Scheme 22.12 Hydrogenation route to ACPC.[63]



Scheme 22.13 Chiral pool route to protected ACPC monomer.[64]

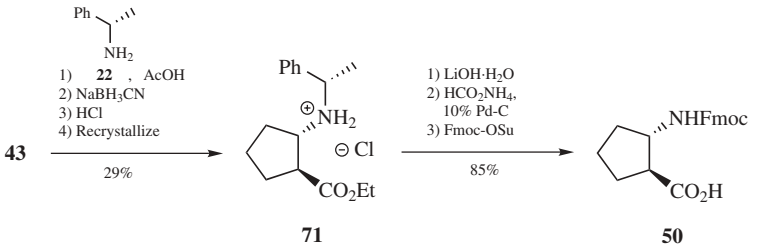
Work in Palmieri's laboratories (Scheme 22.14) inspired the development of our second-generation synthesis of ACPC. Bartoli et al. showed that benzyl imine **66**, derived from **43**, could be diastereoselectively reduced with sodium triacetoxyborohydride to give cis isomer **67** in 89% yield, with only 7% production of trans



Scheme 22.14 Diastereoselective routes to racemic[65] and optically active[41] ACPC derivatives.

diastereomer **68**.[65] Under similar conditions, Cimarelli et al. diastereoselectively reduced imino ester **69**, formed by imination of **43** with *ent*-**22**, to *cis*-β-amino ester **70**.[41] Sodium reduction of **66**, however, gave primarily trans product **68**.[65]

LePlae et al. took advantage of these developments and others to develop a new synthetic route to the protected ACPC monomer (Scheme 22.15).[58] Sodium cyanoborohydride reduction of enamine **69**, following the precedent of Lee et al.[66]

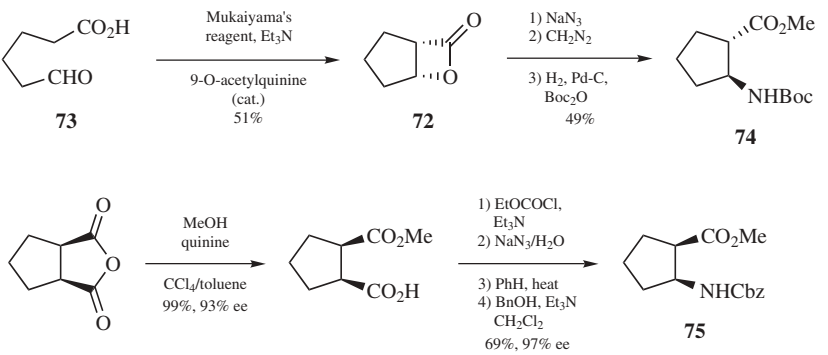


Scheme 22.15 Second-generation route to protected ACPC monomer.[58]

for the APC monomer (discussed below), gave chloride salt **71** in enantiomerically pure form after a three-step recrystallization. This route is easily scalable, requires no chromatography, and gives protected monomer **50** in either form.

It should be noted that the published procedure for conversion of **71** to **50** specifies hydrogenation with H_2.[58] We have since developed an improved procedure relying on transfer hydrogenation with ammonium formate, which gives a better yield, allows simpler purification, and is less hazardous.

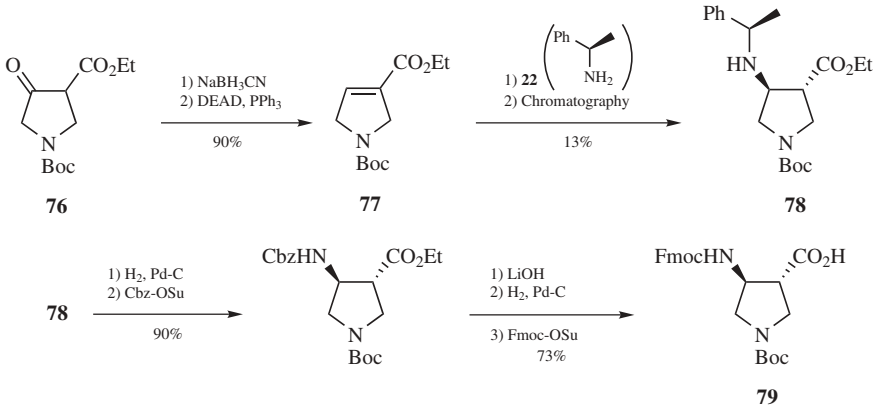
Alternative routes to ACPC have been reported (Scheme 22.16). Yokota et al.[67] converted **72**, accessible by catalytic asymmetric tandem aldol-lactonization from **73**,[68] into protected ACPC monomer **74**. Bolm et al.'s asymmetric anhydride



Scheme 22.16 Aldol-based route[67,68] and anhydride route[46,69] to ACPC monomer.

opening[69] has been used to generate protected cis monomer **75**,[46] which could provide *trans*-ACPC via epimerization.

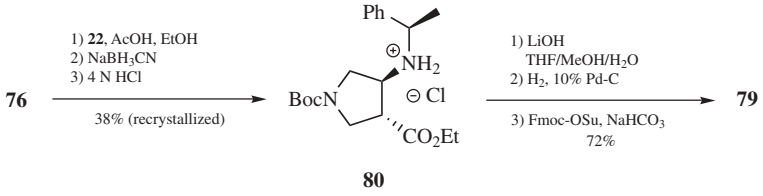
Our first-generation synthesis of the APC monomer[70] (Scheme 22.17) began from known β-ketoester **76**.[71] Wang et al.[70] reduced the ketone carbonyl following literature precedent for a related compound[71]; Mitsunobu elimination gave **77** (similar to undesired ACPC synthesis by-product **48** in Scheme 22.10). In contrast



Scheme 22.17 First-generation route to protected APC monomer.[70]

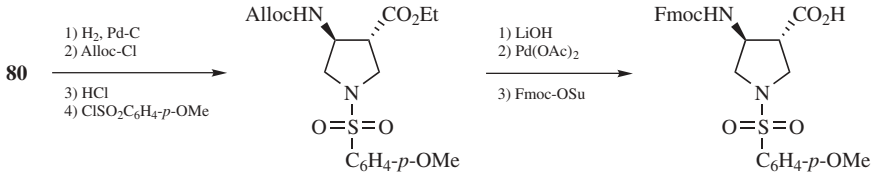
to the ACPC synthesis in Scheme 22.10 but similarly to that in Scheme 22.11, the achiral unsaturated intermediate was a substrate for enantioselective Michael addition by chiral amine **22** to provide **78**, analogous to ACPC intermediate **54**. Intermediate **78** was separated chromatographically from the other three diastereomers produced in this reaction. Monomer **79**, suitable for solid-phase oligomer synthesis, was obtained via a series of protecting group manipulations.

The inefficiencies of this first-generation route as well as the scale-limiting chromatographic step spurred the development of a shorter, more scalable route (Scheme 22.18) [66] that is directly analogous to the second-generation route to Fmoc-ACPC (Scheme 22.15). Lee et al.[66] reduced the enamino ester formed from **76** and **22** to give crystalline hydrochloride salt **80** after workup. Removal of the chiral auxiliary and protecting group manipulation gave **79** without the need for chromatographic separation.



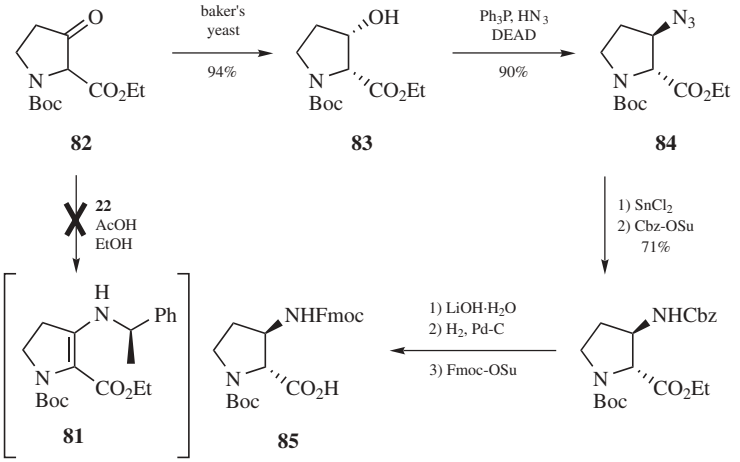
Scheme 22.18 Second-generation synthesis of protected APC monomer.[66]

Sulfonylation of the ring nitrogen of APC provides a class of side-chain-bearing β-peptide building blocks that we designate S-APC monomers. S-APC monomers are prepared from intermediate **80** via a route that includes multiple protecting group manipulations (Scheme 22.19).[72] Other S-APC derivatives, including the *S*-isopropyl and *S*-methyl derivatives, have been synthesized by similar routes (Dr. H.-S. Lee, unpublished results).



Scheme 22.19 Conversion of **80** to a representative S-APC monomer.[72]

AP, another heterocyclic β-peptide building block, is an isomer of APC. The AP monomer, unfortunately, could not be synthesized by routes analogous to our second-generation syntheses of ACPC and APC. Allylic strain apparently prevents the formation of enamino ester **81** from **82** and **22**, even under forcing conditions. On the other hand, a baker's yeast reduction of **82** (Scheme 22.20), following

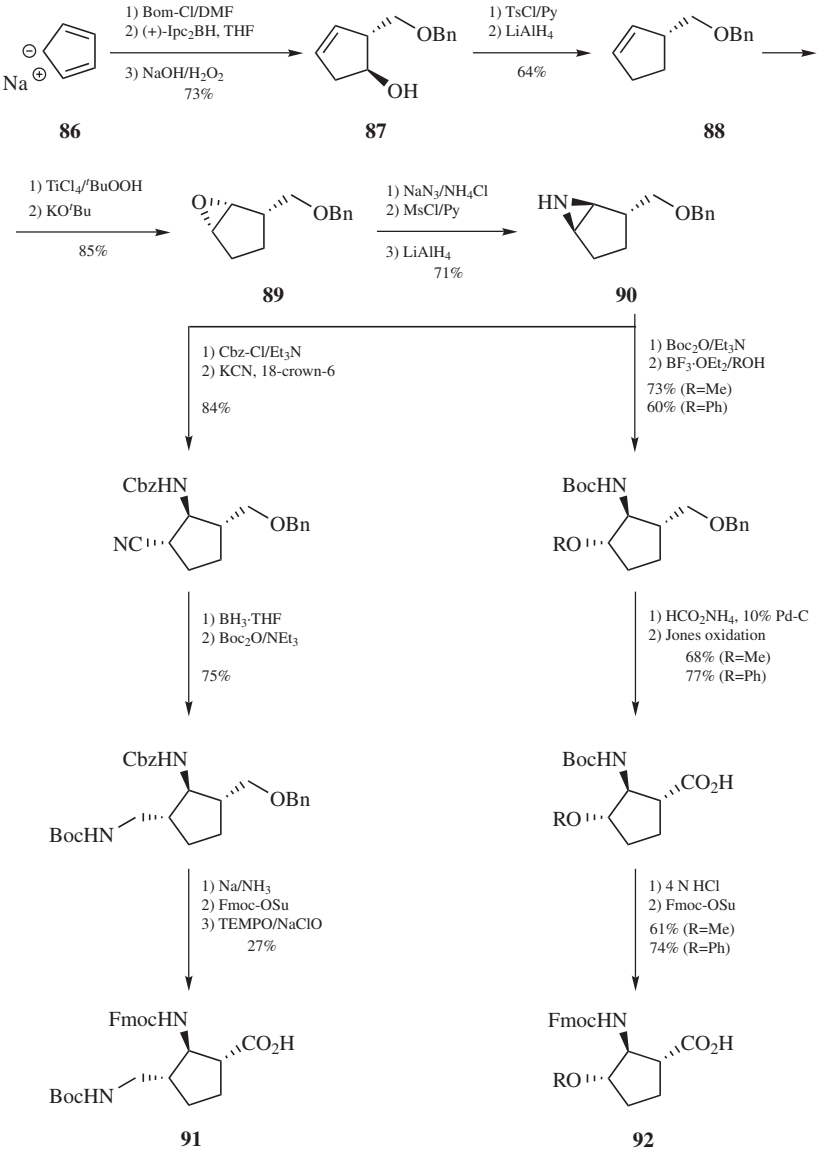


Scheme 22.20 Synthetic route to protected AP monomer.[74]

precedent,[73] gave **83**, which was carried on to azide **84**, by analogy to the Tilley et al.[56] route to ACPC. Elimination is disfavored in this system, presumably because of product allylic strain. Tin chloride reduction and protecting group manipulation yielded appropriately protected monomer **85**.[74] Whereas **50** and **79** are available in either enantiomeric series, via **22** and *ent*-**22**, monomer **85** is currently accessible only as the (*R,R*)-enantiomer. It should be noted that, although the AP residue used for synthesis of β-peptide oligomers was only 89% *ee*, in all cases the

desired β-peptide diastereomer was isolated as the single major product.[74] The presumed inability of stereochemically heterogeneous β-peptide impurities to form 12-helical structure may have increased their chromatographic separability from the desired product.

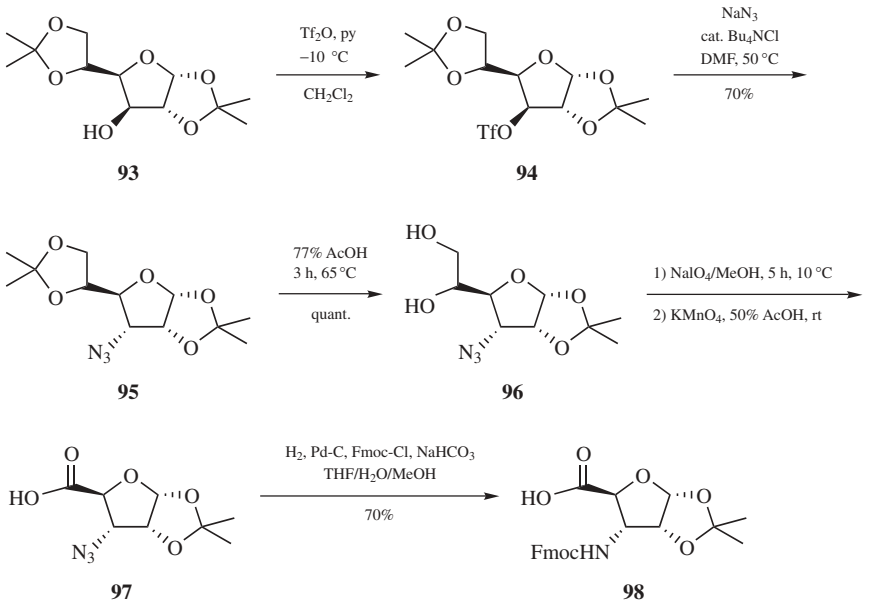
Woll et al. developed a stereoselective route to 3-substituted ACPC derivatives (3-ACPC) from sodium cyclopentadienide **86** (Scheme 22.21).[75] Because the borane



Scheme 22.21 Enantioselective route to protected 3-ACPC monomers.[75]

used to break the symmetry of alkylated **86** is available in either enantiomeric series, this route can lead to either enantiomer of **87** and hence to both (2*R*)- and (2*S*)-series ACPC derivatives. Reduction to **88** followed by epoxidation to **89** and conversion of the epoxide to aziridine **90** establishes the required three contiguous stereocenters while introducing the nitrogen atom. Depending on the type of functional group desired at the 3-position, the protected aziridine may be opened with cyanide or an alcohol. Redox and protecting group manipulations can then give amino derivative **91** or alkoxy derivative **92**.

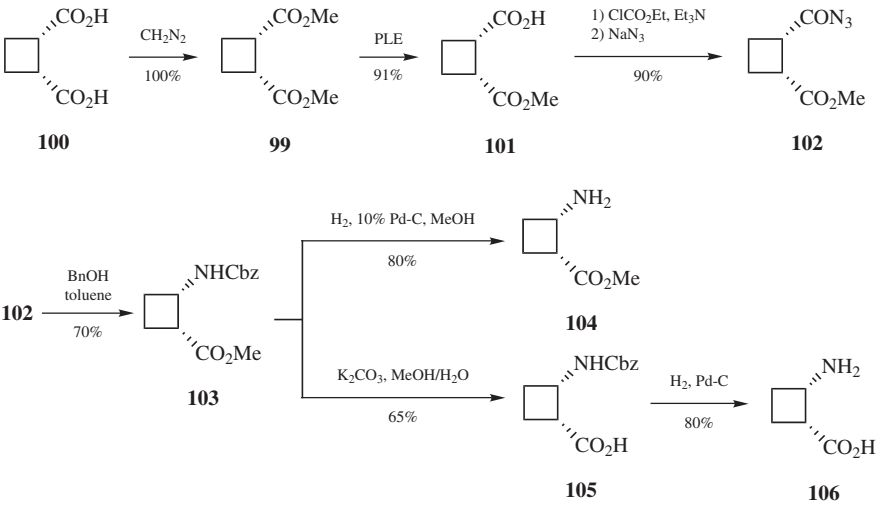
Before leaving the synthesis of 5-constrained residues, we note that some amino furanose derivatives are β-amino acids. Impressive routes have been devised to overcome some of the chemoselectivity issues inherent in transformation of the densely functionalized sugar precursors.[77] Other routes, such as a two-step route from AZT to one such amino furanose derivative,[78] may be of particular interest to researchers interested in nucleobase-bearing β-peptides. A recent synthesis by Gruner et al.[76] provides access to a protected sugar-derived amino acid (Scheme 22.22). The free hydroxyl of diacetone glucose **93** was activated as triflate **94**, then displaced with azide to give **95**. Selective deprotection of the non-ring-fused acetonide was achieved with acetic acid, and diol **96** was oxidized to **97**. Simultaneous azide reduction and Fmoc protection gave monomer **98**.



Scheme 22.22 Route to a sugar amino acid.[76]

22.2.3 4-Constrained Residues

Martín-Vilà et al. reported the first synthesis of a 4-constrained β-amino acid in 1998.[79] Their route (Scheme 22.23) relied on the enzymatic resolution of meso diester **99**, obtained by treatment of **100** with diazomethane. (A later report detailed



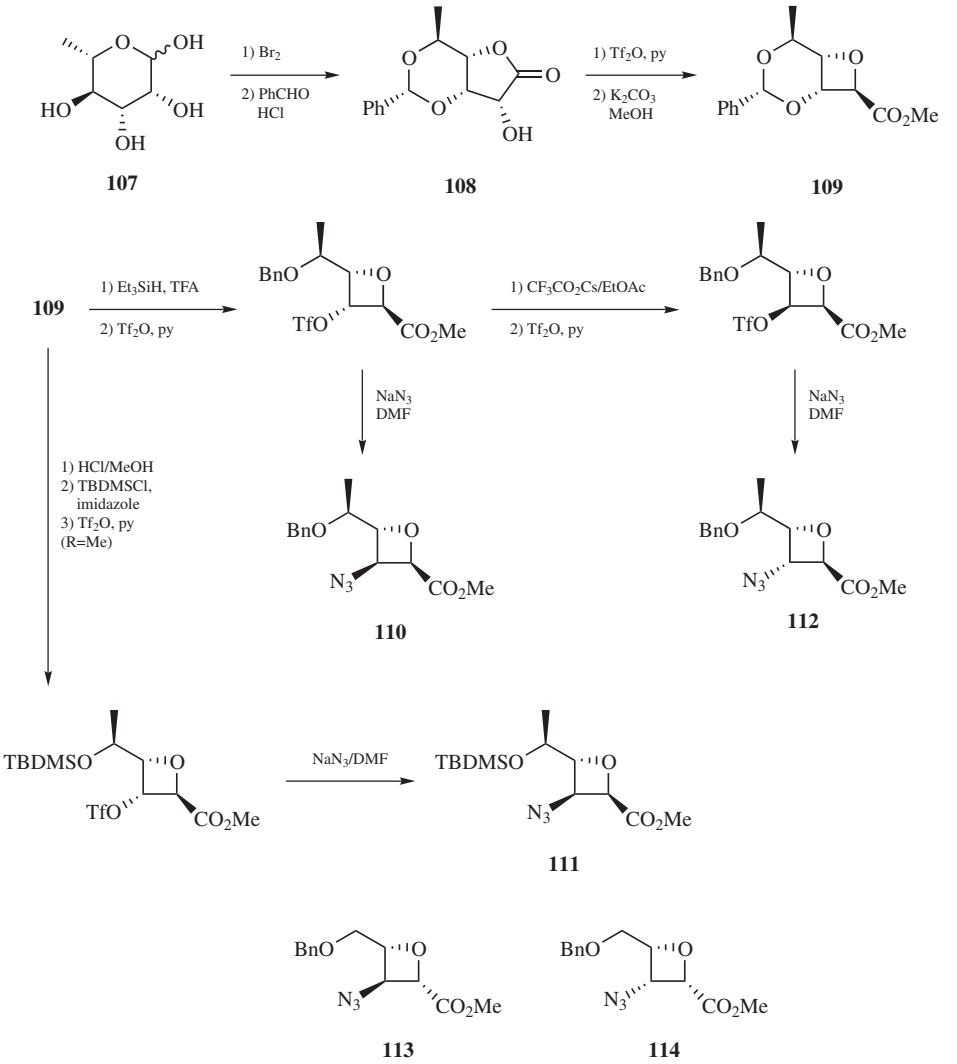
Scheme 22.23 Route to *cis*-4-constrained residue.[79]

a protecting group manipulation that converted **101** to the *t*-butyl hemi ester of the other acid moiety, providing access to the enantiomeric β-amino acid.[80]) Acyl azide **102** was subjected to Curtius rearrangement to give **103**. This bis-protected intermediate could then be deprotected to give **104**, **105**, or **106**.

Oxetane-constrained β-azido esters were synthesized in a stereodivergent fashion by Barker et al. as a precursor to β-peptides (Scheme 22.24).[81] Rhamnose **107** was oxidized and protected to **108**, then transformed to oxetane **109**. Protecting group manipulation and functional group interchange, with or without conformational inversion, yielded *cis*-azido esters **110** and **111** and *trans*-azido ester **112**. The same transformations, performed on xylose (which lacks the methyl group of rhamnose and has inverted stereochemistry at C-3 and C-4), gave the nor-(C-1-epi) monomers **113** and **114**.

22.2.4 *N*-Constrained Residues

Although hydrogen bonding is the driving force for the most common types of α-protein secondary structure, sequences rich in the secondary amino acid proline



Scheme 22.24 Synthesis of oxetane β-azido esters.[81]

form non-hydrogen-bonded helical structures, such as polyproline I and II helices.[82] These structures rely on the residues' inherent conformational rigidity to enforce a particular conformation. This alternative driving force for folding has provided the impetus for studies on oligomers of β-amino acids that cannot form hydrogen bonds; because these residues are constrained by a ring involving the amide nitrogen, we will refer to them as "*N*-constrained."

β-Amino acid monomers of interest for the study of non-hydrogen-bonded secondary structure include β^3-homoproline (β^3HPro, Fig. 22.5), nipecotic acid

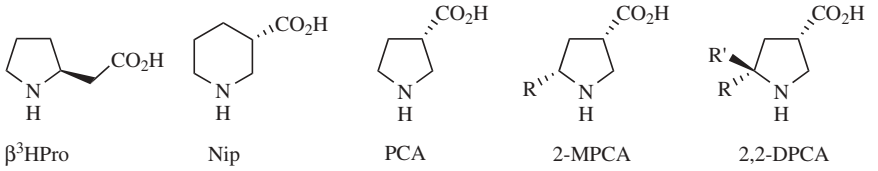
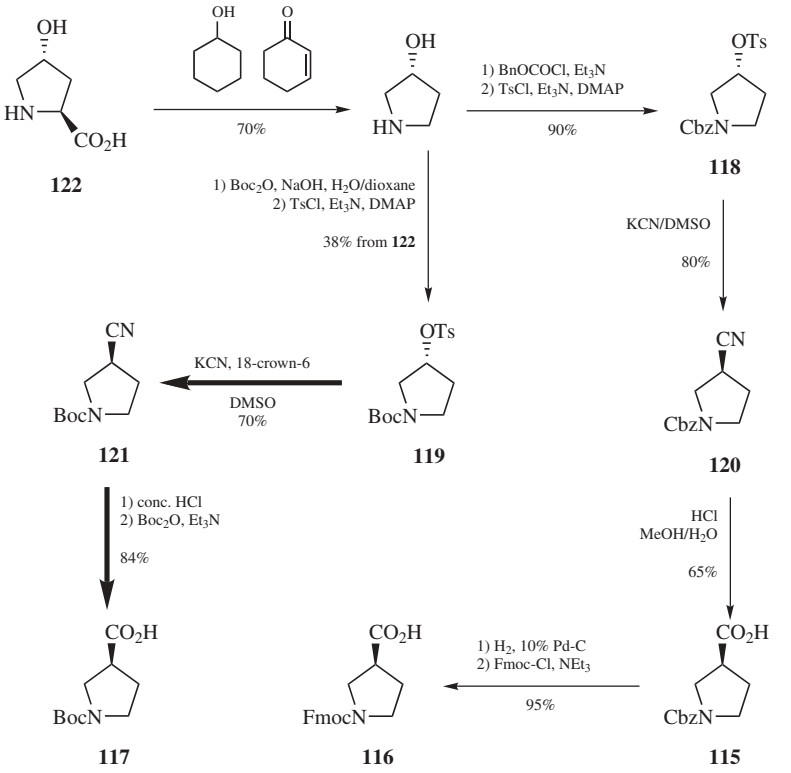


Figure 22.5 *N*-constrained residues.

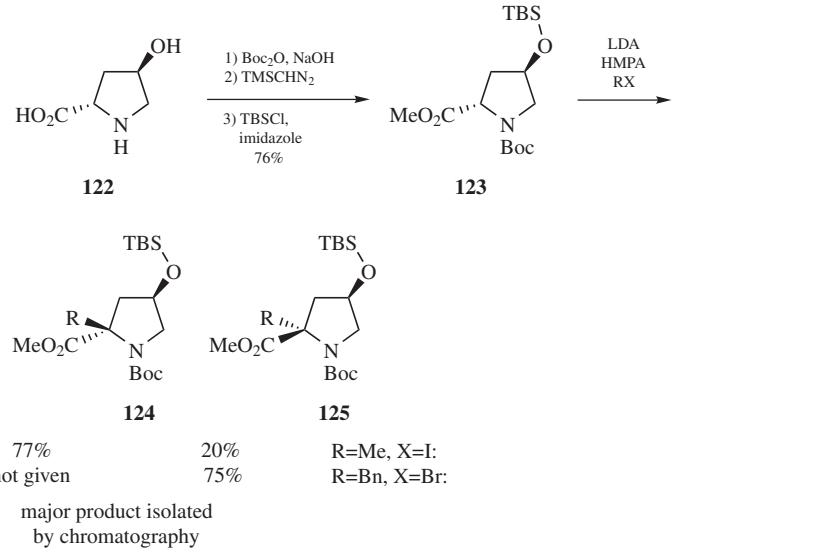
(Nip), and pyrrolidine-3-carboxylic acid (PCA).[11,83] The β^3HPro monomer is accessible in a straightforward fashion via Arndt–Eistert homologation of proline.[84] Racemic Nip-OEt may be resolved using tartrate,[85] or Nip itself may be resolved by recrystallization with camphorsulfonic acid.[10] PCA requires a multistep route for synthesis. Our group has used the route of Klein et al.[86] to prepare protected (*S*)-PCA monomers **115**, **116**, and **117** from 4-hydroxy-proline (Scheme 22.25).[87]

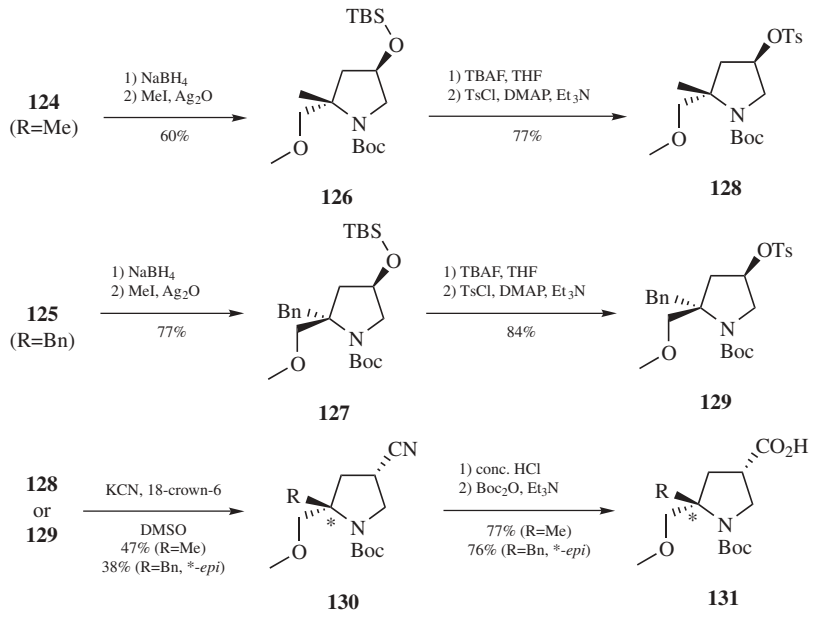


Scheme 22.25 Routes to *N*-protected PCA monomers. The route of Klein et al.[86] is shown with thin arrows; bold arrows are Huck's application of this route to generate the Boc-protected monomer.[87]

The key transformation in this route is displacement of the tosylate in **118** or **119** with cyanide anion to give **120** or **121**, respectively.

To restrict rotation around the amide bond of PCA-based oligomers, PCA derivatives with one or two substituents were synthesized via a divergent strategy (Scheme 22.26).[87] Formally, these monomers are described as 2-mono- and

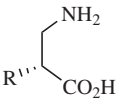




Scheme 22.26 Synthesis of substituted PCA monomers.[87]

2,2-disubstituted pyrrolidine-4-carboxylic acids (2-MPCA and 2,2-DPCA). Beginning from **122**, triple protection yielded **123**, which could then be alkylated[88] with alkyl, allyl, or benzyl (opposite diastereoselectivity) halides to give diastereomeric mixtures of **124** and **125**, which were separable by column chromatography. Reduction of the ester and silver-promoted alkylation under nonbasic conditions (to avoid formation of a cyclic carbamate) generated compounds exemplified by **126** and **127**. These intermediates were *O*-deprotected and tosylated to **128** and **129**, then allowed to react with potassium cyanide to give **130**. Acid hydrolysis and reprotection gave disubstituted PCA monomers **131**.

22.2.5 β^2-Residues



β^2HXaa

Our studies of 12-helical β-peptides have led us to investigate synthetic routes to β^2-amino acids. Multiple methods for the synthesis of β^2-amino acids have been reported. The majority of these methods rely on enolate formation from a carboxyl group bearing a chiral auxiliary (amide or ester). Major examples may be classified by disconnection (Fig. 22.6) or by the nature of the chiral auxiliary (Evans oxazolidinone,[89–91] Oppolzer sultam,[92] pseudoephedrine,[93] pyrimidinone[94]). The asymmetric C–H activation strategy of Davies and Venkataramani, which employs a chiral catalyst rather than a chiral auxiliary, is quite distinct from these routes and provides access to aryl- or vinyl-substituted β^2-amino acids.[95] More recently,

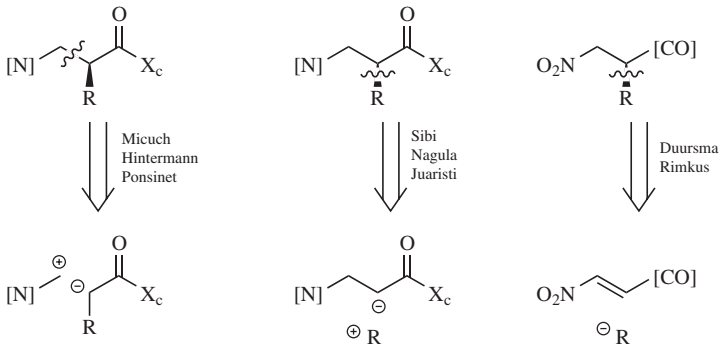
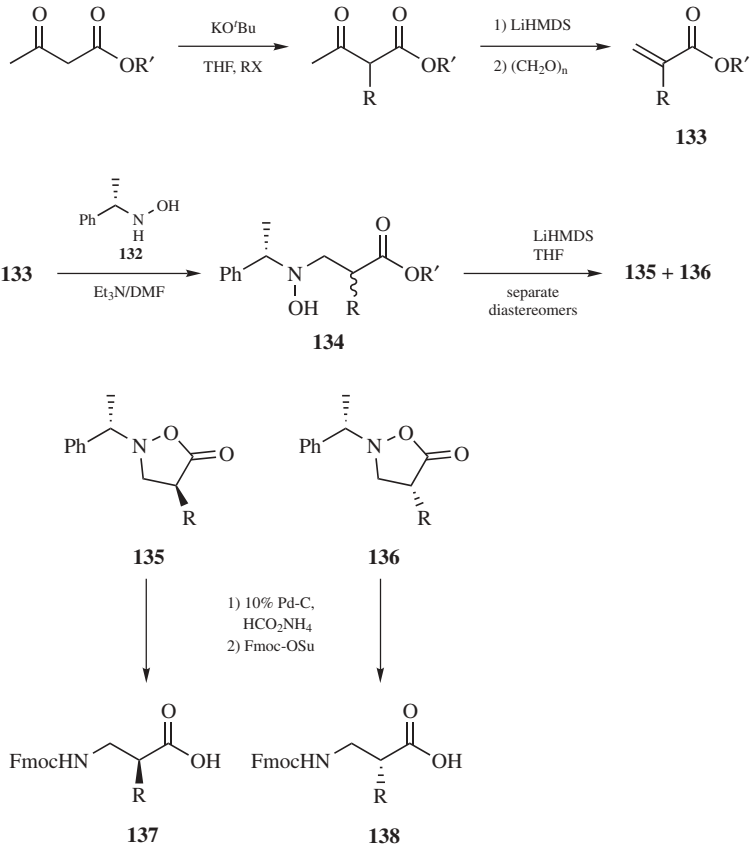


Figure 22.6 Classification of enolate-based routes to β^2-amino acids of Micuch and Seebach,[89] Hintermann and Seebach,[90] Ponsinet et al.,[92] Sibi and Deshpande,[91] Nagula et al.,[93] and Juaristi and Quintana,[94] and the Michael addition routes of Duursma et al.[96] and Rimkus and Sewald.[97] [CO], carboxylate precursor (acetal or ester).

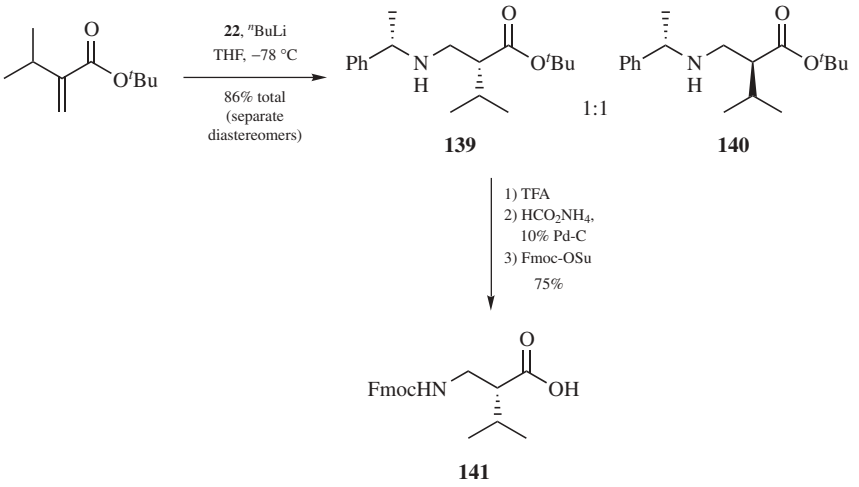
Duursma et al.[96] and Rimkus and Sewald[97] reported highly enantioselective routes via catalytic addition of dialkylzinc reagents to nitroolefins.

Removal of the chiral auxiliaries employed in the methods summarized in Figure 22.6 often requires harsh conditions that can lead either to epimerization at the newly generated stereocenter or to loss of acid-sensitive *t*-butyl-based side-chain protecting groups. Lee et al.[98] (Scheme 22.27) employed hydroxylamine **132**[99] as a chiral ammonia equivalent to develop a new route to β^2-amino acids.



Scheme 22.27 Chiral hydroxylamine addition route to Fmoc-β^2HXaa-OH.[98]

The α-alkylacrylates **133** were generated by alkylation of acetoacetate esters followed by deacylative methylenation. Michael addition of **132** gave adducts **134**, which were cyclized to a mixture of diastereomeric isoxazolidinones **135** and **136** (dr ∼ 1.5 : 1). These diastereomers have proven to be easily separable by chromatography in every case examined to date. Hydrogenation served both to remove the chiral auxiliary and to cleave the N–O bond, leading after protection to the



Scheme 22.28 Methylbenzylamine addition route to Fmoc-β^2HVaa-OH.[98]

β^2-homoamino acid derivatives **137** and **138**; **137** is in the chiral series compatible with a left-handed 12-helix. An alternate route to β^2HVal (Scheme 22.28) involved use of chiral amine **22** to generate the diastereomeric Michael adducts **139** and **140**. Although no diastereoselectivity was observed in this addition, the adducts were separable by chromatography, providing access in reasonable overall yield to Fmoc-protected (*R*)-β^2HVal **141** and its (*S*)-enantiomer (not depicted).

22.2.6 *syn*-Disubstituted Residues

Synthetic routes to *syn*-disubstituted residues are many and varied. We will provide a brief summary and classification of these routes here (Fig. 22.7), with a more detailed treatment of routes that our group has used successfully in the synthesis of *syn*-$\beta^{2,3}$-amino acids.

Enantioselective routes to *syn*-$\beta^{2,3}$-amino acids may be classified by disconnection. Because two stereocenters must be established, these syntheses pose a significant challenge. The C-2 and C-3 stereocenters may be set simultaneously by forming the bond between them[100,101] or by stereoselective hydrogenation of an unsaturated ester.[102] The C-2 stereocenter is frequently introduced last, by alkylation[15,53,103–105] or protonation of an enolate.[106] When the C-2 stereocenter is fixed first with enolate chemistry, the C-3 stereocenter can be installed subsequently using radical chemistry.[107] In a diastereoselective synthesis, Minter et al. fixed C-2 with a cycloaddition to a chiral allylic alcohol starting material, then set C-3 reductively.[108] Some of these routes, however, are limited in scope or proceed with poor stereoselectivity. Others may involve chiral auxiliaries or protecting groups that, for removal, require basic conditions (rendering C-2 prone to epimerization) or acidic conditions (incompatible with common *t*-butyl side-chain protection).

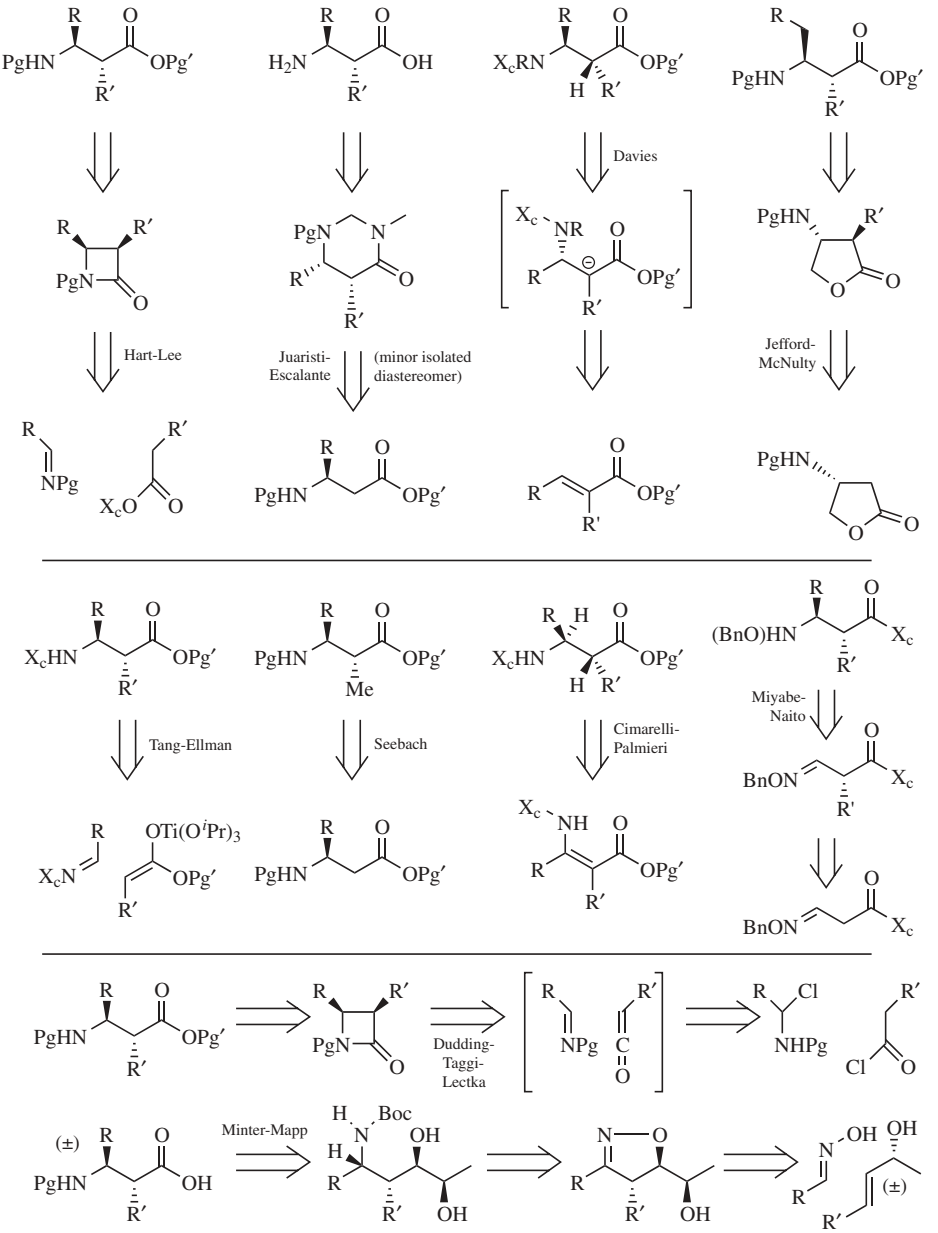
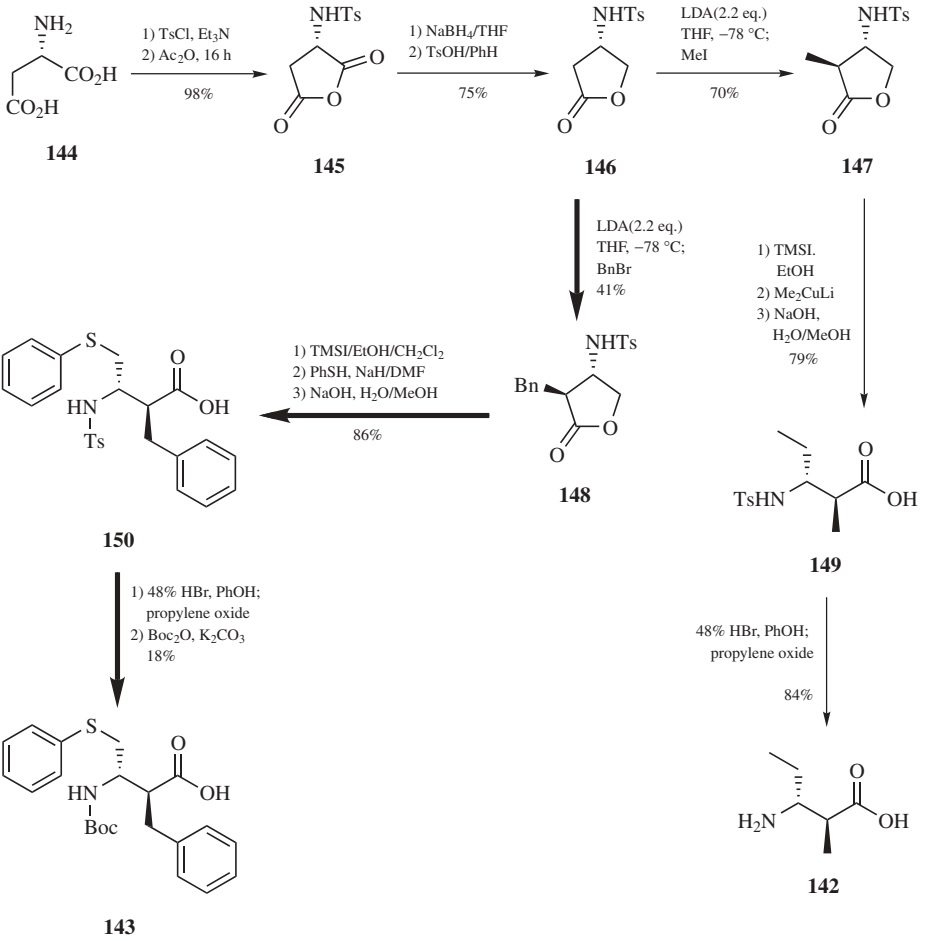


Figure 22.7 Retrosynthetic routes to *syn*-β[2,3]-amino acids of Hart et al.,[101] Juaristi and Escalante,[104] Davies et al.,[103,106] Jefford and McNulty,[105] Tang and Ellman,[100] Seebach et al.,[15,53] Cimarelli and Palmieri,[102] Miyabe et al.,[107] Dudding et al.,[109a] and Minter et al.[108]

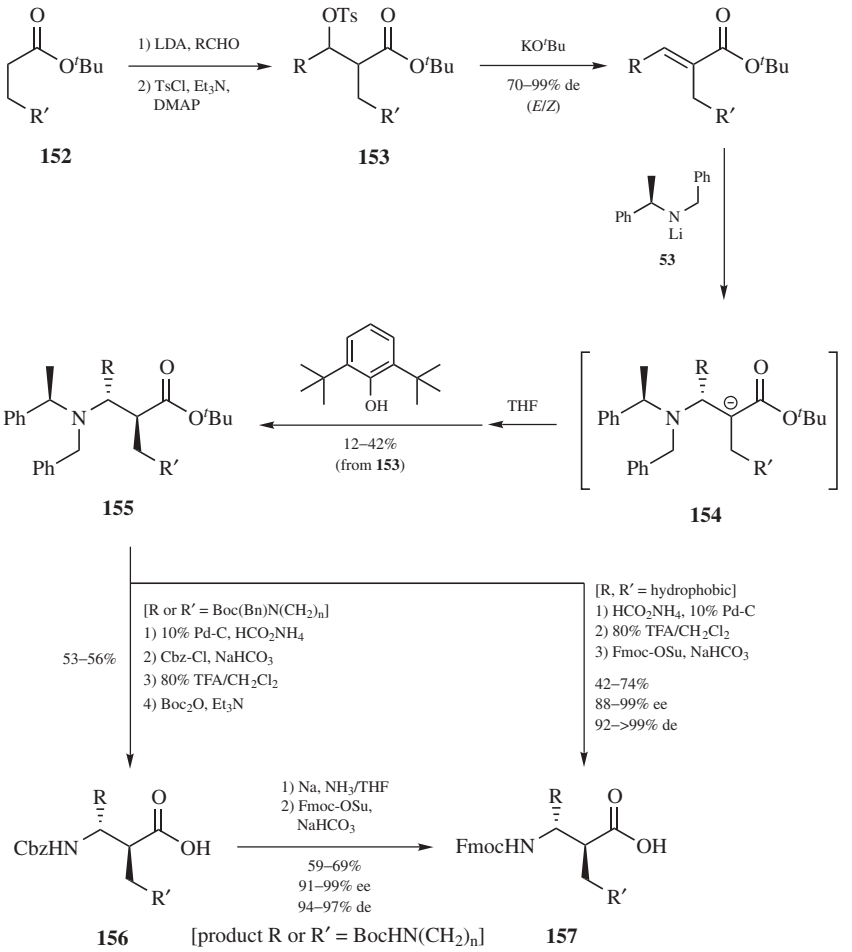


Scheme 22.29 Jefford–McNulty route to **142**,[105] with divergent route of Krauthäuser et al. to **143** (bold arrows).[26]

For our own initial studies of sheet-forming β-amino acids, we utilized the route of Jefford and McNulty[105] to **142**, modifying it to provide **143** as well (Scheme 22.29). (L)-Aspartic acid **144** was protected and cyclized to anhydride **145**, which was reduced regioselectively to yield **146**. This intermediate could then be alkylated to **147** or **148**. These lactones were opened by S_N2 reaction with iodide, and the resulting iodides were displaced with lithium dimethylcuprate (**147** → **149**) or thiophenolate (**148** → **150**), then hydrolyzed to the free acids. Protecting group manipulations gave the final products.

Diastereomeric contamination in intermediate **147** and low yields of **143** as well as similar difficulties encountered when attempting to extend this chemistry to syn-disubstituted monomers with other side chains spurred us to search for a superior

synthetic method. Ultimately, the route developed by Davies et al.[103,106] was selected for further study. This route relies upon diastereoselective protonation of an enolate generated by Michael addition of a chiral ammonia equivalent to an α-alkyl-α,β-unsaturated ester (see Scheme 22.11 for Davies et al.'s application of this route to a 5-constrained residue). Langenhan and Gellman[110] used a dehydrative aldol strategy to generate unsaturated esters **151** from substituted *t*-butyl propionates **152** via tosylation to **153** and elimination (Scheme 22.30). Addition



Scheme 22.30 Langenhan's application of the Davies route to syn-disubstituted monomers.[110]

of chiral ammonia equivalent **53**, as employed by Davies et al., gave enolate adduct **154**, which was protonated by 2,6-di-*t*-butylphenol to give **155**.

Because the conjugate addition did not proceed in the presence of a side-chain carbamate proton, side-chain amines were double protected with a *t*-butyl

carbamate (Boc) and a benzyl group. Removal of the chiral auxiliary and protecting group manipulation was straightforward for hydrophobic side chains, but successful deprotection of the doubly protected amine required a convoluted six-step procedure via **156**. Nevertheless, this route provides *syn*-$\beta^{2,3}$-amino acids **157** in sufficient quantity and of sufficient stereochemical purity for β-peptide synthesis.

22.3 β-PEPTIDE SYNTHESIS

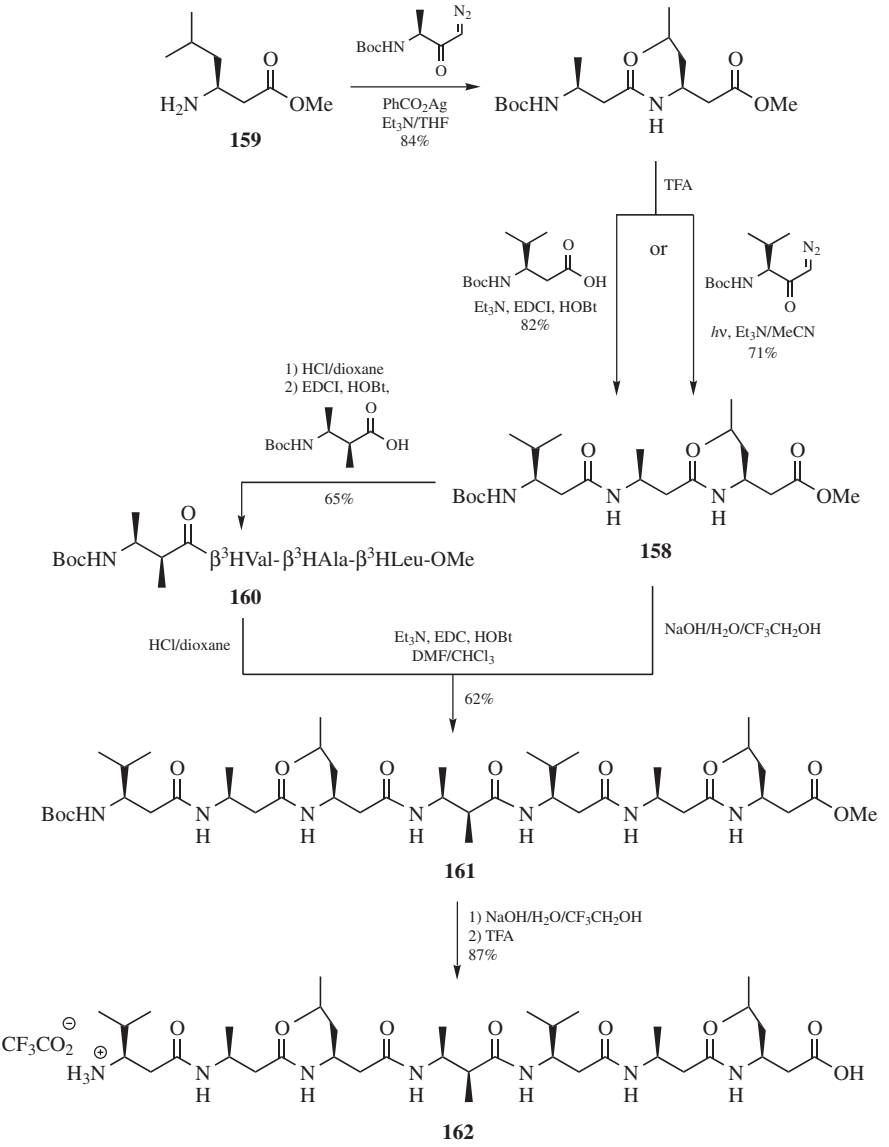
Multiple strategies exist for the synthesis of α-peptides.[111] These various strategies may also be applied to β-peptide synthesis. Some of the decisions to be made in planning the synthesis of a β-peptide are as follows:

- Sequential versus convergent synthetic strategy
- Solution-phase versus solid-phase chemistry
- Protecting group scheme
- Final deprotection (and resin cleavage) conditions and purification
- Coupling and deprotection conditions:
  a. Coupling reagent
  b. Additives
  c. Stoichiometry (of coupling reagent, amino acid, additives)
  d. Solvent
  e. Coupling reaction time
  f. Temperature
  g. Deprotection reagent
- Intermediate purification conditions (resin washing for solid-phase synthesis, extraction/chromatography for solution-phase synthesis)
- ''Difficult residue'' coupling and deprotection conditions

As of this writing, no comprehensive study of these variables has been reported in the Medline- or Chemical Abstracts–covered literature. Here we will anecdotally discuss the development of β-peptide synthesis, with special attention paid to syntheses of β-peptides containing constrained residues.

22.3.1 Solution-Phase Synthesis

Aside from early polymerization work,[112] the first reported syntheses of β-peptide oligomers were performed in solution by a convergent strategy using a Boc protection scheme. Seebach et al.[12] prepared Boc-β^3HVal-β^3HAla-β^3HLeu-OMe tri-β-peptide **158** (Scheme 22.31), not through traditional amide coupling chemistry, but by use of a β-amino acid or β-peptide free amine (e.g., **159**) as the nucleophile to capture the ketone generated in the Wolff rearrangement step of an Arndt–Eistert homologation. Because the side chains did not require protection,



Scheme 22.31 Syntheses of trimer **158**[12] and heptamer **162**[53] by Seebach et al. via standard coupling conditions or Wolff rearrangement conditions.

and because strongly basic conditions would not lead to epimerization at the β^3-position, solution-phase fragment coupling could be carried out using Boc protection for the amino terminus and methyl ester protection for the carboxyl terminus. Protected tetra-β-peptide **160** and hepta-β-peptide **161** were poorly soluble in standard peptide coupling solvents, requiring further reactions to be

carried out in trifluoroethanol (TFE) and impairing yields; solubility was better for deprotected β-peptide **162**.[53]

Later solution-phase syntheses in the Seebach group, including the synthesis of an all-anti hepta-$\beta^{2,3}$-peptide,[15] were carried out entirely by standard amide bond formation. Because epimerization was reported at C-2, triethylamine was replaced by the weaker base *N*-methylmorpholine in the coupling conditions. Also, the trifluoroacetate salts produced by *N*-deprotection were preneutralized. Finally, to obviate the need for strongly basic deprotection conditions, the C-terminal protecting group was changed from methyl ester to benzyl ester, which was removed by hydrogenolysis.

Appella et al.[9] used a convergent solution-phase strategy, with Boc *N*-protection and benzyl ester C-protection, to synthesize a hexamer of ACHC residues via dimer and tetramer fragments. Because Boc-$(ACHC)_6$-OBn was poorly soluble in eluents compatible with silica gel, silicic acid chromatography was employed for the purification of this hexamer. Appella et al. also synthesized the related hexa-β-peptide H-$(DCHC\text{-}ACHC)_3$-OH.[57] Because monomer **19** had Boc "side-chain" protection and Cbz "main-chain" protection, a methyl ester was used as the C-terminal protecting group. Coupling of Cbz-DCHC(Boc)-OH to H-ACHC-OMe gave a dimer soluble only in TFE, and hydrolysis of the methyl ester required forcing conditions. Dimer–dimer coupling gave disappointing yields; in a related system, fragment coupling using a Cbz strategy also proceeded poorly past the trimer stage (T. Raguse and P. R. LePlae, unpublished observations). Ultimately, **14** and **19** were successfully used in a sequential solution-phase strategy. For this synthesis using EDCI·HCl as coupling agent, yield showed a strong dependence on acidity of the coupling solution, with an optimum near pH 7; at more basic pH, a less active tautomer of the EDCI coupling agent predominates in solution.

The first reported syntheses of 12-helical β-peptides were also performed in convergent fashion in solution. Appella et al. coupled **47** and **49** with EDCI·HCl and DMAP in DMF to give a protected di-β-peptide.[13] To promote crystallinity, the ethyl ester was converted to a benzyl ester at the di-β-peptide stage, and further fragment couplings yielded tri-, tetra-, hexa-, and octa-β-peptides.

Chung et al. synthesized homochiral (*R*)-Nip-(*R*)-Nip and heterochiral (*R*)-Nip-(*S*)-Nip di-β-peptides in solution using EDCI·HCl, HOBt, and triethylamine in DMF.[10] These di-β-peptides were then coupled under similar conditions to βHGly residues or *syn*-$\beta^{2,3}$ residues (vide infra, Fig. 22.19). Abele et al. used similar solution-phase conditions, with benzyl ester rather than methyl ester protection, to generate homochiral all-(*S*) Boc-$(\beta^3HPro)_n$-OBn ($n = 2, 3, 6, 12, 18$) and heterochiral Boc-[(*S*)-β^3HPro-(*R*)-$\beta^3HPro]_n$-OBn ($n = 1, 2, 3$) oligomers.[83] The same group used ethyl ester protection to construct Boc-[(*S*)-Nip]$_n$-OEt ($n = 2, 3, 6$).

Huck et al.[113] investigated various reagents for peptide coupling to *N*-constrained residues and found that bis(2-oxo-3-oxazolidinyl)phosphinic chloride, or BopCl, was superior to more common solution-phase coupling agents EDCI·HCl, HBTU, and HATU. Thus, BopCl (1.5 eq.) and DIEA (5 eq.) were used as standard solution-phase fragment-coupling conditions to construct Boc-$(Nip)_n$-OMe ($n = 2, \cdots, 6$). BopCl and DIEA were also used to synthesize Boc-$(PCA)_n$-OMe

($n = 2, 4, 6$). Even with more forcing stoichiometry (2 eq. BopCl, 6 eq. DIEA), yields of PCA couplings (~60%) were lower than those for Nip couplings (~80%).

Initial studies of sheet secondary structure in β-peptides focused on hairpin-forming tetra-β-peptides. These compounds were synthesized via solution-phase couplings of appropriately protected **142** and **143** either with a proline–glycolic acid linker (below, Fig. 22.19),[26] which has been shown to support formation of a type II β-turn,[114] or with a heterochiral di-Nip reverse-turn unit (below, Fig. 22.17).[10,11] Pro-Glyco-containing oligomers **193–195** (below, Fig. 22.19) were prepared by sequential coupling, but the di-Nip turn was introduced into β-peptides **191** and **192** (and their stereoisomers) as a dipeptide fragment in order to perform the difficult coupling of two tertiary amines at the earliest possible stage. A similar Boc-based solution-phase strategy was used to prepare parallel hairpin model system **196** (below, Fig. 22.20).

22.3.2 Manual Serial Solid-Phase Synthesis

Regardless of the advances made in solution, the benefits of solid-phase peptide synthesis dictated that eventually solid-phase techniques would need to be developed for the synthesis of β-peptides. All such reports have adopted a main-chain Fmoc/side-chain *t*-butyl protecting scheme, which has become common in modern solid-phase α-peptide synthesis.[115] The methodology of Marti et al. involved capture of Wolff rearrangement ketene intermediates by resin-bound β-peptide free amines.[116] Guichard et al. soon followed, using the highly acid labile 2-chlorotrityl resin (with loading by esterification of a free β-amino acid) or the less acid labile Wang resin (with loading by ketene capture).[117,118] Liu and DeGrado adopted similar conditions, substituting HBTU for the toxic BOP coupling reagent employed by Seebach[119]; Berkessel et al. substituted PyBOP instead and omitted the HOBt coupling additive.[120] Hamuro et al. coupled tri-β-peptide fragments on solid phase in the synthesis of some highly sequence redundant β-peptides.[121] Seebach et al. also reported the synthesis of a hexa-β-peptide hairpin containing two strands of syn-$\beta^{2,3}$ residues on solid phase.[25]

Guichard et al. noted a few drawbacks in their manual solid-phase procedure.[117] First, epimerization was often seen at C-2 in β^2-residues. This epimerization is likely due to the basicity of the coupling conditions. Second, Guichard et al. found that the Kaiser test for free amines is unreliable for β-peptides bound to resin, a result we have reproduced in our own studies. Guichard et al. used the 2,4,6-trinitrobenzenesulfonic acid (TNBS) test instead. We have found the TNBS test to be useful in manual solid-phase Fmoc β-peptide synthesis, although it can also be unreliable for some sequences (T. Raguse, unpublished observations).

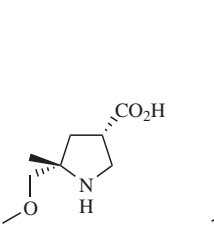
Removal of the Fmoc protecting group sometimes required the stronger base DBU in addition to piperidine. Our group's experience has been that Fmoc deprotection is difficult at certain points (always between residues 4 and 8) of some sequences with moderate (~33%) ACHC content. This difficulty varies with sequence and appears to depend sensitively on the placement of ACHC residues. It is possible that Fmoc removal problems arise from steric issues caused by

secondary-structure formation in the resin-bound β-peptides. Heating the deprotection reaction to 60°C in *N*-methylpyrrolidinone (NMP) improves yield.[37] Synthesis on grafted PEG-PS resin appears to alleviate the need for strenuous deprotection conditions, at least for some sequences, but couplings to strongly 14-helical β-peptides involving ACHC may still be difficult (T. B. Potocky, unpublished observations).

Meanwhile, Wang et al. investigated Fmoc solid-phase couplings of 5-constrained residues on Rink amide resin (to give C-terminal carboxamides) in custom-made glass fritted shaker vessels,[70] in an effort to reduce scale and increase diversity. Wang et al. found that 5-constrained residues coupled quite efficiently on solid phase using 3 eq. each of amino acid, PyBOP coupling reagent, and HOBt additive. Following standard TFA cleavage (with water and 1,2-ethanedithiol as scavengers) and high-performance liquid chromatography (HPLC) purification, these authors obtained left-handed 12-helical β-peptides Ac-(APC-ACPC)$_n$-NH$_2$ for $n = 2$, 3, 4 (the tetra-, hexa-, and octa-β-peptides).[70]

Lee et al. used these methods to synthesize related hexa-β-peptides in which the ACPC residues were replaced by S-APC residues.[72] Porter et al., in a further demonstration of the efficiency of the methodology, performed the manual solid-phase synthesis of a 17-residue β-peptide (see **204** below, Fig. 22.23).[122] Gruner et al. used similar methods, with a different coupling reagent (HATU) and base (2,4,6-collidine), to synthesize a protected hexa-β-peptide, Fmoc-(**98**-βHGly)$_3$-OH, which contains 5-constrained residues but forms a 12/10-helix rather than a 12-helix.[123]

For the synthesis of 2,2-DPCA oligomers, Huck compared solid-phase synthesis with Boc or Fmoc main-chain protecting group schemes.[87] Without the use of specialized apparatus for HF handling, cleavage from the solid support of β-peptides prepared by the Boc strategy requires the use of trifluoromethanesulfonic acid. These highly acidic conditions appeared to lead to β-peptide decomposition. Therefore, Huck used manual Fmoc solid-phase synthesis, with PyBrOP as coupling reagent, to generate β-peptides Ac-(**163**)$_n$-NH$_2$ ($n = 4$, 6, 8) and a number of heterooligomers, including **164**. The attempted synthesis of a tetra-β-peptide on an Applied Biosystems model 432A (Synergy) instrument (vide infra) failed, perhaps because the instrument is limited to the use of HBTU as coupling agent rather than PyBrOP. Arnold et al., however, reported incorporation of an (*R*)-Nip-(*S*)-Nip sequence into an α-peptide using Fmoc chemistry[124]; in this case, a non-β-peptide context or fewer difficult secondary-amine couplings may have made the difference between success and failure.



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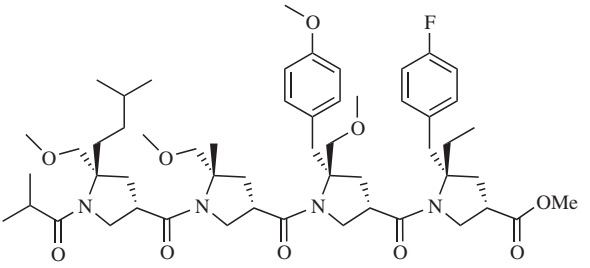

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22.3.3 Automated Serial Solid-Phase Synthesis

The next logical step in the solid-phase synthesis of β-peptides was the employment of automation. We turned from manual to automated solid-phase synthesis as the scope of our studies of 12-helical β-peptides expanded.[74,75,125,126] Commercial peptide synthesizers, while preconfigured for α-peptides, often feature built-in flexibility in order to deal with ''difficult'' couplings or sequences. Our protocol, detailed by Raguse et al.,[127] uses an Applied Biosystems model 432A (Synergy) synthesizer, with the instrument's standard HBTU/HOBt coupling reagents. Coupling times are extended to 2 h; the coupling step is repeated with a second batch of reagents (''double coupling'') where necessary. Studies performed with manual solid-phase synthesis showed that coupling times longer than 3 h led to decreased β-peptide purity (M. A. Gellman, unpublished observations). Also, trials with 90-min coupling times on the Synergy instrument showed evidence of incomplete couplings (N. Umezawa, unpublished observations). The deprotection time is extended where necessary, but manual heated deprotection may still be necessary for the most recalcitrant deprotection steps (T. Raguse, unpublished observations).

In our group's experience, the solid-phase synthesis of β-peptides containing 5-constrained residues has been more straightforward than that of β-peptides containing 6-constrained residues, using either automated or manual methods. Failed syntheses occur in both series, but when automated syntheses of sequences designed to form the 12-helix do not give a single major product by HPLC with correct mass, the difficulty can generally be traced to monomer impurity, monomer decomposition, or a mechanical fault in the synthesis instrument. In contrast, the synthesis of certain 14-helical β-peptide sequences may fail due to unusually difficult coupling or deprotection reactions (vide supra).

22.3.4 Other Strategies for β-Peptide Synthesis

Watts et al. demonstrated increased yields for ultramicroscale solution-phase synthesis of di- and tri-β-peptides in a microreactor using electroosmotic flow.[128] They postulated that the improvement might be due to an electrochemical effect; although there are clear hurdles in yield and scope to be overcome, the principle shows intriguing promise for the construction of large libraries from scarce synthetic β-amino acid monomers.

22.4 CONFORMATIONAL DATA

22.4.1 14-Helical β-Peptides

The elegant studies of Seebach et al. on β-peptides constructed from mono- and disubstituted (β^2, β^3, and acyclic anti-$\beta^{2,3}$) β-amino acids have been extensively reviewed and constitute a foundation for much work on the conformational analysis of β-peptides.[7,16,29] Here, we will focus mainly on the use of six-membered rings to enforce the 14-helical conformation.

The 14-helix was the first regular secondary structure demonstrated via high-resolution methods for β-amino acid oligomers.[6,12] Some oligomers composed solely of β^3-homologues of (L)-amino acids adopt left-handed 14-helical structure in solution,[12,53] and a circular dichroism (CD) signature of 14-helical β^3-peptides in methanol has been determined.[53] The CD spectra of Seebach et al.'s left-handed 14-helical β^3-peptides, built from (L)-α-amino acid–derived residues, shows a spectral maximum at 197 nm and a minimum at 215–216 nm. This signature was decreased by modifications intended to disrupt hydrogen bonding (*N*-methylation, backbone amide-to-ester change) or sterically block the 14-helix (inversion of chirality or $\beta^{3,3}$-disubstitution). Inclusion of an acyclic $\beta^{2,3}$-anti-disubstituted residue also decreased CD signal intensity, possibly due to gauche steric interaction of the substituents.[53]

"Mixed" β-peptides composed of alternating β^2- and β^3-residues may adopt either 14-helical or 12/10-helical structure.[15] The structure adopted depends sensitively on sequence and on terminal protecting groups, even though the stereochemistry at both the β^2 and β^3 side chains should occupy sterically allowed "lateral" positions on a left-handed 14-helix. Even a dodeca-β-peptide composed entirely of β^3-residues, which showed a 14-helical CD signature in methanol, gave a 12/10-helical signature (a maximum, for a left-handed 14-helical β-peptide, at 202 nm) in aqueous solution.[130] However, structural conclusions based solely on CD data must be regarded as tentative.[131]

This last result may be explained by reference to the structural features of the 14-helix itself (Fig. 22.8). As compared to the α-helix, which has 3.6 residues per turn,[132] the 14-helix has only 3.2 residues per turn.[30] This difference has the effect of making the 14-helix slightly more squat (pitch of 5.1 vs. 5.4 Å for the α-helix),

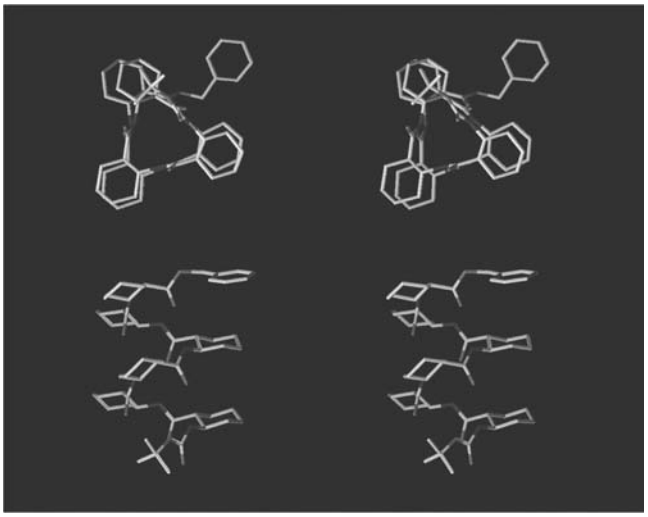


Figure 22.8 Right-handed 14-helical Boc-[(*R*,*R*)-ACHC]$_6$-OBn oligomer in end-on and side-on relaxed-eye stereoviews from crystal structure data.[6]

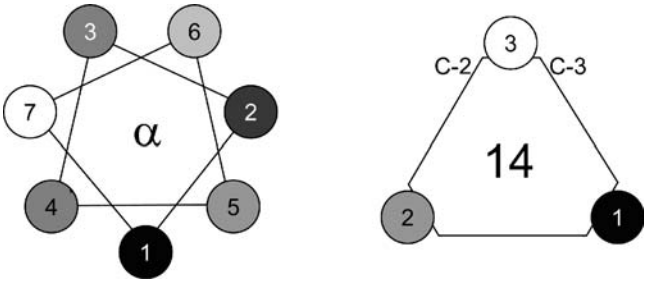


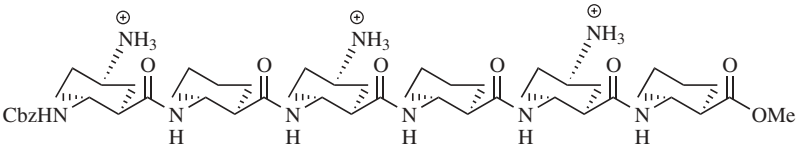
Figure 22.9 Simplified helical wheel diagrams for α-peptide α-helix (left) and β-peptide 14-helix (right). Residue 1 is farthest from the viewer; closer residues are more lightly shaded.

despite having almost the same axial translation (rise per residue, 1.6 vs. 1.5 Å for the α-helix). The near-integral number of residues per 14-helical turn means that the ''helical wheel'' for a 14-helix can be approximated by a truncated triangle (Fig. 22.9), although there is a slight twist to the helix in solution. Thus, in the dodeca-β-peptide[130] H-β^{3}HLys(ε-acylated)-β^3*HPhe*-β^3**HTyr**-β^{3}HLeu-β^3*HLys*-β^3**HSer**-β^{3}HLys-β^3*HPhe*-β^3**HSer**-β^{3}HVal-β^3*HLys*-β^3**HAla**-OH, the residues in roman type would form a ''column'' on one face of a 14-helix, those in italics would form a second column, and those in boldface would form a third column. Schreiber and Seebach[130] noted that the residues here boldfaced are neutral, while the other two columns contain both hydrophobic and β^{3}HLys (cationic) residues. They hypothesized that the 12/10-helix may allow more effective burial of hydrophobic groups than does the 14-helix, which would lead to a preference for the 12/10-helix in water, but not in methanol. Working with a series of β^3-peptides in which the 14-helical conformation would be amphiphilic, Liu and DeGrado observed 14-helical structure only in the presence of phospholipid vesicles.[119]

When β^3-peptides do not adopt a 14-helical structure on their own, ACHC and/or other 6-constrained residues can be employed to induce this conformation. Dimer Cbz-DCHC-ACHC-OMe is too short to form a single turn of helix, but it showed a weak 14-helical CD signal,[38] suggesting that the ACHC and DCHC residues partly populate conformations compatible with 14-helix even in the absence of intramolecular hydrogen bonding. This conformational preorganization is believed to be largely responsible for the strong stabilizing effect of 6-constrained residues on 14-helical conformations of β-peptides. All-(*R,R*) β-homopeptides Boc-(ACHC)$_4$-OBn and Boc-(ACHC)$_6$-OBn display 14-helical conformations in the solid state[6,9] and in organic solvents.[133] The CD spectra of these β-peptides were expected to be mirror images of their all-(L) α-amino acid–derived β^3-peptide counterparts reported by Seebach et al.,[54] and, indeed, they show the expected CD maximum at 217 nm. At shorter wavelengths (195–205 nm), however, the signal is weak, in contrast to the minimum observed for 14-helical β^3-peptides.[134] This difference may reflect different intrinsic CD properties of the individual residues or it could indicate that the more flexible β^3-peptides populate a minor conformer that gives rise to the shorter wavelength extremum.

Incorporation of even a single 6-constrained residue (ACHC or Seebach et al.'s 1,2-dithiane residue) can significantly stabilize the 14-helix in aqueous solution.[54] 14-Helical structure is further enhanced by substitution of additional 6-constrained residues for β^3-residues (Fig. 22.10).[38] All-6-constrained β-peptide **165** maintained its 14-helical CD signal even at 80°C, indicating an extremely robust conformation. Signal intensity decreased in the order **165** > **166** > **167**, with a very weak and non-14-helical signal for all-β^3-peptide **168**. A solution NMR structure of β-peptide **166** confirmed 14-helical folding. In a related study, Raguse et al.[37] substituted ACHC residues into a β^3-peptide modeled after amphiphilic sequences of Liu and DeGrado. Only the ACHC-containing β-peptides showed a 14-helical CD signal in aqueous solution, and signal intensity increased dramatically as ACHC content increased from one-third to two-thirds of the residues.[37]

Raguse et al.[127,135,136] demonstrated the generality of the ACHC substitution strategy by synthesizing β-peptides **169–171** (Fig. 22.11; helical wheel diagrams



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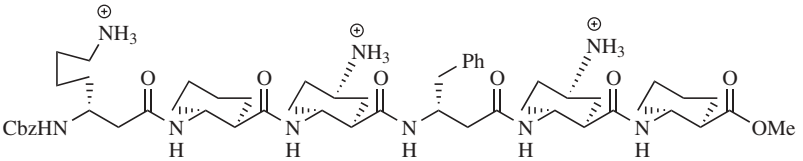

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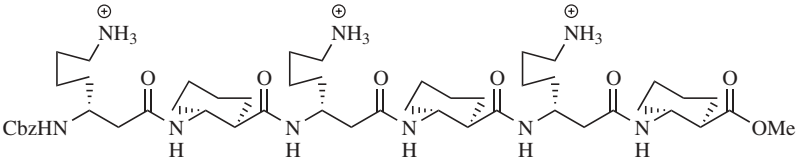

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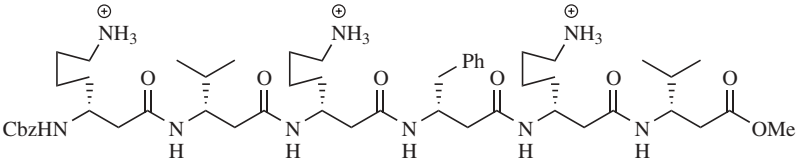

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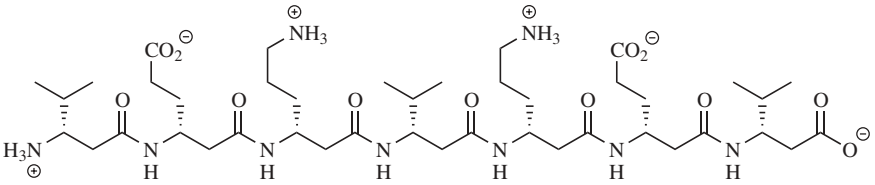
Figure 22.10 β-Peptides synthesized by Appella et al. that formed 14-helical structure in aqueous solution.[38]



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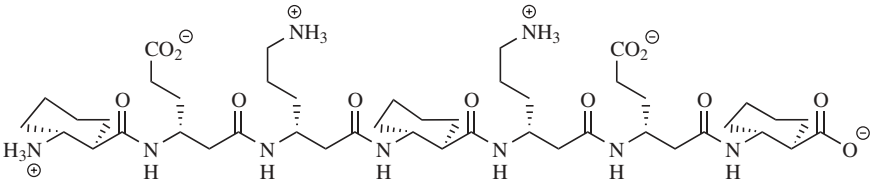

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H-β^{3}HTyr-βHGly-ACHC-β^{3}HLys-ACHC-β^{3}HGlu-β^{3}HGlu-ACHC-β^{3}HLys-β^{3}HLys-ACHC-β^{3}HGlu-NH_2

171

H-β^{3}HTyr-β^{3}HLeu-β^{3}HLeu-β^{3}HLys-β^{3}HLeu-β^{3}HLeu-β^{3}HLys-β^{3}HLeu-β^{3}HLeu-β^{3}HLys-NH_2

172

H-β^{3}HTyr-β^{3}HVal-β^{3}HVal-β^{3}HLys-β^{3}HVal-β^{3}HVal-β^{3}HLys-β^{3}HVal-β^{3}HVal-β^{3}HLys-NH_2

173

H-β^{3}HTyr-β^{3}HLeu-β^{3}HLeu-β^{3}HLys-β^{3}HLeu-ACHC-β^{3}HLys-β^{3}HLeu-β^{3}HLeu-β^{3}HLys-NH_2

174

H-β^{3}HTyr-β^{3}HLeu-ACHC-β^{3}HLys-β^{3}HLeu-ACHC-β^{3}HLys-β^{3}HLeu-ACHC-β^{3}HLys-NH_2

175

H-β^{3}HTyr-ACHC-ACHC-β^{3}HLys-ACHC-ACHC-β^{3}HLys-ACHC-ACHC-β^{3}HLys-NH_2

176

Figure 22.11 β-Peptides synthesized by Raguse et al. to study the effect of ACHC on 14-helical conformation. Note: All β-peptides, including **171–176**, were composed entirely of (*R*)-β^3 residues and (*R,R*)-cyclic residues.[127,135,136]

in Fig. 22.12).[37,127,136] The enantiomer of **169** had been shown by Arvidsson et al. to adopt partial 14-helical structure in water only at neutral pH, most likely due to a salt-bridge effect.[137] Replacement of β^{3}HVal residues by ACHC gave **170**, which showed a more intense 14-helical signature than did **169** in water at pH 7, maintained its CD signal even at pH 2 and pH 12 (where **169** shows little or no

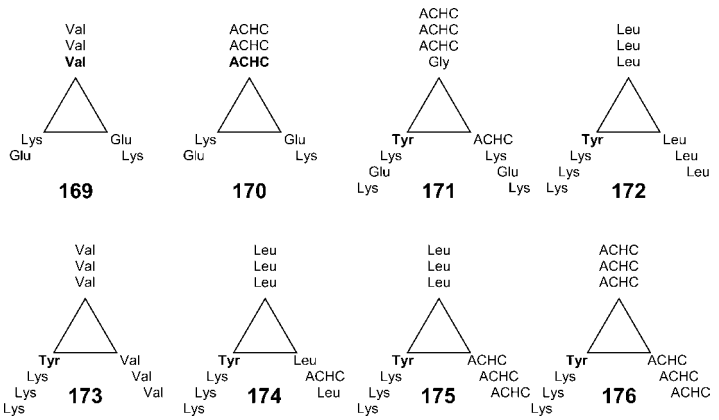


Figure 22.12 Helical wheel diagrams for β-peptides **169–176**. Bold: N-terminal residue. N → C, clockwise.

14-helicity, presumably because there are no salt bridges), and showed interresidue NOEs consistent with the 14-helix.[135] Similarly, **171**, related to a β^3-peptide design of Cheng and DeGrado,[138] showed a strong pH-independent 14-helical CD signature.[135] In both **170** and **171**, there was little difference in the CD signal intensity in methanolic versus neutral aqueous solution, suggesting that these β-peptides may approach 100% 14-helix population in water.

The series **172–175** (Fig. 22.11; helical wheel diagrams in Fig. 22.12) showed the flexibility of most β^3-residues and illustrated a surprising effect of the side-chain-branched residue β^3HVal. β-Peptide **172** showed a heretofore-unseen CD signature (strong maximum at 203 nm and weak minimum at 220 nm, for the (*R*)-β^3-series β-peptide) in methanolic and aqueous solution, while related β-peptide **173** showed a 14-helical CD signal. The 14-helix-promoting effect of β^3HVal, which has been noted by others,[121,139] stands in contrast to α-peptide systems, where β-branched residues discourage α-helix formation.[140] Mutation of a single β^3HLeu residue in **172** to ACHC, giving β-peptide **174**, resulted in a CD spectrum explainable as a weighted average of those for **172** and **173**. This phenomenon could reflect two populations of **174** molecules adopting different conformations or a uniform population of **174** molecules with different regions adopting different conformations.

Deca-β-peptide **176**, which appears to be 14-helical by CD, displayed concentration-dependent NMR data, suggesting that this molecule self-associates. Analysis of variable concentration analytical ultracentrifugation (AU) data indicated the presence of at least two equilibrating species; the data were best modeled by a monomer–hexamer equilibrium.[136] Among conventional α-peptides, self-association of amphiphilic α-helices is regarded as an important step toward helix-bundle tertiary structure,[141] and electrostatically complementary β-peptide helices have demonstrated increased 14-helical CD signal when tethered to each other by a disulfide (as compared to disulfide-reduced control).[142] Thus, the

self-association of **176**, which is presumably driven by hydrophobic surface area burial, suggests a strategy for designing β-peptides with discrete helical bundle tertiary structure. Further studies suggest that **175** also self-associates, but **172** does not.

22.4.2 12-Helical β-Peptides

In contrast to the 14-helical structure, which may be seen in β-peptides containing no conformationally constrained residues, the 12-helical secondary structure appears always to require the use of specialized residues, namely 5-constrained residues. In 1997, Appella et al. demonstrated the 12-helical structure in the solid state and solution for protected ACPC oligomers (Fig. 22.13).[22] The NMR data for an ACPC hexamer and octamer showed medium-range NOEs between residues in an $(i, i + 2)$ relationship, confirming the 12-helical structure in organic solution.[133] This well-defined structure is seen despite the significant conformational flexibility of the cyclopentane ring.[143]

Substituents on the five-membered ring restrict conformational freedom and fix the θ angle (Fig. 22.1). Applequist et al.[20] proposed that a skew θ angle of 94.3° would be seen in an idealized 12-helix of βHGly residues. Christianson modeled a 12-helical ACPC oligomer and computed a theoretical θ angle of 88°.[19] Hill et al. analyzed θ angles in an ACPC oligomer crystal structure and estimated that they varied between 78° and 113°,[7] spanning a range that includes both the Applequist and Christianson predictions.

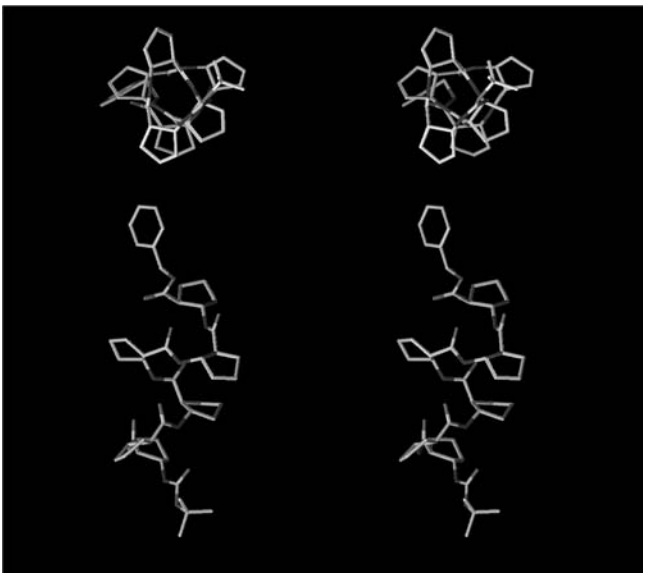


Figure 22.13 Left-handed 12-helical Boc-[(*R*,*R*)-ACPC]$_6$-OBn oligomer in end-on and side-on relaxed-eye stereoviews from crystal structure data.[22]

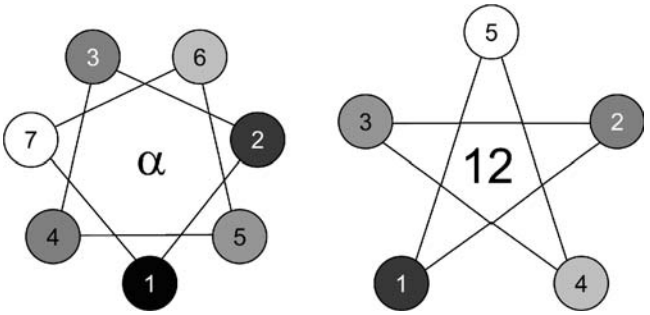


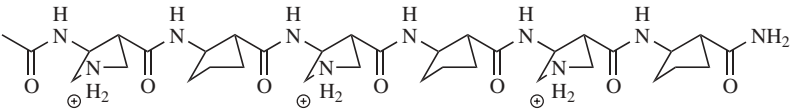
Figure 22.14 Simplified (α-helix shown with 3.5 rather than 3.6 residues per turn) helical wheel diagrams for α-helix (left) and 12-helix (right). Residue 1 is farthest from the viewer; closer residues are more lightly shaded.

The structural characteristics of the 12-helix differ significantly from those of the 14-helix and are in many respects more similar to those of an α-peptide α-helix (Fig. 22.14).[20] With an axial translation of 2.1 Å per residue and 2.6 residues per turn, the 12-helix has a pitch of 5.4 Å per turn. The (*S*,*S*)-ACPC 12-helix, like the L-residue α-helix, is also right-handed, whereas the (*S*,*S*)-ACHC 14-helix is left-handed. The 12-helix has approximately five residues in two helical turns, while the α-helix has approximately seven residues in two turns. Finally, the helical dipole direction (N → C) is identical for the 12-helix and the α-helix but opposite that for the 14-helix.

A characteristic CD signature, first reported for ACPC hexamer in methanol, has been shown to correlate with the 12-helical conformation based on NMR structural studies. The 12-helical CD signal becomes more intense on a per-residue basis for longer ACPC oligomers (dimer, trimer, tetramer, and hexamer), suggesting cooperativity in 12-helical folding.[13] For left-handed 12-helical oligomers in methanol, the CD signal has a maximum near 204 nm, a zero crossing near 214 nm, and a minimum near 221 nm.[22] The maximum, which is slightly blue shifted in aqueous solution (to 201 nm),[70] is well modeled by theoretical calculations.[20] The amide n–π^* transition, which is the likely source of the minimum, was not included in the calculations, so neither the minimum nor the zero crossing can be compared with theory.

5-Constrained residues other than ACPC are compatible with the 12-helix. β-Peptides Ac-(APC-ACPC)$_n$-NH$_2$ show intensity correlation with β-peptide length, consistent with a two-state conformational model.[70] For $n = 3$ (alternating hexa-β-peptide **177**), interresidue NOEs in methanol and water are consistent with the 12-helical conformation. Similarly, hexa-β-peptide **178** (Fig. 22.15) shows a number of interresidue NOEs consistent with the 12-helix, sufficient to force 12-helical conformation in an NOE-restrained dynamics simulation.[72] Similar CD spectra are seen for related β-peptides **179** and **180**.

The CD analysis of hexa-β-peptides **181** and **182**, which contain the AP residue, suggested that this residue is also compatible with the 12-helix.[74] β-Peptide **182** also showed characteristic 12-helical interresidue NOEs. Conformational analysis



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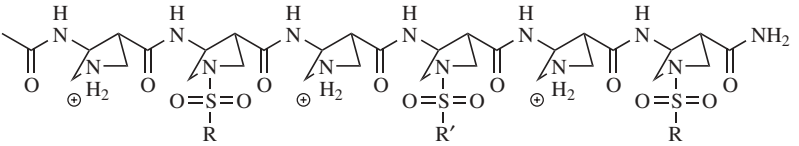
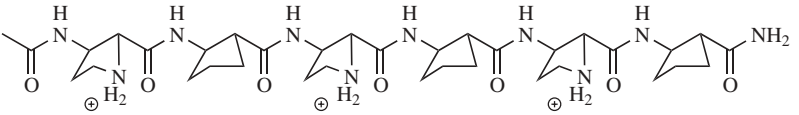


178 R=^{i}Pr, R′=*p*-tolyl

179 R,R′=^{i}Pr

180 R,R′=*p*-tolyl



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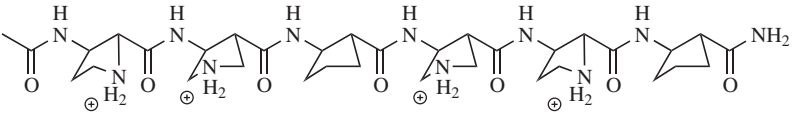

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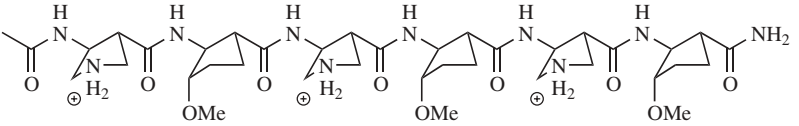

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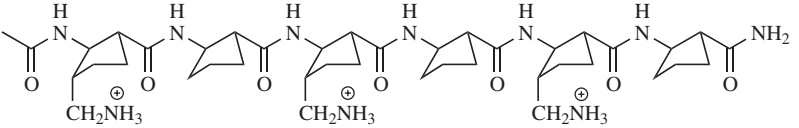

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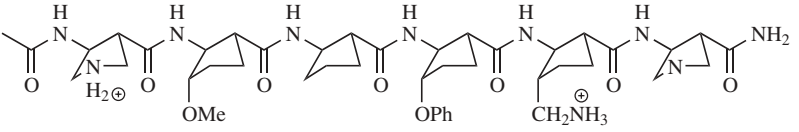


185

Figure 22.15 A series of hexa-β-peptides investigated by NMR and CD.[72,74,75]

Tag-ACPC-APC-ACPC-APC-ACPC- β^3HLys-ACPC-NH_2

186

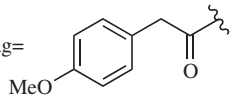
Tag-ACPC- β^3HLys-ACPC-APC-ACPC- β^3HLys-ACPC-NH_2

187

Tag-ACPC- β^3HLys-ACPC- β^3HLys-ACPC- β^3HLys-ACPC-NH_2

188

Tag=



Ac-ACPC-ACPC- β^3HLeu-APC- β^3HLeu-APC-APC- β^3HLeu-ACPC-
β^3HLeu-APC-ACPC- β^3HLeu-APC- β^3HLeu-ACPC-APC-NH_2

189

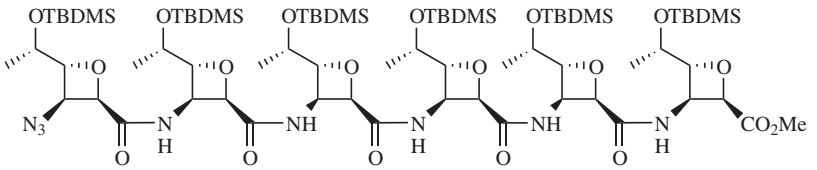
Figure 22.16 Series of β-peptides containing 5-constrained and β^3-residues.[125]

of hexa-β-peptides **183–185** confirmed that substituted 3-ACPC residues support the 12-helical conformation.[75] The NMR analysis of **185** gave abundant NOE evidence for the 12-helix.

β-Peptides **186–189** (Fig. 22.16, helical wheel diagram for **189** in Fig. 22.24) were examined in order to determine whether β^3-residues could be incorporated into the 12-helix.[125] The CD and NMR evidence supports at least partial 12-helical folding for all of these β-peptides (**186–189**) in methanol, and all but **188** show a 12-helical CD signature in aqueous solution. Thus, a 12-helical hepta-β-peptide tolerates no more than two β^3-residues in aqueous solution. Recently, a similar study on mixed β-peptides of 5-constrained and β^2-residues suggested that only one or, in some cases, two β^2-residues can be incorporated into a hepta-β-peptide without the loss of 12-helical structure in water or methanol; in borderline cases, a 12-helical CD signature is seen in methanolic but not aqueous solution.[144] On the other hand, Gruner's sugar-derived hexa-β-peptide Fmoc-(**98**-βHGly)$_3$-OH (see Scheme 22.22 for residue structure), which contains 5-constrained residues in alternation with the flexible βHGly residue, appears to be 12/10-helical in CH_3CN by CD and NMR.[123]

22.4.3 10-Helical β-Peptides

The recent report of a 10-helical conformation for oligomer **190**, which is composed of cis 4-constrained oxetane residues,[18] is an exciting development in the field of β-peptide chemistry, as it represents a new secondary structure for β-peptides.



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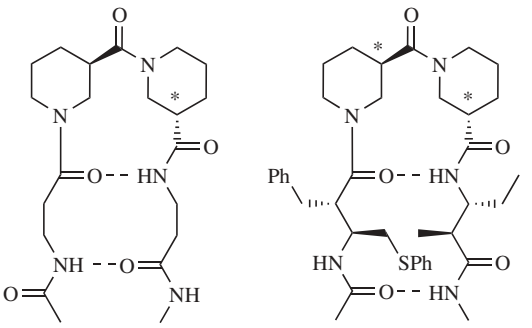
As of this writing, the only structural data reported for a β-peptide containing a carbocyclic 4-constrained residue are those of **105**-βHGly-OMe (see Scheme 22.23 for residue structure).[145] This β-peptide aggregated in solution, but a crystal structure showed a hairpin bend with a **105** residue θ angle of −22.2°. Gas-phase theoretical calculations suggested an intraresidue hydrogen bond for the **105** residue.

Claridge et al. examined hexamers of the 4-constrained residues **110**, **111**, and **114** (see Scheme 22.24 for residue structure) by IR and NMR.[18] Each of these hexamers showed significant deshielding of internal amide protons in $CDCl_3$, consistent with the formation of a hydrogen-bonded structure. Also, the IR amide stretch region for each hexamer showed a strong absorbance at 3302 cm^{-1}, indicative of strong hydrogen bonding. For **190** (an oligomer of **111**), the β-peptide with the best resonance dispersion, a regular pattern of interresidue (i, $i + 2$) NOEs was observed in d_6-benzene solution. An NOE-restrained dynamics simulation indicated the adoption of 10-helical conformation, providing the first example of this new secondary structure for β-peptides.

22.4.4 Non-Hydrogen-Bonded Structures

N-Constrained residues have been evaluated as elements of local secondary structure, that is, reverse turns. Computational evaluation suggested that a heterochiral (*R*)-Nip–(*S*)-Nip sequence would induce a reverse-turn structure characterized by a 12-membered hydrogen-bonded ring (as shown in the context of longer β-peptides in Fig. 22.17).[19] The simulation also predicted that a homochiral Nip–Nip segment would *not* form a reverse turn. Indeed, Chung et al. observed an IR N–H stretch band consistent with strong hydrogen bonding for Ac-(*R*)-Nip-(*S*)-Nip-NHMe but not for Ac-(*R*)-Nip-(*R*)-Nip-NHMe in CH_2Cl_2, results that are consistent with the computational predictions. For both di-β-peptide derivatives, amide bond rotamers



191 **192**

Figure 22.17 Tetra-β-peptides synthesized to explore the Nip–Nip turn. Epimers at the starred carbons and the bis-epimer of **192** were also synthesized.[10,11]

complicated the ^{1}H NMR analysis, but only the major rotamer of the heterochiral di-β-peptide showed an amide proton chemical shift consistent with strong intramolecular hydrogen bonding.

When examined by IR and NMR as a turn unit in the tetra-β-peptide Ac-βHGly-(*R*)-Nip-(*R* or *S*)-Nip-βHGly-NHMe (**191** or its epimer, Fig. 22.17), the heterochiral turn unit promoted a hairpinlike conformation to a greater extent than did the homochiral di-β-peptide.[10] These two Nip–Nip di-β-peptides and their enantiomers were also evaluated as turn units in a tetra-β-peptide context between syn-$\beta^{2,3}$-residues.[10,11] Infrared, NMR, and crystallographic evidence showed hairpin formation for the tetra-β-peptides linked by heterochiral Nip–Nip sequences (**192** and its diastereomer containing an (*S*)-Nip–(*R*)-Nip sequence) but not for those linked by homochiral Nip–Nip sequences (diastereomers of **192** containing (*R*)-Nip–(*R*)-Nip or (*S*)-Nip–(*S*)-Nip sequences; vide infra for a further discussion of β-peptide hairpins). The (*S*)-Nip–(*R*)-Nip turn also significantly populated both rotamers around one of the tertiary Nip amide bonds. Thus, the (*S*)-Nip–(*R*)-Nip turn promoted the hairpin conformation to a lesser extent than did (*R*)-Nip–(*S*)-Nip.

Circular dichroism studies of *N*-constrained β-peptide homooligomers have provided some intriguing results. Homochiral oligomers of β^3HPro, Nip, and PCA each show CD signatures[83,113] that, in the case of Nip and PCA, reach a maximum per-residue intensity near six residues in oligomer length.[113] Data from a crystal structure of a β^3HPro trimer led Abele et al. to construct a speculative model of a regular helical structure, actually a twisted extended chain, for β^3HPro homooligomers.[83] However, NMR studies of all three types of N-constrained oligomers showed the presence of rotamers around the tertiary amide bond.[83,87] This phenomenon, also seen for proline residues in α-peptides, complicates NMR analysis and shows that observation of a limiting per-residue CD signature in a variable-length series is not a reliable indicator of secondary-structure formation.[146]

Oligomers of 2,2-DPCA (but not 2-MPCA) each show a single set of ^{13}C NMR resonances, indicating that a single major rotameric state is populated about each amide group.[146] The CD spectroscopic data obtained on all-(*S*,S) *i*-PrCO(**163**)$_n$-OMe ($n = 2, \cdots, 6$) show a signature with maximum at $\sim$ 200 nm, zero crossing at $\sim$ 208 nm, and minimum at $\sim$ 216 nm, which increases in intensity with increasing oligomer length. Quantum mechanical calculations on a bis(2,2,-DPCA) derivative suggested that the ϕ, θ, and ω angles are well constrained but the ψ angle [the exocyclic backbone Cβ-C(O) torsion] can adopt two different values, one of which leads to a largely extended structure and the other to a more compact structure. A crystal structure of a bis(2,2,-DPCA) derivative showed that the N-terminal residue ψ torsion adopted the ''compact'' conformation. However, an NMR structure of **164** derived by NOE-restrained dynamics indicated that two residues were in an ''extended'' conformation, whereas a third ψ angle adopted the ''compact'' conformation seen in the di-β-peptide crystal structure. Thus, in this case, the enforcement of a single regular structure may require yet further constraints on residue conformation.

22.4.5 Hairpins

As mentioned above, the syn-$\beta^{2,3}$-substitution pattern induces the θ torsion to adopt an anti-periplanar conformation, in contrast to the gauche-type θ preference enforced by small rings. This conformation, in turn, supports the formation of extended strand structures.

As discussed above, hairpin population by Nip–Nip segments follows the relationship (*R*)-Nip–(*S*)-Nip > (*S*)-Nip–(*R*)-Nip ≫ (*R*)-Nip–(*R*)-Nip ≈ (*S*)-Nip–(*S*)-Nip.[10] Here, we will consider the effect of syn-$\beta^{2,3}$-residues on hairpin conformational stability.

Tetra-β-peptides **191** and **192**, along with the (*R*)-Nip–(*R*)-Nip epimer of **191** and all three Nip diastereomers of **192**, were synthesized and examined by IR and NMR in CH_2Cl_2.[10] Both IR and amide chemical shift data on **192** indicated the formation of intramolecular hydrogen bonds in a "dipole-additive" pattern, analogous to that shown at the left of Figure 22.18. In this pattern, all four amide dipoles in the sheet portion are aligned parallel to one another, giving the structural unit a large net dipole. A crystal structure of the Boc-protected tetra-β-peptide precursor to **192** was also acquired. This crystal structure showed a folded dipole-additive hairpin conformation in which both intramolecular hydrogen bonds were well formed; NOE data for **192** were consistent with the conformation observed in the precursor crystal structure.[11] On the other hand, while a crystal structure of **191** showed a dipole-additive hydrogen-bonding pattern, solution amide chemical shift data supported the alternative hydrogen-bonding pattern drawn at the right of Figure 22.18, in which successive amide dipoles along each strand are antiparallel to each other. This so-called dipole-canceling pattern, in which the structural unit has a near-zero net dipole, is conformationally accessible for **191** if both strand θ angles adopt gauche values but would lead to steric clash for syn-$\beta^{2,3}$-residues in **192**.

Chimeric depsipeptides **193–195** were synthesized and evaluated by NMR.[26] Amide chemical shift data and observed NOEs suggest that **193** adopts the dipole-additive hydrogen-bonded conformation drawn in Figure 22.19, which is also observed in the solid-state structure. The amide chemical shifts of **195**, on the other hand, suggest that gauche θ angles are adopted as for **191**, leading to the dipole-canceling conformation. Intermediate case **194**, where the strand elements are

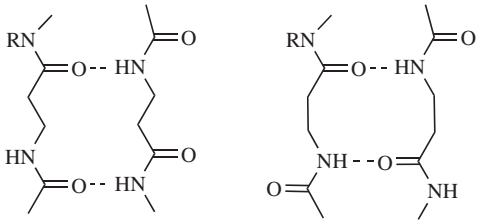
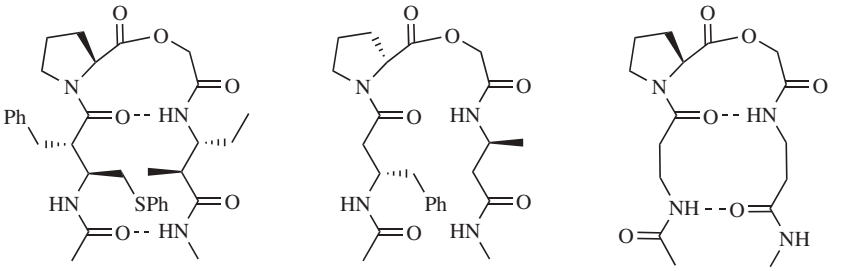


Figure 22.18 Two types of antiparallel hairpin conformation.[26]



193 194 195

Figure 22.19 Tetra-β-peptides synthesized for studies on antiparallel hairpin conformations. See also Figure 22.17.[26]

β^3-residues, shows intermediate amide chemical shift values suggestive of a conformational equilibrium between the dipole-additive and dipole-canceling hairpins.

Langenhan et al. prepared compound **196** (Fig. 22.20), which contains a (D)-Pro-DADME linker.[147] This linker has been shown to support the formation of a parallel hairpinlike structure between α-peptide[148] or γ-peptide strands,[149] and a crystal structure of **196** showed the intramolecular hydrogen-bonding pattern expected for parallel sheet secondary structure involving the two syn-$\beta^{2,3}$-residues. In methanol solution, two sets of peaks were observed for **196**, and these were assigned to rotamers around the tertiary amide bond. For the major (93%) conformer, a number of interresidue NOEs consistent with the hairpin conformation were observed; no NOEs inconsistent with hairpin structure were observed for this conformer. Interestingly, in the (L)-Pro-containing epimer *epi*-**196**, similar NOEs were observed, but the major rotamer was less highly populated (74%). This observation suggests that β-peptide hairpins do not depend as sensitively on turn configuration as do their α- and γ-counterparts, which are predisposed to accept only one turn configuration by the helical twist of their strand structures.

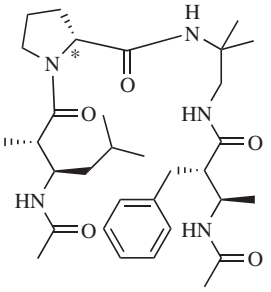


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Figure 22.20 Parallel hairpin synthesized by Langenhan et al.[147] The starred carbon has the opposite stereochemistry in *epi*-**196**.

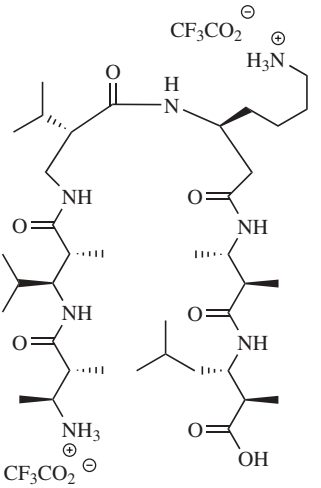

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Figure 22.21 Hairpin synthesized by Seebach et al.[25]

Seebach et al. developed an alternative turn structure in which the loop is formed by a β^2-residue and a β^3-residue in sequence, giving a 10-membered hydrogen-bonded ring[25] rather than the 12-membered ring seen with the di-Nip turns. Hairpin **197** (Fig. 22.21) was characterized in methanol by NMR.[25] The NOEs observed were consistent with hairpin structure, and coupling constants indicated that the *syn*-$\beta^{2,3}$-residue θ angles adopted anti conformations. These results were supported by molecular dynamics simulations, which suggested that the hairpin conformation is roughly 20–30% populated under the experimental conditions.[150]

22.5 BIOLOGICAL APPLICATIONS

Biological applications of β-peptides have mainly focused on designed amphiphilic helices, that is, helices in which one face is composed of lipophilic residues and the opposite face is hydrophilic, usually charged. The amphiphilic α-helix is a recurring motif in intermediate-size bioactive natural peptides, including hormones and toxins, as well as in apolipoproteins.[151,152] Amphiphilic helical β-peptides have been designed to inhibit cholesterol and fat uptake by enterocytes and to kill bacteria.

22.5.1 Cholesterol and Fat Uptake Inhibition

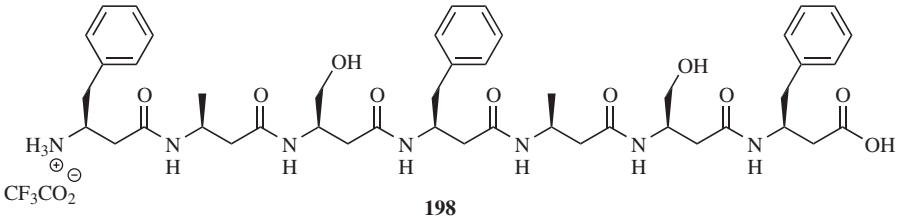
Uptake of dietary lipids and cholesterol in the small intestine is facilitated by the scavenger receptor protein SR-BI.[153] This uptake is inhibited by the 243-amino-acid protein apolipoprotein A-I (apo A-I),[154] which contains repeating structural

elements capable of forming amphiphilic α-helices.[151] Because the inhibition can be reproduced using either enantiomer of a short designed amphiphilic α-helical α-peptide with minimal homology to natural sequences,[153,154] it was hypothesized that any amphiphilic helix would be competent to inhibit lipid uptake. To test this hypothesis, Werder et al. synthesized β-peptides **198**–**203** (Fig. 22.22).[155] Three of these β-peptides (**198**–**200**), which are capable of adopting amphipathic 14-helical conformations, inhibited SR-BI-mediated uptake of cholesterol by a vesicle model system and by a cultured cellular monolayer. On the other hand, β-peptides **201** (the 14-helical conformation of which would not be amphiphilic), **202** (predicted to form sheetlike structure, vide supra), and **203** (predicted not to form regular secondary structure) were inactive. Controls suggested that the mechanism of inhibition was receptor mediated. The inhibitory concentrations were roughly millimolar, as compared to micromolar for lipoproteins and an α-peptide inhibitor; however, these β-peptides are shorter than the natural α-peptides, and the length difference may explain the lower activity of the β-peptides. The β-peptides are much more resistant to protease degradation than are α-peptides prepared from (L)-residues, which is promising with respect to this and other biomedical applications. These β-peptide results provide strong support for Kaiser and Kedzy's hypothesis that amphiphilicity is a determining criterion of many α-peptide biological activities.[151]

22.5.2 Antimicrobial Activity

Antimicrobial α-peptides have been characterized in a wide range of animal and plant species.[156] These α-peptides contribute to innate immunity and, in some species, also serve as toxins. One major class of antimicrobial α-peptides adopts amphiphilic α-helical structure[157]; this class includes the frog magainins[158] and the insect cecropins.[159] These α-peptides are believed to act on bacterial cell membranes, associating with or intercalating into lipid bilayers and causing changes in membrane curvature and thickness, formation of transient ''toroidal'' pores, and ultimately membrane disruption and collapse.[156,160] Modifications that increase amphiphilicity tend to increase potency.[161] The enantiomers of magainins and cecropins retain the parent structures' antimicrobial activity, which suggests that the mode of action does not involve binding to a specific protein receptor.[162] Because antimicrobial activity appears to depend only on the presence of an amphiphilic helix, efforts were undertaken to design amphiphilic helical β-peptides as potential antimicrobials.

Hamuro et al.[121] and Liu and DeGrado[119] designed two related classes of antimicrobial β-peptides based on repeating tri-β-peptide sequences of β^3HVal-β^3HLys-β^3HLeu ($^{\beta}$VKL), β^3HLeu-β^3HLys-β^3HLeu ($^{\beta}$LKL), or β^3HAla-β^3HLys-β^3HVal ($^{\beta}$AKV). β-Peptides with at least three trimer repeats showed 14-helical conformation by CD in the presence of lipid micelles and inhibited the growth of *Escherichia coli* at micromolar concentrations [except $(^{\beta}\text{LKL})_{5-6}$, which aggregated in phosphate-containing media]. β-Peptides with only two repeats were not



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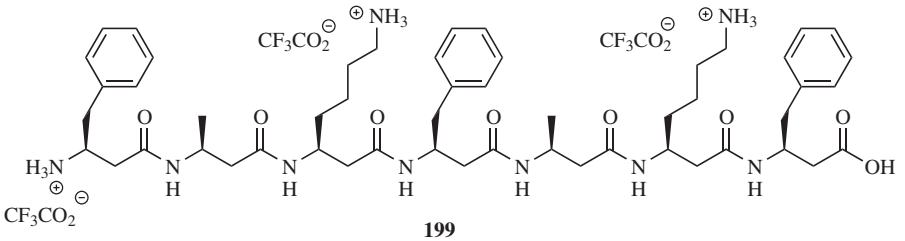

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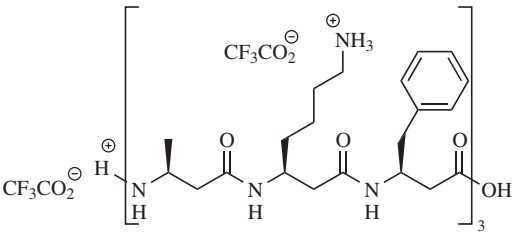

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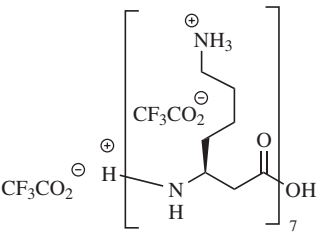

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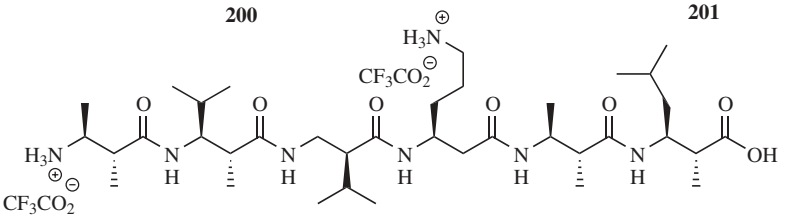

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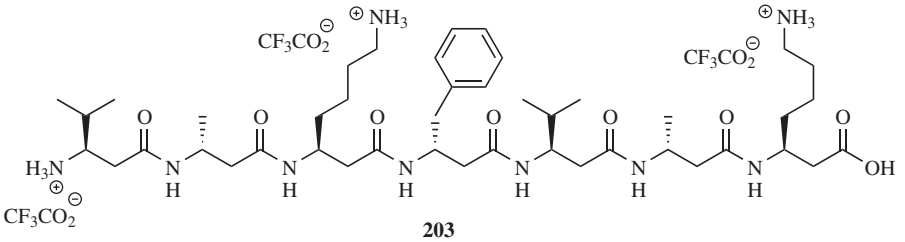


203

Figure 22.22 β-Peptides synthesized by Werder et al. for lipid uptake inhibition studies.[155] **198**–**200** should be competent to form amphiphilic 14-helix; **201**–**203** should be incapable of doing so.

helical in the micellar environment and showed no antibacterial activity. The relative IC_{50} values (concentrations required to inhibit 50% of bacterial growth) of the dodeca-β^3-peptides tested followed the relationship Fmoc-($^{\beta}$VKL)$_4$ > H-($^{\beta}$LKL)$_4$ > H-($^{\beta}$VKL)$_4$ > H-($^{\beta}$AKV)$_4$, suggesting a correlation between hydrophobic content and antimicrobial potency.

As a model for toxicity to mammalian cells, the hemolytic activities of these β-peptides against human erythrocytes were evaluated. The same qualitative order of activity was observed for these β-peptides, but hemolytic activity dropped off much more steeply than antibacterial activity with the same decrease in hydrophobic content. Thus, whereas the IC_{50} against *E. coli* of H-($^{\beta}$AKV)$_4$ was double that of H-($^{\beta}$VKL)$_4$, HC_{50} (concentration at which 50% of red blood cells are hemolyzed) for H-($^{\beta}$AKV)$_4$ was 25-fold higher than that of H-($^{\beta}$VKL)$_4$.[119] Therefore, H-($^{\beta}$AKV)$_4$ is roughly 10-fold more selective for bacterial cells over mammalian cells, suggesting that a trade-off exists between activity and selectivity. These differences in cytolytic activity correlated with differences in β-peptide binding to anionic and zwitterionic phospholipid vesicles, which are simplistic models for bacterial and mammalian cell membranes, respectively. Hexa-β^3-peptides, which were incompetent to form 14-helix in the presence of micelles, showed no hemolytic activity, suggesting that helicity is required for cytolytic activity against both bacterial and mammalian cells.[121]

Using Hamuro's H-($^{\beta}$VKL)$_3$ as a point of comparison, Raguse et al. investigated whether using ACHC to force 14-helical conformation would affect cytolytic activity against four bacterial species and human erythrocytes.[37] β-Peptides were generally synthesized with C-terminal amides, because amidation is known to increase the potency of some antimicrobial α-helical α-peptides.[163] These workers examined an unamidated β-peptide, all-(*R*)-H-($^{\beta}$VKL)$_3$, and found it to be 10- to 100-fold less potent than its amidated counterpart. Because this work was undertaken before the development of the third-generation ACHC synthesis, the β-peptides examined belonged to the right-handed 14-helical series; a single left-handed 14-helical control, all-(*S*)-H-($^{\beta}$VKL)$_3$-NH_2, showed activity indistinguishable from that of its enantiomer. A nonamphiphilic ''scrambled'' β-peptide, in which ACHC and β^3HLys residues alternated, showed only minimal activity, which demonstrates the importance of global amphiphilicity for antimicrobial activity.

The four bacterial species examined included two laboratory strains (JM109, an *E. coli* K-strain, and *Bacillus subtilis* BR151) and clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE). Two series of β-peptides were examined: a nona-β-peptide series of all-(3*R*) H-($^{\beta}$VKL)$_3$, all-(3*R*) H-($^{\beta}$CyKL)$_3$, and all-(3*R*) H-($^{\beta}$CyCyK)$_3$ (where Cy = ACHC), and a deca-β-peptide series **172**, **175**, and **176** (Fig. 22.11). Despite wide variation in the intensity of the aqueous 14-helical CD signal within each series, all six of these β-peptides showed indistinguishable activity (MIC, minimum concentration required to inhibit bacterial growth) against each bacterial species. This consistent activity correlates with the uniformly 14-helical CD spectra of these β-peptides in 60% TFE, a structure-promoting solvent[164] that has been suggested to

mimic the membrane environment.[165] Similar activity for the three nona-β-peptides was also seen in a cell leakage assay with *B. subtilis*. Hemolytic activity seemed to correlate slightly with ACHC content and aqueous 14-helicity for the nona-β-peptide series, but not for **172**, **175**, and **176**. Thus, it appears that constrained residues do not improve the cytolytic activity of 14-helical β-peptides.[37] This conclusion dovetails with results obtained with heterochiral and cyclized α-peptides that suggest that conformational stability per se is not a major determinant of activity.[166]

As Hamuro et al.[121] were developing their 14-helical antimicrobial β-peptide designs, Porter et al.[122] investigated an amphiphilic 12-helical design for the same purpose. β-Peptide 17-mer **204** (Fig. 22.23), also referred to as "β-17," was predicted to form a left-handed 12-helix with two-fifths of its helical circumference occupied by cationic (*R*,*S*)-APC residues and the remaining three-fifths occupied by hydrophobic (*R*,*R*)-ACPC residues (Fig. 22.24). This β-peptide was assayed for inhibitory activity (MIC) and cell killing (MBC, minimal bactericidal concentration) against *E. coli*, *B. subtilis*, MRSA, and VRE. For each species, the activity of **204** was comparable to that of a synthetic magainin derivative, which served as positive control. Shorter analogs of **204**, with 12 or 7 residues, showed little or no activity, respectively.[126] Like the ACHC-containing 14-helical antimicrobial β-peptides, **204** showed remarkably low hemolytic activity, lower than that of the magainin derivative. In vesicle model systems, **204** showed stronger binding and lytic activity toward anionic phospholipid vesicles (a model for prokaryotic cell membranes) than toward zwitterionic vesicles (a model for eukaryotic cell membranes).[168] This result is similar to those obtained for 14-helical β-peptides.[119]

In an effort to optimize the activity of 12-helical antimicrobial β-peptides, variant sequences **205**, **207**, and **208** (Fig. 22.23) were examined. Nonamphiphilic

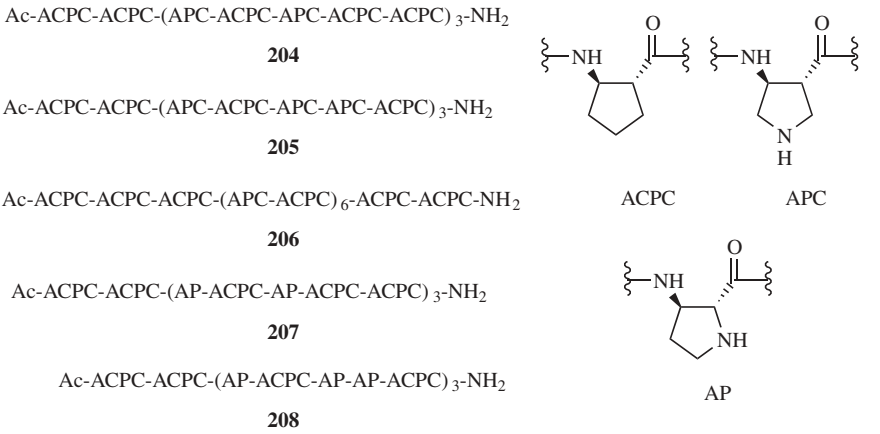


Figure 22.23 A series of 17-residue β-peptides constructed entirely of 5-constrained residues.[167]

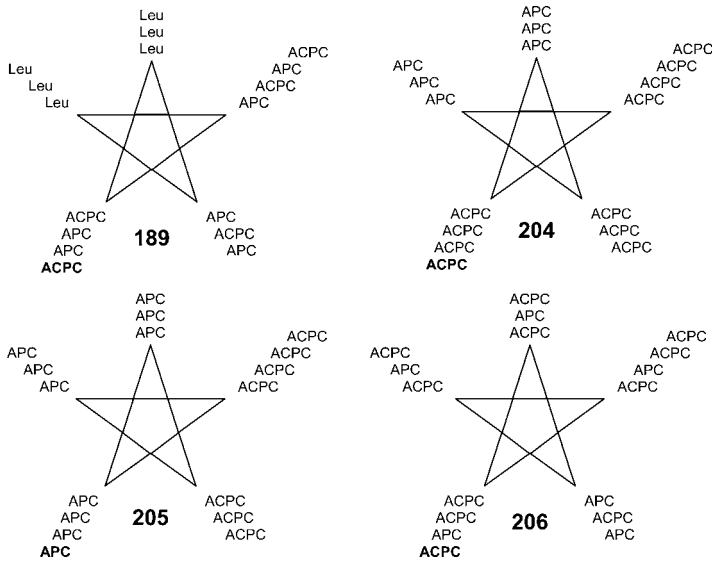


Figure 22.24 Helical wheel diagrams for **189** and **204**–**206**. Boldface: N-terminal residue. N → C direction is counterclockwise.

''scrambled'' sequence **206**, which has cationic residues evenly distributed around the helical circumference, was examined as a negative control.[167] β-Peptide **189** (Fig. 22.16), which incorporates β^3-residues along with 5-constrained residues, was also studied.[125] In sequence **205**, the helical circumference is three-fifths APC and two-fifths ACPC, giving a larger sector of cationic residues than in **204** (Fig. 22.24). β-Peptides **207** and **208** are analogs of **204** and **205**, respectively, in which APC is replaced by the isomeric AP residue. The design of **189** is distinct from that of **204**, **205**, **207**, and **208** in its hydrophobic/lipophilic pattern: **189** spreads six APC residues over three-fifths of the helical circumference and concentrates six β^3HLeu residues on two-fifths of the circumference as a hydrophobic sector.

Replacement of APC in **204** by AP, to give **207**, caused a modest decline in activity. However, both β-peptides with smaller hydrophobic sectors (**205** and **208**) had very limited activity. Porter et al. hypothesized[167] that the ACPC residue is less hydrophobic than the alkyl residues that form the hydrophobic helical faces of antimicrobial α-peptides, for which a smaller hydrophobic sector is optimal.[157] β-Peptide **189** showed activity similar to that of **204**,[125] but it is difficult to draw conclusions from these data because **189** differs from the **204**–**208** series in both residue identity and cationic residue distribution. The similarity of **204** and **189** does show, however, that a highly preorganized 12-helix is not required for antimicrobial activity.

Hydrophobicity is believed to correlate more highly with hemolytic activity than with antimicrobial potency.[169] In support of this hypothesis, **207** and **208** were not hemolytic.[167] The more hydrophobic **204** and to a lesser extent **205** were hemolytic,

but less so than the magainin derivative, an α-peptide positive control for antimicrobial activity. Scrambled β-peptide **206**, included as a nonamphiphilic negative control, was also nonhemolytic. β-Peptide **189**, on the other hand, was more hemolytic than **204** and roughly as hemolytic as the magainin analogue, suggesting that the β^3HLeu residue may be more hydrophobic than ACPC in a membrane context.[125]

The mechanistic basis for 12-helical β-peptides' cytotoxic activity has been investigated. Both **204** and **205** permeabilized *B. subtilis* cell membranes, as assayed by leakage of a cellular enzyme, with similar potency to magainin and to melittin, a cytotoxic amphiphilic α-peptide found in bee venom.[167] Leakage induced by **204** was studied further using large unilamellar vesicles (LUVs) of varying lipid compositions.[168] These studies showed that leakage correlated with the measured intrinsic negative curvature of the membrane lipids. Calorimetric data confirmed that **204** decreases membrane curvature, an effect opposite to the toroidal-pore-forming effect of magainin.[170] The significance of this result is poorly understood and a subject for future study.

22.5.3 Protein Prosthesis

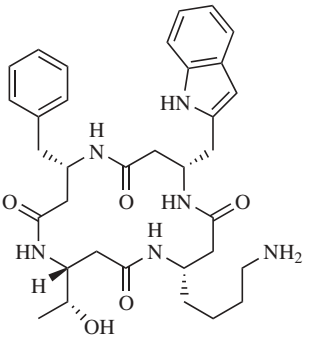
Huck et al. have reported IR and NMR evidence that the (*R*)-Nip–(*S*)-Nip reverse turn can replace the loop region in an α-peptide hairpin model system, that is, a molecule in which α-amino acid residues form the strands, rather than the syn-$\beta^{2,3}$-residues in **192**.[171] Arnold et al. carried this finding further, using expressed protein ligation to construct a semisynthetic analog of ribonuclease A (RNase A) in which the Asn113–Pro114 di-α-peptide segment, which forms the center of a type VI reverse turn, is replaced by (*R*)-Nip–(*S*)-Nip.[124] Enzymatic activity of this chimeric protein was indistinguishable from that of wild-type RNase A, and the chimeric protein showed slightly increased conformational stability, as evidenced by an increased T_m. On the other hand, replacement of Asn113–Pro114 by a homochiral (*R*)-Nip–(*R*)-Nip sequence almost completely inactivated the protein. This result raises the possibility that other secondary structural elements in proteins can be replaced by unnatural foldamer segments.

22.5.4 Hormone Mimicry

The β-peptide backbone has been employed by Gademann et al. as a scaffold for mimicry of the human hormone somatostatin.[172] Cyclic tetra-β-peptide **209**, composed entirely of β^3-residues, adopts a conformation similar to that of the pharmaceutical somatostatin analog octreotide, a cyclic α-peptide. Cyclic tetra-β-peptide **209** also binds all five human somatostatin receptor subtypes with micromolar affinity, one to five orders of magnitude less tightly than does octreotide.

To take fuller advantage of the structure-forming capabilities of β-peptides, Gademann et al. also synthesized linear tetra-β-peptide **210**, which contains a β^2HLys residue.[173] Circular dichroism and NMR spectroscopy suggest that **210**

may adopt a turn structure similar to that seen in **197** (see above, Fig. 22.21). Intriguingly, although linear tetra-β-peptide **210** bound modestly if at all to somatostatin receptor subtypes 1, 2, 3, and 5, it displayed selective mid-nanomolar affinity for somatostatin receptor subtype 4, a receptor of uncertain clinical significance which is the subject of ongoing investigation. This binding was abolished in linear all-β^3 analog **211**, where neither the putative turn-forming constraint of the β^2–β^3 sequence nor the constraint of cyclization is present.



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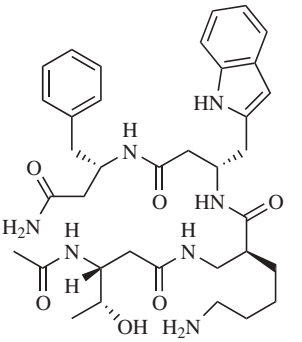
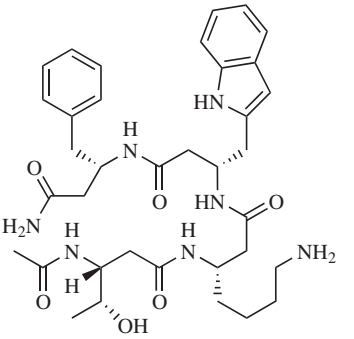


210



211

22.5.5 Other Biological Applications of β-Peptides

The proteolytic stability of β-peptides has inspired additional studies into their possible biological applications. An undeca-β^3-peptide was recently reported to bind the HIV-1 TAR RNA hairpin, a response element which controls a critical step in the viral life cycle, with nanomolar affinity.[174] The β-peptide also showed better selectivity for wild-type TAR RNA over a mutant RNA than did α-peptide analogs.

Several groups, inspired by reports of cationic α-peptides that enable protein or drug payloads to cross cell membranes,[175] have investigated the cell uptake of highly cationic β-peptides. Fluorescence-labeled oligomers of β^3HLys have been reported to enter cells and localize to the nucleus.[176,177] β^3HArg oligomers were internalized to a greater extent, but β-peptides bearing less positive charge were not internalized.[176] Although one report has shed some doubt on cell viability and membrane integrity in early α- and β-peptide experiments, recent studies of the fluorescein-labeled trideca-β-peptide Fl-βHGly-$(\beta VRR)_4$-NH_2 confirm that at least some cationic β-peptides are taken up by living cells with intact membranes and point to an endosomal escape mechanism for peptide access to the cytoplasm.[178]

22.6 NEW FRONTIERS FOR β-PEPTIDE STRUCTURE

The future should hold advances in β-peptide chemistry on at least four fronts:

1. Improvements in the synthesis of β-amino acids will both increase the pool of viable monomers for β-peptide synthesis and decrease the still-significant costs, in materials and labor, associated with generating an appropriate monomer pool. In particular, 3-constrained β-amino acids[145,179] may generate new and unexpected structures.
2. The field of β-peptide synthesis will mature. Conditions will be optimized for the synthesis of difficult sequences. The synthesis of large libraries ($\sim$10,000 members) may become feasible.
3. Insight will be gained into subtle effects of β-peptide sequence on conformation. Novel secondary structures, such as the 8-helix,[23] will be developed to allow maximum residue diversity while still enforcing stable, robust, regular conformations. Elements of secondary structure will be combined to create tertiary structure and β-peptide oligomers that fold with proteinlike complexity.
4. Finally, new applications to biology and medicine will be successfully addressed by β-peptides.[4,180] Among the promising fields for such applications are biomaterials, signal transduction, artificial biocompatible catalysts, and gene delivery.

These prospects make it an exciting time to be working with β-amino acids and β-peptides. The structural control afforded by constrained residues is sure to play a key role in future advances.

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CHAPTER 23

β^2-Amino Acids with Proteinogenic Side Chains and Corresponding Peptides: Synthesis, Secondary Structure, and Biological Activity

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23.1 INTRODUCTION

The field of peptidomimetics has been revolutionized by the work of Seebach, Gellman, and others, who have shown that β-peptides adopt secondary structures analogous to those found in proteins and α-peptides.[1] Furthermore, it has been shown that these unnatural peptides possess remarkable stability against a wide range of proteolytic enzymes, making them possible targets for pharmaceutical applications. The goal of this chapter is to provide an overview of the relevance and development of β-peptides as peptidomimetics through the use of β^2-amino acids with proteinogenic side chains as chiral building blocks, and it is intended to complement Matthews's report on β^3-amino acids in the previous edition of this book.[2] Clearly, when generally referring to β-amino acids and corresponding peptides, one must consider Seebach's work fundamental, since he has discovered and extensively investigated such conformationally unrestricted foldamers. His foresight deserves the best credit, considering that prior to his seminal elucidation of the 3_{14}-helical structure of β-peptides in 1996, experts believed that the degrees of rotational and conformational freedom introduced by additional CH_2 units in a peptide backbone would lead to destabilization of secondary structure. It is

This chapter is dedicated to Professor Dieter Seebach.

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presumably because of this destabilization effect that Gellman and others[3] have chosen to use cyclic, conformationally restricted amino acids for the construction of β-peptides. On the contrary, the merit of Seebach's approach further stands out in view that only a methylene unit has been incorporated onto natural α-amino acids. This small tactical change has allowed him to make a fair comparison between α- and β-peptides,[4] a fact that he has ingeniously exploited to make numerous biologically active β-peptides.

The relevance of β^2-amino acids in the architecture of β-peptides can only be realized by understanding the general rules dictating the secondary structure of peptides. Contrary to α-peptides, the secondary structure of which is governed by finely tuned sequences of α-amino acids,[5] the secondary structure of β-peptides is not so much determined by sequence specificity but rather by amino acid type/substitution [e.g., β^2, β^3, $\beta^{2,3}$, *trans*-2-aminocyclopentanecarboxylic acid (ACPC), *trans*-2-aminocyclohexanecarboxylic acid (ACHC)]. For instance, the architecture of turns in acyclic α-peptides invariably contains the elements Pro and/or Gly,[5] whereas Seebach has shown that, by using a β^2/β^3-amino acid motif, various sequences of amino acids, carrying Try, Lys, and Val side chains, can be used in the construction of β-peptidic turns.[6] A similar argument can be used to describe helix behavior*. Thus β^2-amino acids are valuable building blocks for the engineering of β-peptides because, when properly incorporated, they generate novel secondary structures such as turns and 3_{14}- and 10/12-helices. Thus, recently, the Seebach group has devoted considerable effort to the enantioselective synthesis of β^2-amino acids with the 20 proteinogenic side chains.[7]

23.2 SYNTHESIS OF β^2-AMINO ACIDS

Given the significance of β-amino acids, it is not surprising that their enantioselective synthesis has become an important and challenging endeavor for organic chemists. Numerous methodologies have appeared in the literature, and the subject has been extensively reviewed.[8]

However, a new challenge has recently emerged with the preparation of β^2-amino acids carrying proteinogenic side chains. Most syntheses of β^2-amino acids to date involve the use of chiral auxiliaries, and although many of these strategies lead to enantiomerically pure amino acids, their scope is usually limited to amino acids with the (trivial) side chains of Val, Ala, Phe, and Leu. Furthermore, for applications involving state-of-the art solid-phase peptide synthesis, it is crucial to have access to properly derivatized β^2-amino acids. Fortunately, Seebach et al. have addressed these issues and reported the synthesis of β^2-amino acids with 17 of the 20 proteinogenic side chains. In addition, the preparation of nine β^2-amino acids for Fmoc solid-phase peptide synthesis has also been described.[7]

*It turns out that for β-peptides amino acid type/substitution determines helix structure (3_{14}, 2.5_{12}, 10/12, etc.); however, amino acid sequence is still important for the stabilization of such secondary structures (salt bridges, hydrogen bonding, etc.).

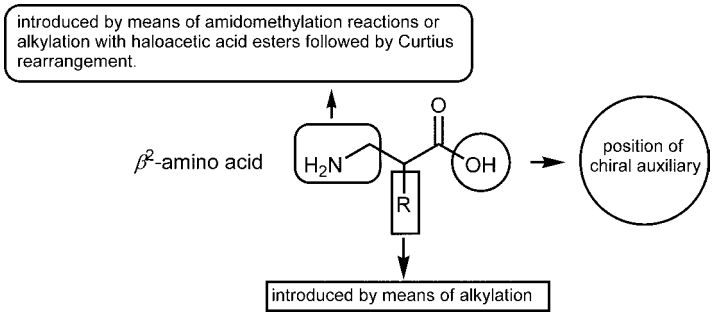


Figure 23.1

23.2.1 Synthesis of β²-Amino Acids Based on Chiral Auxiliaries

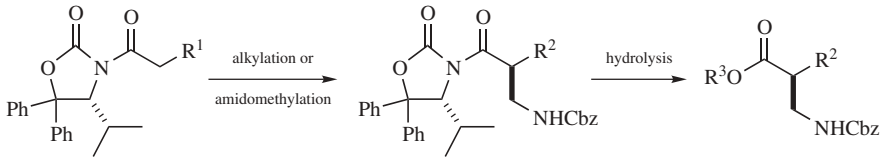
Synthetic approaches to β^2-amino acids based on chiral auxiliaries generally involve the use of either diastereoselective alkylation of 3-aminopropionic acid derivatives to introduce the desired side chain in the α-position of the amino acid or amidomethylation reactions (Mannich-type reactions) to introduce the aminomethyl moiety to α-substituted ethanoic acid derivatives. Alternatively, the amino group can be introduced by means of consecutive alkylation with haloacetic acid esters and subsequent *Curtius* rearrangement of this functionality (Fig. 23.1).

23.2.1.1 Methods Based on Evans's Auxiliary (Type) Derivatives

Evans's methodology is by far the most widely used strategy in the preparation of β^2-amino acids due to the efficiency and high degree of stereoselectivity. Furthermore, this type of auxiliary is easily introduced through activated carboxylic acid derivatives (acid chlorides or anhydrides) and is then removed under basic conditions. Evans et al. were also the first to demonstrate that $^{+}CH_2NH_2$ synthons such as $BzNHCH_2Cl$ and $CbzNHCH_2OMe$ can be effectively used as electrophiles in the amidomethylation of oxazolidinone-3-acyl enolates to prepare β^2-amino acid (β^2-Glu) precursors.[9]

Methods Based on 4-Isopropyl-5,5-diphenyloxazolidin-2-one (DIOZ) The DIOZ auxiliary developed by Seebach is a very useful variation of Evans's chiral auxiliary, which has the following desirable characteristics: (1) its reactions display a high degree of diastereoselectivity; (2) its derivatives are highly crystalline; (3) it is easily removed under basic conditions; (4) it is easily recovered and purified. Seebach has thoroughly demonstrated the use of 3-acyl-DIOZ derivatives for the synthesis of β^2-amino acids (Scheme 23.1). His strategy makes use of diastereoselective amidomethylation (Mannich-type reactions), aldol reactions, or alkylation reactions of corresponding 3-acyl-DIOZ enolates.

Furthermore, to have functional group compatability during these C–C bond-forming reactions, it was necessary to employ enolates of Li, B, or Ti depending on the side chains of the corresponding amino acids. Specifically, boron enolates



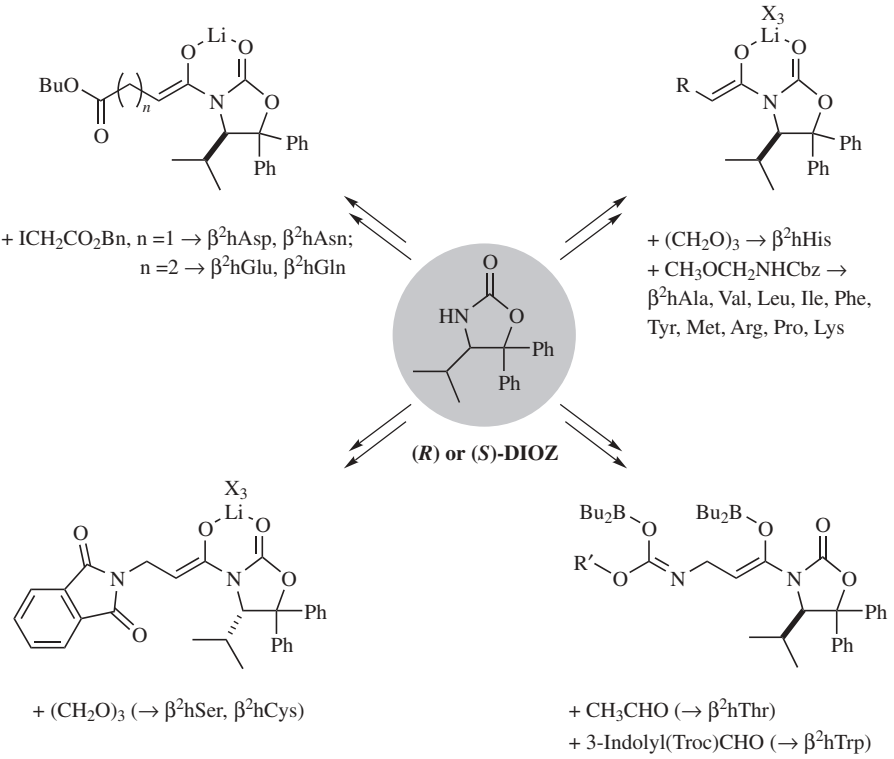
3-acyl-DIOZ derivatives

R^2 = alkyl or functionalized alkyl

R^1 = alkyl or functionalized alkyl or CH_2NHCbz

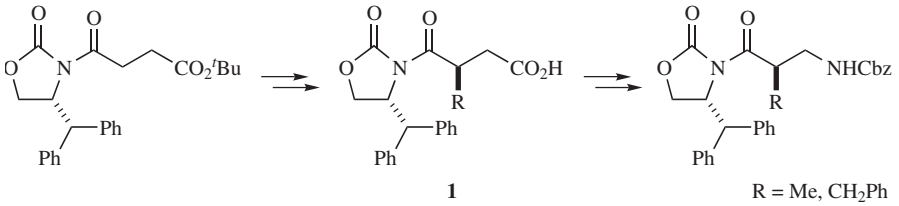
Scheme 23.1 Use of 3-acyl-DIOZ derivatives for preparation of β²-amino acids.

served for aldol reactions in the preparation of β²hTrp and hThr.[7] Lithium enolates were used for alkylation reactions in the preparation of β²hAsp, hAsn, hGlu, and hGln.[10] Titanium enolates were employed for amidomethylation and aldol reactions in the preparation of β²hAla, hVal, hLeu, hIle, hPhe, hTyr, hMet, hArg, hPro, hLys, hSer, hHis, and hCys.[7,11] Total yields range between 55 and 90% with diastereoselectivities generally >80% (Scheme 23.2).



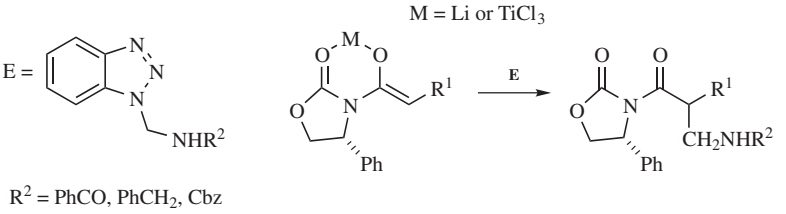
Scheme 23.2 Preparation of β²-amino acids by use of Ti, Li, or B enolates derived from 3-acyl-DIOZ derivatives.

Methods Based on 4-Diphenylmethyl-oxazolidin-2-one Sibi and Deshpande used succinic acid derivatives for the preparation of β²-hAla and hPhe.[12] The method is based on the diastereoselective alkylation of 3-acyl-4-diphenylmethyl-oxazolidin-2-one followed by *Curtius* rearrangement of advanced intermediate **1** to introduce the amino functionality (Scheme 23.3).[12]



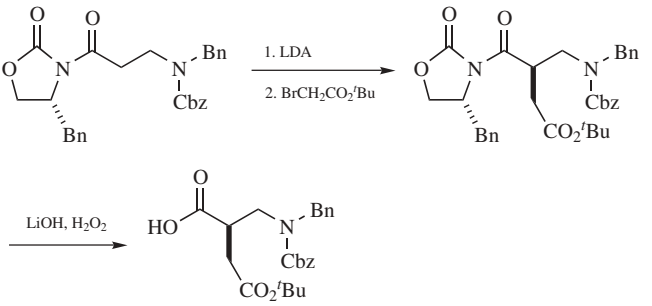
Scheme 23.3 Preparation of β²-amino acids using succinic acid derivatives.

Methods Based on 5-Methyl-4-phenyloxaxolidin-2-one Arvanitis et al. have examined the use of various $^{+}CH_2NH_2$ synthons in *Mannich*-type reactions with 3-acyl-5-methyl-4-phenyloxazilidin-2-one (Scheme 23.4).[13] In general, the benzotriazole derivatives **E** were found to be unreactive toward Ti enolates when the α-substituent (R^1) was other than an aromatic; nevertheless this shortcoming was circumvented by employing Li enolates instead. Alternatively, in the case of substrates having alkyl substituents, it was also possible to use Ti enolates in combination with the more reactive $ZNHCH_2OAc$ electrophile. This approach led to β²hAla and hPhe.



Scheme 23.4 Use of different electrophiles for amidomethylation of 3-acyl-5-methyl-4-phenyloxazilidin-2-one enolates.

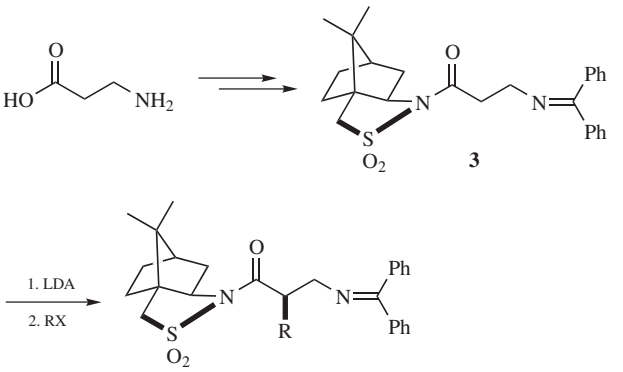
Methods Based on 4-Benzyloxazolidin-2-one Xue and co-workers have prepared a β²hAsp derivative as an intermediate for the synthesis of piperidinedicarboxylic acids.[14] This β²-amino acid intermediate was prepared by diastereoselective alkylation of 3-aminopropionic acid derivatives with *tert*-butyl bromoacetate. Removal of the oxazolidinone chiral auxiliary under basic conditions led to the desired β²hAsp intermediate **2** (Scheme 23.5).[14]



Scheme 23.5 Alkylation of 3-aminopropionic acid derivatives with *tert*-butyl bromoacetate.

23.2.1.2 Methods Based on Oppolzer's Sultam Chiral Auxiliary

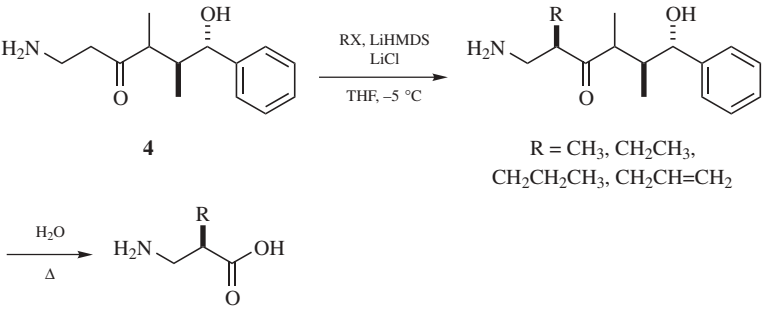
Ponsinet and co-workers[15] have used diasterereoselective alkylations of lithium enolates derived from sultam-β-alaninates **3** in the preparation of Boc-β²(hAla, hLeu, and hPhe). One advantage of this procedure is complete diastereoselectivity of alkylation, which afford enantiomerically pure amino acids after removal of the chiral auxiliary and *N*-deprotection (Scheme 23.6).



Scheme 23.6 Preparation of β²-amino acids using sultam-β-alaninates.

23.2.1.3 Methods Based on Pseudoephedrin as Chiral Auxiliary

Myers et al.[16] have shown that pseudoephedrine can be used as an inexpensive chiral auxiliary in the stereoselective synthesis of β²-amino acids. The key step involves alkylation of lithium enolates generated from **4**. Unfortunately this method suffers a major drawback, namely separation of corresponding diastereomers, which was not possible to achieve even by high-performance liquid chromatography (HPLC). For this reason the enantioselectivity (75–99% ee) was determined by gas chromatography (GC) on a Chirasil-Val capillary column using trifluoroacetamide derivatives (Scheme 23.7).[17]

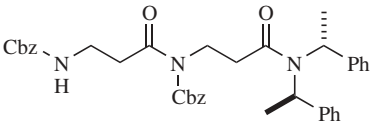


Scheme 23.7 Use of pseudoephedrine as chiral auxiliary.

23.2.1.4 Synthetic Methods Based on Stereoinduction of α-Phenylethyl Groups For the preparation of β²-amino acids (β²hAla and β²hPhe), Juaristi et al.[18] have explored the use of α-phenylethyl groups as stereoinducing moiety in diastereoselective alkylations of β-aminopropionic acid derivatives. Their investigation screened a number of α-phenylethyl groups (Masamune's theory) and found that substrate **5** was particularly effective, giving rise to 80% ds. It is worth mentioning that Akssira et al. also previously explored double stereoinduction of menthyl- and 2-hydroxypinan-3-ylidene moieties in the methylation of 3-aminopropionic acid derivatives for the preparation of β²hAla (Figure 23.2).[19]

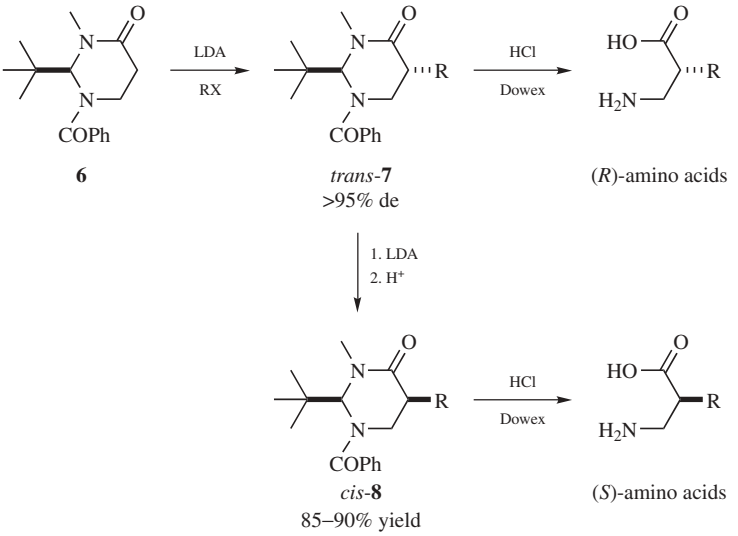
23.2.2 Synthesis of β²-Amino Acids Based on Pyrimidinone Derivatives

23.2.2.1 Methods Based on 2-tert-Butylperhydropyrimidin-4-one Derivatives The alkylation of heterocyclic 2-*tert*-butylperhydropyrimidin-4-one **6**, prepared from commercially available L-asparagine, has been extensively studied by Juaristi et al.[20] The addition of various electrophiles to enolates derived from **6** gave high stereoselective control (>95% de) providing the trans-alkylated products **7** in good yields (Scheme 23.8). Hydrolysis of these intermediates (**7**) to the corresponding (*R*)-β²-amino acids (β²hAla, hPhe) was accomplished under acidic conditions. Alternatively, the corresponding (*S*)-β²-amino acids were prepared from the cis adducts **8**, which in turn were conveniently derived from



5

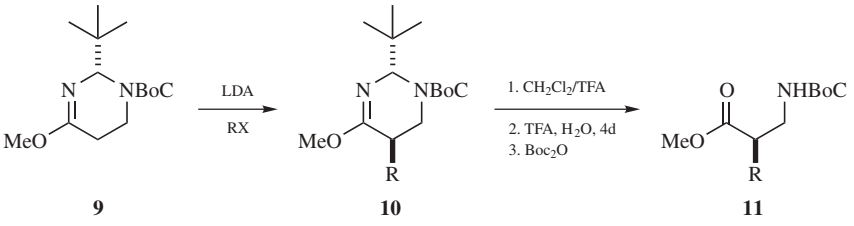
Figure 23.2



Scheme 23.8 Preparation of β²-amino acids using 2-*tert*-butylperhydropyrimidin-4-ones.

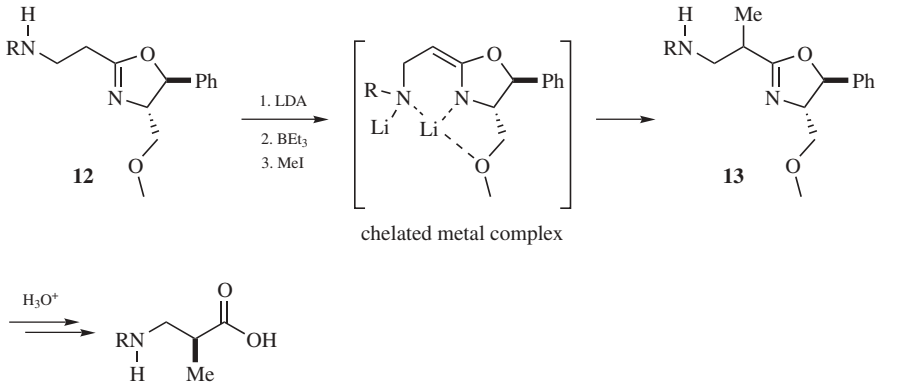
the trans adducts **7** using diastereoselective protonation of the corresponding enolates (Scheme 23.8).

23.2.2.2 Methods Based on 2-tert-Butyltetrahydropyrimidine Derivatives Seebach et al.[21] have prepared β²-amino acids by stereoselective alkylation of hydropyrimidine **9** enolates. The pyrimidine derivative **9** was first obtained as a racemic mixture from 3-amino propanoic acid and was subsequently resolved by chiral chromatography. Alkylation of enolates derived from **9** proceeded smoothly with complete stereocontrol (electrophile attacks the less hindered phase of the enolate) and high yields (Scheme 23.9). The β²-amino esters **11** (β²hAla, β²hPhe) were obtained after a three-step deprotection sequence from **10**.



Scheme 23.9 Preparation of β²-amino acids using 2-*tert*-butyltetrahydropyrimidine.

23.2.2.3 Methods Based on 2-(N-Benzenesulfonylaminoethyl)-4-(methylmethoxy)-5-phenyloxazoline Rottman and co-workers prepared β^2hAla using diastereoselective methylation of the lithium enolate derived from **12**.[22] First attempts to alkylate such enolates gave poor yields and low diastereoselectivities due to intramolecular metal chelation, so it was necessary to use BEt_3 as an additive to break up the complex (Scheme 23.10).[22] Thus, the methylation was improved from 20% yield and diastereomeric ratio of 64:36 to 80% yield and diastereomeric ratio of 90:10 upon BEt_3 addition. The *N*-benzenesulfonylamino acid was obtained after hydrolysis of the oxazoline **13**.

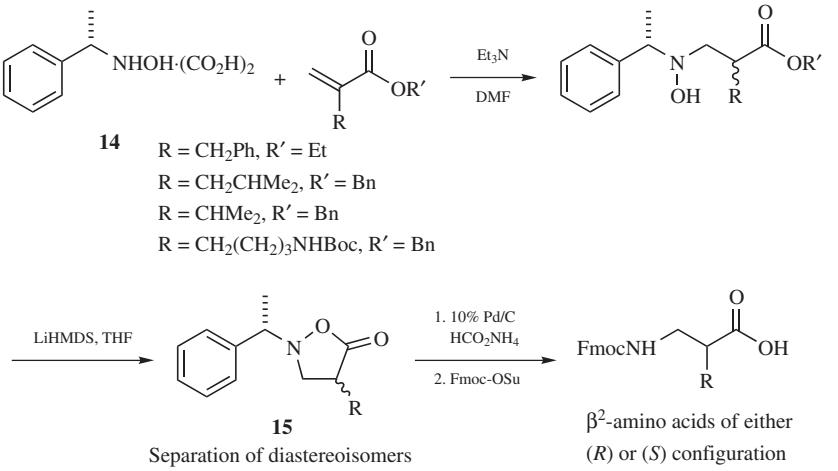


Scheme 23.10 Preparation of β^2-amino acids using 2-(*N*-benzenesulfonylaminoethyl)-4-(methylmethoxy)-5-phenyloxazoline.

23.2.3 Synthesis of β²-Amino Acids Based on 1,4-Conjugate Additions

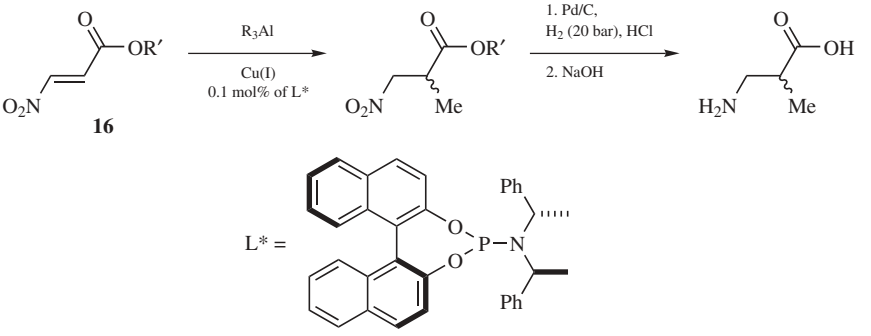
23.2.3.1 Methods Based on Nitrogen Nucleophiles Lee and co-workers have reported a practical and scalable method for the preparation of β^2-amino acids.[23] This approach uses a nondiastereoselective 1,4-addition of chiral hydroxylamine **14** to 2-substituted acrylate esters followed by base-promoted cyclization of the Michael adducts to the corresponding isoxazolidinone derivatives **15**, which were obtained as mixtures of diastereomers. The diastereomers were subsequently separated by column chromatography and transformed to β^2-amino acids (hLeu, hPhe, hVal, and hLys) of either (R) or (S) configuration after functional group deprotection by hydrogenolysis over Pd on carbon (Scheme 23.11).[23] A similar approach based on the resolution of methyl *N*-α-methylbenzyl-3-amino-2-methylpropionate obtained by 1,4-addition of *N*-α-methylbenzylamine to 2-methyl acrylates was employed in the preparation of β^2hAla.[24]

23.2.3.2 Methods Based on Carbon Nucleophiles The Cu-catalyzed stereoselective Michael addition of trialkyl aluminum to 3-nitro acrylates **16** has



Scheme 23.11 Preparation of β²-amino acids based on diastereoisomeric resolution of isoxazolidinone derivatives.

been used to prepare β²-amino acids (β²hAla and β²hLeu) with enantiomeric excesses up to 92%. Chemical yields and stereoselectivities were strongly dependent upon the nature of the alkyl aluminum reagent, being optimum for trimethyl aluminum (Scheme 23.12).[25] A similar Cu-catalyzed addition of diethylzinc to nitroolefins has also been reported.[26]

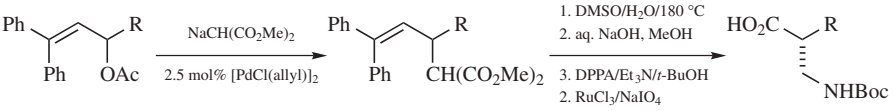


Scheme 23.12 Enantioselective addition of trialkyl aluminum to 3-nitro acrylates.

23.2.4 Synthesis of β²-Amino Acids Based on Nucleophilic Substitution of π-Allylpalladium Intermediates

Williams and co-workers have explored a unique approach to β²-amino acids (β²hAla) which employs the well-established palladium-catalyzed asymmetric allylic substitution with malonate nucleophiles.[27] The desired homoallylic malonate

intermediates **17** were obtained in good yields and high enantioselectivity (>95% ee). Ester hydrolysis and decarboxylation of **17** followed by *Curtius* rearrangement and oxidative cleavage of the double bond led to β^2-amino acid derivatives **18** without loss of enantioselectivity (Scheme 23.13).[27]



17
95–99% ee

18

Scheme 23.13 Preparation of β^2-amino acids by Pd-catalyzed asymmetric allylic substitution.

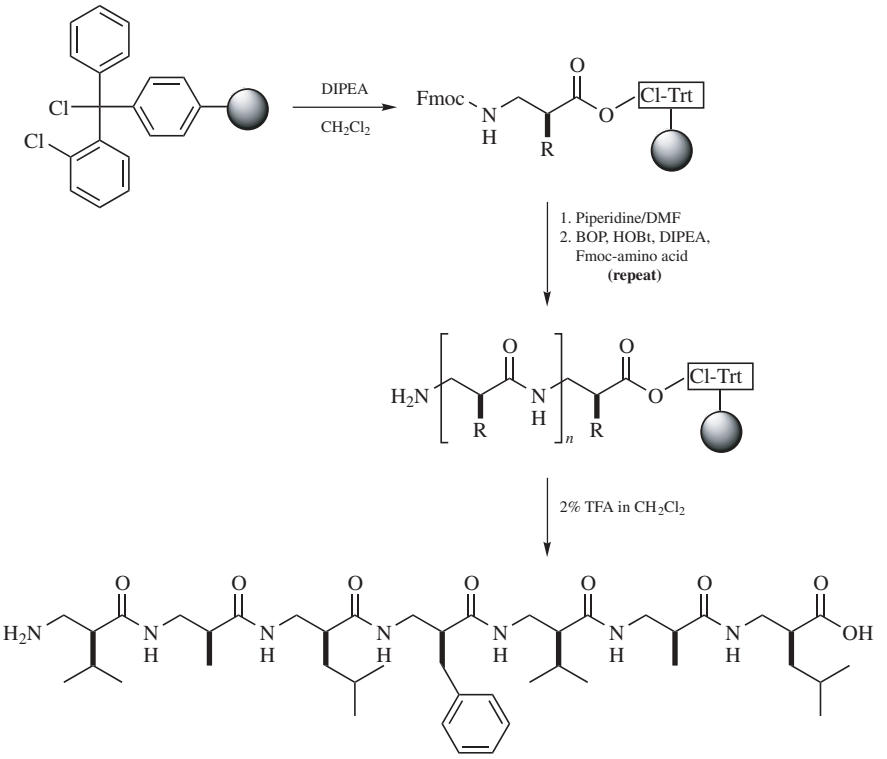
23.3 SOLUTION AND SOLID-PHASE SYNTHESIS OF PEPTIDES CONTAINING β^2-AMINO ACIDS

β-Peptides have been prepared by the two well-established methodologies developed for α-peptides: (1) in solution synthesis and (2) in solid-phase peptide synthesis (SPPS). Thus, it is not surprising that modified procedures used for α-peptide synthesis are also commonly applied to β-peptides. Nevertheless, β-peptide synthesis requires special consideration due to either high cost or limited availability of β-amino acids. For instance, in the case of β^3-amino acids bearing proteinogenic side chains, 18 out of 20 are now commercially available, but their prices are still considerably high compared with α-amino acids. In the case of β^2-amino acids only 4 (β^2hAla, β^2hLeu, β^2hPhe, and β^2hPro) are currently on the market in enantiomerically pure form. From this point of view, SPPS procedures, in particular, must be customized to minimize the amount of amino acid required in each step. Another potential problem is the possibility of racemization during coupling of β^2-amino acids, which can occur by a mechanism similar to that of α-amino acids.[28]

Solution synthesis is most often used for the preparation of short peptides or for the coupling of preassembled peptidic fragments. Although this method is highly desirable due to the high efficiency of the coupling steps, requiring roughly a one-to-one stoichiometry of the coupling partners, the approach is quite laborious due to the need for purification of the peptide intermediate after each coupling step. The protocol usually involves the coupling of *N*-Boc-protected amino acid with a benzyl ester of another using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimidehydrochloride/1-hydroxy-1*H*-benzotriazole (EDC/HOBt) followed by purification and proper deprotection for the next coupling step. This procedure was used in the preparation of β^2- and β^2/β^3-tripeptides segments, which were then appropriately coupled to make hexa- as well as nonapeptides containing aliphatic side chains of Ala, Val, and Leu.[29] As a precautionary measure to reduce the risk of epimerization during synthesis, a weaker base *N*-methylmorpholine (NMM) was

used in place of Et_3N for the couplings steps. This method was also successfully applied for the challenging synthesis of a (*S*)-β²hPro hexapeptide using fragment condensation of two tripeptides.[30]

For the assembly of larger peptides, SPPS becomes the method of choice. This protocol does not require the purificacion of peptide intermediates. Therefore, not only is it more time efficient but also the common problems associated with peptide solubility are avoided all together during synthesis. Another advantage of this method is that the conditions required to cleave the final peptide from the resin simultaneously deprotects the functionalities of the side chains, yielding the fully deprotected peptide. Heptapeptide **19** was prepared from (*S*)-β²-amino acids by solid-phase peptide synthesis using an *ortho*-chlorotrityl-chloride resin as the solid support.[31] The resin was first loaded by esterification with *N*-Fmoc-protected β²hLeu, and after carrying out the routine series of Fmoc deprotections followed by amino acid couplings, the desired peptide **19** was isolated (Scheme 23.14). Unfortunately, the peptide contained some amounts of C-2 epimers, which made its purification tedious.



19

Scheme 23.14 Solid-phase peptide synthesis of β-peptides.

To avoid the problem of epimerization during couplings, Arvidsson and co-workers[28] developed a combined solution- and solid-phase approach for the preparation of peptides containing β^2-amino acids. Fmoc-protected dipeptide building blocks were first synthesized in solution and purified by conventional methods and subsequently used in solid-phase synthesis. This approach also makes the peptide synthesis more convergent and thus significantly reduces the number of steps, which is especially important in the preparation of longer peptides. For the SPPS of peptides containing β^2-amino acids, it is also common to use the Wang resin as solid support; for example, Rossi and co-workers prepared a hairpin-inducing β-octapeptide containing a single β^2hVal using such a resin.[32]

23.4 SECONDARY STRUCTURES OF PEPTIDES CONTAINING β^2-AMINO ACIDS

Before discussing details on secondary structure, one must understand that the local conformation about the C_α–C_β bond of component β-amino acids has a strong influence in the global secondary structure of β-peptides. Briefly, gauche conformations along the C_α–C_β bond favor helix formation as well as turns, while the trans conformation promotes sheet formation (Fig. 23.3).[33]

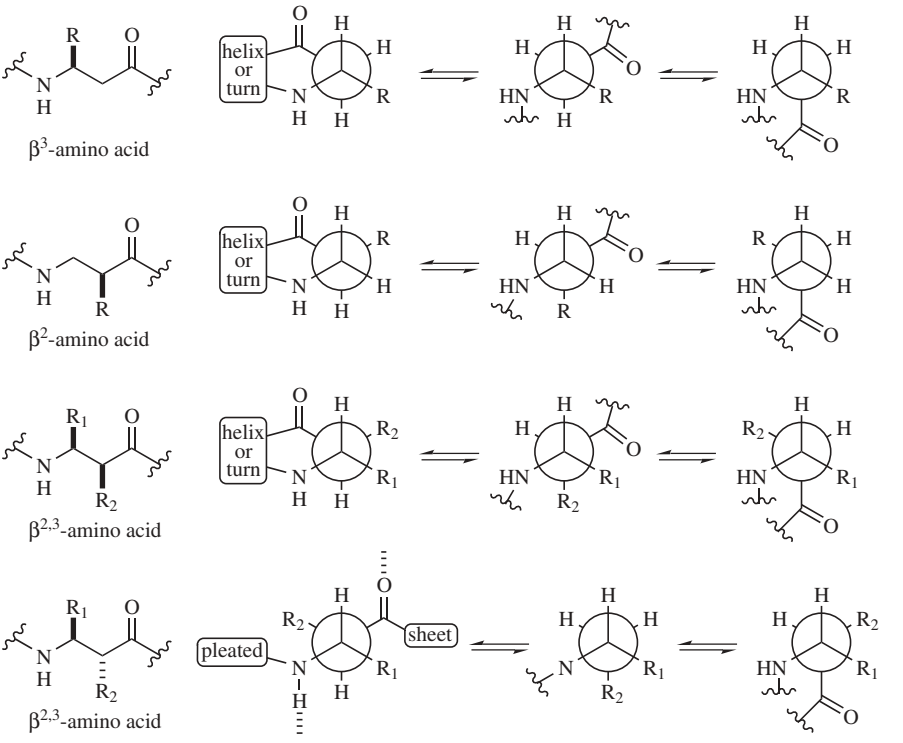


Figure 23.3 β-Amino acid conformations.

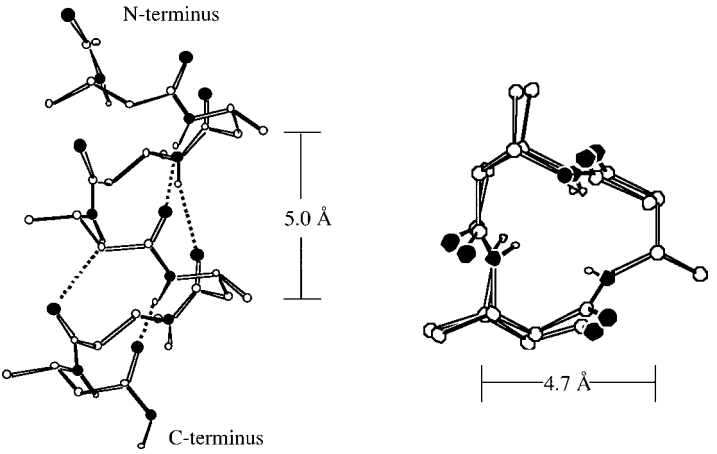


Figure 23.4 Side and top view of a 3_{14} helix.

Therefore, as a first approximation, the folding propensity of β-peptides can be envisaged based on amino acid type/substitution. Thus, as compared with α-peptides, modeling secondary structure of β-peptides[34] is relatively simple, which may partly explain why this peptidomimetic has attracted so much attention and has rapidly expanded.

23.4.1 Helix

23.4.1.1 The 3_{14}-Helix The geometrical characteristics of the 3_{14}-helix include a 5.0-Å pitch and a 2.4-Å radius with 14-membered hydrogen-bonded rings formed between the NH of residue i and the C = O of residue $i + 2$, which ultimately directs the helix macrodipole from the C- to the N-terminus. Furthermore, there are three amino acids per turn, placing residues i and $i + 3$ on top of one another. Figure 23.4 shows a schematic representation of a (M)-3_{14}-helix formed by peptides containing homochiral β^3-amino acids.[35] Helix handedness is actually determined by amino acid configuration, thus peptides containing (*R*)-β^3-amino acids (derived from corresponding (L)-α-amino acids) fold into (P)-helices while (*S*)-amino acids give rise to (M)-helices.

Seebach proposed that analogous peptides containing β^2-amino acids should also adopt a 3_{14}-helical conformation.[4] Nonetheless, the unfavorable positioning of the side chains in a helix formed by a β^2-peptide leaves the hydrogen donor NH groups more exposed to solvolysis than a β^3-peptide. To clarify this point, a top view of the helices formed by β^3- and β^2-peptides containing homologated amino acids derived from the corresponding (L)-α-amino acids Val, Ala, and Leu is shown in Figure 23.5.

Notice that the side chains of β^3-peptides provide more steric hindrance around the NH groups than that of corresponding β^2-peptides. As a result, β^2-peptides are expected to adopt less stable 3_{14}-helices. In agreement with these predictions,

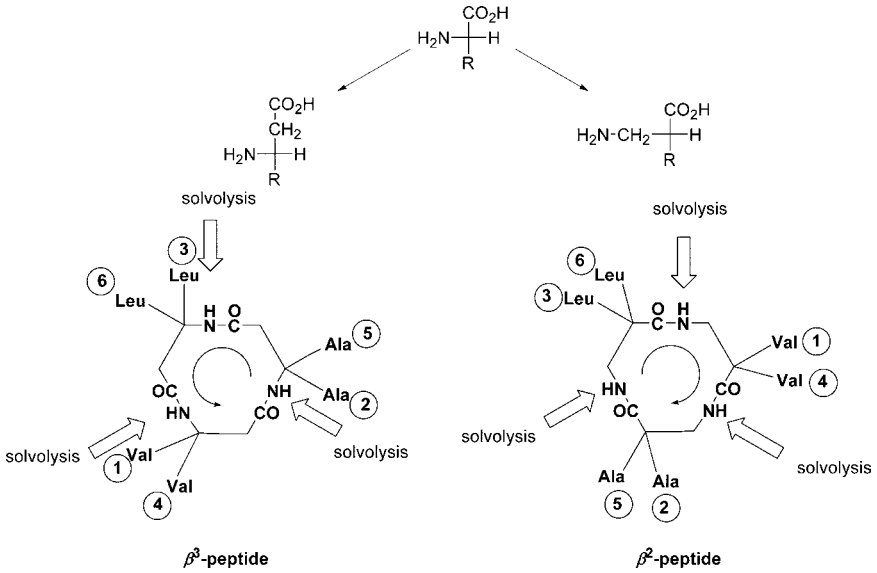


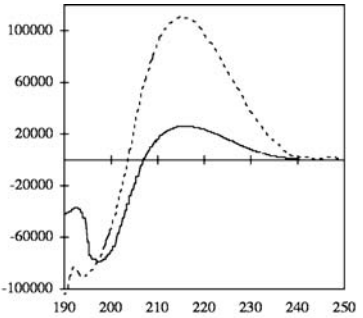
Figure 23.5 Top view of helices formed by β^3- and β^2-peptides.

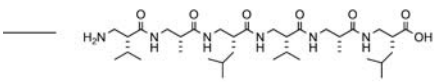
circular dichroism (CD) spectral measurements in MeOH confirmed that the β^2-hexamer **20** does fold into a (P)-3_{14} helix showing the typical helix pattern: (1) minimum at ~216 nm; (2) zero-point crossing at ~209 nm and; (3) maximum at ~197 nm; while a relatively weak cotton effect indicated poor helix stability (Fig. 23.6).[7a]

Unfortunately, nuclear magnetic resonance (NMR) structure elucidation failed with this peptide due to insufficient secondary-structure stability, which resulted in peak broadening originating from internal dynamics. The helix stability was improved by introducing a single strongly helix-inducing $\beta^{2,3}$-amino acid in the middle of the β^2-sequence, as suggested by the CD spectrum (Fig. 23.6). Ultimately, NMR studies revealed that heptapeptide **21** indeed folds into a (P)-3_{14}-helix in MeOH (Fig. 23.7).[29a]

23.4.1.2 The 12-Helix It is worth mentioning that Park et al. have incorporated β^2-amino acids with the proteinogenic side chains of Lys, Phe, and Val into β-peptides made almost entirely of conformationally restricted ACPC and *trans*-3-aminopyrrolidine-4-carboxylic acid (APC) chiral units (Fig. 23.8).[36] As expected for peptides containing amino acids with a five-membered ring constraint, such oligomers adopted a 12-helical conformation in MeOH and H_2O, although the helix stability was compromised by the number of flexible β^2-amino acids being incorporated into the peptides.

23.4.1.3 The 10/12- or 12/10-Helix The 10/12- or 12/10-helix is a unique and novel structure with no precedent in nature. This structure was stumbled upon





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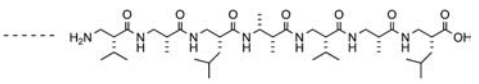


21

Figure 23.6 CD spectra of two helix-inducing β²-peptides.

when mixed β²/β³-peptides, which were originally designed to fold into 3_{14}-helices, gave rise to an unusual CD pattern with a single maximum at ~205 nm.[37] Thus, peptides containing an alternating β²/β³-amino acid motif of like configuration adopt an intercalating sequence of 10 and 12 hydrogen-bonded rings arranged in a

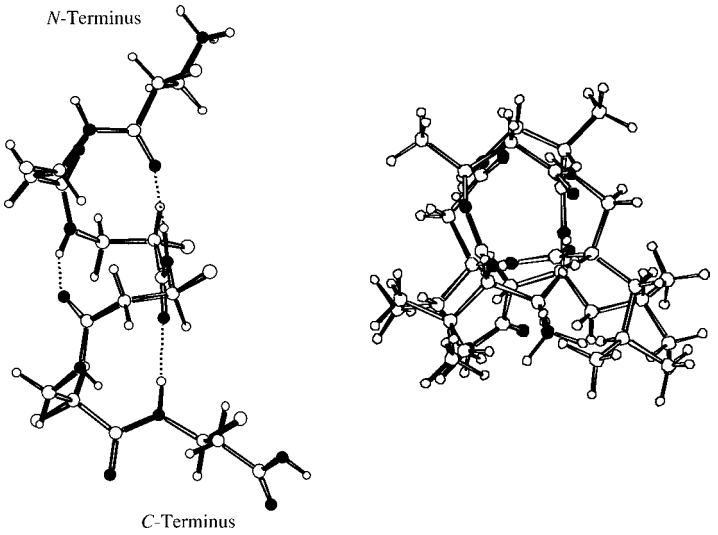


Figure 23.7 NMR structure of heptapeptide **21**.

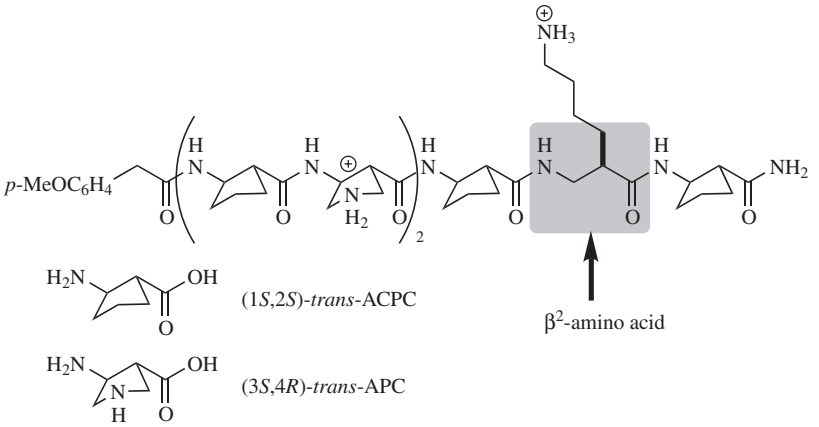


Figure 23.8 Example of peptide containing both conformationally restricted β-amino acids as well as β^2-amino acids.

helical structure with the following characteristics: (1) 10-membered hydrogen-bonded rings between amides surrounded by methylenes $(i, i+2)$; (2) 12-membered hydrogen-bonded rings between amides surrounded by side chains $(i+2,\ i+3)$; (3) the C=O groups, which form 12-membered hydrogen-bonded rings, point toward the C-terminus along the helix axis while the C=O groups, which form 10-membered hydrogen-bonded rings, point toward the N-terminus, and (4) this motif is repetitive in longer peptides (Fig. 23.9).[29]

Peptides adopting the 10/12-helix have reduced polarity (as compared with other helical conformations), which is due to the antiparallel arrangement of the amide groups along the helix axis; as a result, such peptides have surprisingly high solubility in common organic solvents, such as EtOAc. Furthermore, it has been postulated that upon terminal group deprotection the generated dipole promotes

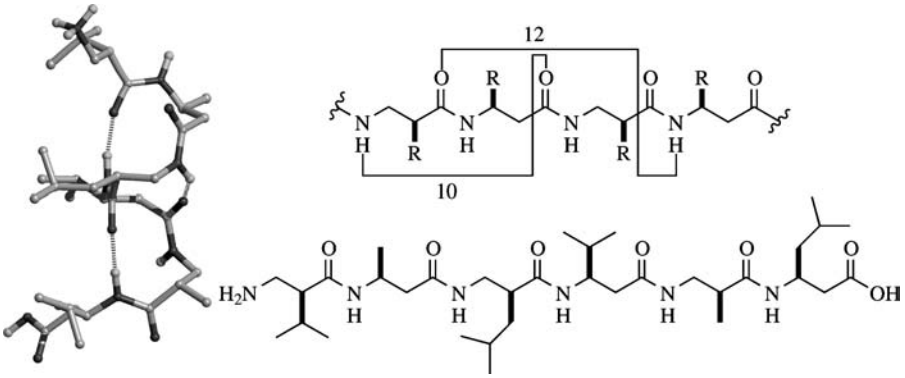
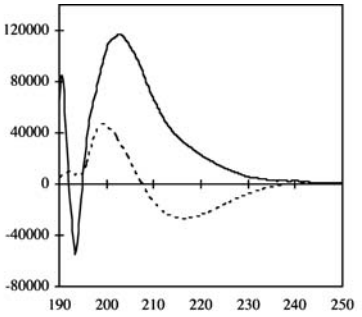
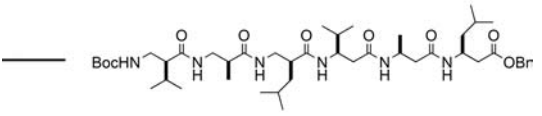
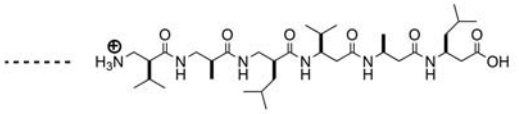


Figure 23.9 Model of 10/12/10-helix.





22a



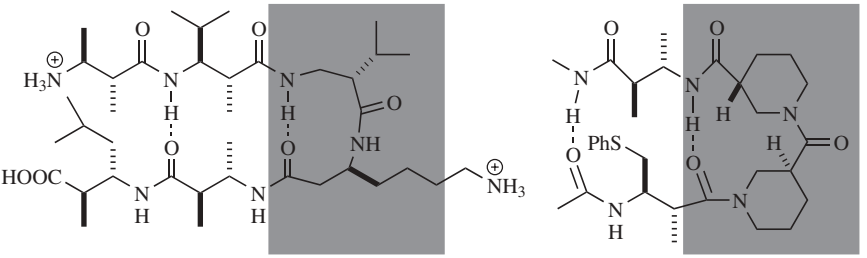
22b

Figure 23.10 CD spectra of protected and deprotected β-peptide **22**.

population of the 3_{14}-helical state in such pepides, making the 10/12-helix appear less stable.[29,37] Figure 23.10 shows the change in CD pattern of peptide **22a** upon terminal group deprotection (peptide **22b**). Notice that the CD pattern of peptide **22b** resembles a 3_{14}-helix.

23.4.2 Turns

23.4.2.1 Hairpin Turn After discovering the 10/12-helix, Seebach et al. realized the potential of using a β^2/β^3-amino acid sequence as a turn-inducing motif.[6] To stabilize such a turn, they introduced sheet-inducing peptidic segments made of $\beta^{2,3}$-amino acids of unlike configuration to hold both ends of the turn in place. The NMR studies in MeOH revealed that peptide **23** indeed folds into the expected strand–turn–strand conformation, which is typically known as a hairpin turn[6] (Fig. 23.11). As expected, the turn-inducing section of the peptide is initiated by the β^2/β^3-amino acid sequence, which folds into a 10-membered hydrogen-bonded ring, making a 180° directional change along the peptide's backbone. Alternatively, it has been proposed that a similar hairpin turn can be induced by a histidine-containing peptide upon complexation with Zn^{2+} ions.[32] Peter et al. have demonstrated that dipeptides containing the β^2/β^3-unit also form stable β-peptidic turns.[38]



23 Turn inducing **24** Turn inducing

Figure 23.11 Hairpin-inducing peptides synthesized by Seebach et al. (left) and by Gellman et al. (right).

In general, the CD pattern of β-peptides adopting such turns resembles that of a 10/12-helix, namely a single maximum at 205 nm. This is not at all surprising considering that such turns are indeed a segment of a 10/12-helix.

Gellman et al. have also reported β-peptides capable of adopting a hairpin turn conformation by the use of conformationally restricted nipecotic acid (β^2hPro).[34,39] They based their peptide design on computational studies suggesting that a heterochiral dinipecotic acid (β^2hPro) unit has a strong propensity to induce turns. Again the key elements in the architecture of peptide **24** include a strand-inducing section made of $\beta^{2,3}$-amino acids with unlike configuration, which are linked to the C- and N-termini of a turn-inducing section made of (*R*)-Nip–(*S*)-Nip. It was demonstrated by NMR studies in CD_2Cl_2 that the peptide folded into the expected strand–turn–strand conformation (Fig. 23.11). In this case, the turn-inducing section forms a 12-membered hydrogen-bonded ring.

23.4.2.2 Other Conformations Although there is scarce solid experimental evidence, it is has been suggested, based on CD measurements, that peptides made entirely of nipecotic acid (β^2-proline) form stable secondary structures in solution. It is also important to mention that such (unknown) secondary structures should not be stabilized by hydrogen bonds.[30]

23.5 BIOLOGICALLY ACTIVE PEPTIDES CONTAINING PROTEINOGENIC β^2-AMINO ACIDS

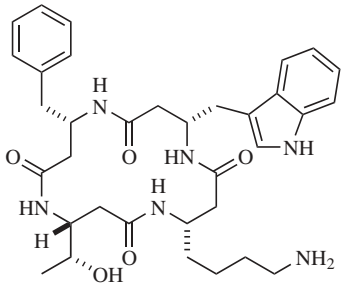
There are a number of examples of naturally occurring peptides containing substituted β-amino acids, isolated especially from marine organisms and prokaryotes.[40] However, if one considers peptides containing β^2-homoamino acids with proteinogenic side chains, examples are sparse. The dipeptide carnosine is an example of a mammalian peptide containing a β-amino acid, with the sequence βhGly-His.[41] β^2hAla is another naturally occurring amino acid, present in for example, γGlu-β^2hAla dipeptide found in several plant species and in bovine

brain.[42] Occurrence of β-amino acids in mammalian metabolism has also been already reviewed.[43] In this section, we focus on biologically active synthetic peptides containing β^2-amino acids with proteinogenic side chains.

Apart from their excellent structural stability, β-peptides also exhibit a remarkable stability toward proteolytic enzymes. Frackenpohl and co-workers[44] have subjected 36 linear and cyclic β-peptides comprised of 2–15 amino acids to 15 commercially available peptidases of bacterial, fungal, and eukaryotic origin. Under conditions of complete cleavage of the α-peptide within 15 min, the β-peptides were stable for at least 48 h. Comparable results were obtained with in vivo studies using ^{14}C-labeled β^3-nonapeptide in rats.[45] Even the insertion of one β^2- or β^3-amino acid into α-peptide significantly increases its stability against peptidases.[46] This proteolytic stability of peptides built from homologated amino acids is a precondition for their potential use as peptidomimetic drugs. As was already mentioned, they form secondary structures with as few as four amino acid residues, so there is a possibility of mimicking biologically active α-peptides with certain structural characteristics. The idea of replacing one amino acid in an α-peptide with its β-homologated analog (usually β^3-homoamino acid) to improve its proteolytic stability was used several times to prepare various receptor agonists and antagonists, including angiotensin, gastrin, oxytocin, and bradykinin. (For a review on the use of β-amino acids as peptidomimetic, see Ref. 47.)

Somatostatin is a natural α-peptide hormone with various biological functions, including regulation of growth hormones and insulin. Octreotide (Sandostatin) is a cyclic α-octapeptide which is nowadays clinically used as a somatostatin analog. Initially, the cyclic β^3-peptide **25** was shown to have micromolar affinity for somatostatin receptors (hsst1–5).[48] Further studies led (Seebach) to the synthesis of a linear β^2/β^3-tetrapeptide **26**, which folds into a hairturn structure where the amino acids β^3hTrp and β^2hLys are strategically located in the loop section (Fig. 23.12). This compound shows a nanomolar affinity $(K_D = 83\,\text{nM})$ for the human sst4 receptor, which is approximately 20 times higher than the value for octreotide but still about 20 times lower than that of natural somatostatin.[7d]

After having recognized that formation of a turn with tryptophan and lysine residues is the key element for optimal binding to somatostatin receptors, a series of



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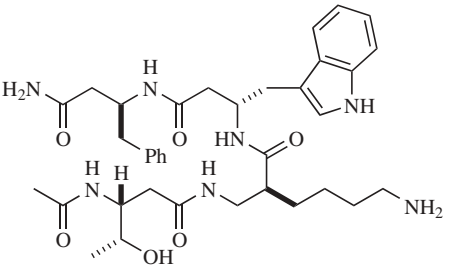

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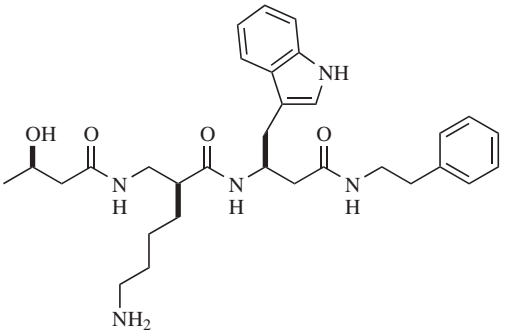
Figure 23.12 Somatostatin analogs.



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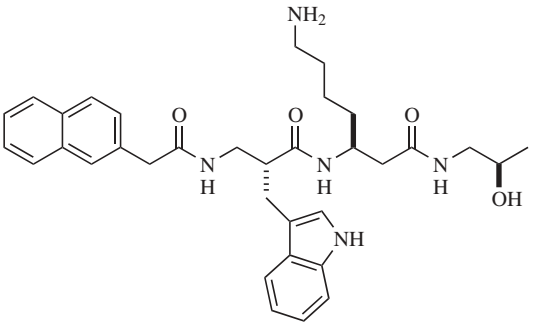

29

Figure 23.13 Dipeptidic somatostatin analogs.

β^2/β^3-dipeptides was prepared in solution.[49] They have retro- as well as natural sequences of hLys and hTrp. Dipeptide **27** displayed good binding affinity to the cloned human somatostatin receptor hsst4 ($K_D = 245\,nM$), while its epimer has greatly reduced affinity ($K_D > 5\,\mu M$). Dipeptide **28**, having the so-called natural sequence, binds with $K_D = 724\,nM$, while several other variations of terminal protecting groups and configuration resulted in compounds with significantly reduced binding (Fig. 23.13).

Cellular uptake studies with β-peptides have shown that β^3- and β^2/β^3-peptides without (or just a few) basic side chains are not transported into 3T3 mouse fibroblast cells. On the other hand, polycationic β^3-oligolysine and β^3-oligoarginine peptides readily translocate through the cell membrane.[50] Independently, Gellman and co-workers[51] reported similar results with a β^3-analog of human immunodeficiency virus (HIV) Tat 47-57 peptide.

Several other biological evaluations have been performed mainly with β^3-peptides, such as antimicrobial and hemolytic assays[52] showing some antimicrobial activity and very little or no hemolytic activity. Additionally, β-peptides have been shown to inhibit intestinal cholesterol and fat absorption.[53] Recently, Arvidsson et al.[54] reported a β^2/β^3-peptide capable of folding into a 12/10-helical secondary structure displaying good antibiotic activity against *Staphylococcus*

and *Streptococcus*. Some cyclo-β³-tripeptides display antiproliferative activity by inhibiting the growth of several cancer cell lines.[55]

23.6 CONCLUSIONS

β²-Amino acids have proven to be key elements in the design of β-peptides with novel secondary structures. Many obstacles had to be overcome before such amino acids could be efficiently incorporated into peptides. Presently, the lack of commercial availability of β²-amino acids and the time and cost of their preparation represent major disadvantages to overcome as their demand increases. Nevertheless, great progress has been made not only in the preparation of β²-amino acids with all 20 proteinogenic side chains in enantiomerically pure form but also in developing protocols for their incorporation into peptides. It is now fair to say that we possess the required empirical and theoretical level of understanding to move on to the next dimension of β-peptides: tertiary structure.

ABBREVIATIONS

ACHC	*trans*-2-Aminocyclohexanecarboxylic acid
ACPC	*trans*-2-Aminocyclopentanecarboxylic acid
APC	*trans*-3-Aminopyrrolidine-4-carboxylic acid
Boc	*tert*-Butoxycarbonyl
BOP	(1*H*-Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
Cbz	Benzyloxycarbonyl
DIPEA	Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
EDC	1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Fmoc	[(9*H*-Fluoren-9-yl)methoxy]carbonyl
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxy-1*H*-benzotriazole
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
NMM	*N*-Methylmorpholine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TNBS	2,4,6-Trinitrobenzenesulfonic acid

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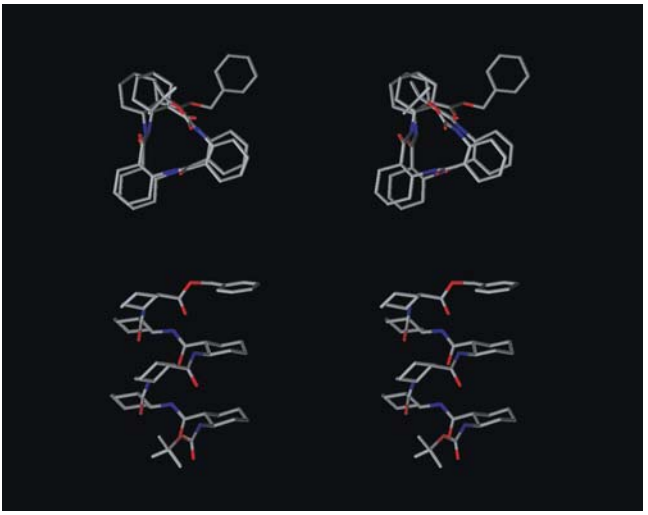

Figure 22.8 Right-handed 14-helical Boc-[(*R*,*R*)-ACHC]$_6$-OBn oligomer in end-on and side-on relaxed-eye stereoviews from crystal structure data.[6]

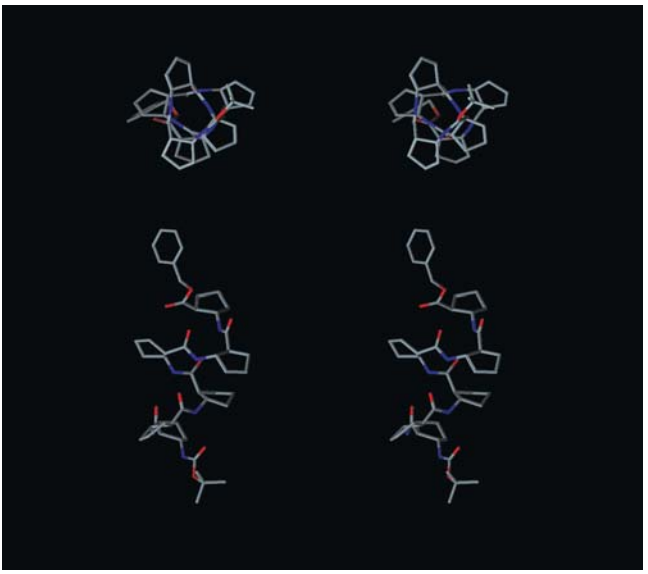

Figure 22.13 Left-handed 12-helical Boc-[(*R*,*R*)-ACPC]$_6$-OBn oligomer in end-on and side-on relaxed-eye stereoviews from crystal structure data.[22]