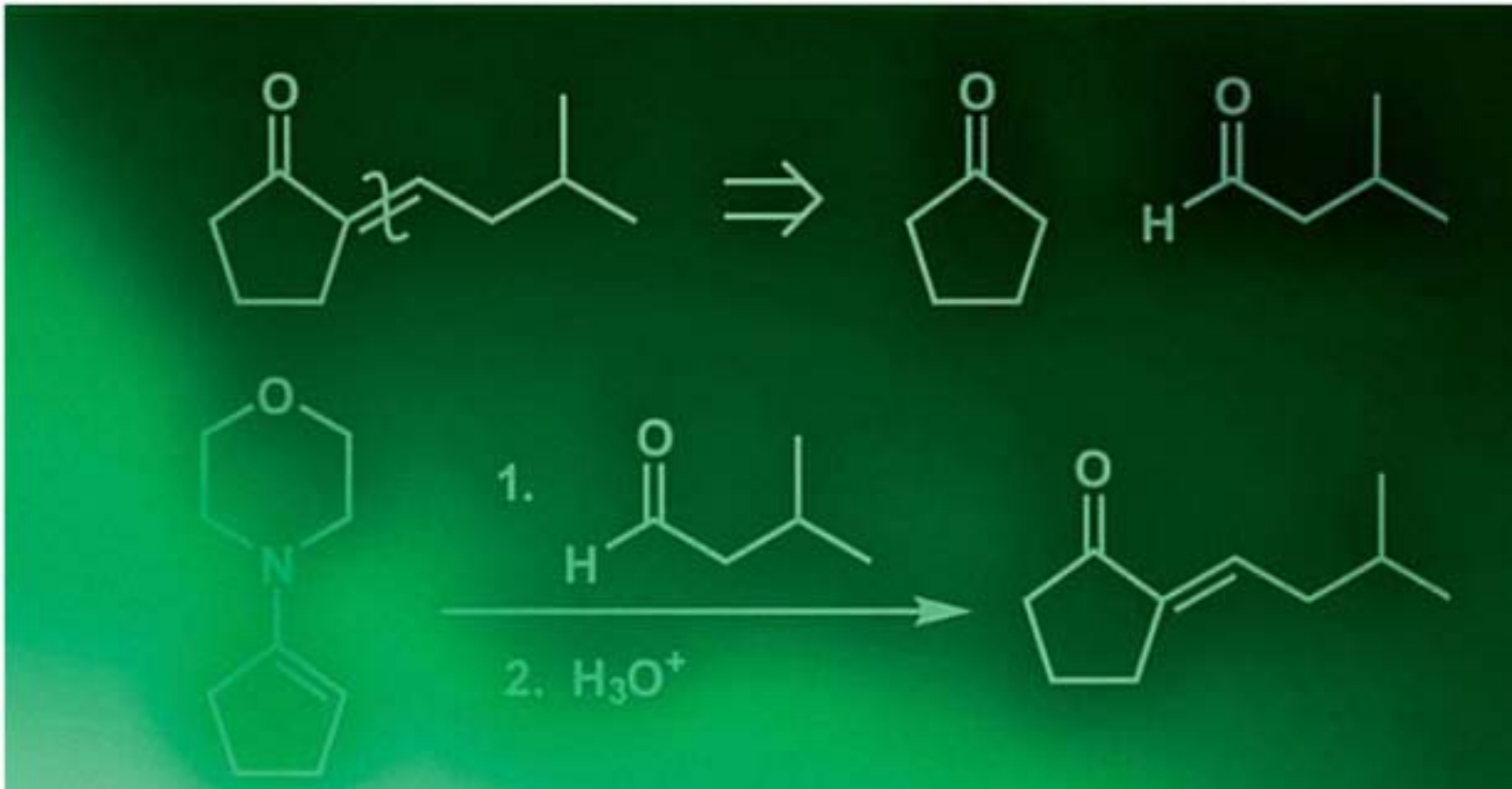

Stuart Warren · Paul Wyatt

Workbook for ORGANIC SYNTHESIS

The Disconnection Approach

Second Edition

WILEY

Workbook for Organic Synthesis: The Disconnection Approach Second Edition

Stuart Warren
Reader in Organic Chemistry, Department of Chemistry,
University of Cambridge, UK

and

Paul Wyatt
Reader and Director of Undergraduate Studies, School of Chemistry,
University of Bristol, UK

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Contents

Preface

In the 26 years since Wiley published *Organic Synthesis: The Disconnection Approach* and the accompanying Workbook, this approach to the learning of synthesis has become widespread while the books themselves are now dated in content and appearance. In 2008, Wiley published the second edition of *Organic Synthesis: The Disconnection Approach* by Stuart Warren and Paul Wyatt for which this is the accompanying *Workbook*.

This workbook contains further examples, problems (and answers) to help you understand the material in each chapter of the textbook. The structure of this second edition of the workbook is the same as that of the textbook. The 40 chapters have the same titles as before but all chapters have undergone a thorough revision with some new material. The emphasis is on helpful examples and problems rather than novelty. Many of the problems are drawn from the courses we have given in industry on 'The Disconnection Approach' where they have stimulated discussion leading to deeper understanding. It makes sense for you to have the relevant chapter of the textbook available while you are working on the problems. We have usually devised new problems but some of the problems in the first edition seemed to do such a good job that we have kept them. Usually, the answers are presented in a different and, we hope, more helpful style.

It is not possible to learn how to design organic syntheses just from lectures or from reading a textbook. Only by tackling problems and checking your answers against published material can you develop this skill. We should warn you that there is no single 'right answer' to a synthesis problem. Successful published syntheses give some answers that work, but you may well be able to design others that have a good chance of success. The style of this second edition is to give more discussion of alternative routes.

Stuart Warren and Paul Wyatt
2009

General References

Full details of important books referred to by abbreviated titles in the chapters to avoid repetition.

Clayden *Organic Chemistry*: J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry*, Oxford University Press, Oxford, 2000.

Disconnection Textbook: S. Warren and P. Wyatt, *Organic Synthesis: The Disconnection Approach*, Second Edition, Wiley, Chichester, 2008.

Drug Synthesis: D. Lednicer and L. A. Mitscher, *The Organic Chemistry of Drug Synthesis*, Wiley, New York, seven volumes, from 1977.

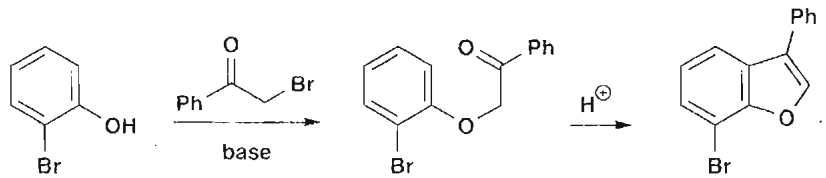
Fieser, *Reagents*: L. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 20 volumes, 1967–2000; later volumes by T.-L. Ho.

Fleming, *Orbitals*: Ian Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976.

Vogel: B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Fifth Edition, Longman, Harlow, 1989.

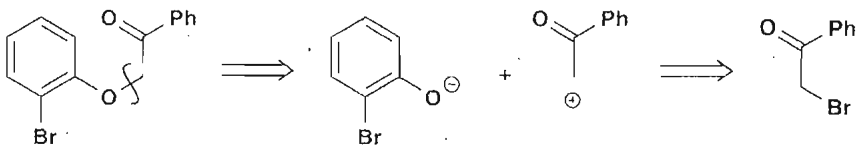
1 The Disconnection Approach

We start with a few simple problems to set you at ease with disconnections. **Problem 1.1:** Here is a two-step synthesis of the benzofuran **3**. Draw out the retrosynthetic analysis for the synthesis of **2** from **1** showing the disconnections and the synthons.



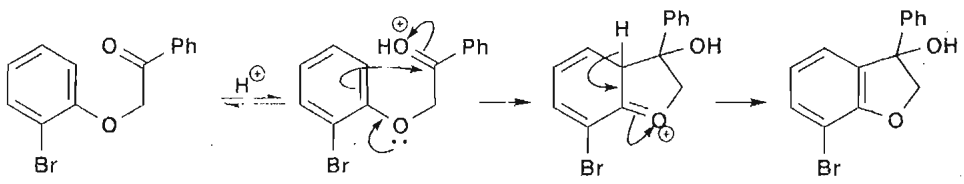
1 2 3

Answer 1.1: As this is a simple S_N2 reaction, the disconnection is of the C–O bond **2a** and the synthons are nucleophilic phenolate anion **4**, which happens to be an intermediate in the reaction, and the cation **5**, which happens not be an intermediate in the reaction but is represented by the α-bromoketone **6**.



2a 4 5 6

Problem 1.2: Draw the mechanism of the cyclisation of **2** to **3**. This is an unusual reaction and it helps to know what is going on before we analyse the synthesis. **Answer 1.2:** The first step is an acid-catalysed cyclisation of the aromatic ring onto the protonated ketone **7**. Loss of a proton **8** completes the electrophilic aromatic substitution giving the alcohol **9**.



2 7 8 9

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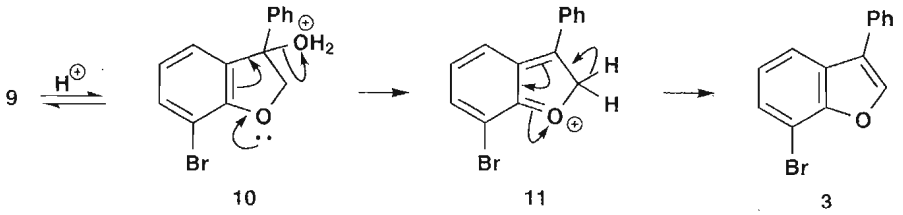
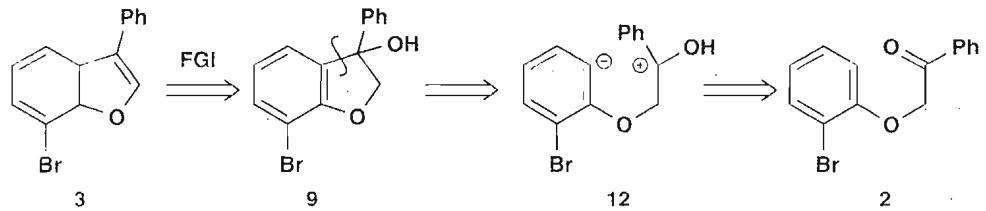
Now protonation of the alcohol leads to loss of water **10** to give a stabilised cation that loses a proton **11** to give the new aromatic system **3**. **Problem 1.3:** Now you should be in a position to draw the disconnections for this step.

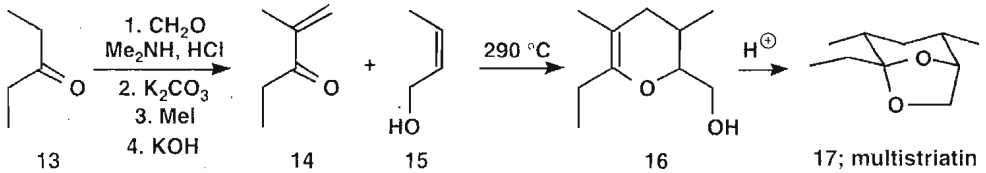


Answer 1.3: We hope you might have drawn the intermediate alcohol **9**. Changing **3** into **9** is not a disconnection but a Functional Group Interconversion (FGI) – changing one functional group into another. Now we can draw the disconnection revealing the synthons **12** represented in real life by **2**.

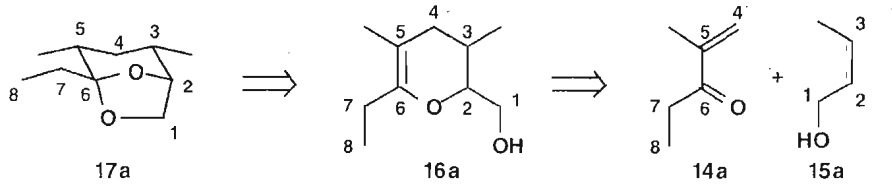


A Synthesis of Multistriatin

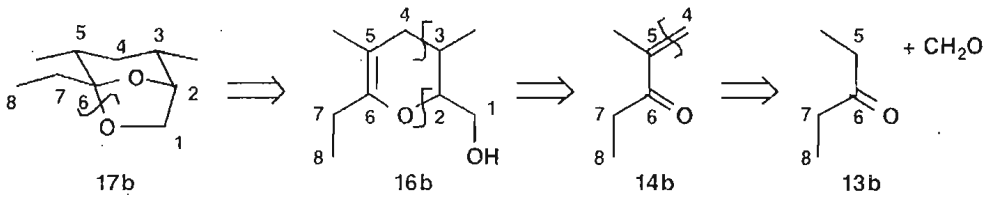
In the textbook we gave one synthesis of multistriatin **17** and here is a shorter but inferior synthesis as the yields are lower and there is little control over stereochemistry.[1] **Problem 1.4:** Which atoms in the final product **17** come from which starting material and which bonds are made in the synthesis? *Hint*: Arbitrarily number the atoms in multistriatin and try to trace each atom back through the intermediates. Do not be concerned over mechanistic details, especially of the step at 290 °C.



Answer 1.4: However you numbered multistriatin, the ethyl group (7 and 8 in **17a**) finds the same atoms in the last intermediate **16a** and the rest falls into place. It then follows which atoms come from **14** and which from **15**. Finally, you might have said that C-4 in our diagrams comes from formaldehyde.



So the disconnections also fall into place. Just one C–O bond was disconnected at first **17b** then one C–O and one C–C **16b** and finally the alkene was disconnected **14b** in what you may recognise as an aldol reaction with formaldehyde. If you practise analysing published syntheses like this, you will increase your understanding of good bonds to disconnect.



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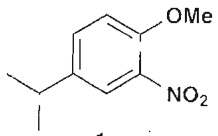
1. W. E. Gore, G. T. Pearce and R. M. Silverstein, *J. Org. Chem.*, 1975, **40**, 1705.

2 Basic Principles: Synthons and Reagents: Synthesis of Aromatic Compounds

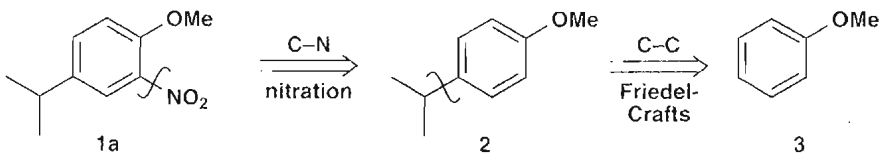
This chapter concerns the synthesis of aromatic compounds by electrophilic and nucleophilic aromatic substitution. All the disconnections will therefore be of bonds joining the aromatic rings to the sidechains. We hope you will be thinking mechanistically, particularly when choosing which compounds can undergo nucleophilic aromatic substitution and the orientation of electrophilic aromatic substitution. Any textbook of organic chemistry[1] will give you the help you need.

Problem 2.1: Compound **1** was needed[2] for an exploration of the industrial uses of HF. Suggest how it might be made. *Hint*: consider which of the three substituents you would rather *not* add to the ring.



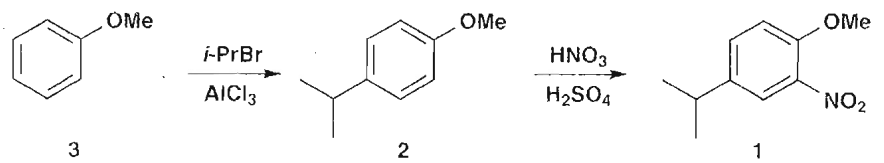
1

Answer 2.1: We can add the nitro group by nitration and the isopropyl group by Friedel-Crafts alkylation (as it is a secondary alkyl group) but we would rather not add the OMe group as there is no good reagent for MeO^+. So we disconnect first the most deactivating group (nitro) **1a** and then the isopropyl group **2**.



1a 2 3

Before writing out the synthesis, we should check that the orientation of the substitution will be what we want. The OMe group is *ortho, para*-directing so alkylation will go mainly *para* because of steric hindrance. Now we have a competition as isopropyl is also *ortho, para*-directing but, since OMe has a lone pair of electrons conjugated with the benzene ring, it will dominate so everything is fine. We therefore suggest:



3 2 1

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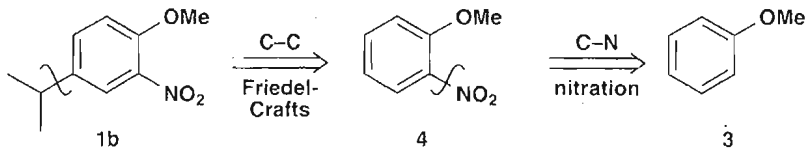
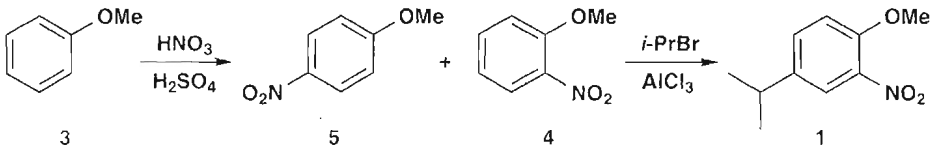
Did you consider the alternative strategy? That is, disconnect the isopropyl group first **1b** to give a new intermediate **4** and disconnect the nitro group second. The starting material, anisole **3**, is the same in both routes.



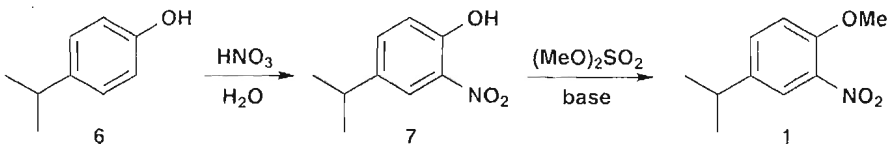
1b 4 3

Again we should check the orientation. Nitration of anisole will give a mixture of *ortho* **4** and *para* **5** products so much depends on the ratio and whether they can easily be separated. The Friedel-Crafts reaction will go *ortho* or *para* to the OMe group and *meta* to the nitro group so that is all right. However the deactivating nitro group might make the reaction difficult.



3 5 4 1

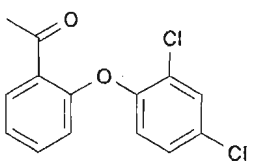
So what did the chemists prefer? One published synthesis[2] used HF as a catalyst to alkylate *ortho*-nitro-anisole **4** with isopropanol. The yield was a respectable 84%. This made sense as they had a supply of **4**. If anisole is nitrated with the usual HNO_3/H_2SO_4, a 31:67 ratio of *ortho:para* products is obtained. If the nitrating agent is an alkyl nitrite in MeCN, the ratio improves to 75:25. The best route nowadays is probably the nitration of available *para*-isopropyl phenol **6**, probably quantitative, and methylation of the product **7** with, say, dimethyl sulfate.

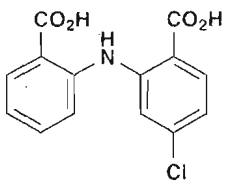


6 7 1

Problem 2.2: These compounds **8** and **9** each have two benzene rings linked by a heteroatom and both are used to make anti-inflammatory drugs. An obvious strategy is to disconnect one C–X bond in each case and combine the two compounds by nucleophilic aromatic substitution. Suggest a synthesis for each compound.

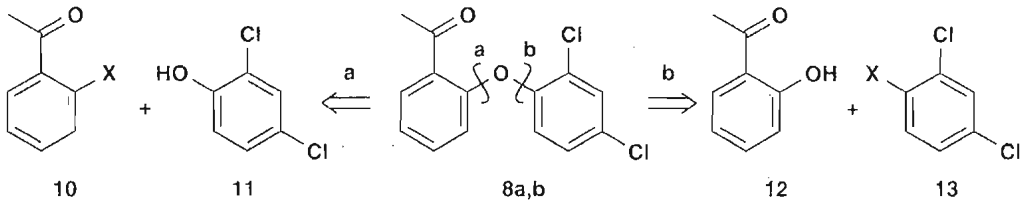
8
anti-inflammatory
lobenzarit





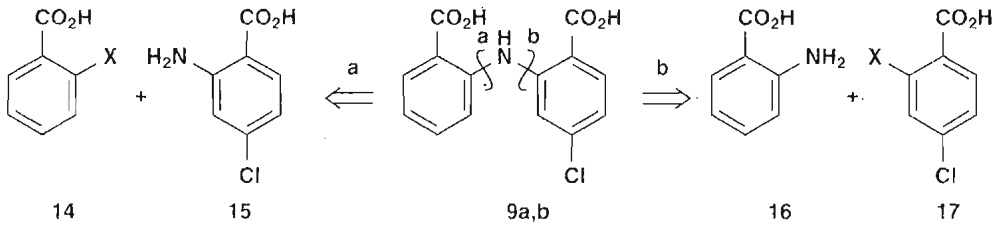
9
needed for the
anti-inflammatory
fenclofenac

Answer 2.2: The two disconnections **8a** and **8b** illustrate the types of molecules needed for the first problem. In each case X is a leaving group such as a halogen and the phenols **11** and **12** would be used as their anions.



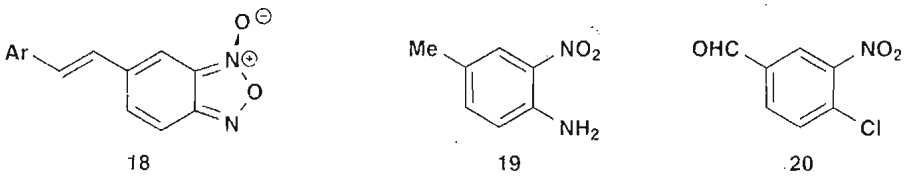
To be successful, nucleophilic aromatic substitution needs an electron-withdrawing group *ortho* or *para* to the leaving group. A chloride, as in **13** is not adequate but the ketone in **10** is perfectly placed. The reported synthesis[3] uses **10**; X = Cl with **11** and Cu/NaOH as catalyst. We might nowadays prefer available **10**; X = F with the anion of the phenol.

The other compound **9** is easier in one way as both disconnections **9a** and **9b** are feasible. Each ring **14** and **15** has an electron-withdrawing CO_2H group in the right position (*ortho* to the leaving group X). Compound **17** has another leaving group (Cl) that is *para* to the CO_2H group so it could react. On the other hand, compound **15** could react with itself and polymerise as it has the nucleophilic amine and the activated chloride in the same molecule.

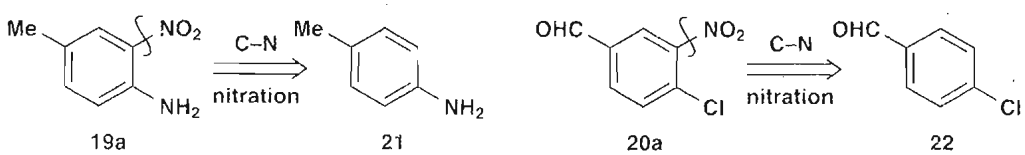


The reported synthesis[4] uses **16** and **17**; X = Cl relying on the CO_2H group to provide regioselectivity at the more electrophilic *ortho* position. It is possible[5] that the fluoro-compound **17**: X = F would be a better way.

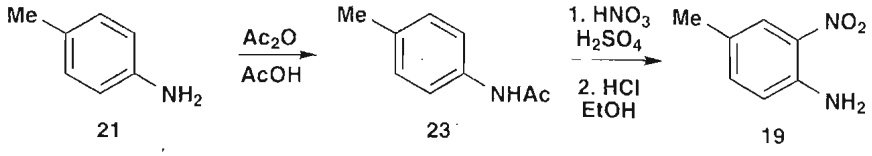
Problem 2.3: Chagas disease causes some 50,000 deaths annually in South America. Drugs based on the structure **18** are urgently needed. You are not expected to understand the chemistry used to make the strange heterocyclic ring but you might appreciate that it could come from an *ortho*-nitro aniline such as **19** or an activated halide such as **20**. Suggest syntheses for these starting materials.



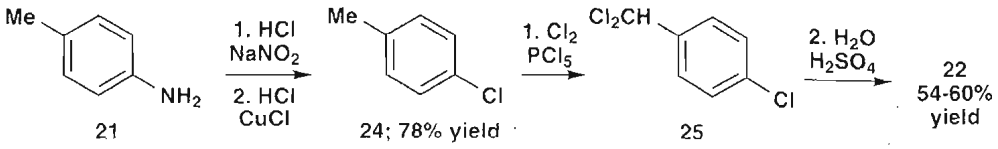
Answer 2.3: In both cases, the initial disconnection of the nitro group **19a** and **20a** is very appealing. The starting materials **21** and **22** should be easily made and nitration will go *ortho* to NH_2 rather than Me in **21** and *ortho* to Cl and *meta* to the deactivating aldehyde in **22**.



The synthesis of **19** is straightforward[6] as the amine **21** is available from the nitration and reduction of toluene. Amide **23** formation reduces the reactivity of the amine so that mono-nitration and hydrolysis give **19**. Nitration of **23** gives **19**.

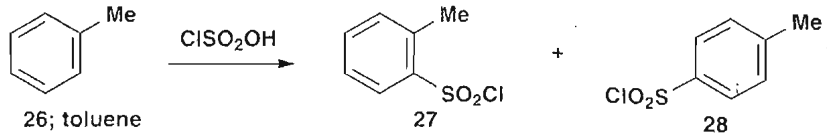


The aldehyde **22** is more difficult as we should need to chlorinate benzaldehyde in the *para* position to get **22**. One solution is to oxidise *para* chloro-toluene **24**, available[7] from **21** via the diazonium salt with, for example, chlorine to give **25** that can be hydrolysed[8] to the aldehyde **22**.

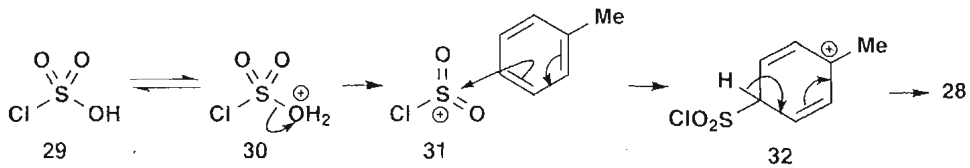


A Problem from the Textbook

When discussing the synthesis of saccharine in chapter 2 of the textbook, we said: 'In practice chloro-sulfonic acid is used as this gives the sulfonyl chloride directly. You may be surprised at this, thinking that Cl might be the best leaving group. But there is no Lewis acid here. Instead the very strong chloro-sulfonic acid protonates itself to provide a molecule of water as leaving group.' The reaction gives a mixture of the *ortho*- **27** and *para*- **28** products. **Problem 2.4:** With those hints, draw a mechanism of the chlorosulfonation.



Answer 2.4: 'Strong' means a strong *acid* here so chloro-sulfonic acid **29** protonates itself to give a cation that loses water **30** to give the reactive cation **31**. This is attacked by toluene in the *ortho*- and *para*-positions to give e.g. **32** that loses a proton to give **28**.



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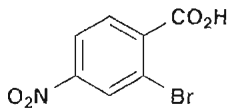
6. W. Porcal, A. Merlino, M. Boiani, A. Gerpe, M. González and H. Cerecetto, *Org. Process. Res. Dev.*, 2008, **12**, 156.
7. *Vogel*, p. 931.
8. W. L. McEwen, *Org. Synth. Coll.*, 1943, **2**, 133.

3 Strategy I: The Order of Events

You should refer to the Guidelines from the textbook when you solve the problems in this chapter.
Guideline 1: Consider the effects of each functional group on the others. Add first (that is disconnect last) the one that will increase reactivity in a helpful way.
Guideline 2: Changing one functional group into another may alter reactivity dramatically.
Guideline 3: Some substituents are difficult to add so it is best to start with them already present.
Guideline 4: Some disubstituted compounds are also readily available and they may contain a relationship (especially *ortho*) that is difficult to achieve by electrophilic substitution.
Guideline 5: Some groups can be added to the ring by nucleophilic substitution.
Guideline 6: If a series of reactions must be carried out, start with one that gives a single product unambiguously and not one that would give a mixture.

Remember that these guidelines may conflict or even contradict each other. THINK!

Problem 3.1: Suggest syntheses of **1** and **2** needed as intermediates: **1** in the synthesis of some brominated acids[1] and **2** to study the mechanism of enzymatic ester hydrolysis.[2]



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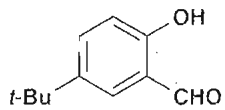
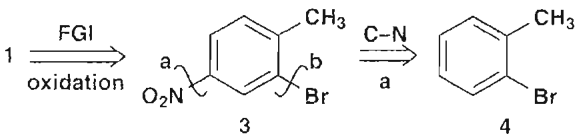
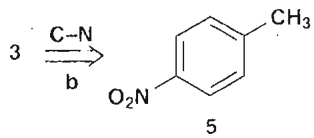


2

Answer 3.1: With two electron-withdrawing groups in **1**, some FGI is needed to control the orientation and gain some reactivity. There are good ways to introduce Br and NO_2 but no easy way to introduce CO_2H. FGI of CO_2H to Me with oxidation in mind would give an *ortho, para*-directing group where we need it **3**. Now we might disconnect NO_2 **3a** or Br **3b** as there are good reagents for adding both. There might be some doubt as to where **4** would be nitrated as both Me and Br are *ortho, para*-directing, but there is no doubt where **5** will be brominated as Me is *ortho, para*-directing while NO_2 is *meta*-directing.

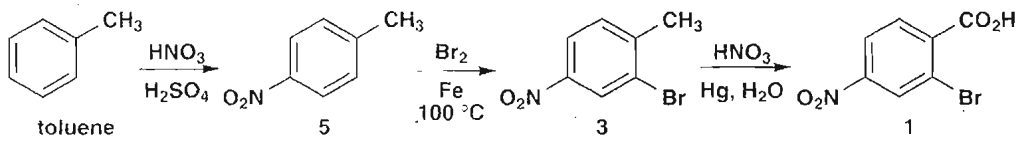


3 4

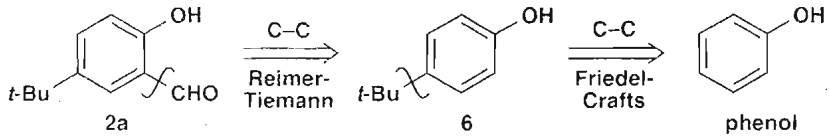


5

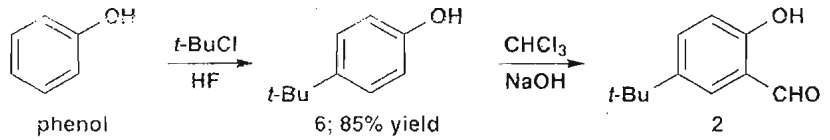
So the synthesis was nitration of toluene (actually **5** is available), separation of **5** from the *ortho* isomer, bromination of **5**, and oxidation of **3** to give the target molecule.[1]



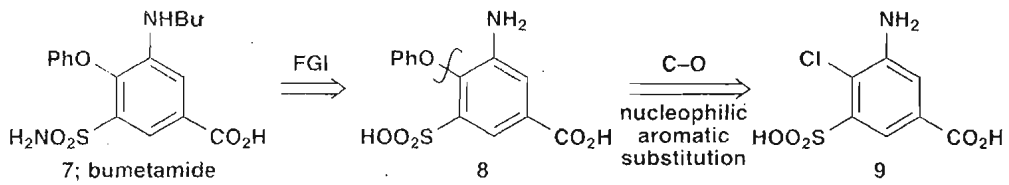
No doubt the CHO group could also be formed by oxidation of a CH_3 group but it can be inserted next to a phenolic OH by the Reimer-Tiemann reaction.[3] Now we can disconnect the *t*-Bu group with Friedel-Crafts alkylation in mind.



The large *t*-Bu group much prefers the *para* position and the Reimer-Tiemann reaction using chloroform as a source of dichlorocarbene (Textbook chapter 30) goes *ortho* to the conjugating OH group.[2,4]

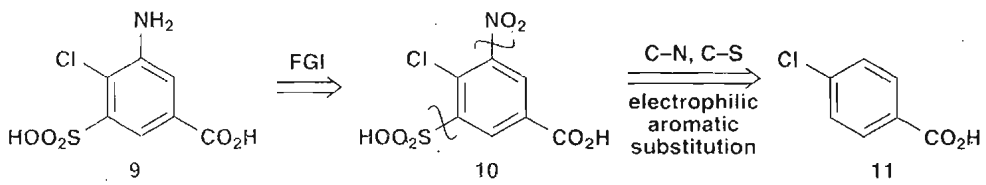


Example and Problem 3.2: Bumetamide **7** is a diuretic from Leo Pharmaceutical Products in Denmark. The synthesis[5] was planned by a number of FGIs to give **8** and then a C–O disconnection to give **9** as a suitable starting material. **Problem 3.2:** Suggest why these FGIs were chosen as a preliminary to disconnection.

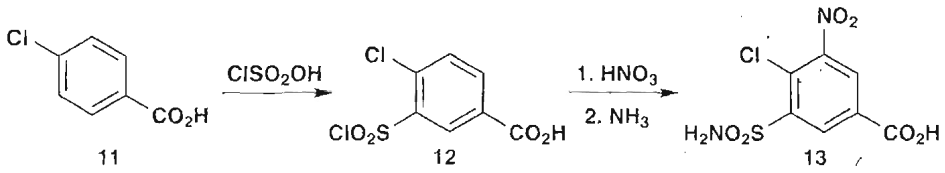


Answer 3.2: The PhO group must be added by nucleophilic aromatic substitution so electron-withdrawing groups are essential. We have two (SO_2X and CO_2H) in the right positions, *ortho* and *para* to Cl in **9**, and could have a third if NH_2 is replaced by NO_2. **Problem 3.3:** Suggest a synthesis of **9**.

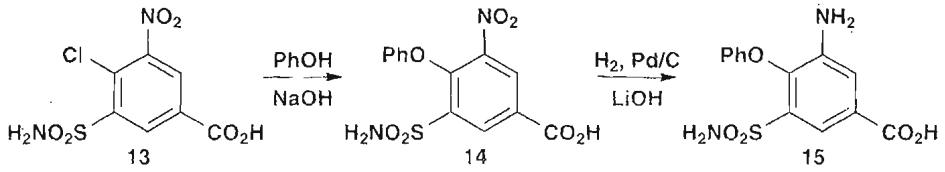
Answer 3.3: Two of the substituents in **9** (SO_2OH and Cl) can be added by electrophilic substitution and we have seen some ways to add the CO_2H group. The most obvious thing to do is to replace NH_2 by NO_2 **10** and disconnect both NO_2 and SO_2OH giving *p*-chlorobenzoic acid **11** as starting material. This compound is available but could be made by chlorination of toluene and oxidation of the methyl group.



Now we need to decide in which order to add the two substituents. The orientation will be decided by the Cl group as it is *ortho, para*-directing. In the published synthesis[5] chlorosulfonation is used followed by nitration and the sulfonamide **13** is formed before the nitro group is reduced to the amine.



With three groups to help nucleophilic substitution, phenoxide was added and catalytic hydrogenation of **14** to the amine **15** was followed by reductive amination (chapter 8) with PrCHO to give bumetamide **7**.



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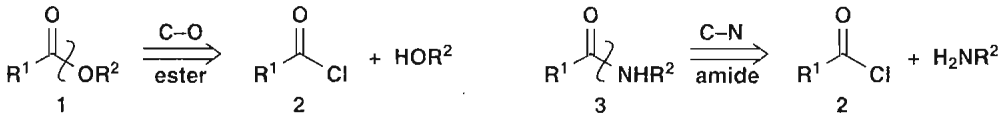
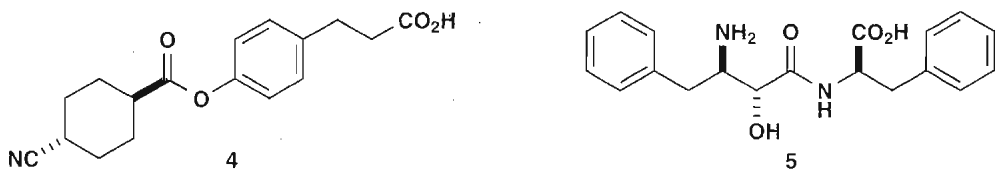
4 One-Group C–X Disconnections

If you have also read chapter 6, you will realise that acid derivatives such as esters **1** or amides **3** are usually made by acylation so that the C–O or C–N bond that is disconnected is the one between the heteroatom and the carbonyl group. In this way we are really using two-group disconnections for these compounds. The synthesis might combine an alcohol or an amine with an acid chloride **2**.



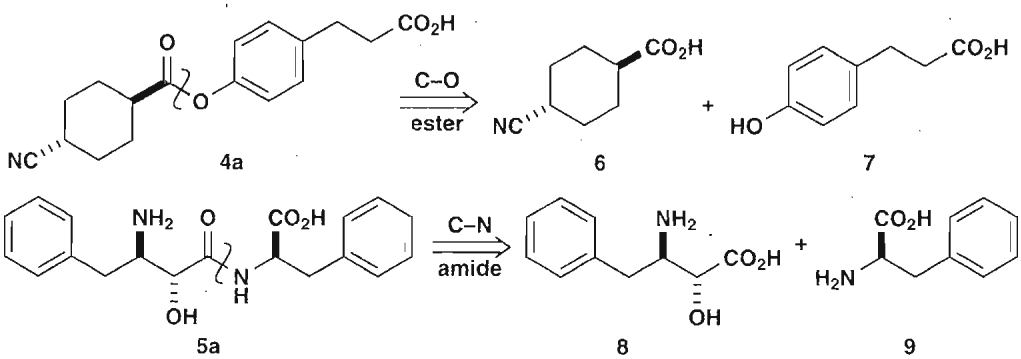
1 2 3 2

Problem 4.1: Suggest which C–X bond would be your first choice for disconnection in these two compounds, explaining your reasons. Draw your proposed starting materials.



4 5

Answer 4.1: Though there are many C–X bonds in both molecules, the first disconnection should be of the ester **4a** and of the amide **5a** both because we know of good ways to make these functional groups and because the disconnections are in the middle of the molecules. You might have drawn **6** and **8** as acid chlorides or as acids, as we have done, deciding to work out the reagents later. **Problem 4.2:** What difficulties do you foresee in carrying out the reaction?



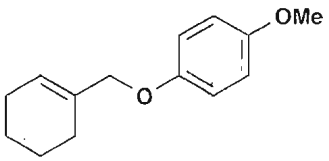
4a 6 7

5a 8 9

Workbook for Organic Synthesis: The Disconnection Approach, Second Edition Stuart Warren and Paul Wyatt

Answer 4.2: Both **6** and **7** have acid groups, so we shall have to activate the CO_2H group in **6** and perhaps protect the CO_2H group in **7**. The situation for **8** + **9** is worse: not only does each compound have a CO_2H group, but **8** also has two nucleophilic groups (OH and NH_2). Again protection and activation will be needed. This second case is not as bad as it seems as **5** is a dipeptide and standard peptide coupling procedures can be used.[1] Stereochemistry is not a problem as the bond-forming steps do not affect any chiral centre.

We shall concentrate mainly on ethers and sulfides where true one-group C–X disconnections will be needed though mechanistic arguments will still be necessary. **Problem 4.3:** Suggest a synthesis for the ethers **10** and **11**.



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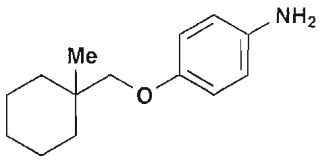
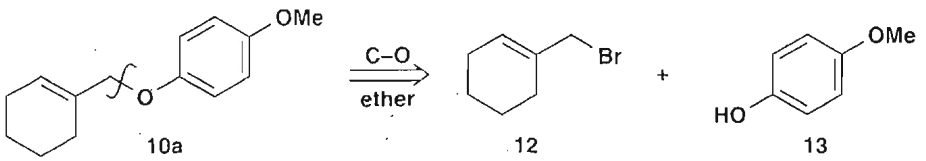


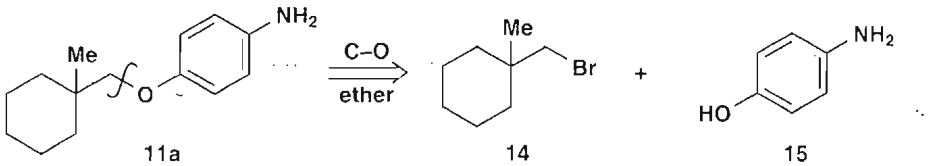
11

Answer 4.3: The first **10** is easy: we much prefer the disconnection on the alkyl side as the aromatic ring is not activated for nucleophilic substitution while the halide **12** is allylic and therefore electrophilic.



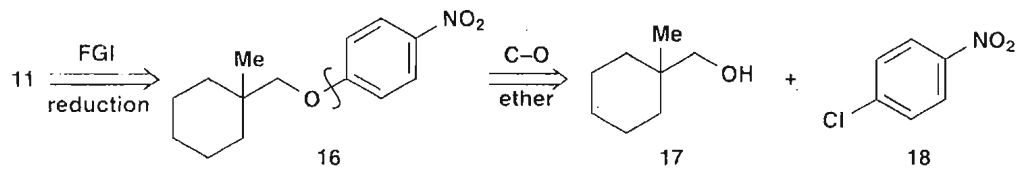
10a **12** **13**

The second **11** requires more thought: The same disconnection **11a** gives a primary halide **14** but it has a quaternary centre joined to it and there will be considerable steric hindrance to an S_N2 reaction. In addition, the amine in **15** is more nucleophilic than the phenolic OH group. Is there an alternative?



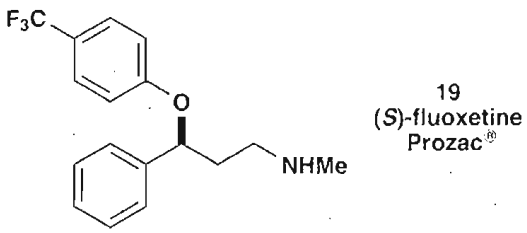
11a **14** **15**

The amine **11** could be made by reduction of a nitro group and now the alternative disconnection **16** corresponding to nucleophilic aromatic substitution becomes possible.[2] There is no longer any ambiguity as there is only one nucleophilic group. In addition, the halide **14** would have to be made from the alcohol **17**. Compounds derived from **11** are used in the treatment of diabetes.

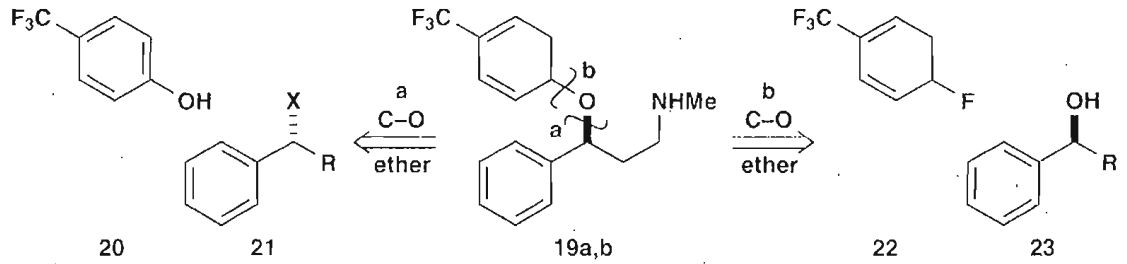


16 **17** **18**

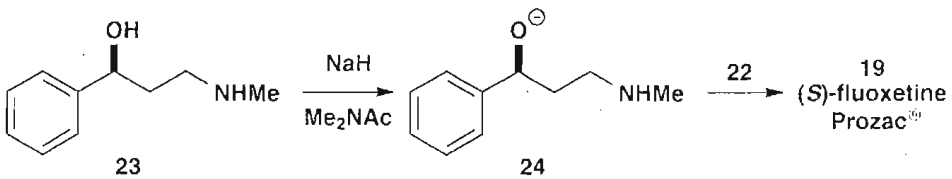
Problem 4.4: Suggest a synthesis of fluoxetine **19**, better known as the antidepressant Prozac®.



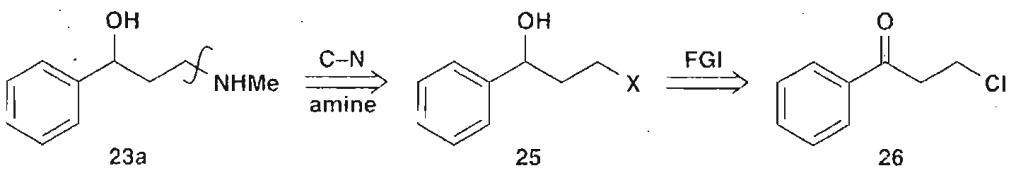
Answer 4.4: We should rather disconnect the ether in the middle of the molecule than the amine at the end and here again either C–O disconnection **19a** or **19b** would serve. The electrophile **21** (X is a leaving group) is benzylic and reactive while the CF_3 group activates the ring for S_NAr by stabilising the intermediate anion in the same way as the nitro group.



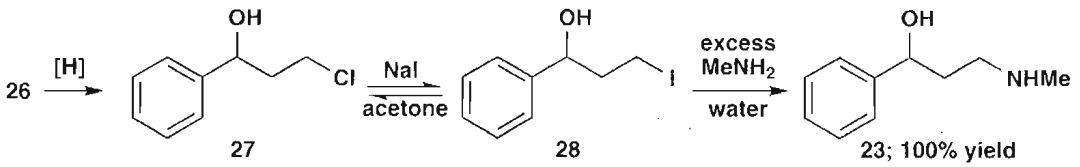
No doubt either synthesis will work but we could consider that the reaction at the chiral centre **19a** might lead to some racemisation while reaction of **23** does not involve the chiral centre. The synthesis has been carried out with a single enantiomer of **23** using NaH as base in an amide solvent.[3] The base gives the anion **24** so that oxygen becomes more nucleophilic than nitrogen.



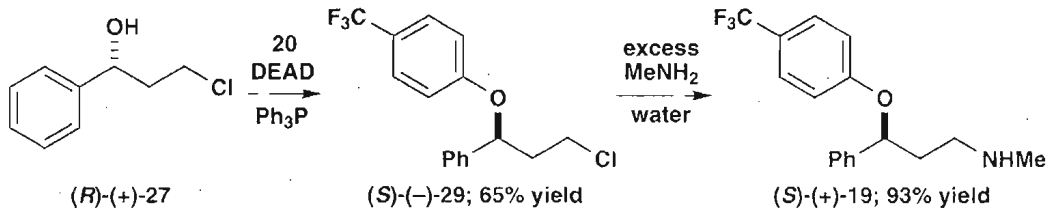
The question remains: how do we make the aminoalcohol **23**? Using a one-group disconnection of the C–N bond, we can displace a leaving group X from **25** and a search of available starting materials reveals the chloroketone **26**.



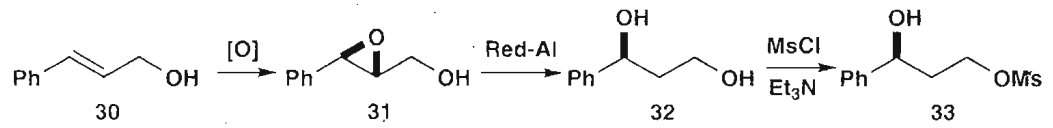
Reduction of the ketone and reaction of the chloride **27** with NaI in acetone (NaCl precipitates from acetone and drives the equilibrium to the right) gave the corresponding iodide **28**. Reaction of **28** with an excess of $MeNH_2$ as its available aqueous solution gave **23** in quantitative yield.[3]



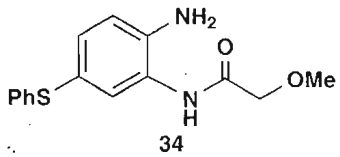
An alternative is to add the second aromatic ring by a Mitsunobu reaction and displace chloride afterwards with aqueous $MeNH_2$. If a single enantiomer, e.g. (*R*)-(+)-**27**, is used, the inverted product (*S*)-(−)-**29** is formed stereospecifically by the Mitsunobu reaction.[4]



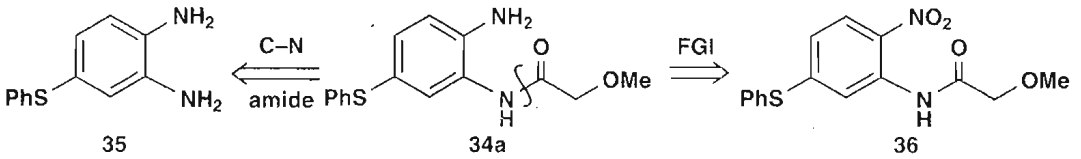
A related route starts with the epoxidation of cinnamyl alcohol **30** and regioselective reduction of the epoxide **31** by Red-Al, $NaH_2Al(OCH_2CH_2OMe)_2$ to give **32** because the aluminium complexes to the primary alcohol and delivers hydride to the nearer end of the epoxide. Mesylation and displacement with aqueous $MeNH_2$ complete the synthesis.[5]



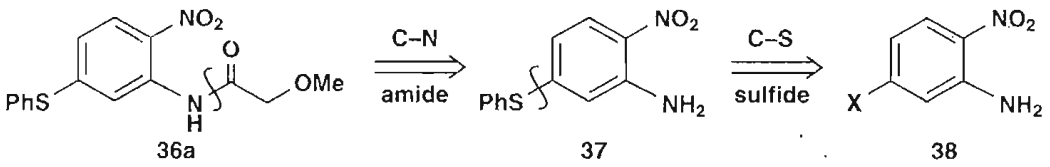
Problem 4.5: Suggest a synthesis of febantel **34** used as an anthelmintic to combat tapeworms and the like.



Answer 4.5: If we do the obvious amide disconnection first **34a**, we have a serious problem of chemoselectivity as we shall have to acylate one of two very similar amines **35**. But if we change the other amine into a nitro group **36**, the problem disappears and also suggests how we might make the sulfide.

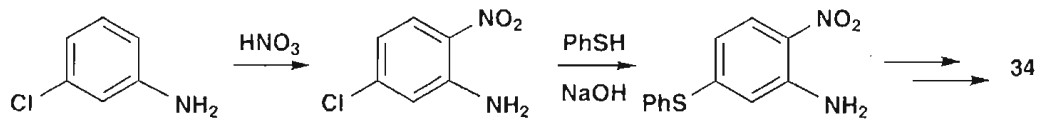


Amide disconnection **36a** reveals a simple nitro-amine with the PhS group in just the right position for C–S disconnection **37** with the nitro group activating a nucleophilic aromatic substitution of a suitable leaving group X.



36a 37 38

As it happens, the chloro-compound **38**; X = Cl is available, though it could easily be made by nitration of *meta*-chloro-aniline **39**. Displacement of chloride with the anion of PhSH gives **37**. Acylation with methoxyacetyl chloride and reduction of the nitro group gives febantel.[6]



39 38; X = Cl 37

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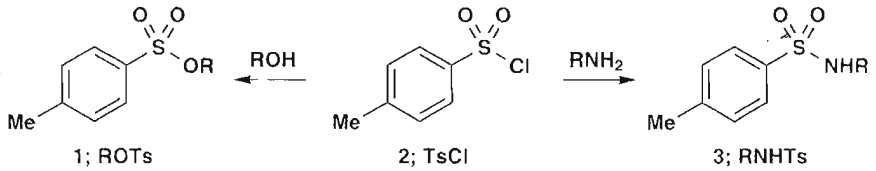
6. *Drug Synthesis*, **4**, 35.

5 Strategy II: Chemoselectivity

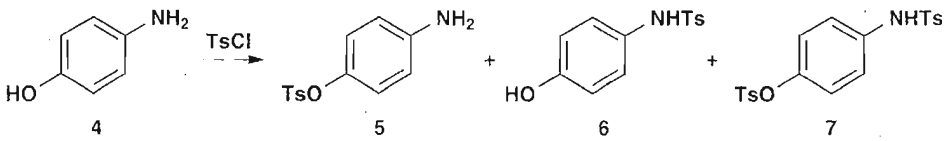
Just to remind you of chemoselectivity: if a molecule has two reactive groups and we want to react one of them and not the other we need chemoselectivity. Under this heading we can consider:

1. The relative reactivity of two different functional groups, such as NH_2 and OH.
2. The reaction of one of two identical groups.
3. The reaction of a group once when it might react twice as in thiol synthesis.

Problem 5.1: Toluene-*p*-sulfonyl chloride **2**, known as tosyl chloride or TsCl, is used to make sulfonate esters **1** from alcohols and sulfonamides **3** from amines.

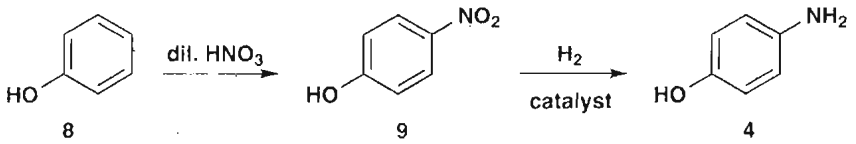


When *p*-aminophenol **4** was reacted with tosyl chloride under a variety of conditions, three products **5, 6** or **7** could be formed. With no catalyst, only **6** was formed (93% yield), with pyridine as catalyst, 76% of **6** was formed with 1% of **4** and 14% of **7**. With Et_3N as catalyst, **5** was the major product (81% yield) with traces of **6** and **7**. Explain.



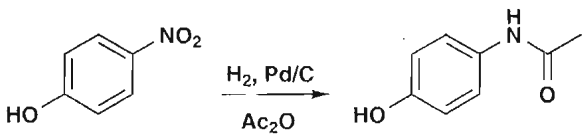
Answer 5.1: The amino group in the neutral compound **4** is more nucleophilic than the phenolic OH and gives only the sulfonamide[1] **6**. Triethylamine (pK_a about 11) can remove (most of) the phenolic proton and the oxy-anion is now more reactive than the amine. Pyridine (pK_a 5.5) is not strong enough to remove the phenolic proton completely but catalyses formation of **7** by removing some of the proton from **6**.

Problem 5.2: We explained in the textbook chapter that *p*-aminophenol **4** was made by nitration of phenol and reduction of *p*-nitrophenol **4** by catalytic hydrogenation.



8 9 4

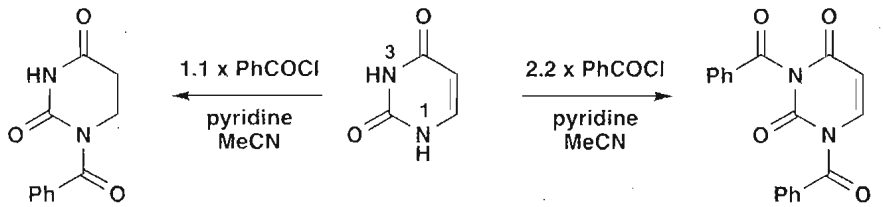
If the reduction is carried out in acetic anhydride (Ac_2O) as solvent, the product is the amide **10** in excellent yield.[2] Explain.



9 10; 79% yield

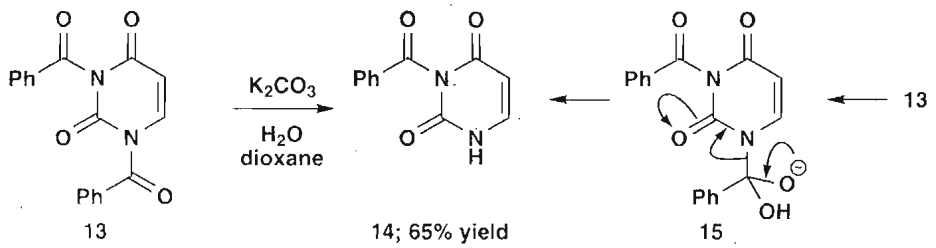
Answer 5.2: The *p*-aminophenol **4** intermediate is trapped as formed by the acetylating agent to give **10** directly without the need to isolate the intermediate **4**. This is an advantage as aromatic amines such as **4** oxidise in the air to give coloured products and hence impure amide **10** upon acetylation.

Problem 5.3: More subtle distinctions can sometimes be achieved. The nucleic acid component uracil reacts with an excess of benzoyl chloride (PhCOCl) to give a dibenzoyl derivative. However, if a very slight excess of benzoyl chloride is used, 1-benzoyl uracil **11** is isolated in excellent yield.[3] Suggest reasons why this selectivity might be observed.



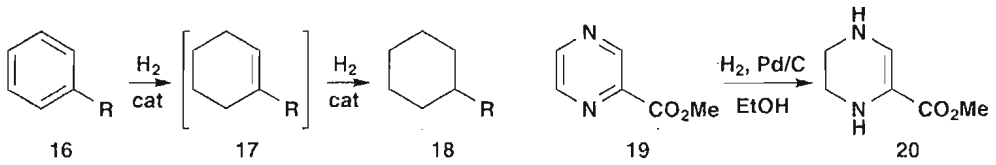
11; 89% yield 12; uracil 13; 65% yield

Answer 5.3: Two reasons spring to mind. If the pyridine removes the relatively acidic (more acidic than the NH protons in **4**) NH proton(s), we should expect the more acidic NH to react. If, on the other hand, the neutral amide reacts, we should expect the more nucleophilic lone pair to react. We can put this greater acidity to use in a hydrolysis of **13**. Thus weakly basic solution removes the 1-benzoyl group to give **14**. It looks as though the decomposition of the tetrahedral intermediate **15** is faster than the alternative. This suggests that the NH proton at N-1 is more acidic. So both mono-benzoyl derivatives can be made chemoselectively.

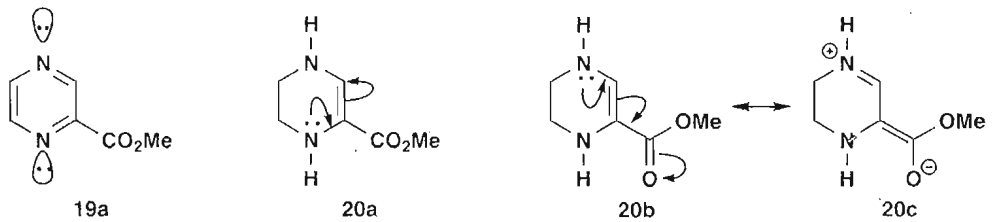


13 14; 65% yield 15

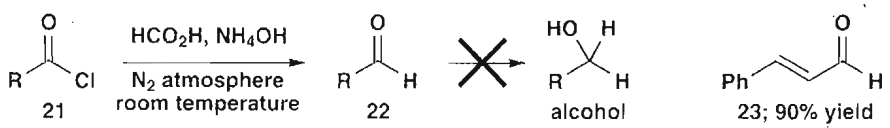
Catalytic hydrogenation usually reduces weak bonds and leaves strong bonds. So alkenes are reduced to alkanes but carbonyl groups are difficult to reduce. Catalytic reduction of benzene rings **16** normally goes all the way to cyclohexanes **18** because intermediates such as cyclohexenes **17** would be reduced more readily than the original benzene as there is less conjugation and no aromaticity. So this is chemoselectivity of type 3. However, when the aromatic heterocycle **19** is reduced catalytically,[4] the product is partly reduced **20**. **Problem 5.4:** Why is the reduction incomplete and why is that particular product formed?



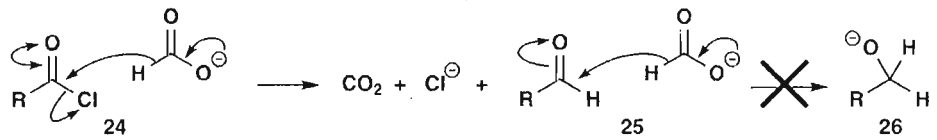
Answer 5.4: There must be some special stabilisation of the alkene in **20**. The starting material **19** is aromatic but there is no conjugation with the lone pairs on nitrogen as they are in the plane of the ring. When the nitrogens are reduced in **20**, the lone pairs can be in p-orbitals and can be conjugated with the alkene, and more importantly, one of them is conjugated through the alkene into the carbonyl group.



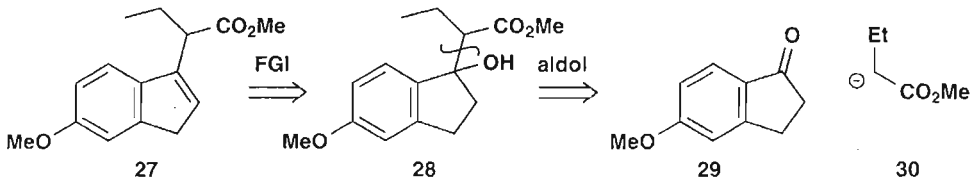
Problem 5.5: Another case where reaction may go too far is in the reduction of acid chlorides **21** to aldehydes **22** without unwanted reduction to alcohols. One successful method is to use salts of formic acid HCO_2H as the reducing agents.[5] This works well for aliphatic (R = Alk), aromatic (R = Ar) and conjugated aldehydes, e.g. **23**. Suggest a mechanism for the reaction and a reason why it stops at the aldehyde.



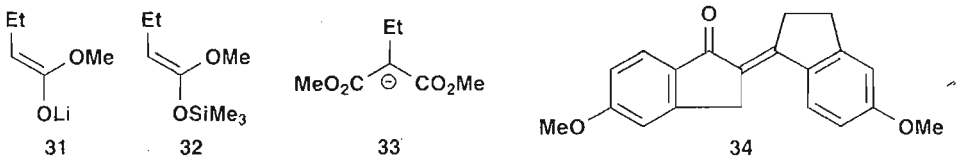
Answer 5.5: The only hydride that can be transferred is that on the formate anion and nucleophilic substitution at the carbonyl group of the acid chloride **24** gives the aldehyde **22**. The second reduction would be a nucleophilic addition to the aldehyde **25**. This is less favourable kinetically because the aldehyde is less electrophilic than the acid chloride and thermodynamically because the product is an oxyanion **26** instead of a chloride ion. These arguments apply to all such reductions of acid chlorides but metal-hydride transfer reagents such as $LiAlH_4$ or even $NaBH_4$ react rapidly with aldehydes. Formate is a less nucleophilic source of hydride than either of these.



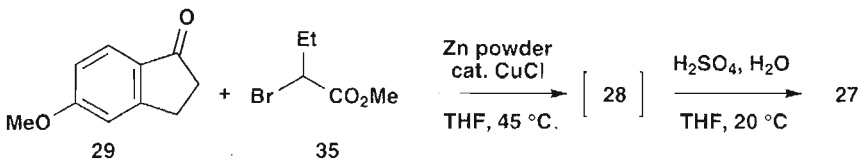
Sometimes chemoselectivity problems arise unexpectedly as in the synthesis of an intermediate **28** needed at Baeyer Health Care AG as part of a drug discovery programme.[6] Dehydration of the alcohol **28** gives **27** and **28** might easily be made by an aldol reaction (chapters 19 and 20) between the ketone **29** and some reagent for the enolate **30**.



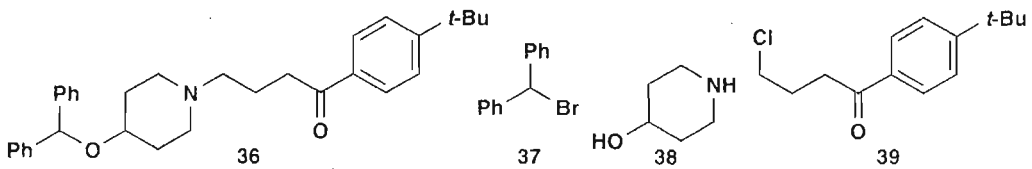
As you may guess, things go wrong with the aldol reaction. The obvious reagents for **30**, the lithium enolate **31** or the silyl enol ether **32** and even the anion **33** of the usually well behaved malonate fail to give any **28** or **27**. Instead the enone **34** is formed. **Problem 5.6:** What is going wrong? How might we make **28** by the aldol reaction?



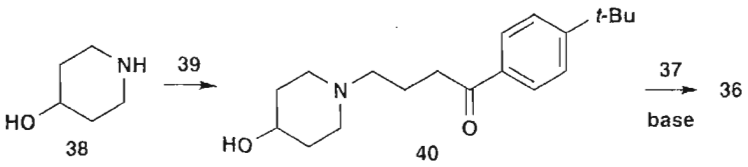
Answer 5.6: Enone **34** is just an aldol self-condensation product of the ketone **29**. Clearly the enol equivalents **31–33** are forming the enol(ate) from some of **29** rather than attacking it as nucleophiles. Two of the reagents **31** and **33** are basic while **32** needs Lewis acid catalysis so we must clearly avoid acids or bases if we want to make **27**. This sounds like a tall order but the Reformatsky method was the answer. It uses a zinc enolate, made from the bromoester **35** and there is neither acid nor base present. The chemists carried the reaction out on a roughly 10 kg scale and got 13.7 kg of **27** (92%) after dehydration in acid.



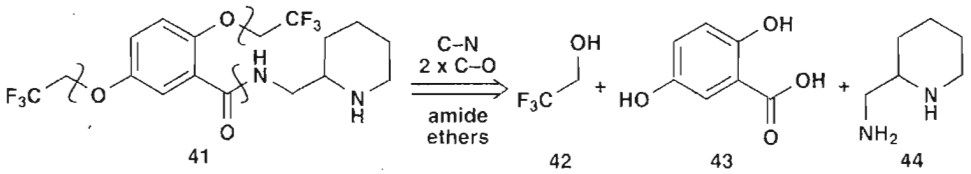
Problem 5.7: Suggest a synthesis for the antihistamine ebastine **36**. Possible starting materials **37–39** are available.



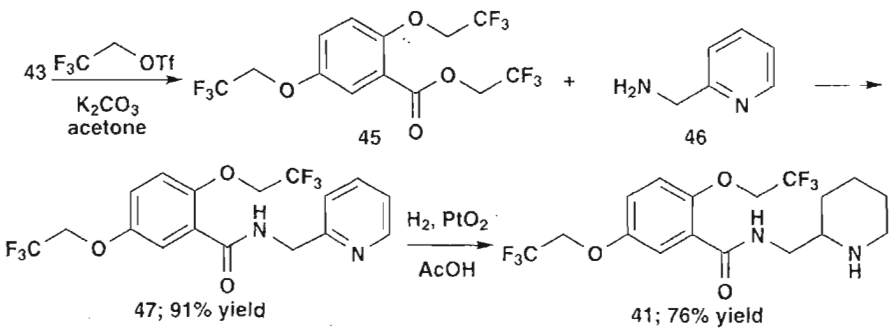
Answer 5.7: Your only problem was to ensure chemoselectivity in the couplings. The amine is more nucleophilic than the alcohol but the anion of the alcohol is more nucleophilic than the amine. This commercial synthesis alkylated on nitrogen first and on oxygen second.[7] This synthesis is from the patent literature so details are not easily available.



Sometimes it is better to react all functional groups and reveal the one wanted by selective cleavage. A case in point is 3M's antiarrhythmia drug **41**. The obvious ether and amide disconnections reveal available 2,5-dihydroxybenzoic acid **43**, the diamine **44**, and trifluoroethanol **42**. There are two main chemoselectivity problems: how do we form an amide with the primary and not the secondary amine in **44** and how do we distinguish between the three nucleophilic groups in **43**?



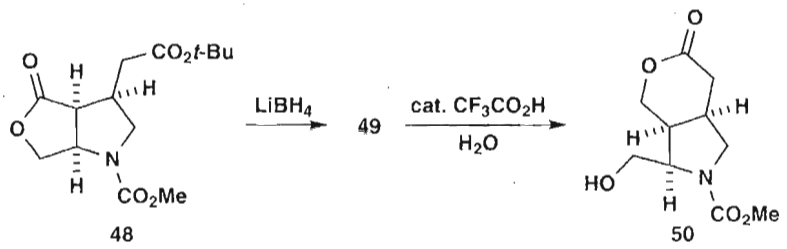
The solutions[8] used by 3M were ingenious. If the amide was formed from the pyridine **46** instead of the piperidine **44**, acylation can occur only at the primary amine. The three hydroxyl groups in **43** were all reacted with trifluoroethyl triflate to make the triple trifluoroethyl derivative **45**. Amide formation with **46** gave the amide **47** and catalytic hydrogenation over PtO_2 gave the target molecule. Note this final piece of chemoselectivity: the pyridine ring in **47** is reduced but not the benzene ring. The reaction is carried out in acetic acid so that the pyridine is protonated: this activates the pyridine towards reduction and prevents the nitrogen atom complexing with the catalyst surface.



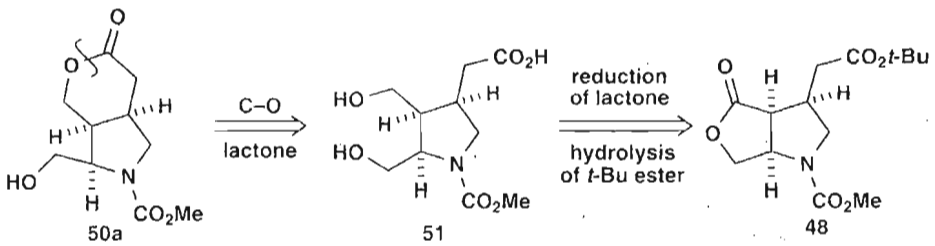
Using Disconnections to Solve Structural and Mechanistic Problems

Sometimes one has to find the chemoselectivity in a published reaction, explain it and see what one can learn from it. It is usually easier to do this than to invent a synthesis.

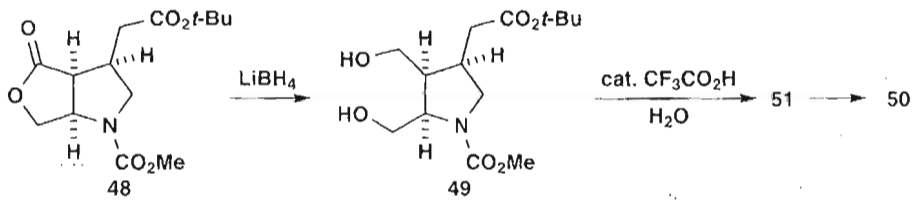
Problem 4.8: Deduce the structure of **49**, identify any chemoselectivity in both reactions, and explain it.[9]



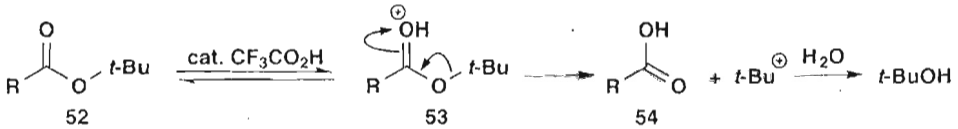
Answer 4.8: It is even possible to solve structural and mechanistic problems by disconnections! The new lactone in **50** must come by C–O lactone disconnection from **51** which must come from **48** by reduction of the lactone and hydrolysis of the ester. But is **51** the same as **49**?



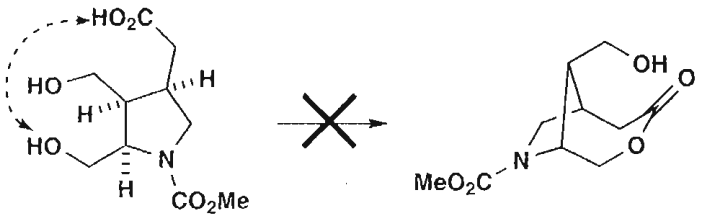
We now need to look at the forward reactions: the first reagent ($LiBH_4$) is a reducing agent while the second, aqueous acid, could hydrolyse an ester. So **49** is the product of reduction of the lactone in **48**, the hydrolysis gives **51** which cyclises to the lactone **50** in the acidic solution.



So what chemoselectivity is there? Reduction by $LiBH_4$ reduces only the lactone in the presence of an ester and a carbamate, aqueous acid hydrolyses only the ester but not the carbamate, and only one of the two primary alcohols cyclises to a lactone. In the reduction, the *t*-butyl ester is sterically hindered towards nucleophilic attack and the carbamate has extra stabilisation from the nitrogen atom. This leaves only the most reactive carbonyl group, the five-membered lactone. Lactones are generally more electrophilic than acyclic esters as they lack the stabilisation of the anomeric effect.[10] The hydrolysis of the *t*-butyl ester occurs by a different mechanism than ordinary ester hydrolysis: more S_N1 in character with no nucleophilic attack on the carbonyl group.



Finally, the lactone **50** has a stable six-membered ring fused *cis* on the five-membered heterocycle. The alternative **55** would have seven- and eight-membered rings bridged across the five-membered ring. This is perfectly possible but not as stable as **50**. The cyclisation is probably reversible and under thermodynamic control.



51a **55**

References

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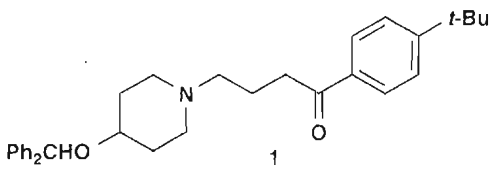
6 Two-Group C–X Disconnections

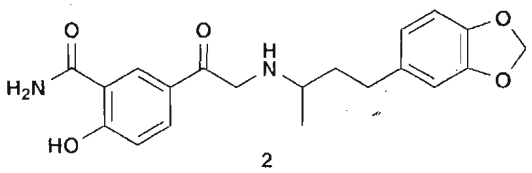
This chapter is particularly important as the counting of relationships between functional groups, the recognition of synthons, and the choice of reagents are central to the whole of organic synthesis. In this chapter we shall be disconnecting C–X bonds but the same principles will soon be applied to C–C bonds.

Counting Relationships between Functional Groups

Problem 6.1: Identify the relationships between the functional groups in these molecules.

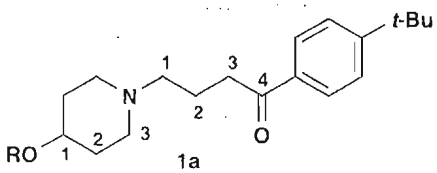


1

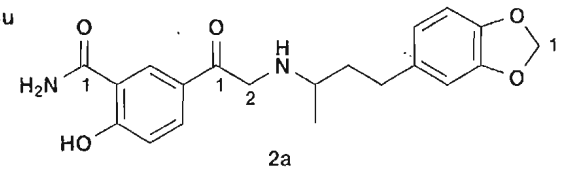


2

Answer 6.1: You may have recognised compound **1** as compound **36** from the last chapter. It has 1,3-diX (whichever way round the ring you go) and 1,4-diX relationships **1a**. The other compound has a simple 1,2-relationship and you probably saw the 1,1-diO relationship in the acetal at the right hand end. You might also have called the amide at the other end a 1,1-diX relationship.

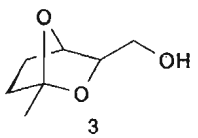


1a



2a

Problem 6.2: Find the 1,1-diX relationships in these molecules and disconnect them, drawing the starting materials. What do you think are your chances of making these molecules this way?



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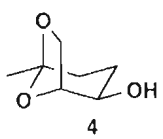
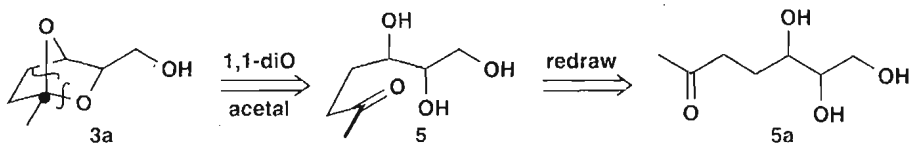
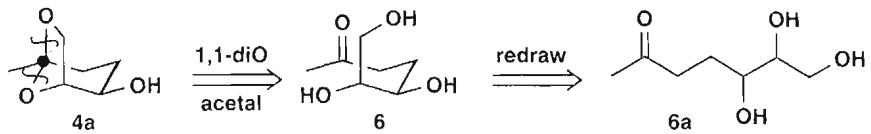


4

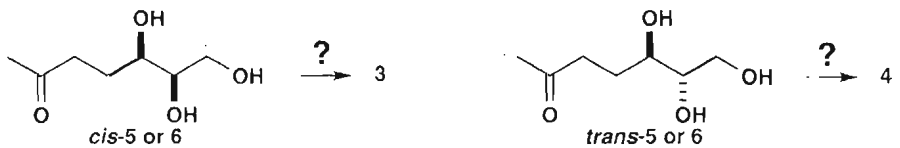
Answer 6.2: We draw the black blob where the carbonyl group is hidden **3a** – you may or may not do this as you choose and the 1,1-disconnection of the acetal reveals a keto-triol **5**, better appreciated as a redrawn **5a**. The synthesis looks good. Although another acetal could in theory be formed from the terminal diol, this would have a seven-membered ring and thermodynamically less likely.



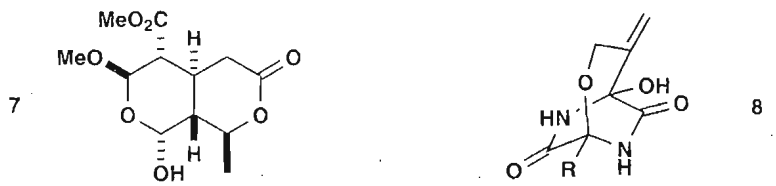
If we do the same thing with **4**, the acetal disconnections **4a** also give a keto-triol **6**, redrawn as **6a**. Again the synthesis looks good but did you notice that **5** and **6** are the same? The acid-catalysed cyclisation of **5** or **6**, whichever you want to call it, will be thermodynamically controlled and will give either **3** or **4** or perhaps a mixture of the two. If our ring size argument is right, **3** may be favoured.



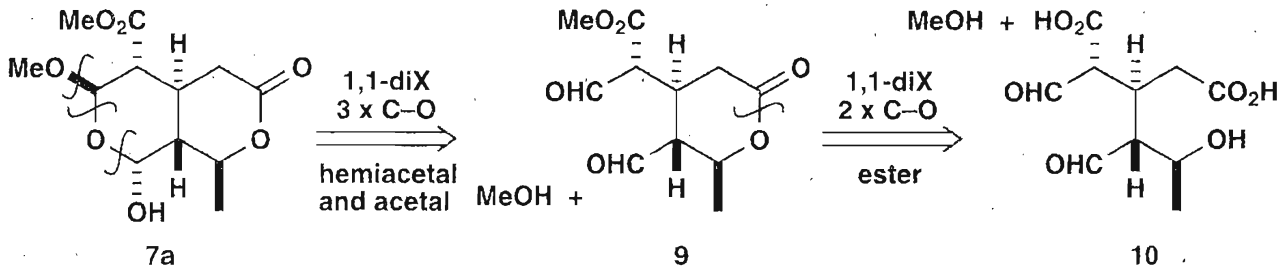
If you suggested that the stereochemistry of the two secondary alcohols could be relevant, you might well be right. The *cis* compound *cis*-**5** or **6** might give **3** while the *trans* compound *trans*-**5** or **6** might give **4**.



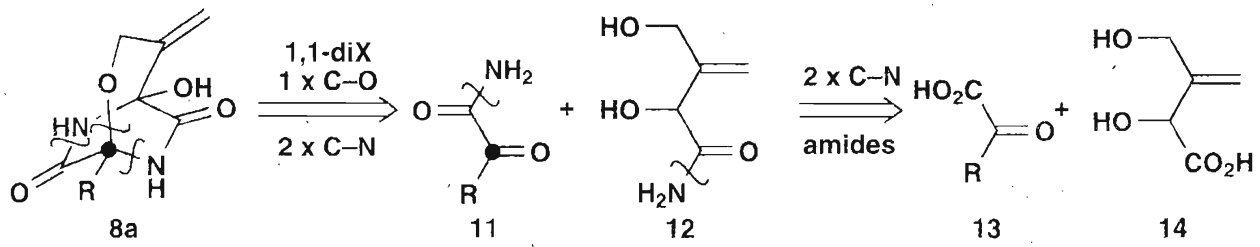
Problem 6.3: This problem may look formidable but just do the disconnections and see what you get. Find the 1,1-diX disconnections in these molecules **7** and **8** and reveal the piece(s) of hidden continuous carbon chain.



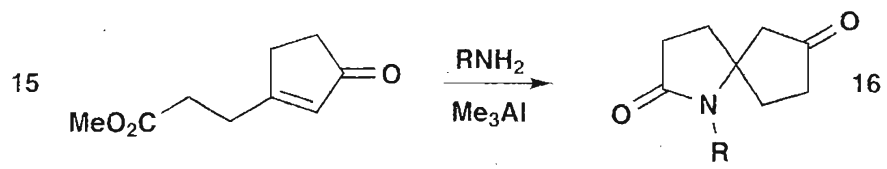
Answer 6.3: There are many ways to tackle compound **7** but they all end up the same way. We thought it best to start with the hemiacetal and the acetal at the SW corner **7a**. This reveals two aldehydes **9** but we still have the two esters so they can be disconnected to give the one piece of carbon skeleton **10**.



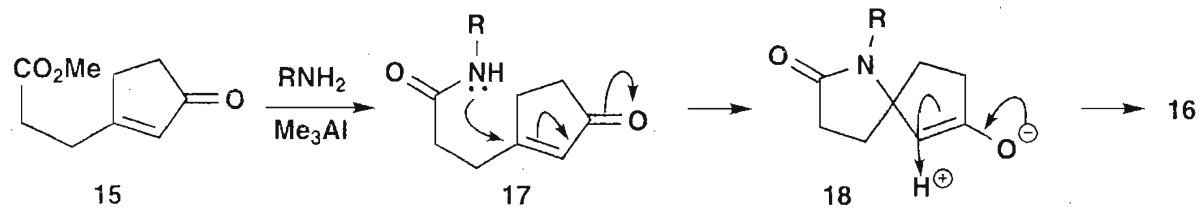
Again, it doesn't much matter where you start disconnecting **8**, but we have chosen one amide and the aminal **8a**. The carbonyl group of the aminal is marked with a black dot. This gives two pieces of carbon skeleton **11** and **12**: disconnection of the amide in each gives two simple carboxylic acids **13** and **14** – an amazing simplification. This problem is just to demonstrate the simplifying power of two-group disconnections. Designing a detailed synthesis of **7** or **8** would be much more difficult.



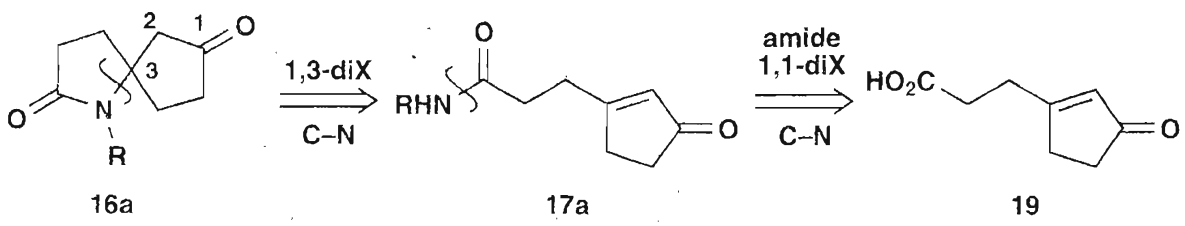
Now we approach syntheses from the other end. **Problem 6.4:** Suggest how this synthesis of spirocyclic lactams **16** might work. What are the disconnections corresponding to this synthesis?



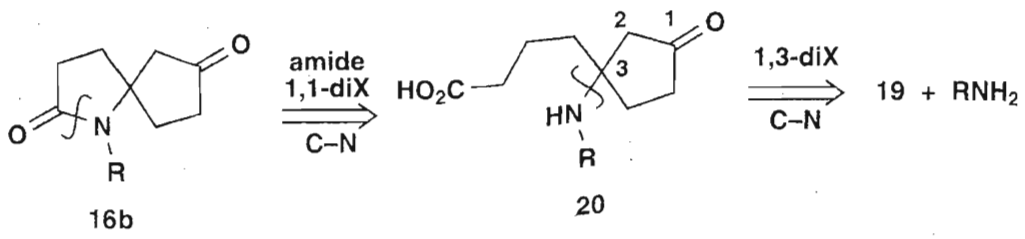
Answer 6.4: Tietze[1] suggests that Me_3Al catalyses the formation of the amide which does a conjugate addition to the cyclic enone **17**.



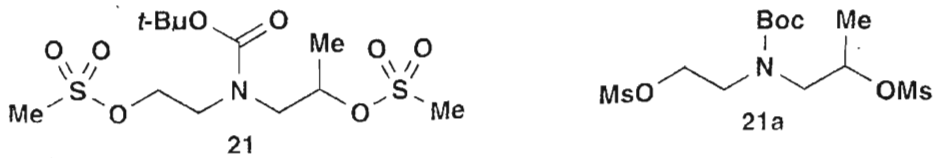
The first disconnection is of the C–N bond (not the amide) **16a** suggested by the 1,3-diX relationship between N and C=O. Then disconnection of the amide gives **19**, whose methyl ester is **15**.



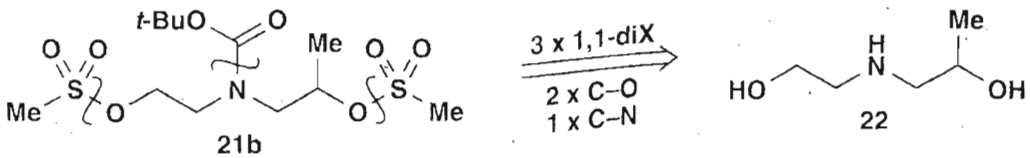
Of course, it would make no difference if you disconnected the amide first **16b**. You would get the amine **20** and now the 1,3-diX disconnection is more obvious giving the same starting materials **19** and RNH_2 but implying a different reaction.



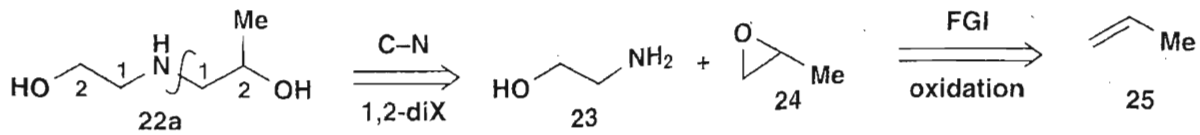
Problem 6.5: Suggest a synthesis of compound **21** needed at Merck for the synthesis[2] of some chemokine receptor antagonists. This is a fully drawn out structure and you might be more used to an abbreviated version **21a**.



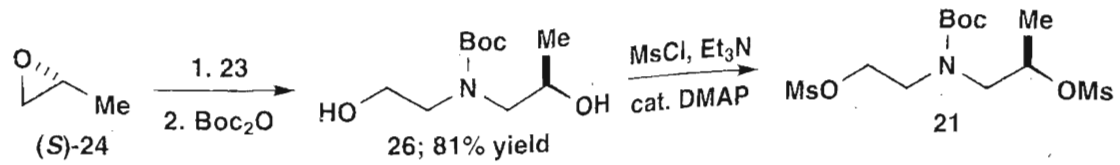
Answer 6.5: You need the full version for your first disconnections **21b** as they are all within the abbreviated groups. Boc derivatives are made from the 'Boc anhydride' Boc_2O and mesylates from mesyl chloride MsCl and Et_3N. So now we can see the real target: the aminodiol **22**.



The aminodiol **22** has two 1,2-diO relationships that we would generally make from amines and epoxides. But as ethanolamine **23** is readily available, it makes sense to disconnect just one **22a** and we shall use the epoxide **24** from propene **25**.

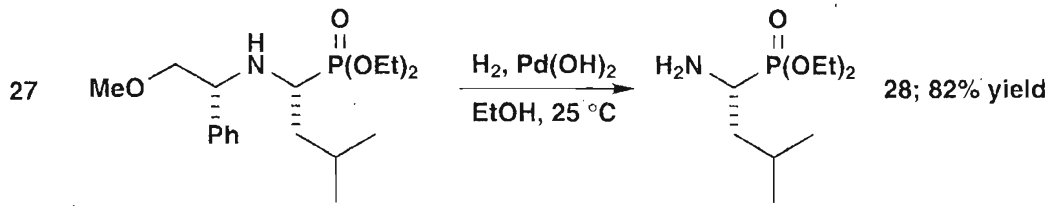


As this epoxide (propylene oxide) is available as either enantiomer, the Merck chemists used *R*-(–)-**24** to make the enantiomer of **21** that they needed. Note that this synthesis works because the epoxide is attacked at the less substituted carbon atom and therefore no inversion takes place at the chiral centre.

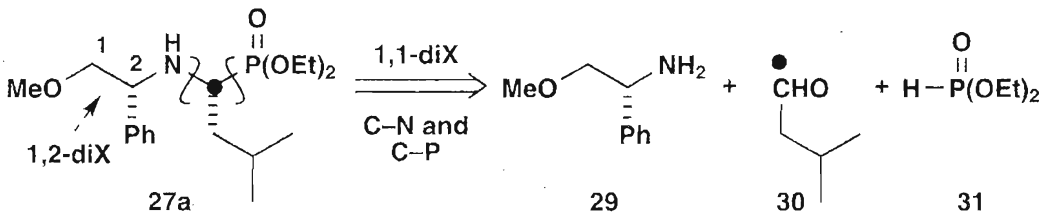


Problem 6.6: Identify the possible 1,n-diX disconnection in this molecule **27** and suggest a synthesis. You do not have to be concerned over the stereochemistry. Though in fact the stereochemistry was important as the TM **27** was hydrogenated to cleave the benzylic C–N bond and

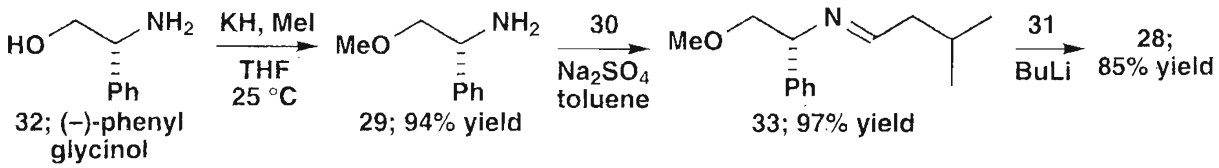
give the phosphorus analogue of leucine, the phosphono-amino ester **28**, which inhibits bacterial growth.



Answer 6.6: There are 1,2-diX and 1,1-diX relationships shown in **27a**. The 1,1-diX is in the middle of the molecule and the carbonyl group (black blob) is very helpful. The three starting materials will be the amino-ether **29**, the aldehyde **30** and diethyl phosphite **31**. The last two are available.[3]

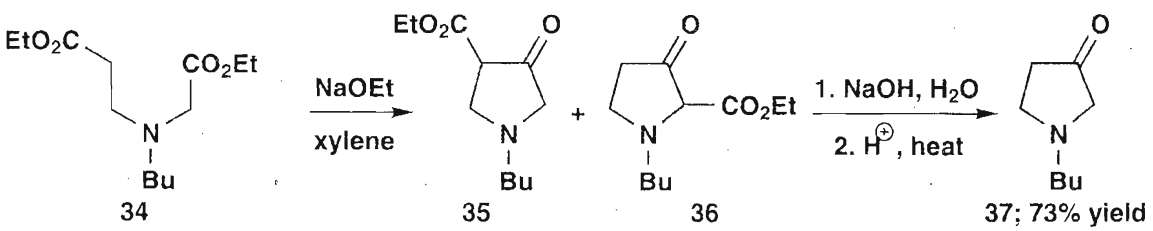


Phenyl glycinol **32** is also available in enantiomerically pure form so it is easy to start with ester and imine formation. Mixing the aldehyde **30** and the amine **29** in toluene with sodium sulfate as dehydrating agent gives the imine **33** which need not be isolated but can be combined immediately with the lithium derivative of diethyl phosphite **31**. It so happens that the chiral amino substituent directs the incoming phosphite anion to the other face of the imine by chelation of the Li atom with OMe and the imine nitrogen atom. All the reactions go in superb yield.

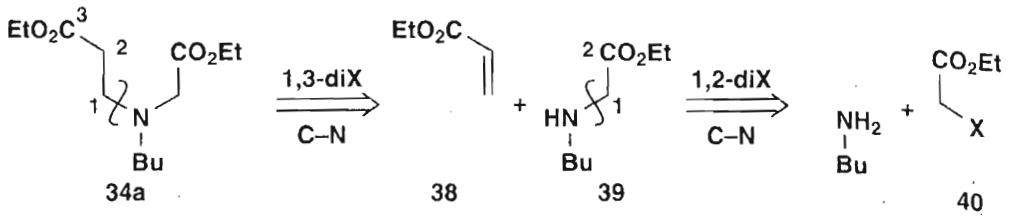


Synthesis of a Heterocycle

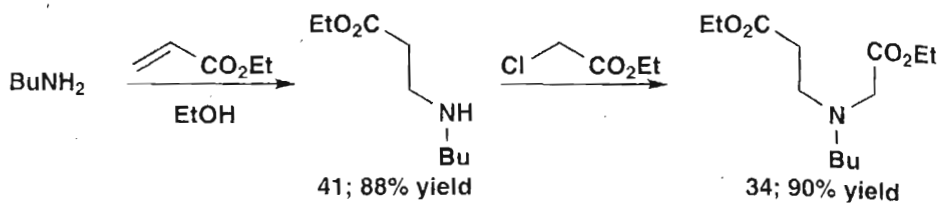
It turns out that the simple pyrrolidine **37** can be made by Claisen ester condensation of **34** and decarboxylation of the two products **35** and **36**. This kind of reaction is treated in more detail in chapter 19. **Problem 6.7:** Suggest a synthesis of the starting material **34**.



Answer 6.7: The nitrogen atom has 1,2- and 1,3-diX relationships to the two carbonyl groups and we can obviously disconnect both C–N bonds by standard methods to reveal ethyl acrylate **38**, butylamine $BuNH_2$ and an α-halo acetic ester **40**. But which reaction should we do first?



The alkylation may go twice on $BuNH_2$ whereas conjugate addition usually occurs once only. So it makes sense to do conjugate addition first and alkylate **41** second when steric hindrance should inhibit a second alkylation of **41** by the chloroester. This works very well[4] with **40**; X = Cl.

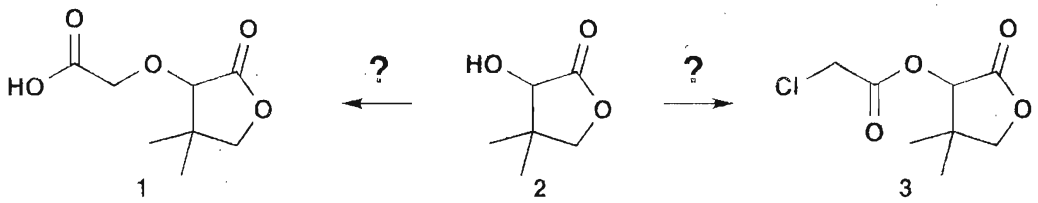


References

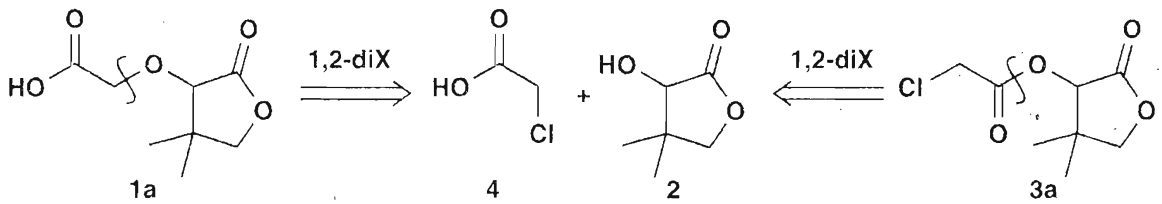
1. L. F. Tietze and P. L. Steck, *Eur J. Org. Chem.*, 2001, 4353.
2. A. Pasternak, D. Marino, P. P. Vicario, J. M. Ayala, M. A. Cascierri, W. Parsons, S. G. Mills, M. MacCoss and L. Yang, *J. Med. Chem.*, 2006, **49**, 4801.
3. A. B. Smith, K. M. Yager, B. W. Phillips and C. M. Taylor, *Org. Synth.*, 1998, **75**, 19; A. I. Meyers, G. S. Poindexter and Z. Brich, *J. Org. Chem.*, 1978, **43**, 892.
4. N. J. Leonard, F. E. Fischer, E. Barthel, J. Figueras and W. C. Wildman, *J. Am. Chem. Soc.*, 1951, **73**, 2371.

7 Strategy III: Reversal of Polarity, Cyclisations, Summary of Strategy

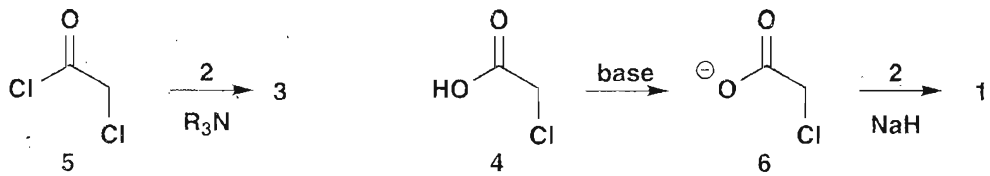
Problem 7.1: How would you convert available pantolactone **2** selectively into the two products **1** and **3**?



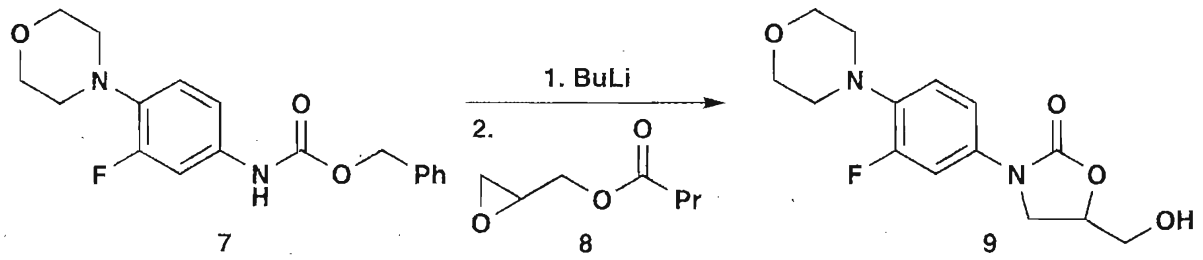
Answer 7.1: The disconnection of each product appears to require some derivative of chloroacetic acid **4** in a selective acylation (for **3a**) or alkylation (for **1a**).



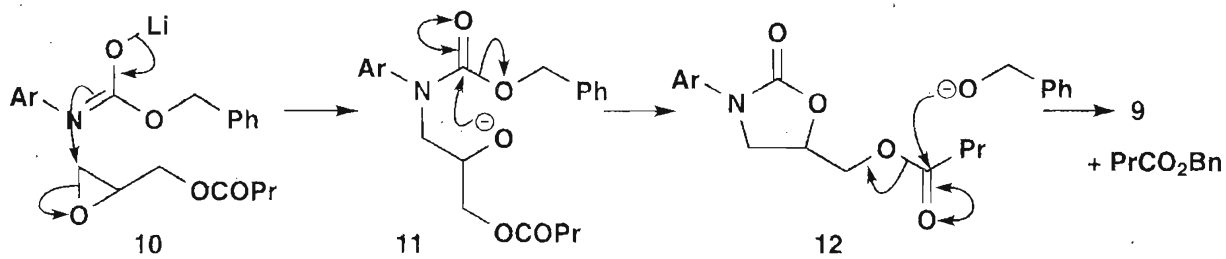
We know that chloroacetyl chloride **5** is available and reaction with this acylating agent in base gives[1] the expected ester **3**. The alkylation is more difficult but using the free acid **4** in basic solution will give the anion **6** that cannot be attacked at the carbonyl group.



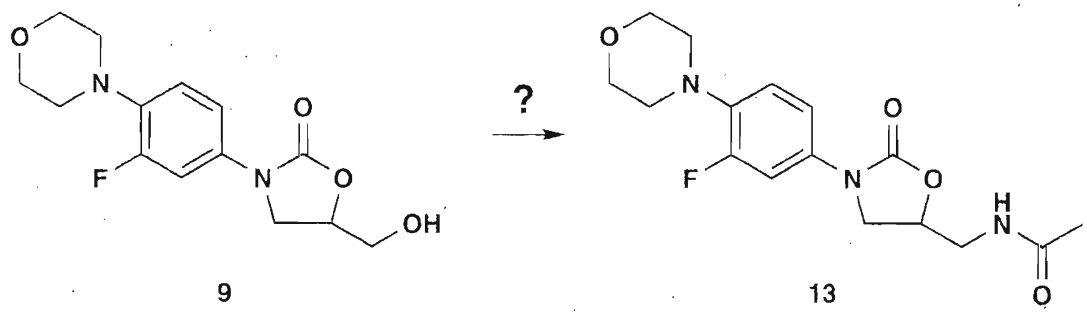
The antibiotic **9** is made[2] by the reaction of **7** with BuLi followed by glycidyl butyrate **8** in 85% yield. **Problem 7.2:** What is the mechanism of the reaction? Why is BuLi used?



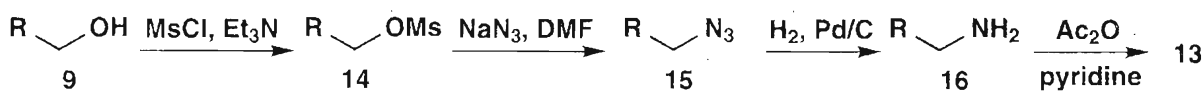
Answer 7.2: There is only one acidic proton in **7** – the NH proton of the amide. Drawing the left hand rings as 'Ar' we can react the lithium derivative with the epoxide **10** to give an alkoxide that cyclises **11** to give the ring and finally the benzyloxide anion deacylates the ester **12** to give the anion of **9**. So why use BuLi? Well, **7** also contains a nucleophilic amine so we need the anion of the amide but perhaps mainly because of this helpful cascade of alkylation and two acylations giving **9** in one step. The anion of BnOH, released in step **11**, is more nucleophilic than BnOH itself.



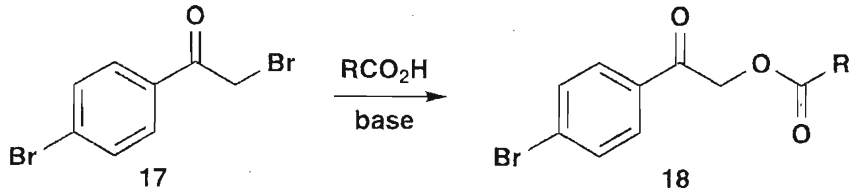
In fact, the antibiotic was not **9** but the amide **13**. **Problem 7.3:** How would you make **13** from **9**?



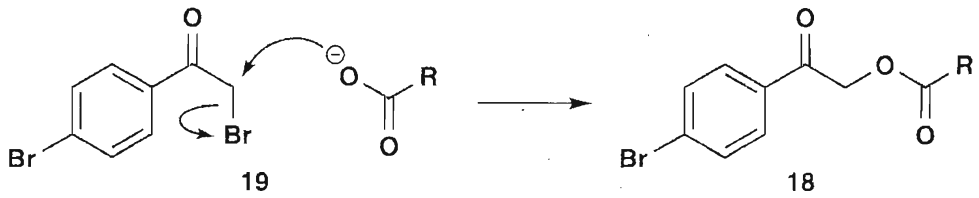
Answer 7.3: You need to convert the OH group into a leaving group, displace it with some nitrogen nucleophile (but not ammonia as you will see in the next chapter) and acylate the amine. The chemists used a mesylate **14**, displaced that with azide ion, reduced the azide **15** catalytically and acylated the amine **16** with acetic anhydride in pyridine.



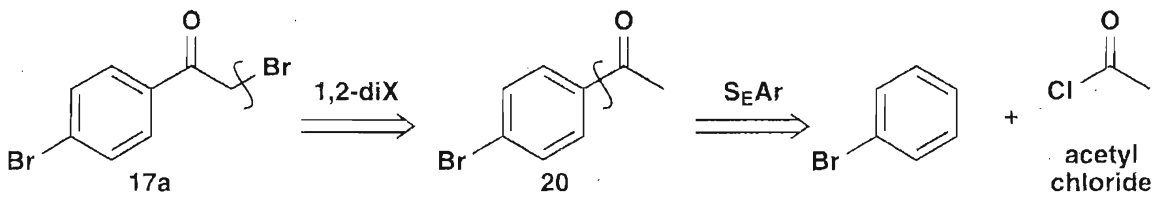
The dibromide **17** is used to make crystalline derivatives **18** of carboxylic acids for X-ray analysis. Ester formation is by an unusual base-catalysed reaction. **Problem 7.4:** How does this method work and why is that bromide displaced?



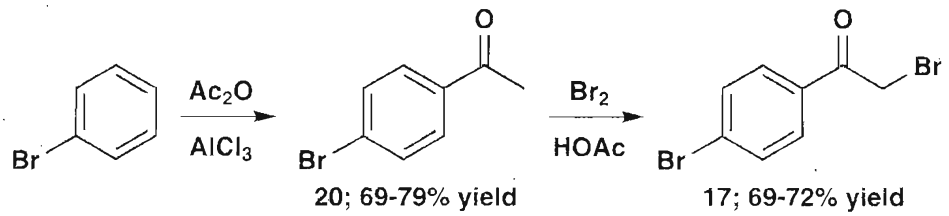
Answer 7.4: The reaction is a simple S_N2 displacement of bromide by carboxylate ion **19**. It is unusual because carboxylate is a weak nucleophile and rarely displaces bromide. However this α-bromo ketone is very electrophilic because of the 1,2-relationship between the two electron-withdrawing groups. It would be possible to displace the aryl bromide by nucleophilic aromatic substitution, also activated by the carbonyl group, but this is a more difficult reaction.
Problem 7.5: Suggest a synthesis for the reagent **17**.



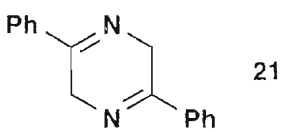
Answer 7.5: We can add the bromine next to the ketone by bromination of an enol of the ketone **20** but we cannot add the other bromine by electrophilic substitution as the ketone is *m*-directing. However, the bromine is *o*, *p*-directing so we can use a Friedel-Crafts reaction.



It turns out to be easier to use acetic anhydride in the Friedel-Crafts reaction and bromination in acetic acid completes the synthesis.[3]

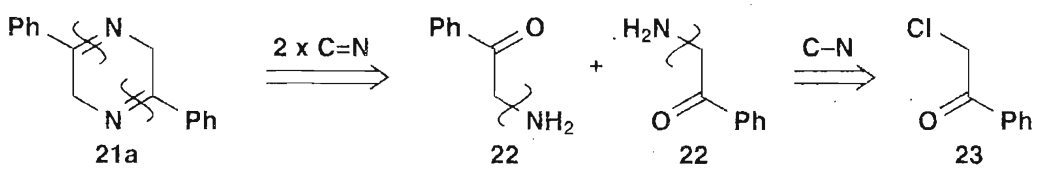


Symmetrical compounds are often easy to make as two molecules of the same starting material often gives the product. **Problem 7.6:** Suggest a synthesis of this heterocycle **21**.

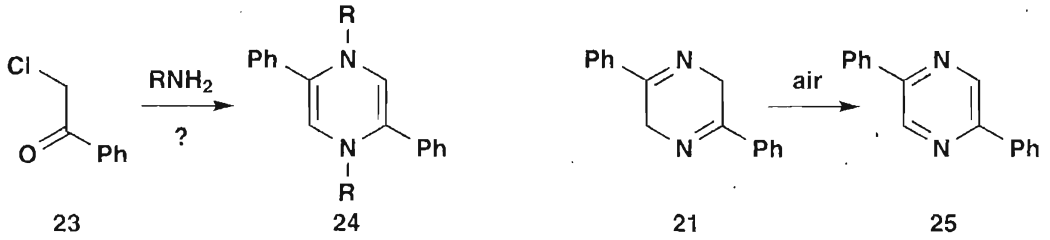


21

Answer 7.6: You could disconnect the two imines first, as we have done, or the two C–N single bonds, but either will get you back to two molecules of the reactive α-halo ketone **23** and two of ammonia. As the product is cyclic, simply mixing **23** and ammonia in equal proportions[4] gives **22** which dimerises to form the stable six-membered ring **21**.



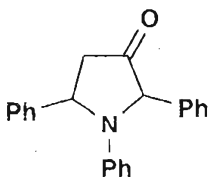
When primary amines RNH_2 are used instead of ammonia in this reaction, it proves difficult if not impossible to isolate the obvious product **24. Problem 7.7:** Why should this be so difficult? *Hint*: Even **21** is unstable and oxidises to **25** on exposure to air.



23 24 21 25

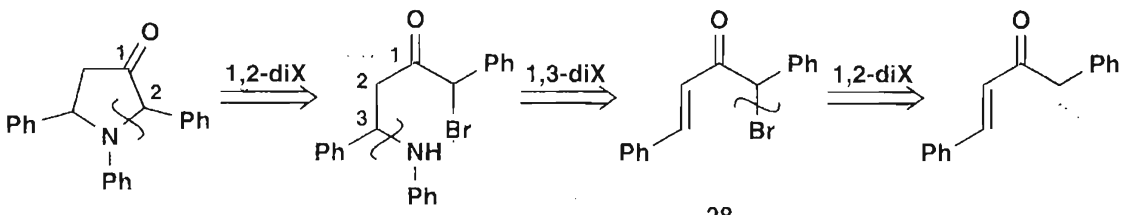
Answer 7.7: The oxidation of **21** gives the aromatic heterocycle **25** with six π-electrons. Compound **24** has *eight* π-electrons: two in each alkene and two on each N atom and, if fully conjugated, would be anti-aromatic. So it lacks the aromatic stability of **25**. What does happen to **24** is quite complicated.[5]

This approach of disconnecting all C–N bonds need not be restricted to symmetrical compounds. **Problem 7.8:** Suggest a synthesis of the five-membered heterocyclic amine **26**.



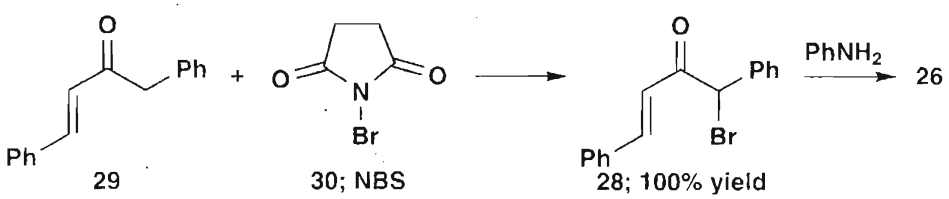
26

Answer 7.8: The other functional group in this compound is the ketone so we need to note the relationship on either side. One is a 1,2-diX and the other a 1,3-diX. It doesn't matter which you do first: the 1,2-diX **26a** gives a bromoketone and 1,3-diX disconnection **27** with conjugate addition in mind leads back to a bromoketone **28** and a simple enone **29**. We'll stop there but you will discover how to make compounds like **29** in chapters 19 and 20.



26a 27 28 29

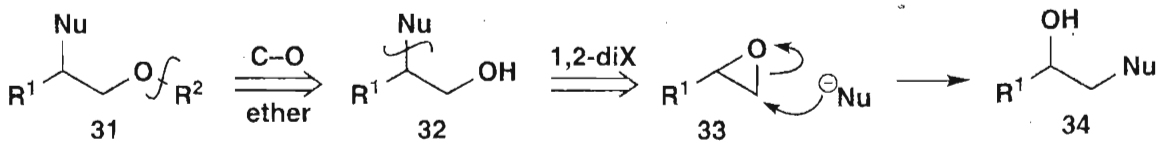
It turns out that NBS **30** is the best reagent for bromination and that reaction of aniline $PhNH_2$ with **28** gives the heterocycle **26** immediately.[6] Whichever reaction happens first is slower than the cyclisation of the product.



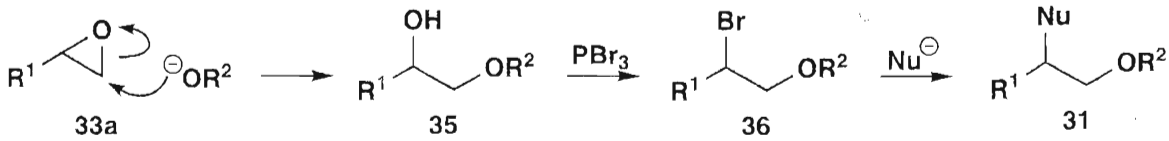
29 30; NBS 28; 100% yield 26

Regioselective Attack on Epoxides

At first sight, the disconnection of **31** seems to lead naturally back to the epoxide **33**, but the nucleophile will actually attack the less hindered end of the epoxide and **34** is the product.

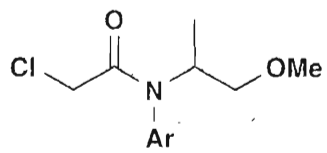


So how do we go about making **31**? In fact it can be made from the same epoxide **33** by using a different nucleophile. If we add the alkoxide from R^2OH **33a**, we get **35** and now we change the free OH group into a leaving group such as bromide **36**, we can displace that with the original nucleophile.



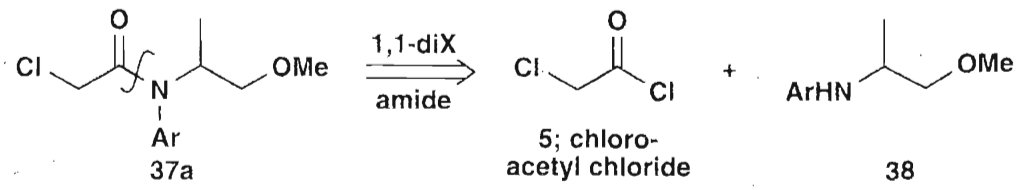
A class of agrochemicals used to inhibit the germination of weeds[7] is based on structure **37**.

Problem 7.9: Suggest how these compounds might be made.

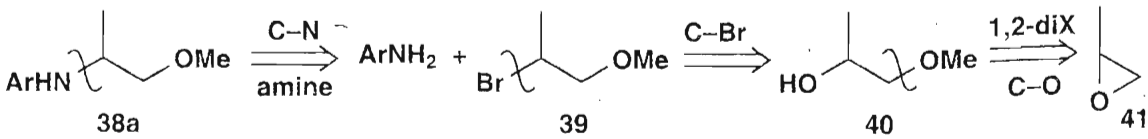


37

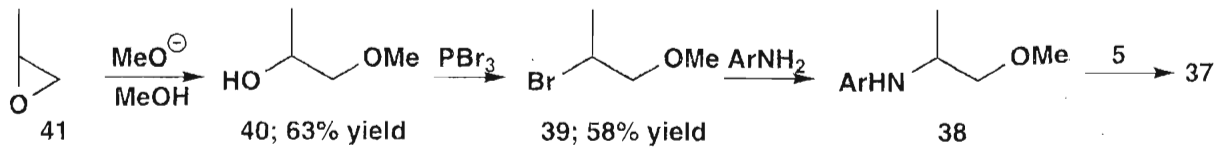
Answer 7.9: Disconnection of the amide reveals one 1,2-diX compound **5** that we can buy and one **38** of exactly the type we have just discussed.



So, following the same line of argument we get back to available propylene oxide **41** by a series of familiar disconnections.



The synthesis[8] follows the lines of the disconnections exactly.



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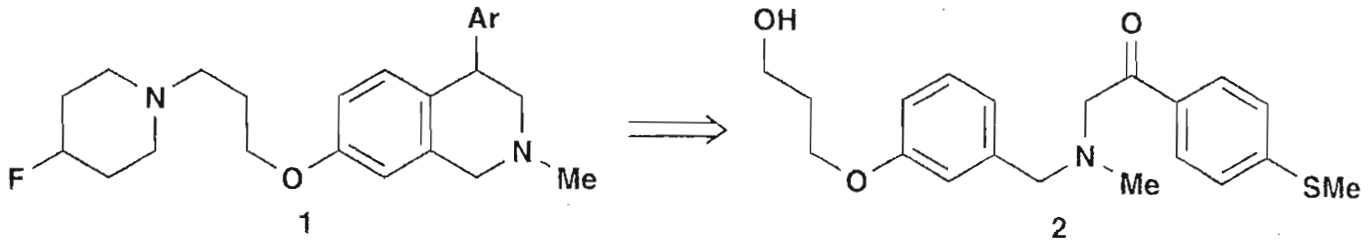
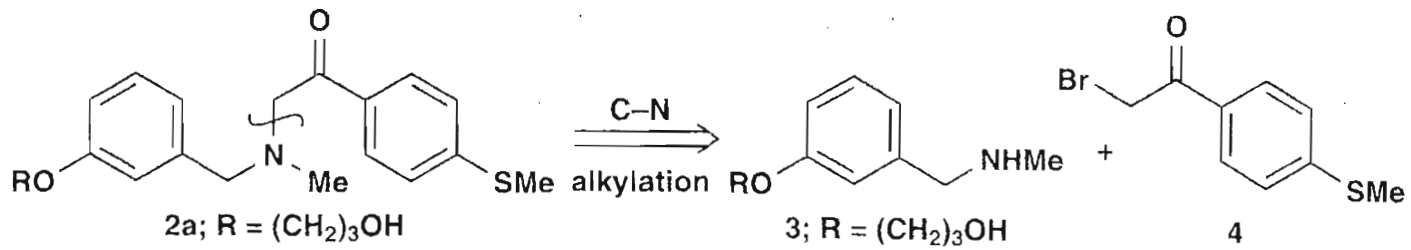
8 Amine Synthesis

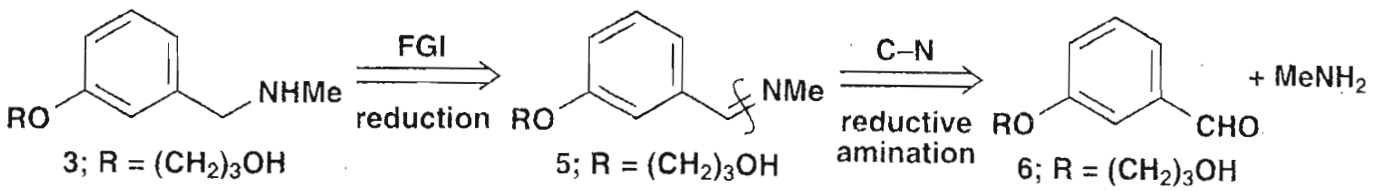
Just to remind you of the main methods for the synthesis of amines, here is a synthesis of a Johnson and Johnson drug **1** that contains two amines.[1] The key intermediate **2** contains only one of the amines: a tertiary amine with three different substituents. Its structure shows what 'Ar' means in diagram **1**.



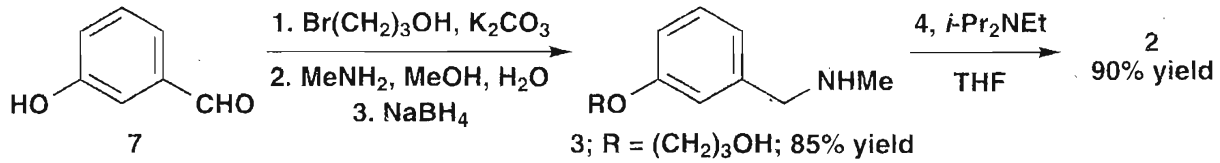
The first disconnection **2a** was of one C–N bond with alkylation in mind: this is a good strategy when adding a reactive alkyl halide to make a tertiary amine. The halide **4** is easily made by bromination of the enol of the methyl ketone.



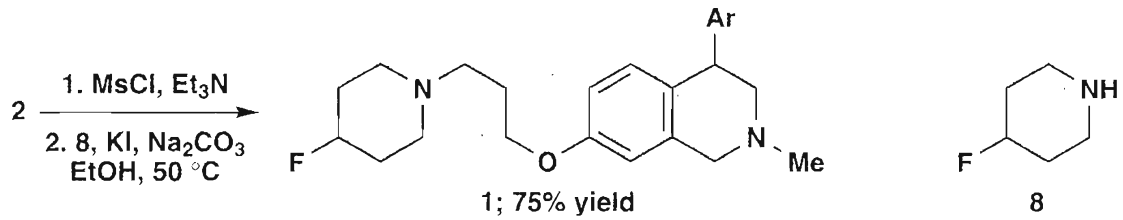
Now a second C–N disconnection is needed and the choice was reductive amination. Here we draw it out in full: the FGI to the imine **5** and C=N disconnection to the aldehyde **6** but we shall not usually bother to draw the imine.



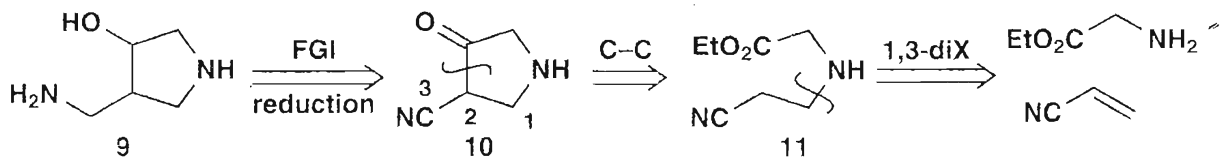
So far the synthesis is straightforward: as it happens that the imine **5** is quite stable and the reduction can be carried out as a separate step with $NaBH_4$. The alkylation is very successful with a hindered amine base.



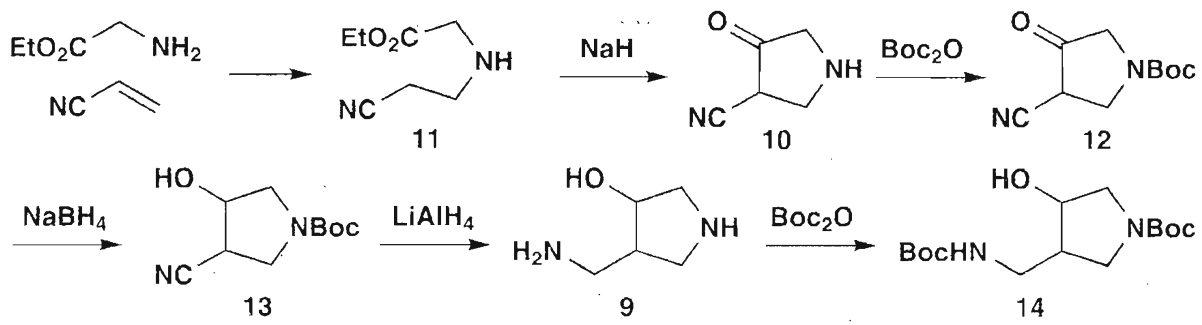
The cyclic tertiary amine was also added by alkylation after converting the primary alcohol in **2** into a leaving group. Providing that the solution was free from chloride ion, coupling to the fluoroamine **8** occurred in high yield.



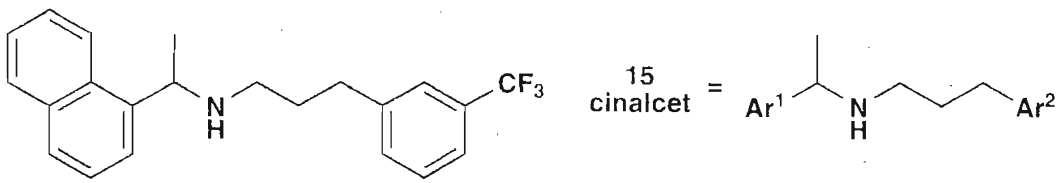
To summarise: alkylation at nitrogen is a possible way to make amines, especially tertiary amines, but reductive amination or reduction of amides or nitriles is generally better as described in the textbook chapter. Perhaps the reduction of nitriles might be the least familiar of these, so here is a simple example. The compound **9** is needed for the synthesis of an antibiotic.[2] Converting the primary amine into a nitrile and the alcohol into a ketone gives a compound suitable for 1,3-C–C disconnection **10**. The idea is to cyclise the anion of the nitrile onto the electrophilic ester. Finally a 1,3-diX disconnection of the amine **11** reveals two available starting materials: acrylonitrile and the ethyl ester of glycine.



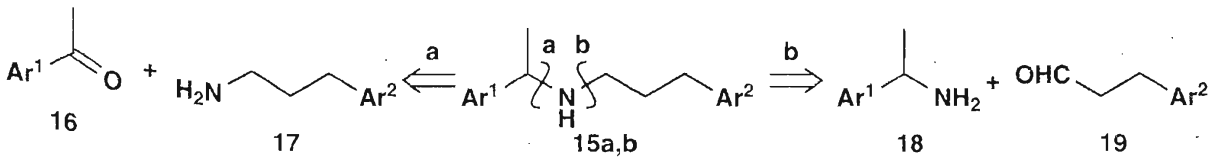
The synthesis required some protection of the amine in **11** and a Boc group was used **12** after the cyclisation. The reduction of the nitrile with $LiAlH_4$ also removed the Boc group **9** but this protection was still useful so it was immediately put back on both amines **14**.



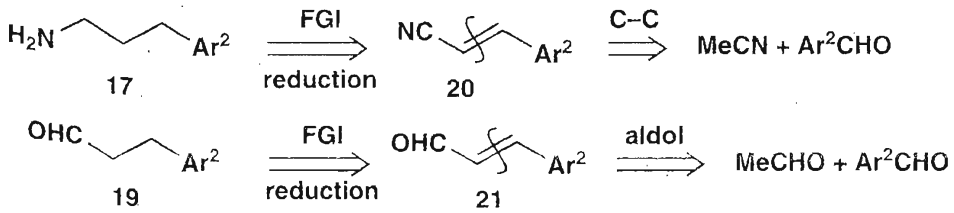
Problem 8.1: Suggest a synthesis of the amine **15**, a drug used to lower calcium levels in diabetic patients.[3]



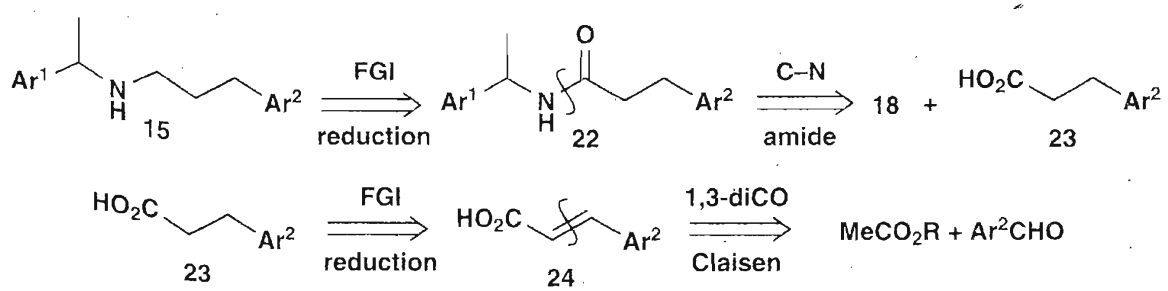
Answer 8.1: You have a very wide choice here! You could use reductive amination on either side of the nitrogen atom **15a,b** cutting the molecule roughly in half and revealing simple primary amines **17** or **18** and ketone **16** or aldehyde **19**.



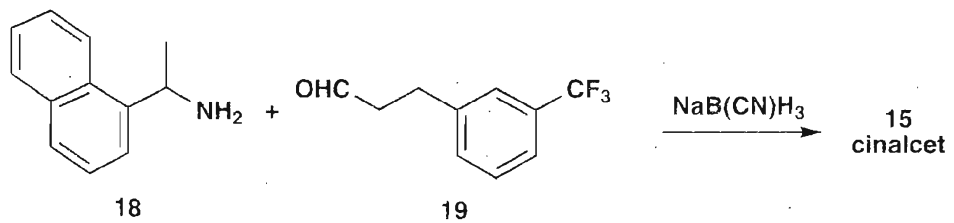
Ketone **16** can be made by a Friedel-Crafts acylation on naphthalene and the amine **18** by reductive amination from **16**. Both **17** and **19** can be made by the kind of condensation discussed in the synthesis of **10** after FGI to introduce an alkene. The starting material for both strategies would be Ar^2CHO with either MeCN or MeCHO. So there is little difference.



But you might have preferred to add a carbonyl group to use the amide **22** which disconnects to **18** and the carboxylic acid **23** that is also available by the aldol/Claisen strategy used to make **18** and **19**.

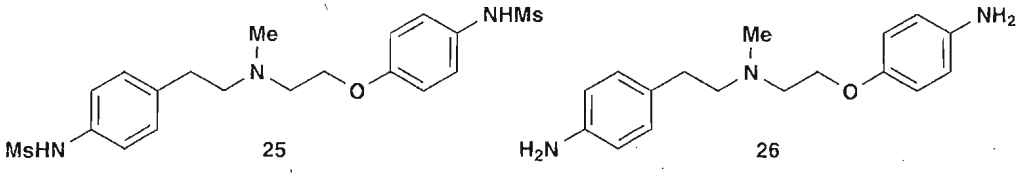


The published synthesis, not necessarily any better than your suggestions, is reductive amination using **16** and **17**. The reduction was done with cyanoborohydride.

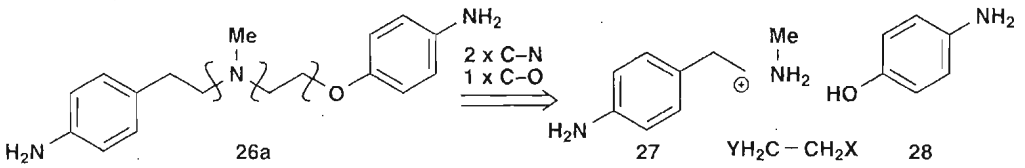


An Example of a Triamine

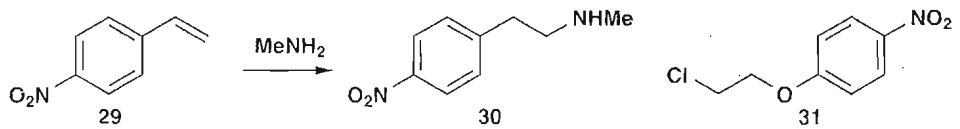
Pfizer have a series of anti-arrhythmic drugs used to treat heart problems.[4] You are invited to consider the synthesis of one of these **25**. As the compound is a *bis*-*N*-mesylate, it is clearly based on the triamine **26**. **Problem 8.2:** What are your initial thoughts?



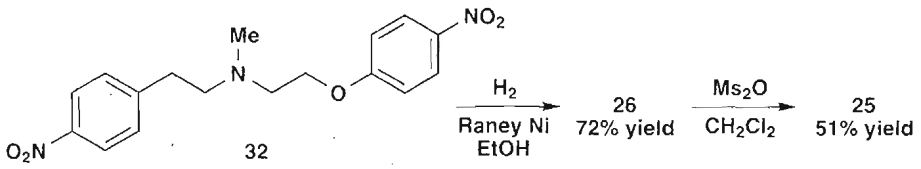
Answer 8.2: The peripheral amines on the benzene ring can probably be inserted by nitration of a suitable precursor. The key disconnections must be around the central nitrogen and probably next to the backbone oxygen. If we do all these at once **26a**, we get an electrophilic synthon **27**, a molecule of $MeNH_2$, *p*-aminophenol **28**, and some two carbon electrophile with leaving groups at each end. Either of the NH_2 groups in **27** or **28** could be nitro groups or sulfonamides.



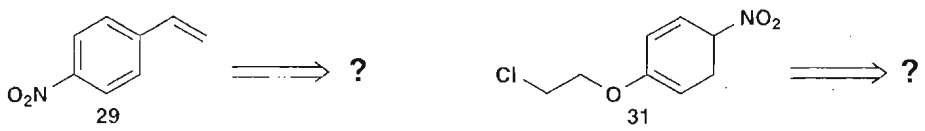
If you have gone further, you have done very well as we feel you are unlikely to have seen a good reagent for **27** so we are going to explain the published synthesis. Naturally, your synthesis may be as good. The workers at Pfizer chose[5] *p*-nitrostyrene as the reagent for **27** as the nitro group makes the alkene electrophilic and conjugate addition of $MeNH_2$ gave the secondary amine **30**. The other half of the molecule came from the chloride **31**. **Problem 8.3:** Why do you think they delayed reducing either nitro group until **30** and **31** were joined together?



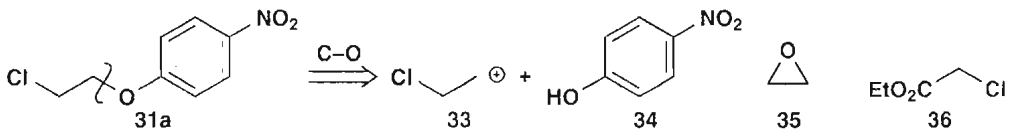
Answer 8.3: If either NH_2 group was present, it might act as the nucleophile for the chloride **31**. The two reagents **30** and **31** were combined in MeCN with K_2CO_3 and iodide ion as catalyst to give **32** in 64% yield. Catalytic reduction and mesylation gave the drug **25**. The yields in these steps are not great but this is a short synthesis and it is convergent (chapter 40).



But we have not yet made the starting materials! **Problem 8.4:** Suggest syntheses for the two starting materials **29** and **31**.

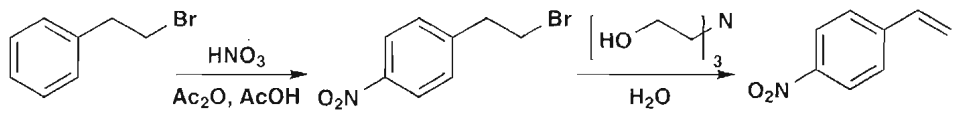


Answer 8.4: You already know the disconnection for **31**: the C–O bond. As *p*-nitrophenol **34** is readily available, you just had to choose a reagent for the two carbon electrophile **33**. You might have chosen 1,2-dichloroethane but a better choice would have been ethylene oxide **35** or the chloro-ester **36**. The product from **36** would have to be reduced to the alcohol (that would be the product from reaction of **34** and **35**) and the alcohol converted to the chloride **31** with PCl_3 or $SOCl_2$.



31a 33 34 35 36

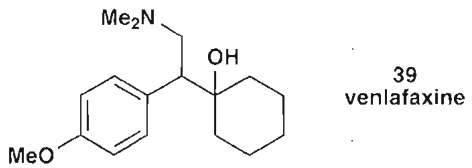
p-Nitrostyrene **29** is more interesting. It is difficult to add vinyl groups to benzene rings and one of the two best ways is to nitrate bromoethyl benzene **37** and eliminate HBr from **38** with the water-soluble base triethanolamine.[6] The other is a Wittig reaction on *p*-nitrobenzaldehyde[7] (chapter 15).



37 38 29; 85-91% yield

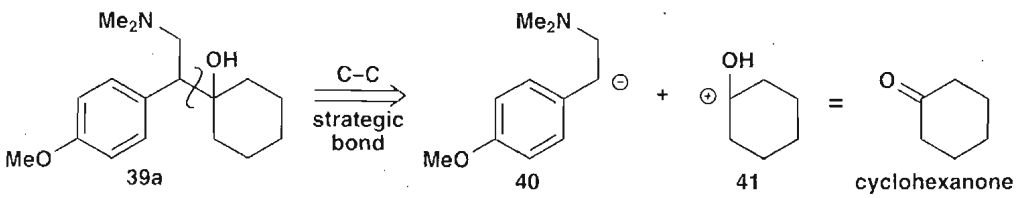
Strategic Bond Disconnection

Venlafaxine **39** is a Wyeth antidepressant.[8] In considering how it might be made, you might identify one bond that would lead to very great simplification – a strategic bond. **Problem 8.5:** Suggest a synthesis for venlafaxine.



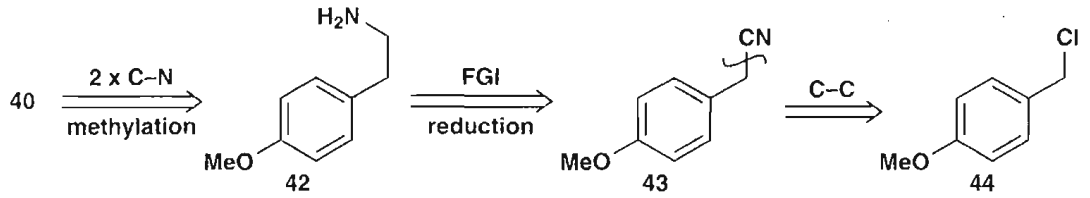
39 venlafaxine

Answer 8.5: The central C–C bond between two branchpoints is the strategic bond **39a**. One half **41** must obviously be electrophilic and is cyclohexanone so we must find a nucleophilic reagent for the other half **40**.

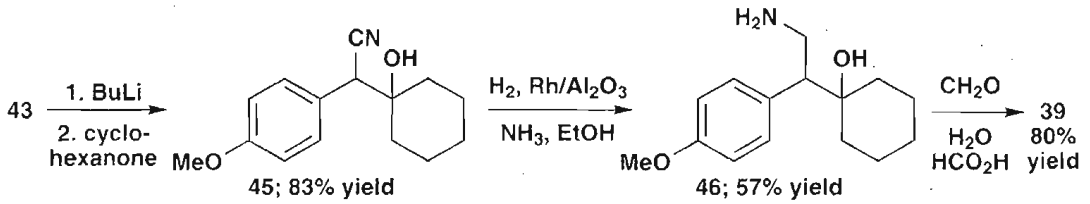


39a 40 41 cyclohexanone

The NMe_2 group does not stabilise an anion, but, if we remove both methyl groups **42**, a cyanide in the same position **43** would stabilise a carbanion. The nitrile **43** is easily made from the available halide **44** and cyanide ion. Actually **43** is also available.

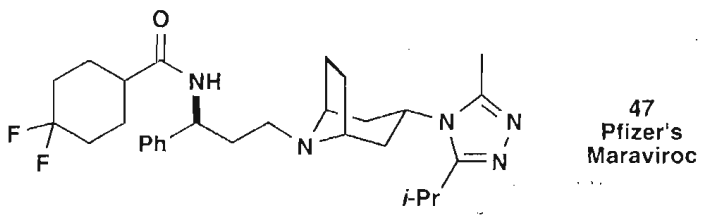


The synthesis is straightforward: treatment of **43** with BuLi gives the lithium derivative that reacts with cyclohexanone to give **45**. Catalytic reduction gave the free amine **46** and methylation gave venlafaxine **39**. Formaldehyde does a kind of reductive amination as it acts as a reducing agent itself, the other product being formic acid. This version of reductive amination is known as Eschweiler-Clarke methylation.[9]



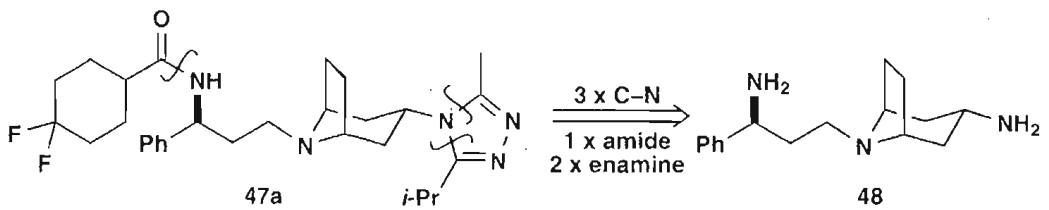
A New Generation Pfizer anti-HIV Drug Maraviroc

The search for anti-HIV drugs that work in different ways from existing drugs was rewarded at Pfizer[10] by the discovery of Maraviroc **47**. This is a more complex molecule than we have tackled before but it is important for you to realise that the methods we are encouraging you to use are exactly those used in the most advanced laboratories today.

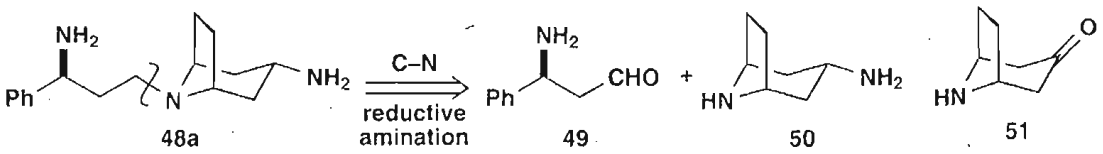


47
Pfizer's
Maraviroc

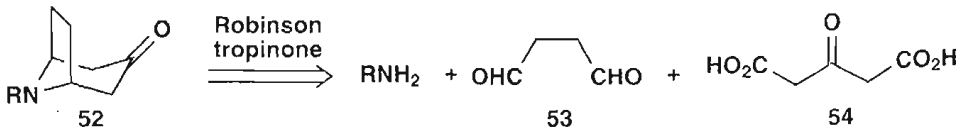
We are not going to consider the synthesis of the difluorocyclohexane on the left, nor that of the triazole on the right but we shall simplify the problem immediately to the key intermediate **48**. This is still a triamine, having two primary and one tertiary amines, and must be made.



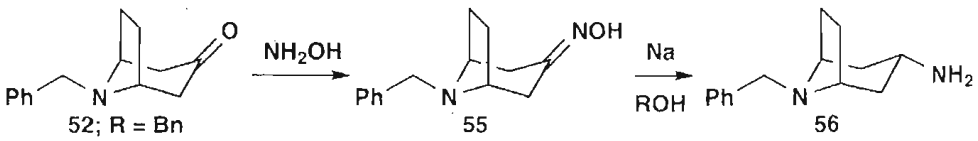
The next most strategic bond joins the cage structure to the chain **48a** and reductive amination is the most obvious way to make this bond using the aldehyde **49** and the bicyclic diamine **50**. Now you might notice the extraordinary similarity of **50** to Robinson's tropinone **51**.



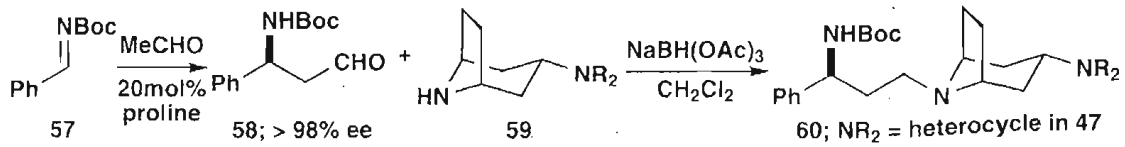
This famous class of compounds was first made by Robinson in 1917 by a variation on the Mannich reaction (chapter 20). He even drew disconnections and this reaction appeared in chapter 1 of the textbook as the Robinson tropinone synthesis.



The workers at Merck chose benzyl as R in **52** and put in the second amine **56** by making and reducing the oxime **55**. The benzyl group could be removed catalytically ready for coupling to **49**.



It turned out that **49** also needed protection and this was put to use in an asymmetric synthesis by organic catalysis discussed more fully in *Strategy and Control*. The reaction being catalysed is another version of the Mannich reaction with a pre-formed imine **58** reacting with the enol of acetaldehyde.[1] The amine **59**, that has the heterocyclic system already in place, is coupled with this aldehyde **50** by reductive amination to give **60** in 75% yield. Removal of the Boc protecting group and amide formation gives Maraviroc.



This synthesis contains two Mannich-like reactions and two reductive aminations. Note the central role of the imines: reduction in the formation of **56** and reaction with a carbon nucleophile in the formation of **52** and **58**. You should now have a feeling for the variety of methods used to make amines and the reasons for choosing one rather than another. The use of Boc and benzyl protecting groups in this last synthesis leads to the next chapter.

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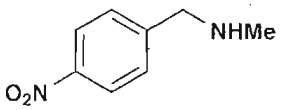
9 Strategy IV: Protecting Groups

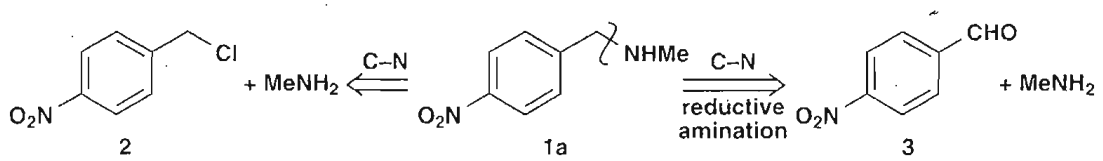
Synthesis without Protection

Continuing the theme of amine synthesis from the last chapter we start by seeing if we can do without protecting groups. **Problem 9.1:** Suggest a synthesis for the simple amine **1** without using protecting groups.



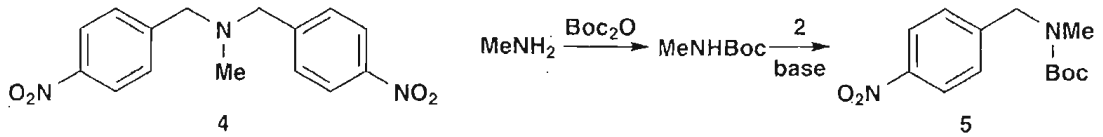
1

Answer 9.1: Surely not difficult! You might have considered alkylation or reductive amination and these two approaches have the same disconnection **1a** – just the reagents **2** and **3** are different.



2 1a 3

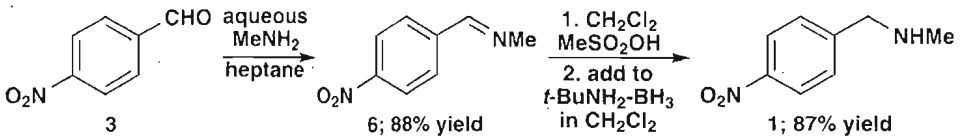
And both work.[1] You probably forecast the problem with the alkylation route – over alkylation. If a 1:1 ratio of $MeNH_2$ to **2** is used, plenty of **4** is formed and even with a 20:1 ratio of $MeNH_2$ to **2**, 3% of **4** is formed and it is difficult to separate **1** from **4**. The only reasonable protection would be by acylation, say with a Boc group, as the product MeNHBoc is not nucleophilic. But a separate alkylation in base would give **5** from which the Boc group would have to be removed. Protection is not worthwhile.



4 5

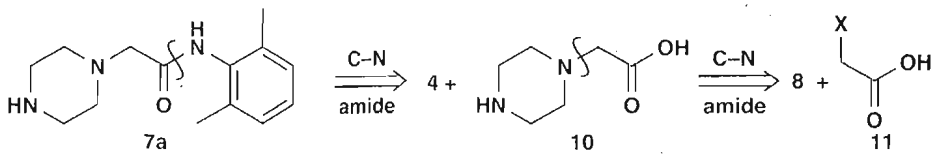
In this case, reductive amination gave the solution but only after some experimentation. As this is to be a commercial process, a cheap reducing agent such as $NaBH_4$ would be ideal, and it works, but it also gave some products from reduction of the nitro group. The usual $NaB(CN)H_3$ and $LiBH(OAc)_3$ were too expensive and the best method turned out to be preparation of the

imine **6** in heptane (the imine dissolves in the heptane leaving the residual $MeNH_2$ in the aqueous layer) and reduction with the borane-*t*-$BuNH_2$ complex.

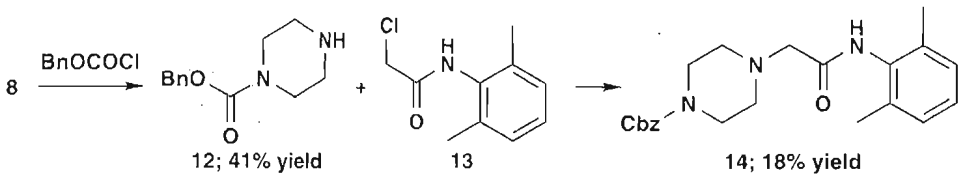


The preparation of **7** is very different. **Problem 9.2:** Suggest two syntheses of this compound **7**, one with protection and one without. Piperazine **8** and the aryl amine **9** are available.

Answer 9.2: The obvious first disconnection is of the amide **7a** and we then just have to make **10** presumably from piperazine **8** and some derivative of a halo-acetic acid **11**. Either step could be performed first. Is there any need for protection?

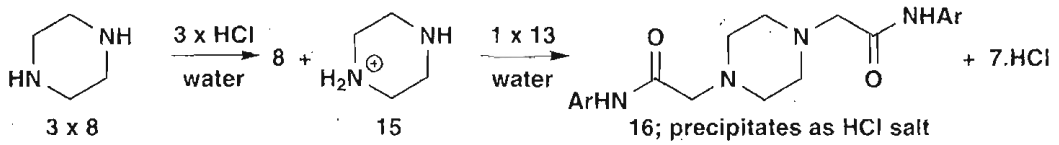


The problem will arise when we try to make a bond to only one nitrogen atom of the piperazine. This is not dialkylation of one N atom as it was with **1**. One solution might be to protect the other nitrogen with, say, Boc or Cbz, so that only one alkylation is possible. This would raise a similar problem: how do we get the protecting group on only one N atom? The problem is that acylation of one N atom does not make much difference to the nucleophilicity of the other and acylation of both nitrogen atoms would be a problem. In fact this has been tried and the results were not encouraging. The amide was made first.[2] The yields were dreadful and the removal of the Cbz protecting group by hydrogenation went in only 29% yield.



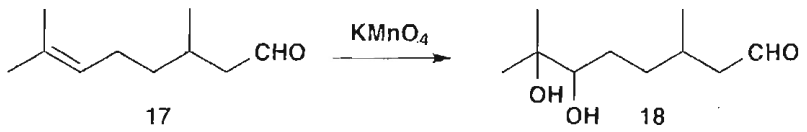
The solution was again to avoid protection and get the conditions right. Three equivalents of piperazine were mixed with three equivalents of HCl in water on a 7.5 kg scale to give a mixture of (mostly) **15** and free **8**. Addition of one equivalent of **13** gave a 97:3 ratio of the HCl salts of **7** and of the diadduct **16**. The diadduct salt precipitated from the aqueous solution and could be removed by centrifugation. Addition of toluene and aqueous NaOH to the filtrate released free **7** extracted into the toluene layer in 99% purity. Protonation of one nitrogen atom **15**

gives a positive charge that affects the pK_a of the other nitrogen more than acylation affects the nucleophilicity of **12**.

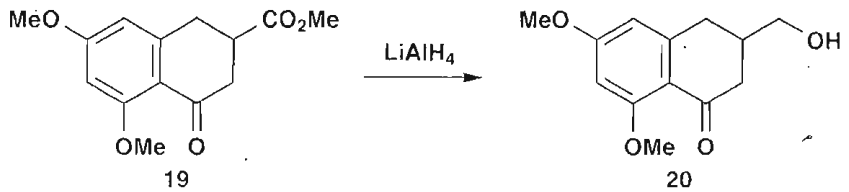


Protection

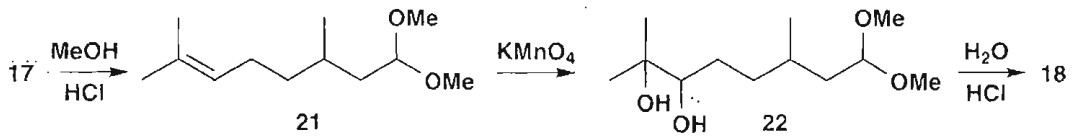
These last two examples set an impossibly high standard and for the rest of the chapter some protection at least will be needed. **Problem 9.3:** What unwanted reaction might happen in the oxidation of **17** to the diol **18** (used in perfumes) and how would you get round this problem?



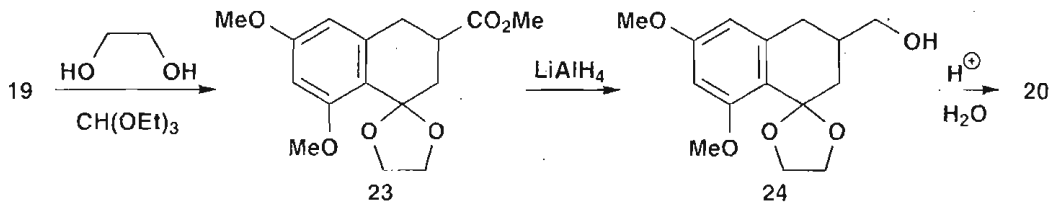
Problem 9.4: What unwanted reaction might happen in the reduction of **19** to the primary alcohol **18** (used in tetracycline synthesis) and how would you get round this problem?



Answer 9.3: The aldehyde is easily oxidised and $KMnO_4$ would give the carboxylic acid. One solution would be to use a different reagent – dihydroxylation with catalytic OsO_4 and NMO (chapter 23) uses oxidative conditions but protection **21** is a safe answer, particularly as aldehydes are easily protected as acetals.[3]

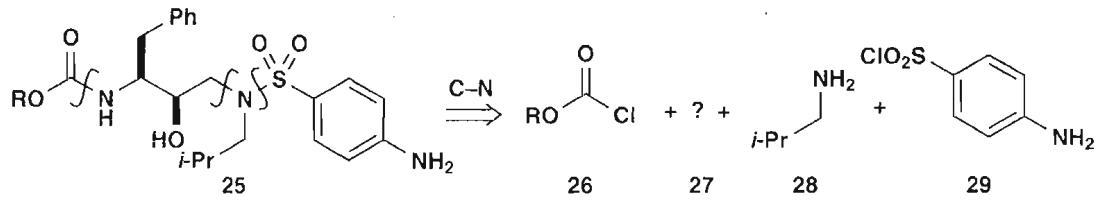


Answer 9.4: The ketone is more easily reduced than the ester so a choice of reagent will not help. Protection as an acetal is again the answer.[4] Notice that a simple acetal can be made from an aldehyde using, say, MeOH but a cyclic one is needed for a ketone. Acetal formation is under thermodynamic control and the bad entropy of *three* molecules (the ketone and *two* molecules of MeOH) giving one is too much for the more stable ketone.

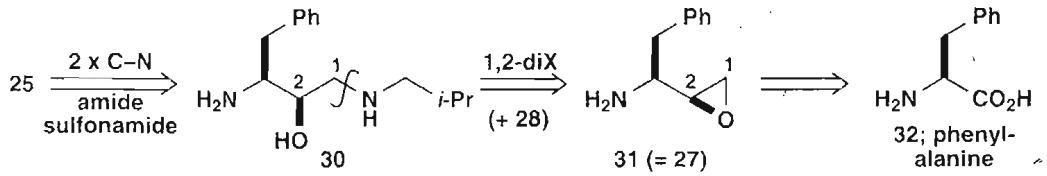


An HIV-Protease Inhibitor as an anti-AIDS Drug

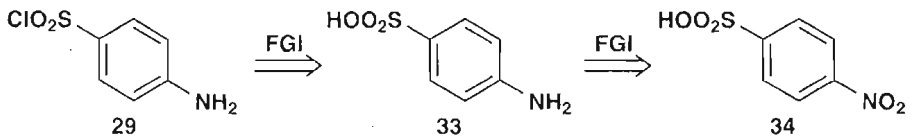
Peptide mimics such as **25** inhibit the protease vital to the HI virus for replication.[5] The disconnections used to make **25** are shown together with some of the possible reagents. **Problem 9.5:** What reagent do you suggest for **27**?



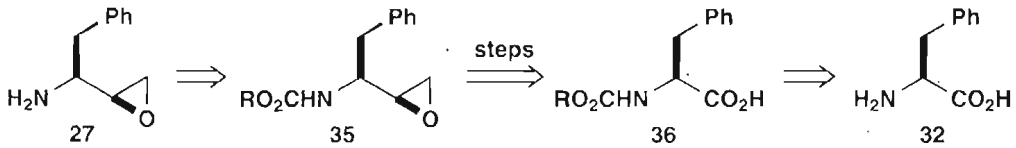
Answer 9.5: Disconnecting the two amides we are left with the central fragment **30** containing the key disconnection and the 1,2-diX relationship should suggest an epoxide **31** as the electrophile **27** to react with the simple amine **28**. In fact this epoxide can be made from the natural amino acid phenylalanine **32**. **Problem 9.6:** What protection will be needed to make **25** from reagents such as **26, 31, 28**, and **29**? Don't forget that some of these reagents may need to be protected. You are not expected to devise a synthesis of **31**.



One reagent **29** is inherently unstable having a nucleophilic amine and an electrophilic sulfonyl chloride and would probably polymerise. It is a derivative of the sulfonic acid **33** which is stable (though not able to carry out the reaction) and might be made from the nitro compound **34**.

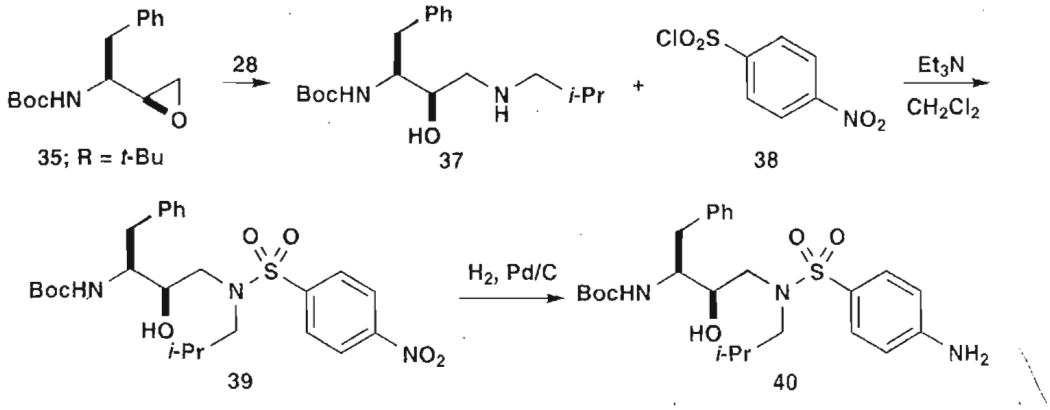


Another reagent **27** also has nucleophilic (NH_2) and electrophilic (epoxide) groups and, as the amine is to be converted into a carbamate anyway, it seems sensible to put that group onto phenylalanine **32** before the epoxide **35** is made. The only remaining reagent is a simple amine **28** needing no protection.



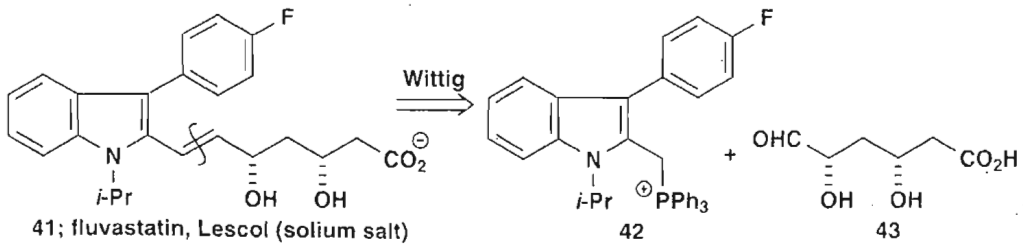
The order of assembling the various reagents is a matter of choice, but the workers at Tibotec[5] chose to put a Boc group on phenylalanine and carry that through the synthesis. So the Boc-protected amino-epoxide **35**; R = *t*-Bu was combined with *i*-butylamine to give **37**. Note that inversion does not occur at the chiral centres in this reaction as they are not involved. Sulfonylation with available *p*-nitrobenzenesulfonyl chloride **38** gives the full skeleton **39** and

it only remains to reduce the nitro group to the amine in **40** and introduce 'RO' in **25** by ester exchange. You were unlucky if you chose a Cbz protecting group as it would be removed in the hydrogenation.

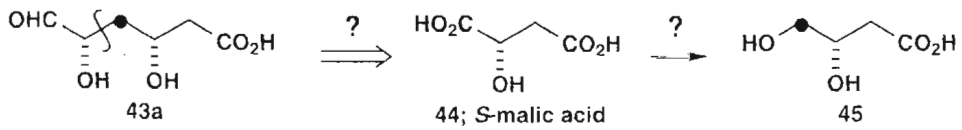


Example: Synthesis of Statins (Cholesterol-Lowering Drugs)

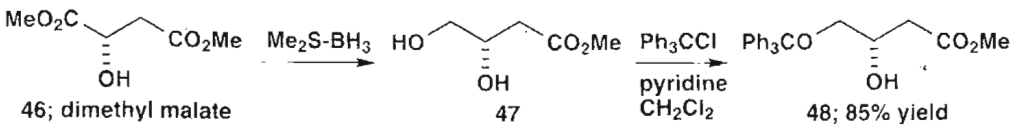
Cholesterol-lowering drugs offer a way to prevent heart disease and the statins, such as Novartis's fluvastatin[6] **41**, act by inhibiting the biosynthesis of cholesterol in the body. These drugs have various structures attached to side chains which contain two chiral centres. Wittig disconnection of the indole from the side chain reveals **42** and that a synthesis of some derivative of the highly functionalised **43** is needed.



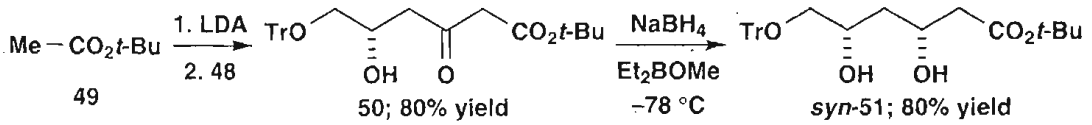
One suggestion is to make **43** from malic acid **44**, an enantiomerically pure acid occurring naturally in fruit. Disconnection **43a** is clearly required and that suggests converting malic acid into some protected form of the diol **45** to get the oxidation level of the carbon atom marked with a black blob right. That alcohol will have to be made into a leaving group.



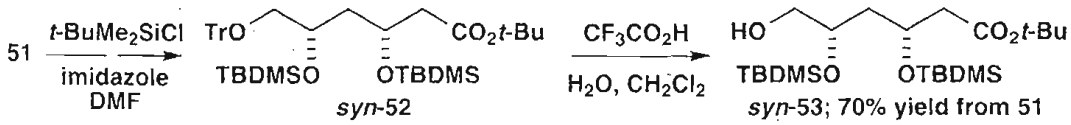
One such route[7] starts with the selective reduction of dimethyl malate **46** with the borane-dimethylsulfide complex. Presumably the free OH guides the borane to the nearer ester group. Now comes the first selective protection: the trityl (Ph_3C = Tr) group is enormous but will add to primary, but not secondary, alcohols by S_N1 to give, in this case, the ether **48**.



The lithium enolate of **49** is acylated by the ester **48** (chapters 19 and 20) to give the required skeleton **50** with a free OH group and a free ketone. Chelation-controlled reduction[8] gives the *syn*-diol **51** with complete control over the stereochemistry.



We now need to protect both secondary alcohols and then release the primary alcohol from its protecting group so we need protecting groups for the secondary alcohols that are cleaved under different conditions from trityl. The answer is the *t*-butyldimethyl silyl group (TBDMS). By this sequence, **51** gives the free primary alcohol **53** with all other functional groups protected.



This alcohol could indeed be oxidised to a protected form of the aldehyde **43** and coupled with the indole by a Wittig-style process. It turned out that a $PO(OMe)_2$ group was better in this reaction than the usual Ph_3P^+ group (chapter 15) and fluvastatin was made in enantiomerically pure form by this route. But you will probably agree that the use of so many protecting groups (we make it two different esters, one ether and one silyl ether) adds many steps. Other routes using different protections have also been successful.[9]

The chosen production route involves almost no protection, deliberately building the side chain with no stereochemistry and introducing stereoselectivity right at the end. The paper describing the evolution of this route makes fascinating reading.[6]

You need to know good protecting groups for OH, CO_2H and NH_2 groups and we have featured the most important in this chapter. You need also to recognise that, while syntheses that avoid protection but still give good yields are best, optimal protection to avoid losses in yields by poor chemo- or regio-selectivity is usually necessary.

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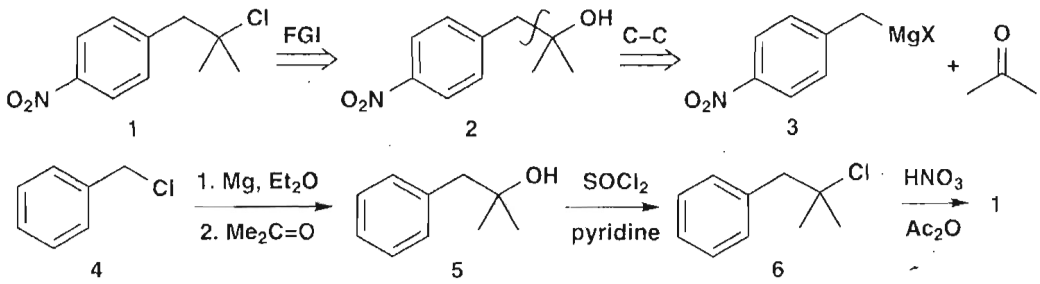
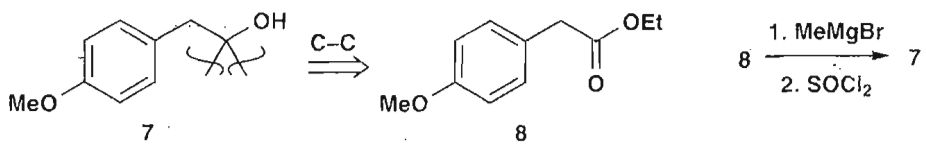
10 One-Group C–C Disconnections I: Alcohols

In the textbook chapter 10, we analysed the tertiary alkyl chloride **1** by FGI to an alcohol and a C–C disconnection **2**. The synthesis was actually carried out by a slightly different route with the nitro group added at the end.



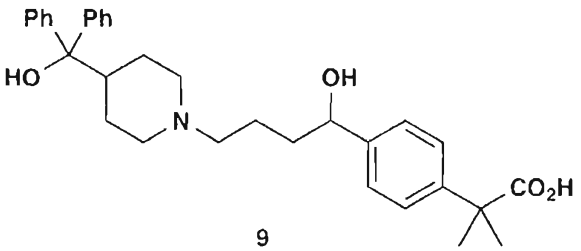
In fact this was just one of many such substituted *t*-alkyl chlorides needed for an investigation into the mechanism of the E2 reaction. All the rest were made by adding a substituted benzyl Grignard reagent to acetone (i.e. the route first envisaged for **1**) or by a different strategy: disconnection of both methyl groups from the tertiary alcohol **7** to reveal an ester **8** of the available phenyl acetic acid.[1]



An Example of Simple Alkylation

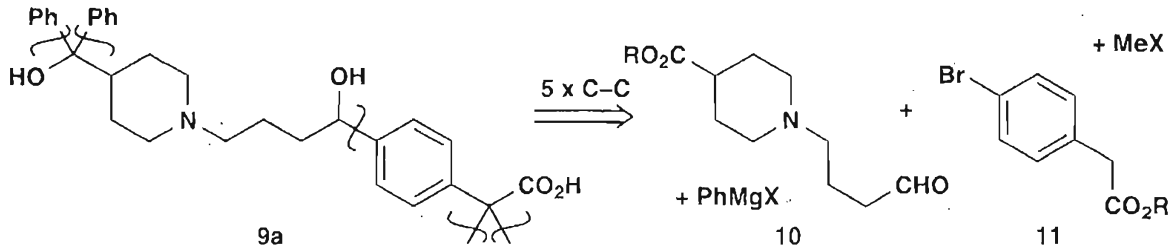
It is important for pharmaceutical companies to discover how their drugs are metabolised in humans in case some metabolite causes side effects. The Sandoz antihistamine terfenadine was found to be metabolised to the carboxylic acid **9** and so a synthesis of this compound was needed.

Workbook for Organic Synthesis: The Disconnection Approach, Second Edition Stuart Warren and Paul Wyatt



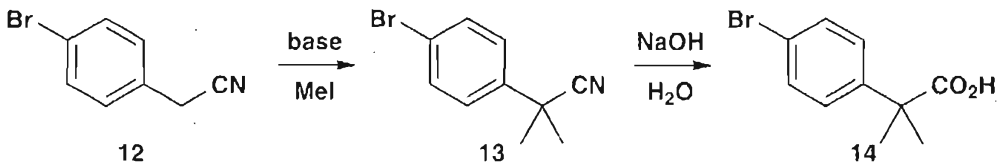
9

Using C–C disconnections with either nucleophilic (RMgX) or electrophilic (RX) reagents in mind **9a** we can break the molecule into two main fragments **10** and **11**. The decision to add the Grignard reagent derived from **11** to the aldehyde **10** might not have been preferred to disconnection on the other side of the OH group as both achieve similar simplification.



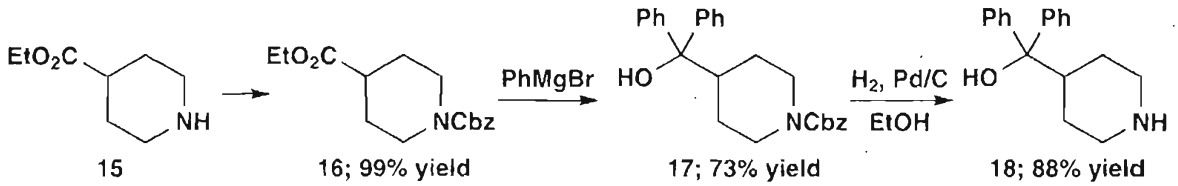
9a 10 11

The right hand part of the synthesis[2] involved the double alkylation of the nitrile **12**, prepared from the benzyl chloride and cyanide ion, with MeI. Hydrolysis of the nitrile **13** gave the carboxylic acid **14**.



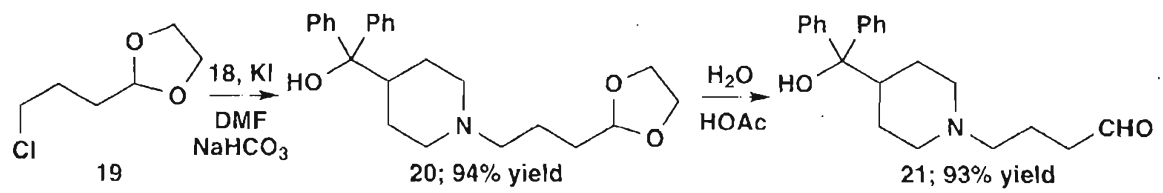
12 13 14

Meanwhile, the available piperidine ester **15** was protected with a Cbz group on nitrogen **16** and reacted with an excess of phenyl Grignard to give the tertiary alcohol **17** and the Cbz group removed by hydrogenation to give the left hand end **18**.



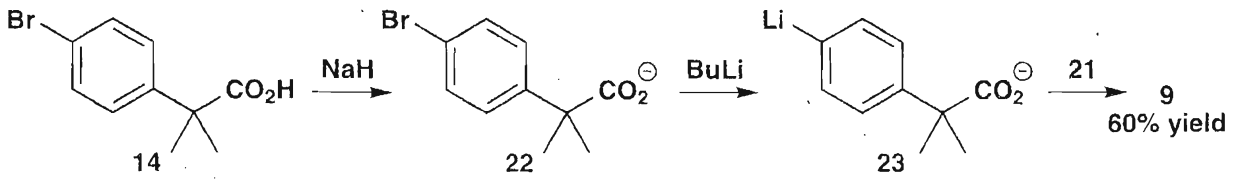
15 16; 99% yield 17; 73% yield 18; 88% yield

The two ends were joined by alkylation of **18** with the protected chloro-aldehyde **19** and the acetal **20** hydrolysed to give **21**. Now all that remains is to couple **21** with **14**.

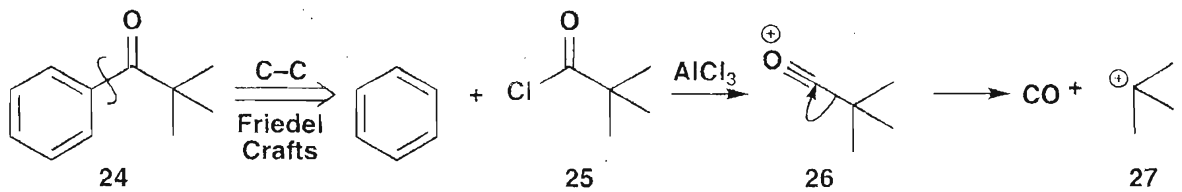


19 20; 94% yield 21; 93% yield

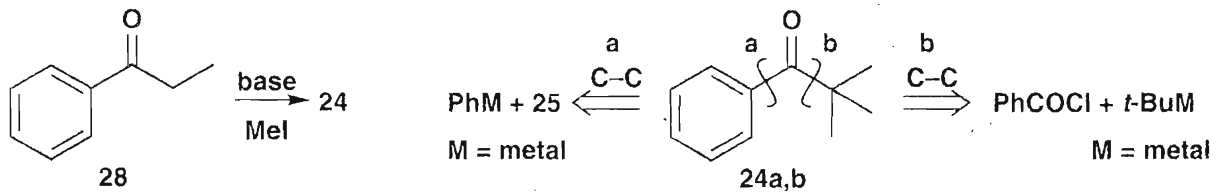
But how can we make a Grignard with **14** when it contains an acidic proton? A similar problem would arise if we tried to make a Grignard reagent from **11** as Grignard reagents react with esters. The solution was to treat **14** with NaH to give the anion **22** and then BuLi to make the lithium derivative **23**. Coupling with **21** gave the target molecule **9**. The synthesis is convergent and makes *five* new C–C bonds.



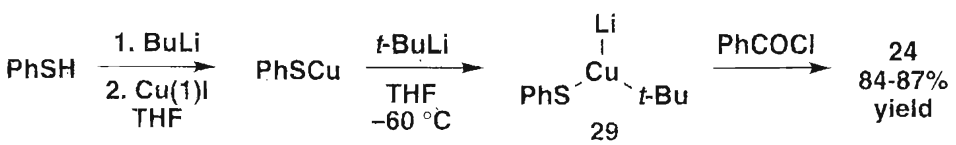
The obvious synthesis of ketone **24** is by a Friedel-Crafts reaction of benzene with the acid chloride **25**. But the main product from this reaction is *p*-di-*t*-butylbenzene as the initially formed acylium ion **26** loses CO to give the *t*-butyl cation. **Problem 10.1:** Suggest a synthesis of **24** that might work!



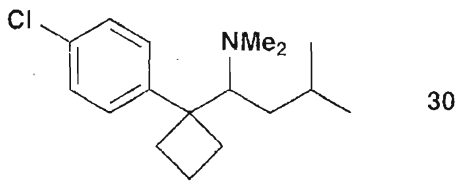
Answer 10.1: There are various possibilities. You might have suggested methylation of the enolate of the ethyl ketone **28** that can be made by the Friedel-Crafts reaction. Another possibility is acylation **24a** or **24b** of a metal derivative, probably M = copper, with a suitable acid chloride.



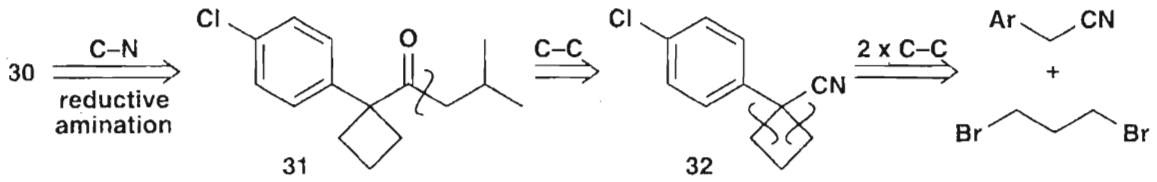
One successful synthesis[3] uses a PhS group to stabilise the cuprate **29** from *t*-BuLi and to acylate with benzoyl chloride. You might have suggested a Grignard reagent with catalytic Cu(I) or a simpler lithium cuprate *t*-Bu_2CuLi or even just *t*-BuCu. Any of these might work fine.



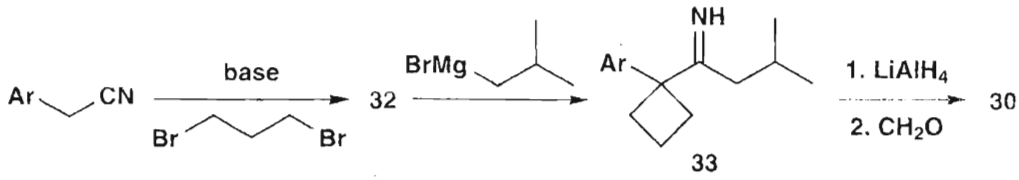
So both alkylation of enolates and addition of organo-lithium compounds are useful reactions. **Problem 10.2:** Can you use both in a synthesis of sibutramine **30** an anti-depressant?



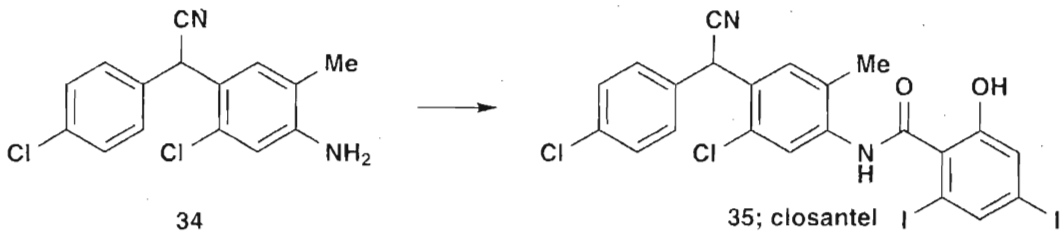
Answer 10.2: Thinking back to chapter 8, reductive amination seems the best way to make the amine and the ketone **31** might come from a Grignard or organo-lithium addition to the nitrile **32**. Now a double alkylation with 1,3-dibromopropane looks ideal.



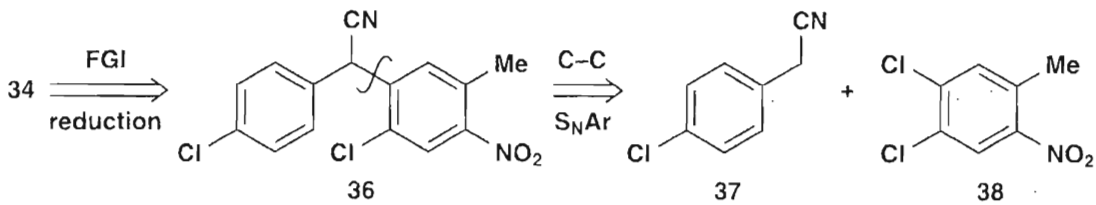
The published synthesis[4] found a short cut. The double alkylation went well and addition of the Grignard to the nitrile **32** led, surprisingly, to the quite stable imine **33** that could be reduced to the primary amine and methylated with formaldehyde.



One-group C–C disconnections are not restricted to alkylations or acylations. **Problem 10.3:** See if you can suggest a synthesis of the amine **34** needed to make the anthelmintic (for killing sheep liver flukes) closantel **35**.

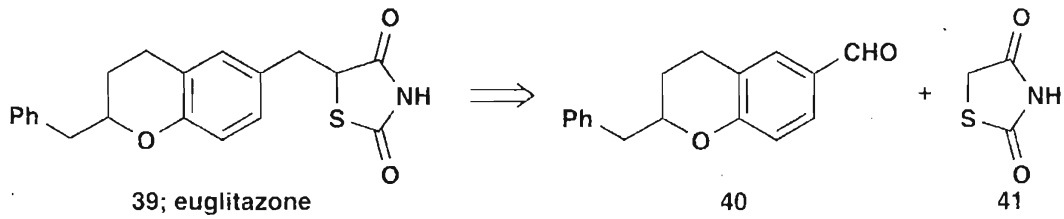


We need a disconnection of one of the C–C bonds between the two benzene rings but neither looks possible at the moment. **Answer 10.3:** But amines are usually made by reduction and, if we replace the aromatic NH_2 group by nitro **36**, things look very different. We can disconnect the nitrile **37** (actually the same as '$ArCH_2CN$' in the previous problem) from the nitro compound **38** as the anion of **37** will be able to displace only the chloride *para* to the nitro group.



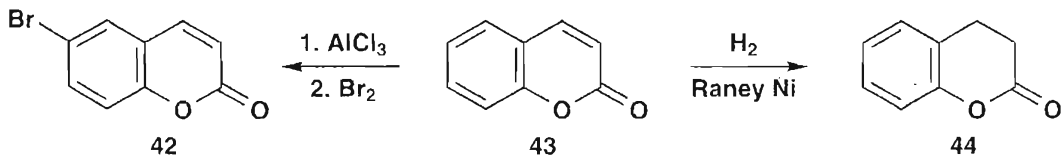
The nitrile **37** can be made from the benzyl chloride and cyanide ion and **38** from nitration of available 3,4-dichlorotoluene and in other ways. Treatment of **37** with base and then **38** gives **36** and catalytic reduction gives the amine[5] **34**.

The drug family of 'glitazones' such as euglitazone **39** are used for the treatment of diabetes. They are made from the heterocycle **41**, and an aldehyde such as **40**, by chemistry we shall not discuss. **Problem 10.4:** Your task is to try and suggest how to approach **40**.



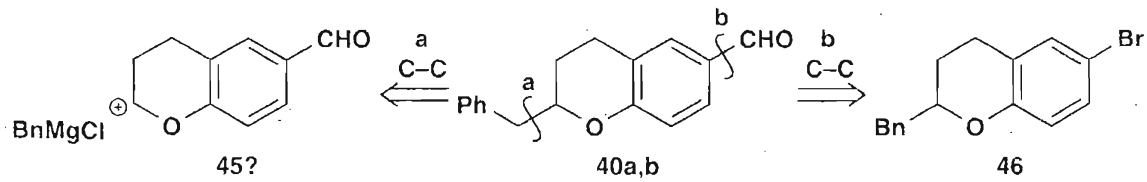
39; euglitazone 40 41

If you want a hint, coumarin **43** is readily available and is brominated[6] to give **42** and reduced catalytically[7] to give **44**.



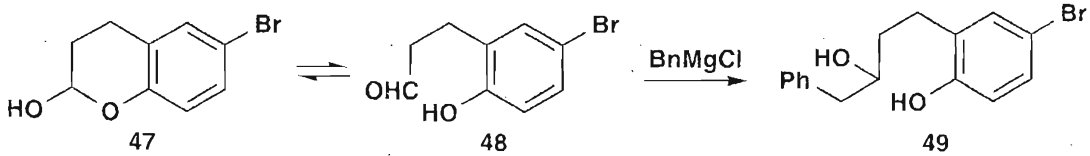
42 43 44

Though we turned the molecule round in the hint, one disconnection **40b** should be obvious. **Answer 10.4:** The aldehyde can be introduced by reaction of DMF (Me_2NCHO) with the lithium derivative from **46**. But what about **40a**? We can use benzyl Grignard but what can represent the electrophilic synthon **45**?



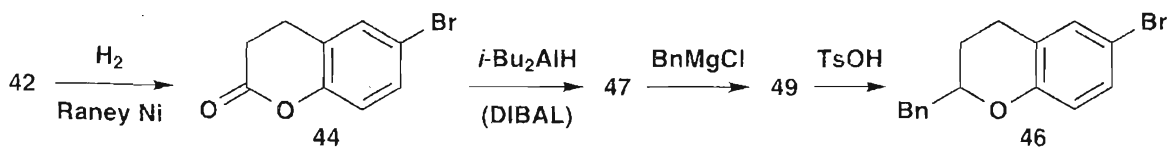
45? 40a,b 46

The answer[8] would be simple if **45** were an aldehyde. But the hemiacetal **47** is in equilibrium with the hydroxyaldehyde **48** and adds benzyl Grignard to give the diol **49** that cyclises in acid to the ether **46**. Two molecules of the Grignard reagent will be needed: one to open the hemiacetal to the anion of **48** and the other to add to the aldehyde. Naturally, we cannot have the second aldehyde present during these reactions so we must have the bromo compounds **47** to **49**.



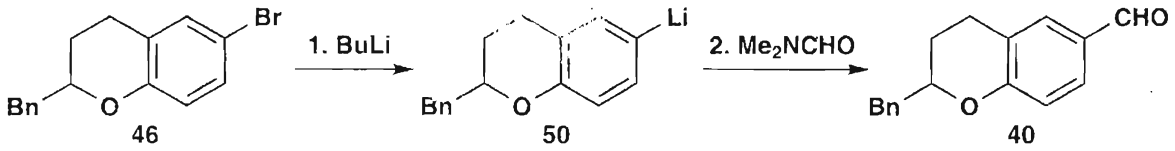
47 48 49

So the first part of the synthesis has only two new reactions: the reduction of the lactone **42** to the lactol **47** and the cyclisation of the diol **49** to the ether **46**.



44 46

The bromo compound **46** is treated with BuLi to give the lithium derivative **50**, quenched with DMF to give the aldehyde **40** ready for coupling with the heterocycle **41**.



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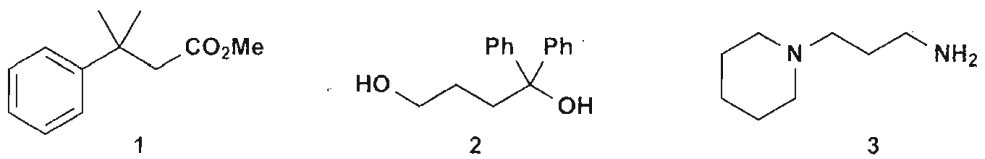
11 General Strategy A: Choosing a Disconnection

In the textbook chapter we offered some general guidelines for choosing disconnections and we shall be following those principles in this chapter too. We may use C–X and/or C–C disconnections from chapters 1–10.

Summary of Guidelines for Good Disconnections

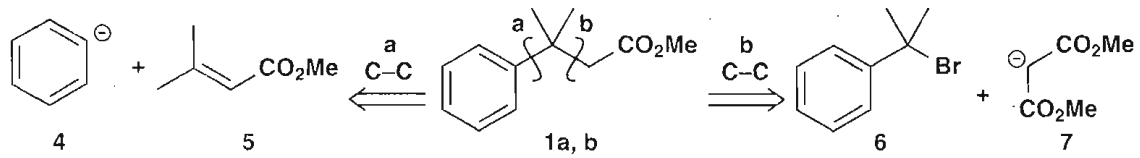
1. Make the synthesis as short as possible.
2. Use only disconnections corresponding to known reliable reactions.
3. Disconnect structural C–X bonds first and try to use 2-group disconnections.
4. Disconnect C–C bonds using the FGs in the molecule
   (a) Aim for the greatest simplification. If possible
      –disconnect near the middle of the molecule
      –disconnect at a branch point
      –disconnect rings from chains
   (b) Use symmetry (if any).
5. Use FGIs to make disconnections easier.
6. Disconnect back to available starting materials or ones that can easily be made.

Problem 11.1: Which bond would you prefer to disconnect in these target molecules? Can you suggest known reliable reactions that will make that bond?



1 2 3

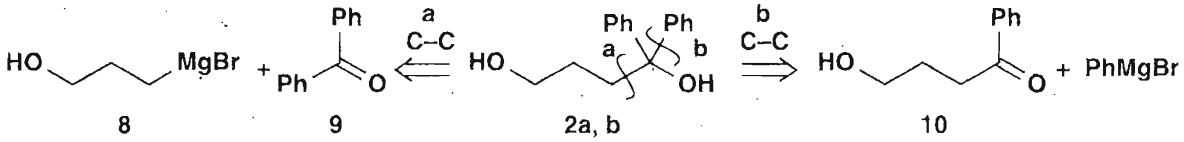
Answer 11.1: We should like to disconnect a C–C bond next to the branch point **1a** or **1b**. The alkylation of, say, a malonate **7** with a tertiary alkyl bromide **7** would probably not be a good reaction but the conjugate addition of some derivative of benzene **4** to the unsaturated ester **5** looks better.



4 5 1a, b 6 7

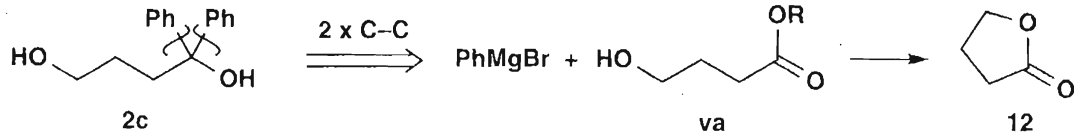
So we suggest the addition of a copper-catalysed Grignard reagent or some copper derivative such as Ph_2CuLi, PhCu or the sulfide complex we saw in chapter 10 to the methyl ester of available 3-methylbutenoic acid.

Again, there are two alternative disconnections next to the branchpoint with Grignard reagents **8** or PhMgBr adding to ketones **9** or **10** respectively. Now there are problems with either route as **8** and **10** will need protection of the OH groups since Grignard reagents and OH groups cannot co-exist.



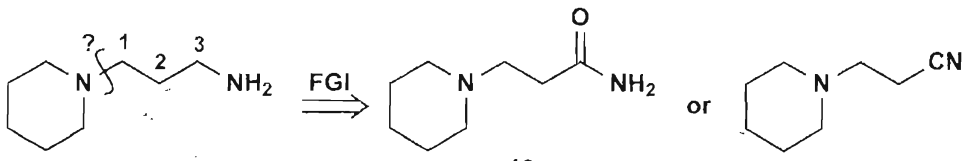
8 9 2a, b 10

However, there is some symmetry in this target molecule so, if we disconnect both phenyl groups **2c** we have a hydroxyester **11** that will exist as the lactone **12** with no acidic Hs. And indeed reaction of this lactone **12** with two equivalents of PhMgBr gives[1] the diol **2**.



2c va 12

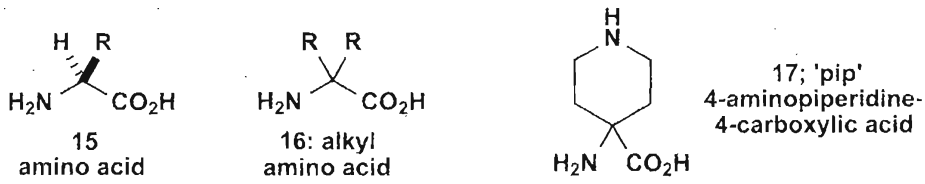
The diamine **3** presents a different style of problem as we prefer to use C–X disconnections where possible. The best disconnection in the middle of the molecule and at a branchpoint is **3a** but what chemistry can we use? As soon as you recognise the 1,3-diX relationship, conjugate addition should come to mind and you had a choice between the amide **13** or the nitrile **14**, either being reduced to **3**, the nitrile by hydrogenation and the amide with $LiAlH_4$ or BH_3. The conjugate addition goes without the need to deprotonate the nitrogen as the amine (piperidine) is a good enough nucleophile not to need any help.



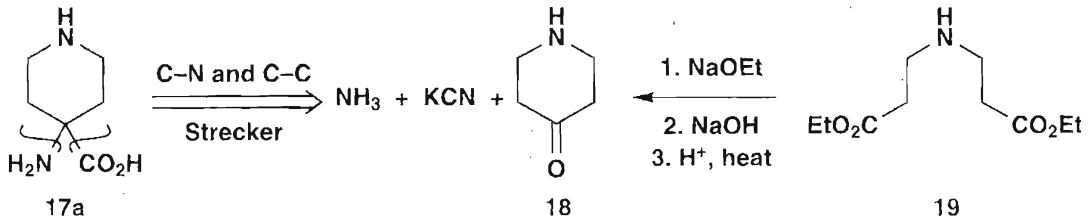
3a 13 14

The Synthesis of an Unusual Amino Acid

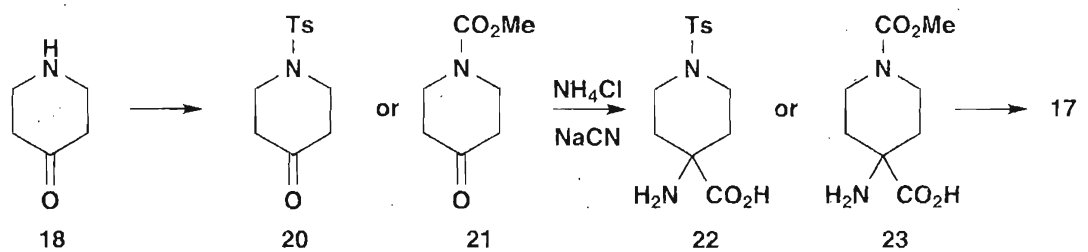
The α-amino acids that make up proteins have one substituent between the NH_2 and CO_2H groups and are chiral **15**. Many variations on this structure have been studied in the design of drugs and we are going to consider the α-amino acids that have two identical alkyl groups between the NH_2 and CO_2H groups and are therefore achiral **16**. In particular, we are going to consider the synthesis of 'pip' **17** having a ring with an extra nitrogen atom positioned so that the molecule is still achiral but that nitrogen makes the compound, and peptides derived from it, more soluble in water. **Problem 11.2:** Suggest how 'pip' **17** might be made.



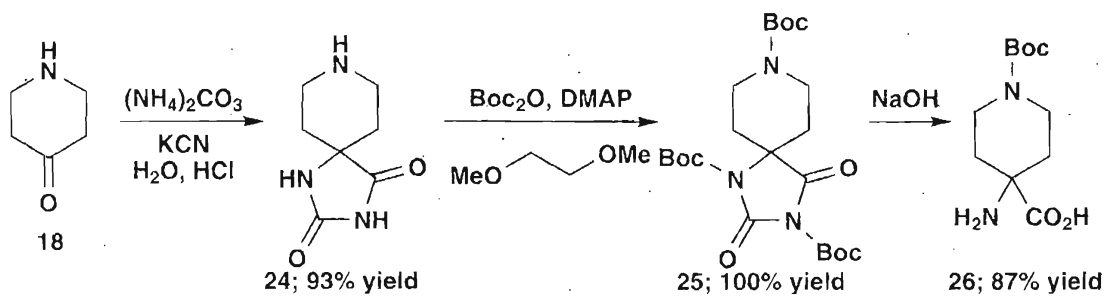
Answer 11.2: If you are familiar with the Strecker reaction, you probably suggested disconnecting both NH_2 and CO_2H groups **17a** and using the easily made ketone **18** as starting material (textbook chapter 19). Cyclisation of the diester **19** (the Dieckmann reaction), ester hydrolysis and decarboxylation give **18**.



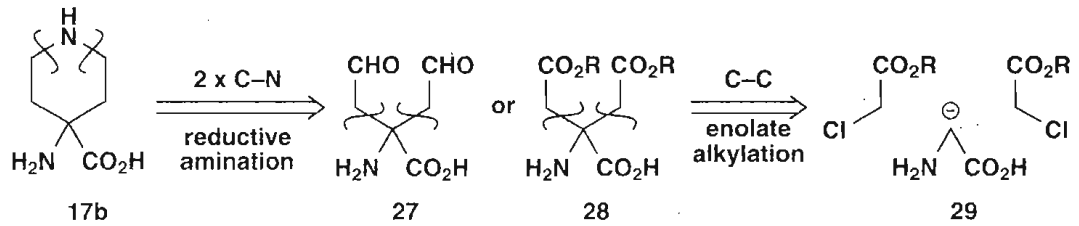
In practice,[2] the Strecker reaction requires protection of the NH in the ring either as a sulfonamide **20** or a methyl carbamate **21**. These groups can be removed from the products of the Strecker reaction **22** and **23** to give **17**. You could not be expected to predict the protecting group but you might have wondered if one was necessary.



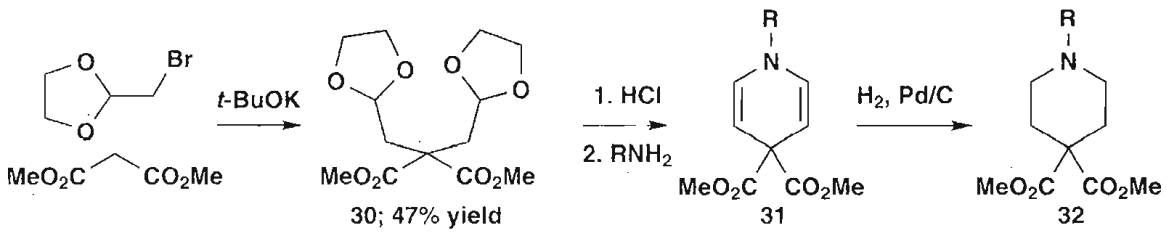
A better version[3] involves direct Strecker-style reaction with KCN and ammonium carbonate. This gives the heterocycle **24** and these workers were able to prepare the protected version **26** of what they really wanted **17** by protecting all the nitrogen atoms **25** and hydrolysing the reactive imide. You were not expected to predict this.



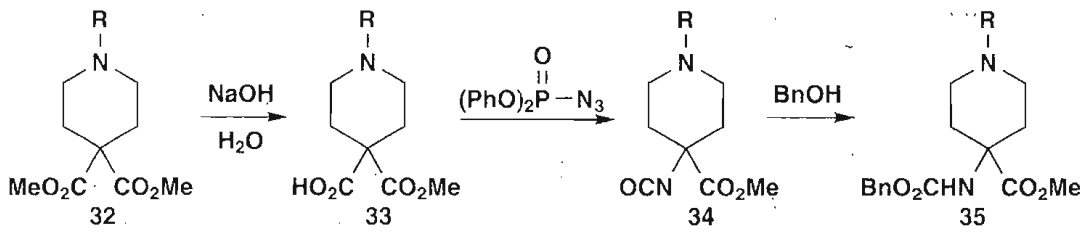
You might otherwise have thought of disconnecting both the C–N bonds in the ring with reductive amination of either the dialdehyde **27** or the diester **28** that could be made by double alkylation of some enolate **29** derived from glycine.



This approach has also been successful but not by alkylation of any derivative of glycine, though many were tried.[4] Instead malonate provided the enolate that was alkylated by the protected bromoaldehyde to give **30** and then the double enamine **31** with any amine you should choose. Catalytic reduction gave the saturated piperidine **32**. You will have seen at once that this is not the target molecule.

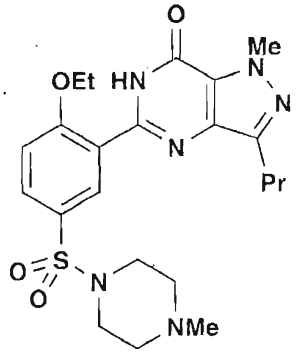


Tanaka's strategy was dominated by the discovery of a good reaction but he still had to change one CO_2Me group into an amine. In fact such a reaction exists. The diester **32** was hydrolysed with aqueous NaOH to give the *mono*-carboxylic acid **33** which was then treated with diphenylphosphoryl azide to initiate a rearrangement to the isocyanate **34** captured by benzyl alcohol to give Cbz-protected **35**. This is a very flexible synthesis.

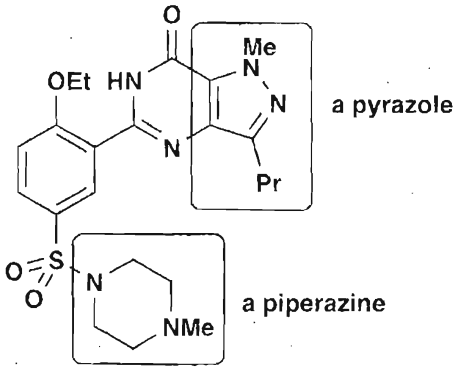


Strategy in the Synthesis of Sildenafil (Viagra®)

The phosphodiesterase inhibitor sildenafil **36**, better known as Viagra®, is one of the best selling drugs of all time and must be made on a large scale. In the discussion that follows, we suggest you ignore the pyrazole ring and the piperazine ring **36a**. **Problem 11.3:** Which C–X bonds would you like to disconnect?

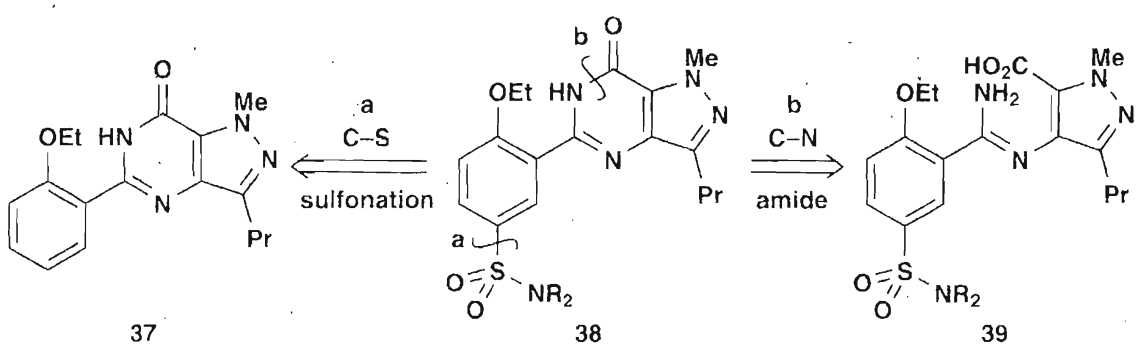


36; sildenafil



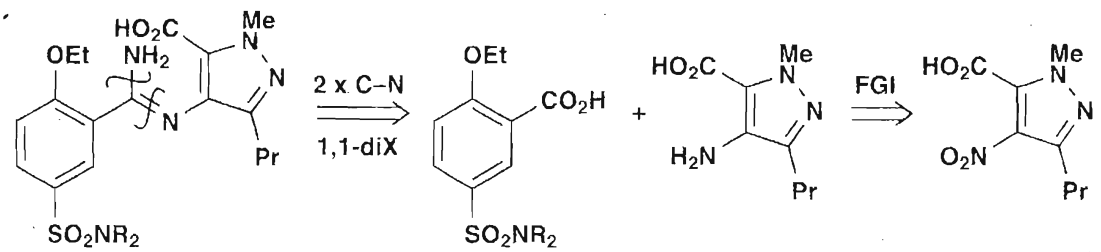
36a

Answer 11.3: You might have chosen the C–S bond of the sulfonamide **38a** with sulfonation of the benzene ring **37** in mind, and/or you might have chosen the amide **38b** as this is always a good place to start. Both are helpful: sulfonation of the benzene ring will certainly be used at some stage and disconnecting the amide starts to break up the six-membered ring in the middle.



37 38 39

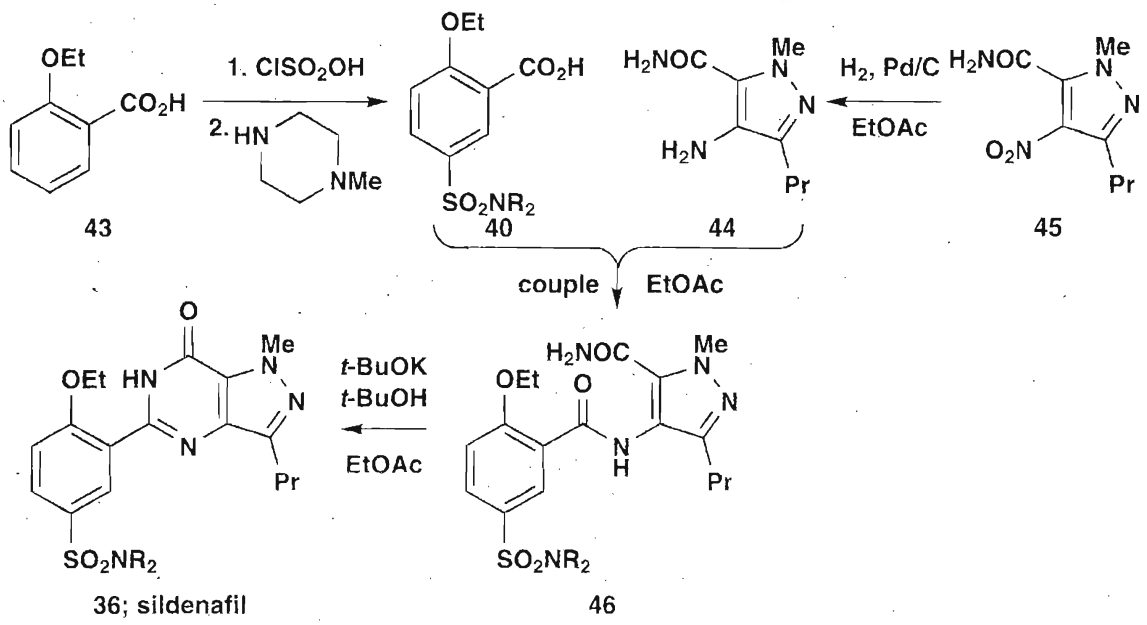
However, **39** is not much of a simplification and you might have chosen the two C–N bonds of the 1,1-diX disconnection to start with, or at this stage **39a** to reveal a much simpler benzoic acid **40** and a pyrazole **41**. If you were prescient, you might have suggested that, as pyrazole is aromatic, the nitro compound **42** might also be a possible starting material.



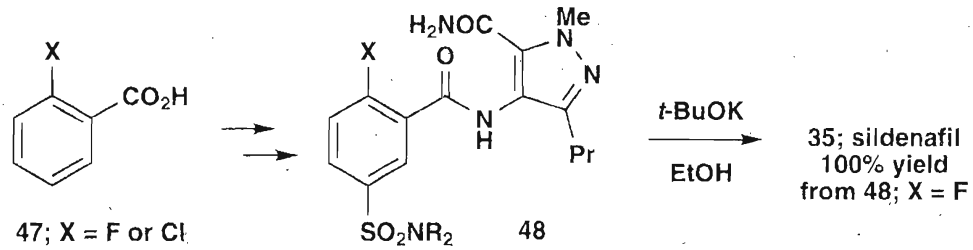
39a 40 41 42

If you got anything like this, you should be very pleased with yourself, as **40** and **42** have indeed been used in several of the published syntheses of sildenafil.[5] The commercial synthesis by Pfizer starts with sulfonation of the available (starting material strategy) acid **43** and formation of the sulfonamide **40**. The amide **45** of **42** was reduced catalytically to give **44**, the amide of **41**,

then **40** and **44** were coupled to give **46** that could be cyclised to sildenafil with base. This synthesis is easy to carry out because the last three steps can all be carried out in ethyl acetate, making work-up easy on a large scale. This review[5] gives many syntheses of sildenafil and makes interesting reading once you have had a few ideas yourself.



One final twist. You might also have considered disconnecting the OEt group to give an intermediate **48**; X = F or Cl as the sulfonamide group activates that position towards nucleophilic attack. The halogen also activates the *para* position for the sulfonation. There are two advantages in this: the halo-acids **47** are cheaper than the ethoxy-acid **43** and the displacement occurs[5] during the final cyclisation of **48**.



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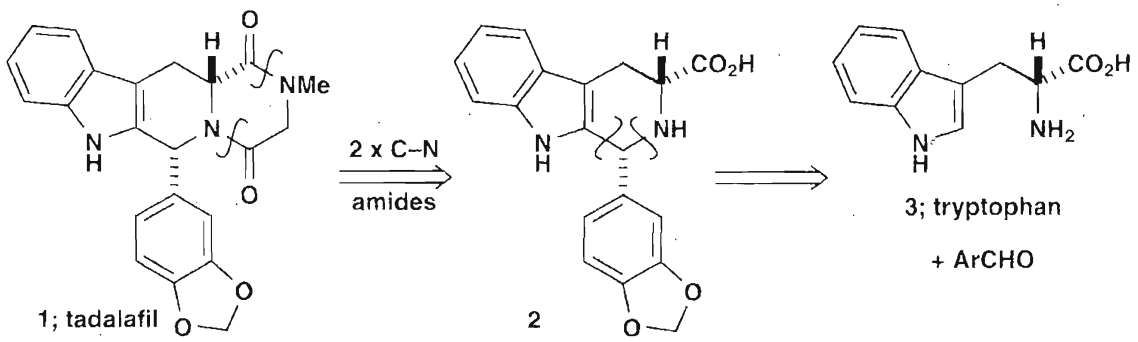
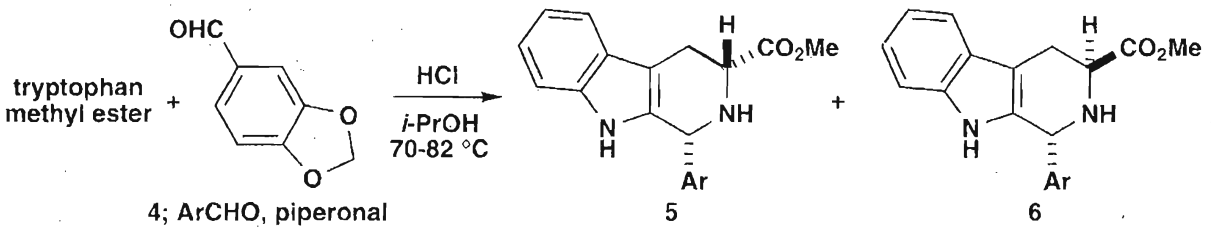
12 Strategy V: Stereoselectivity A

This chapter is unusual in that it contains little but problems and for a good reason. Stereochemical control is the most difficult part of designing syntheses so the need is for exercises in drawing structures and interpreting reactions rather than inventing syntheses.

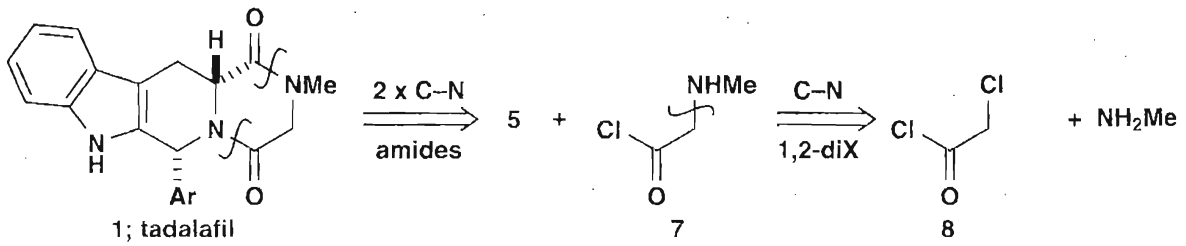
At the end of the last chapter we discussed the synthesis of a phosphodiesterase inhibitor (Viagra) and we start this chapter with another such compound having a very different structure: Lilly's tadalafil[1] (Cialis™) **1**. It also has various heterocyclic rings but the new feature is stereochemistry. Disconnection of the right hand ring reveals the skeleton **2** with the stereochemistry intact and this compound can be made from natural tryptophan **3** and the available aromatic aldehyde 'piperonal' by a Mannich style reaction, the Pictet-Spengler, that you will meet later in the book. But what about the stereochemistry?



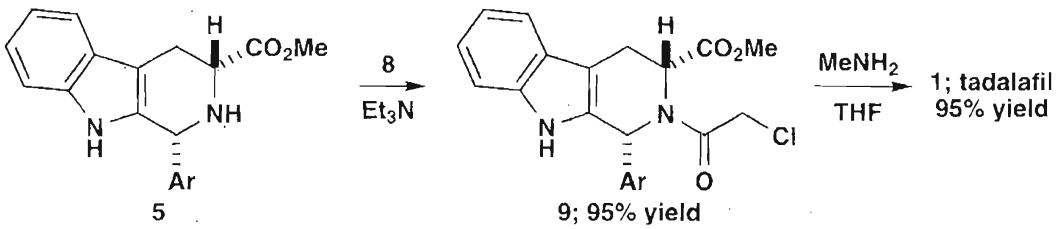
The Mannich reaction with the methyl ester of tryptophan gives, as expected, a mixture of diastereoisomers. These can be separated by chromatography but the best yield was 42% of the *cis* compound **5** and 28% of the *trans* compound **6** when the reaction was run at 4 °C. This highlights two main problems: can the wanted isomer be formed stereoselectively and can it separated from the unwanted? Though **5** and **6** can be separated, the ratio is pathetic and chromatography is not acceptable on a large scale. Luckily, it turns out that the *cis* compound **5** crystallises from the reaction mixture and that **5** and **6** are in equilibrium if the reaction is run at 70–82 °C. A 92% yield of pure **5** is now routinely achieved by this method.[2] **Problem 12.1:** Suggest a reagent that might be used to convert **5** into tadalafil.



Answer 12.1: No new stereochemistry here but some useful revision. We already have the disconnections **1** and the obvious reagent is **7** that can be made from available chloroacetyl chloride **8** and $MeNH_2$.

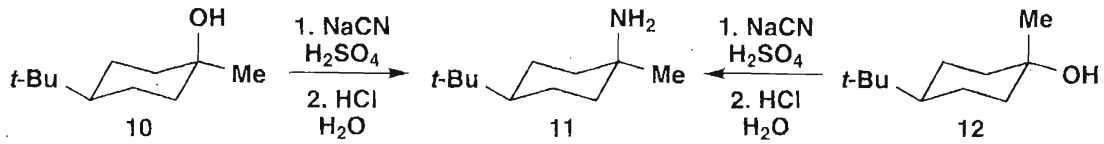


As **7** has both nucleophilic and electrophilic groups, it might polymerise, and it is better to acylate **5** first with **8** and add $MeNH_2$ later. The synthesis is short, the yields are high and the only separation is by crystallisation. **Problem 12.2:** Is the tadalafil made by this synthesis enantiomerically pure?

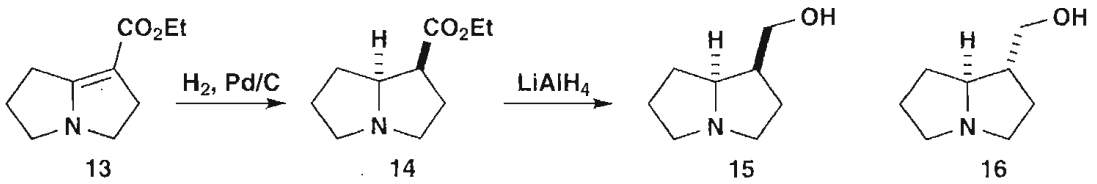


Answer 12.2: The starting material, natural tryptophan, is enantiomerically pure and no racemisation occurs during the synthesis and so therefore tadalafil, made by this method, is also enantiomerically pure. The equilibration of **5** and **6** is an epimerisation (an equilibration between diastereoisomers at one chiral centre) and not a racemisation. This is the strategy of enantiomerically pure starting materials, often called the chiral pool strategy, described in the textbook chapter and developed in *Strategy and Control*. If you want to know whether a product is enantiomerically pure or not, you must ask where it comes from and you must know the details of the synthesis.

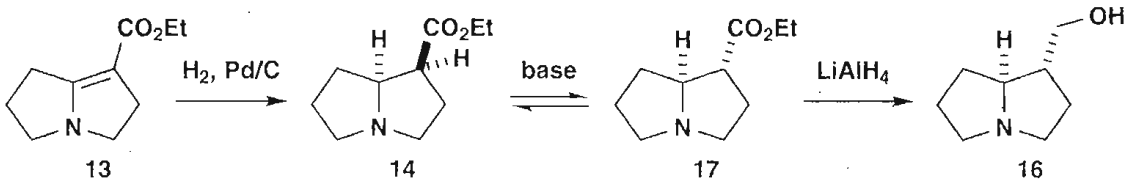
Problem 12.3: Are these reactions stereospecific or stereoselective? Is the product **11** enantiomerically pure?



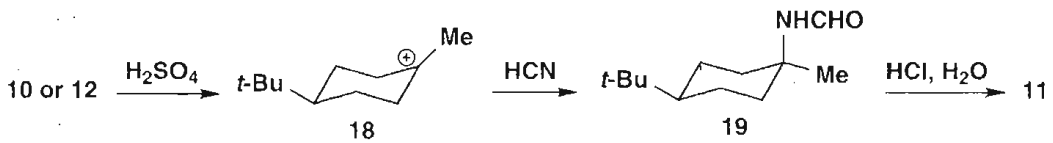
Problem 12.4: Catalytic reduction of **13** followed by treatment with $LiAlH_4$ gives **15**. If **14** is first treated with base and then reduced with $LiAlH_4$, compound **16** is formed instead. Are these reactions stereospecific or stereoselective? Are the products **14, 15**, and **16** enantiomerically pure?



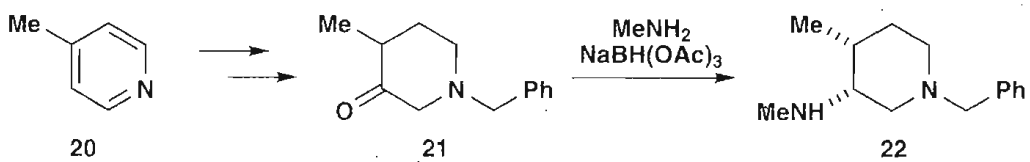
Problem 12.5: How is it possible that **10** and **12** give the same stereoisomer of the product **11**?
Answer 12.3: The starting materials **10** and **12** are diastereoisomers and each gives the same product so the reactions are stereoselective as the stereochemistry of the product does not faithfully reproduce the stereochemistry of the starting materials. The product **11** cannot be enantiomerically pure as none of these compounds is chiral: there is a plane of symmetry in each case bisecting the ring and passing through the *t*-Bu group and the methyl group.
Answer 12.4: The hydrogenation of **13** is stereospecific as both added hydrogen atoms are added to the same side. Equilibration in base, via the enolate anion of **14**, stereoselectively gives the more stable diastereoisomer **17** with the ester group on the outside (convex, *exo*) face of the folded molecule. Reduction with $LiAlH_4$ is stereospecific as no chiral centre is involved. The products **14, 15**, and **16** cannot be enantiomerically pure as the starting material is achiral and no enantiomerically pure reagents are used.



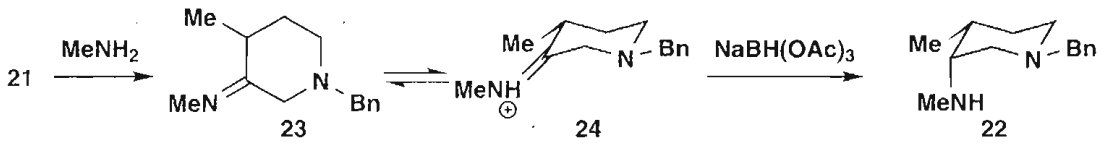
Answer 12.5: The obvious intermediate is the carbocation **18** formed from either **10** or **12** by protonation of the alcohol and loss of water. Addition of HCN in a Ritter reaction (chapter 8) gives the amide **19** which is hydrolysed to the amine **11** in aqueous acid. You were not expected to explain why the axial amine is the favoured product.[3]



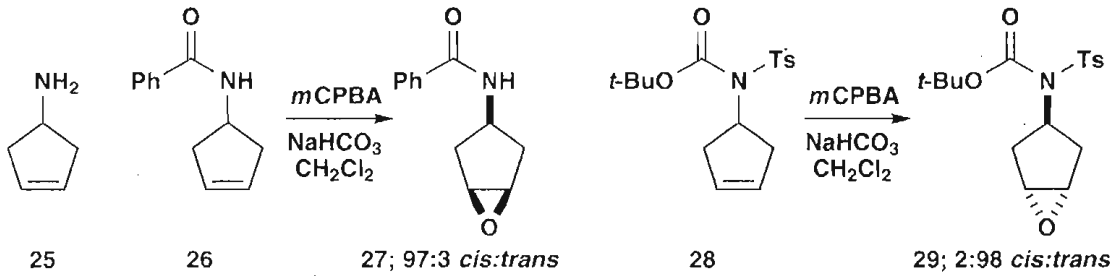
The cyclic ketone **21** can be prepared from the pyridine **20**. **Problem 12.6:** Explain the stereochemistry of the amine **22** formed by reductive amination of this ketone. You will need to consider the step in which stereochemistry appears.



Answer 12.6: The key step is the delivery of hydride from the reagent to the imine salt **24**. The reagent $NaBH(OAc)_3$ is large and, by analogy to the reduction of ketones described in the textbook chapter, we should expect equatorial attack. This will put the $MeNH_2$ substituent in the axial position.[4] The ratio of axial amine to equatorial amine is 97:3.

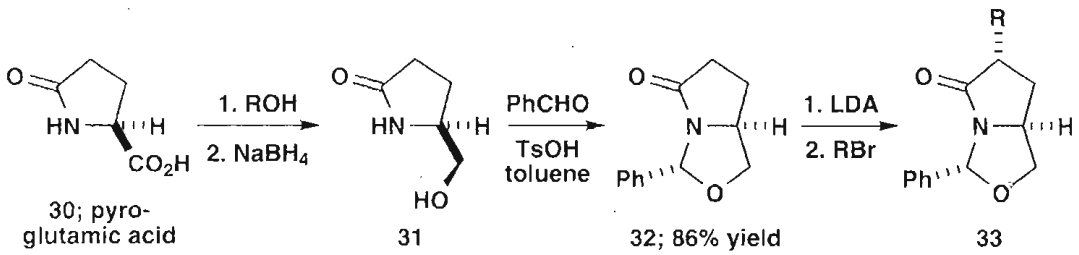


The amine **25** is easily acylated to give the two derivatives **26** and **28**. When these are epoxidised with *m*CPBA, the *cis* epoxide **27** is formed from **26** while the *trans* epoxide **29** is formed from **28**, both with high diastereoselectivity.[5] **Problem 12.7:** Suggest an explanation.

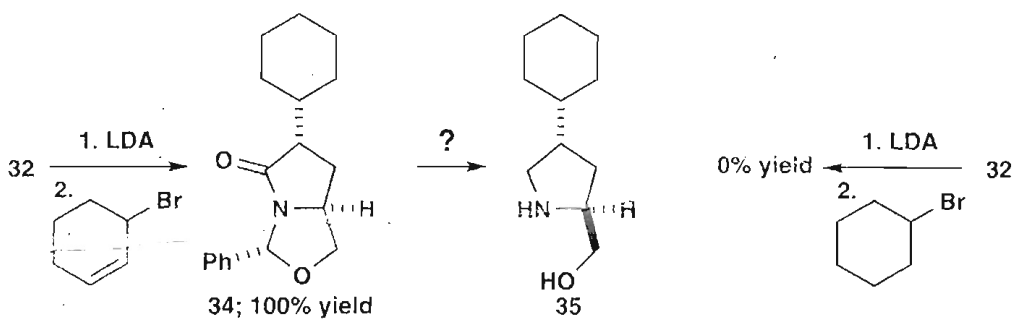


Answer 12.7: You might see a similarity to the contrasted epoxidations at the end of textbook chapter 12. The difference between the two alkenes **25** and **27** is that **25** has a free NH while **28** has not. So steric hindrance from the two large acyl groups in **28** pushes the epoxide to the other face of the ring while the free NH in **26** guides the reagent to the same face by hydrogen bonding.

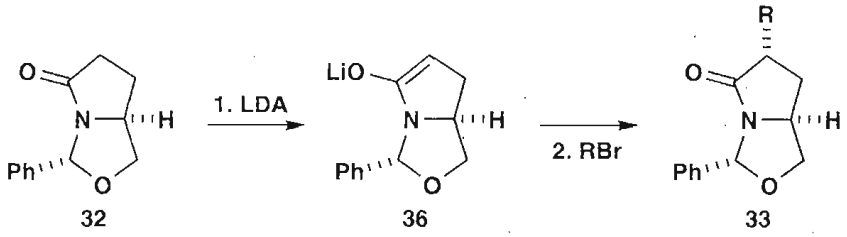
The amido-alcohol **31** can be made easily from pyroglutamic acid **30** derived from natural glutamic acid. Reaction with benzaldehyde under acidic dehydrating conditions gave[6] one diastereoisomer of **32** and alkylation of the lithium enolate of **32** gave one diastereoisomer of **33**. **Problem 12.8:** Explain why these reactions give **32** and **33** with the stereochemistry shown.



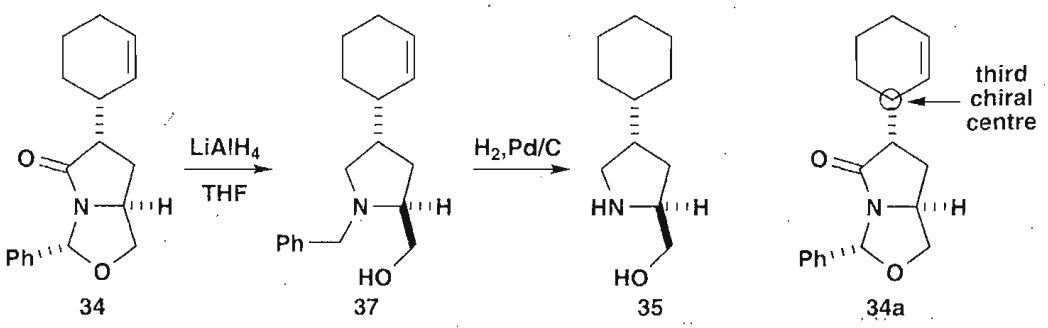
One example, compound **34**, was formed in 100% yield by this alkylation reaction. But in fact the compound these workers wanted to make was not **34** but **35**, the corresponding compound without a double bond in the six-membered ring. This compound, however, could not be made by direct alkylation of **32**. **Problem 12.9:** Suggest why the one alkyl halide reacts well while a very similar one fails. Suggest how to convert **34** into **35** (several steps needed). Why was the stereochemistry of **34** difficult to analyse?



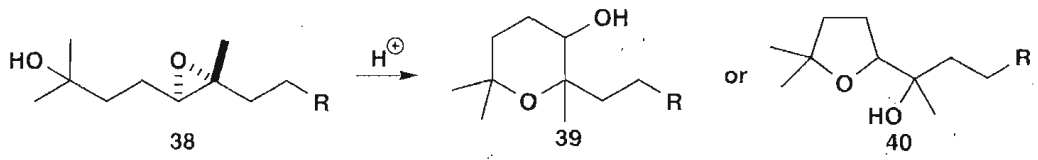
Answer 12.8: The formation of **32** is reversible and controlled thermodynamically (rather like acetal formation). The bicyclic structures **32** and **33** are folded molecules and the large phenyl group prefers to be on the outside (convex or *exo* face) of **32**. The formation of **33** is definitely not reversible and is kinetically controlled. The intermediate lithium enolate **36** is flatter than **32** but still folded and the large electrophile prefers to approach from the same outside (convex or *exo* face).



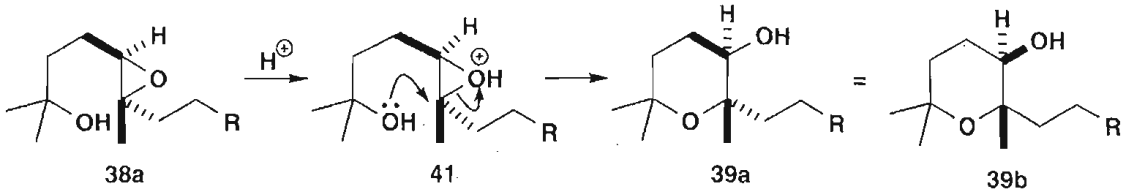
Answer 12.9: Secondary alkyl halides are poor at S_N2 reactions and evidently it is too difficult to add the two hindered molecules to each other. By contrast allylic halides are much more reactive. Converting **34** into **35** involves removing the 'acetal' and reduction of both the amide and the alkene. Any reasonable sequence will do as an answer. In fact they found that reduction with $LiAlH_4$ both reduced the amide and cleaved the benzylic C–O bond of the 'acetal' to give **37**. Hydrogenation then gave **35**. The difficulty with **34** is that it has a third chiral centre **34a** as the cyclohexene ring has no plane of symmetry so, even though the centre that matters is fully controlled, **34** is formed as a 50:50 mixture of diastereoisomers at the ringed centre. Hydrogenation removes that annoyance.



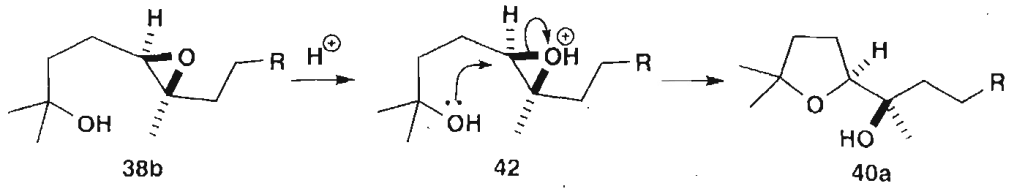
Problem 12.10: The epoxide **38** might cyclise stereospecifically in acid solution to either the five- or six-membered cyclic ether **39** or **40**. What would be the stereochemistry of these products?



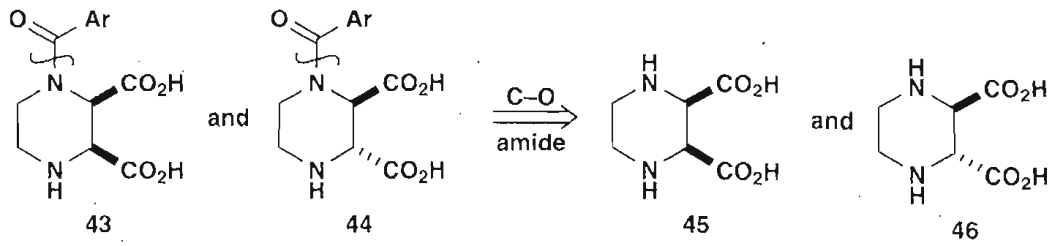
Answer 12.10: The molecules cannot cyclise as they are drawn so it is essential to redraw them in a shape that will allow for cyclisation. A simple way to do that is to draw the starting material in the shape of the product. This is easy to do for **38** as the carbon chain remains in the same extended shape. It is also helpful to draw the reacting bond (the epoxide) in the plane **38a**. Cyclisation of the protonated epoxide **41** with inversion at the centre under attack gives[7] **39a** redrawn as **39b**.



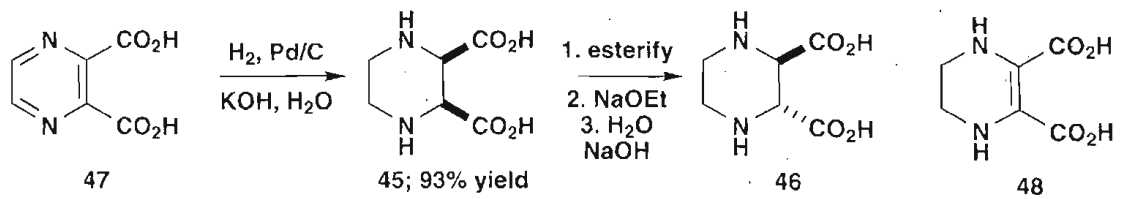
For **40** the best we can do is to distort **38** so that the OH can reach the other end of the epoxide **38b**. Cyclisation **42** then gives **40a**. In both products the alcohol centre shows retention but the centre under attack by OH is inverted. If you had problems with the stereochemistry then you are not alone – drawing the stereochemistry of epoxides is notoriously difficult. Making a model that you can hold in your hand really is the best way to deal with such difficult situations.



A series of drugs was needed[8] in two stereochemical forms: *cis* **43** and *trans* **44**. These compounds may easily be made by acylation of the heterocyclic diacids **45** and **46**. **Problem 12.11:** Suggest ways to control the stereochemistry in compounds **45** and **46**.

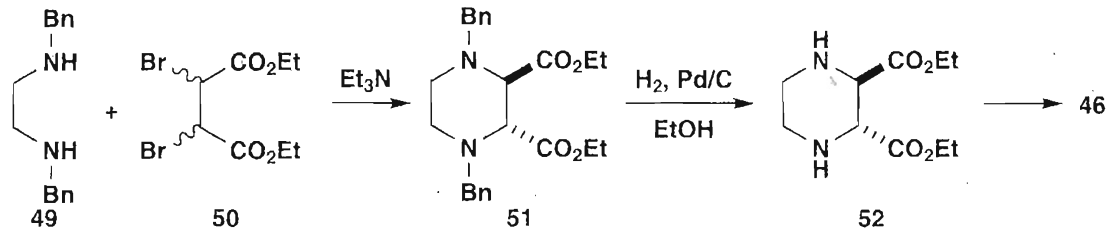


Hint: Have you considered which is the more stable? **Answer 12.11:** The *trans* compound **46** is more stable as it is diequatorial so it may be possible to equilibrate some derivative of **45** (or a mixture of the two) to give pure *trans*. In fact the *cis* compounds **45** is easily made by hydrogenation of the available aromatic heterocycle **43**. The ethyl ester of this compound can be equilibrated with NaOEt via the enolate and hydrolysed to **46**. Probably the last double bond to be hydrogenated is the one remaining in **48** and the last molecule of hydrogen adds *cis* to this.

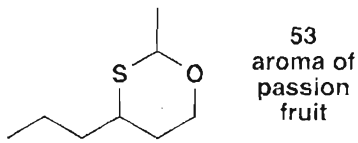


There is another way to make the *trans* diacid **46**. If the diamine **49** is combined with a mixture of diastereoisomers of **50**, only the *trans* compound **51** is formed. This may surprise you as it looks like a stereospecific double S_N2 reaction. But the diastereoisomers of **50** equilibrate under the reaction conditions, either by enolate formation or by elimination of HBr. So the more stable *trans*-**51** is formed fast and the remaining dibromo-ester **50** equilibrates. However, the

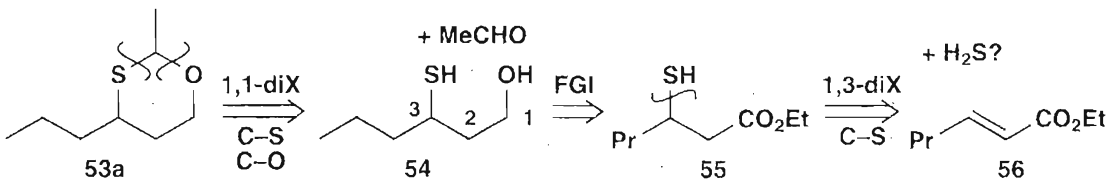
yield is only 32%. Hydrogenation removes the benzyl groups and hydrolysis of the diester **52** gives **46**.



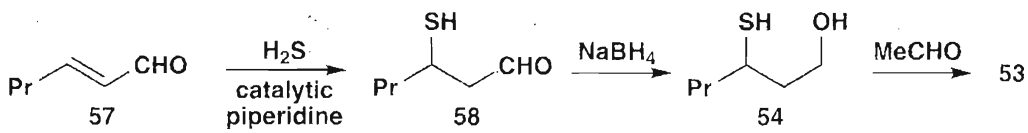
Finally, a normal synthesis problem except that it involves stereochemistry. The smell of passion fruit is largely caused by a simple heterocycle **53**. **Problem 12.12:** Suggest a synthesis of this compound: you need not consider the stereochemistry at this stage. Remember that two-group disconnections are best.



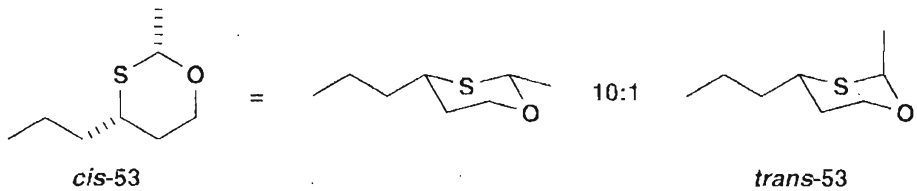
Answer 12.12: The obvious first disconnection is the 1,1-diX of the thioacetal **53a**. This reveals a hydroxy-thiol **54** with a 1,3-relationship between SH and OH. This suggests **55** conjugate addition (chapter 6) of some sulfur nucleophile to an unsaturated carbonyl compound such as **56**.



If fact this synthesis was carried out by addition of H_2S to the unsaturated aldehyde **57** catalysed by piperidine to give **58** which is reduced to **54** with $NaBH_4$. We do not usually use unsaturated aldehydes for conjugate addition but sulfur nucleophiles are good at this reaction and hexenal **57** is available.



Now what about the stereochemistry? The compounds are all racemic as no enantiomerically pure material has been used, so the stereochemistry comes in the thioacetal formation. This is under thermodynamic control and the *cis*-diequatorial isomer is favoured[9] by 10:1. It is not a surprise to know that this is exactly the ratio observed in the passion fruit though these compounds are also the enantiomers shown.[10]



cis-53 *trans*-53

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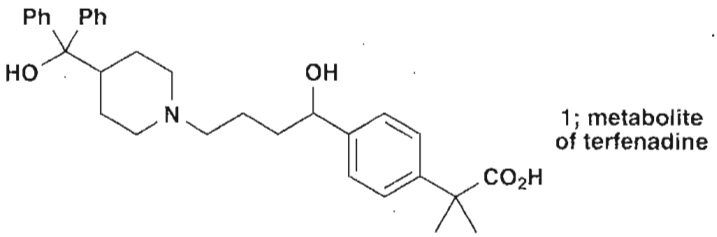
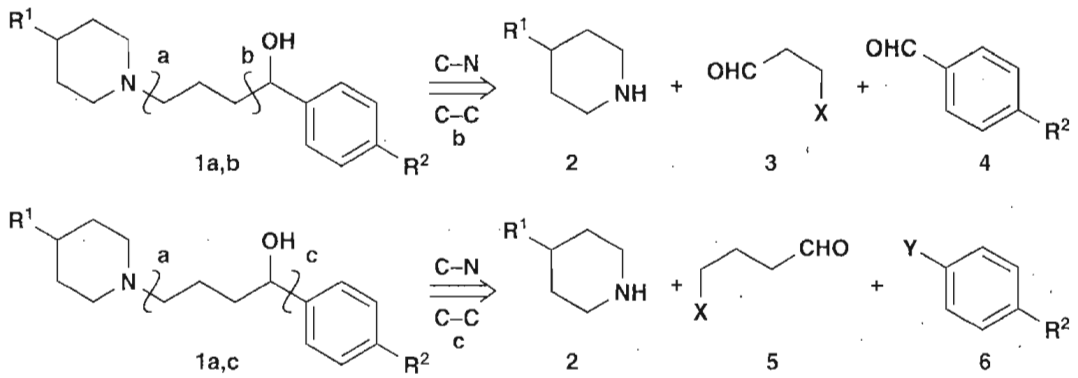
13 One-Group C–C Disconnections II: Carbonyl Compounds

Problem 13.1: The metabolite **1** of Sandoz's non-sedating anti-histamine prodrug terfenadine seems rather a large molecule for you to tackle at this stage. Start by suggesting which bonds you would like to disconnect.

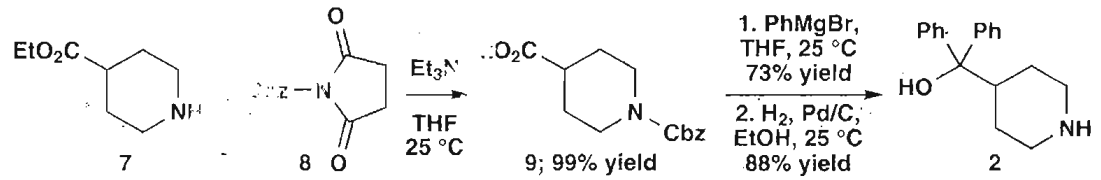


1; metabolite of terfenadine

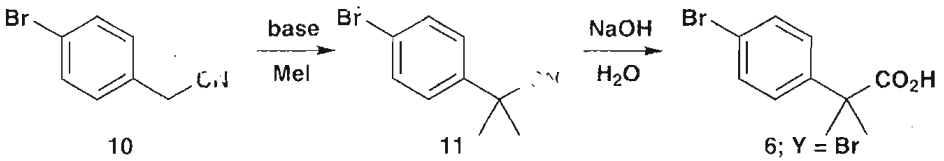
Answer 13.1: There are various bonds around the edges of the molecule that could usefully be disconnected but we should really prefer to break the molecule into three parts by one C–N and one C–C disconnection. The C–N disconnection would give the amine **2** and either the aldehyde **3** (with reductive amination in mind) or the halide **5** (with alkylation in mind). It follows that C–C disconnection **1b** fits best with the first case and **1c** with the second so that we keep our aldehydes separate and our activating groups (X, Y = halide) separate too.



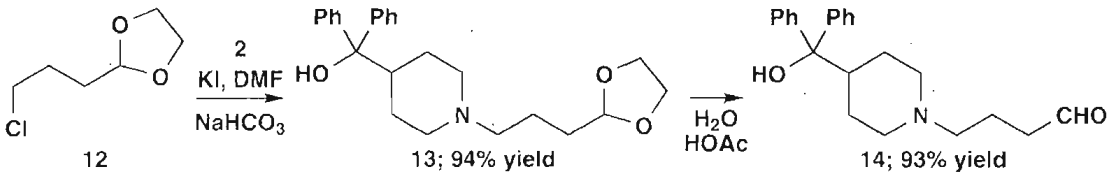
The published synthesis[1] uses strategy **1a,c**. The amino-alcohol **2** was made from the ester **7** by protection and reaction with PhMgBr. Catalytic hydrogenation removed the Cbz group (chapter 9).



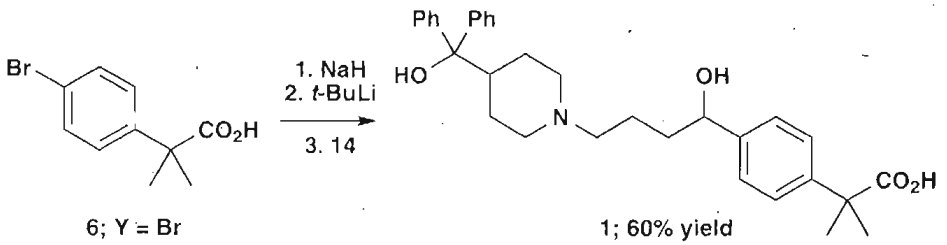
The starting material for the other end of the molecule **6** was made by dimethylation of the nitrile **10** and hydrolysis to the carboxylic acid. Y = Br.



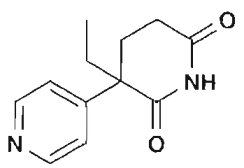
Now the aldehyde **14** needs to be prepared from 2 for coupling with **6**; Y = Br. Alkylation with the protected bromoaldehyde **12** gives an excellent yield of **13**: note that strong base is avoided so that alkylation of OH does not occur. The aldehyde **14** is easily revealed in aqueous acid.



Finally the bromoacid **6**; Y = Br is treated with NaH to deprotonate the acid and with *t*-BuLi to make the lithium derivative from the bromide. Coupling with the aldehyde **14** gives the terfenadine metabolite **1** in reasonable yield. It would of course have been possible to reverse the order of the coupling reactions, alkylating on nitrogen last. This synthesis involves making *five* C–C bonds and introduces two of the main methods used in this chapter. Other strategies are possible.[2]

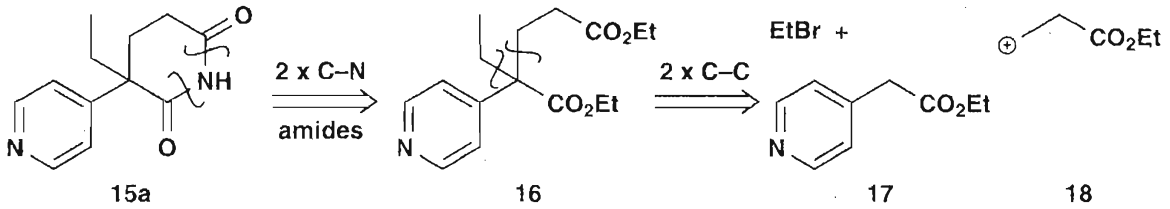


And now to remind you of the third important method used in C–C disconnections to make carbonyl compounds, we study a potential breast cancer drug pyridoglutethimide. **Problem 13.2:** Suggest a synthesis of pyridoglutethimide **15**.



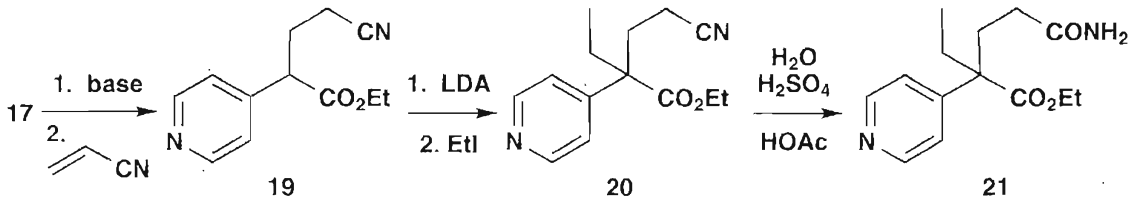
15
pyrido-
glutethimide

Answer 13.2: The first thing to do is to disconnect the two structural C–N bonds **15a** to reveal a simple pyridyl acetic ester **17**, a molecule of EtBr, and a synthon **18**.



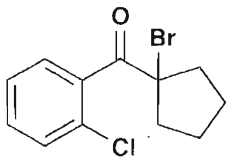
15a 16 17 18

We hope you have already realised what type of reagent to use for **18**: an unsaturated carbonyl compound. In fact the unsaturated nitrile was preferred to the unsaturated ester in the published synthesis and EtI to EtBr. Hydrolysis of the nitrile **20** gave the amide **21** that could be cyclised[3] to **15** with *t*-BuOK. Conjugate addition of carbon nucleophiles to unsaturated carbonyl compounds and nitriles is the third important method of C–C bond formation.



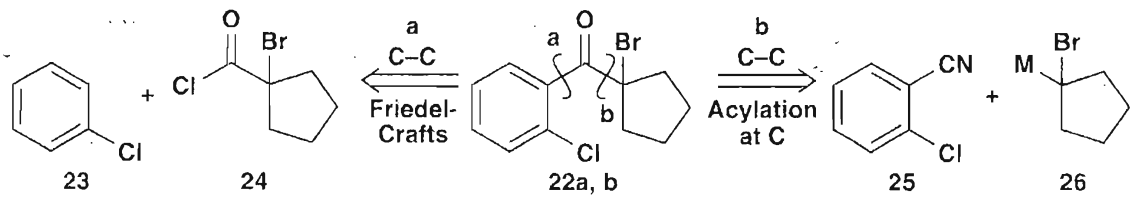
19 20 21

Now for some more general problems. **Problem 13.3:** Suggest two syntheses for compound **22**, each using a different C–C disconnection.



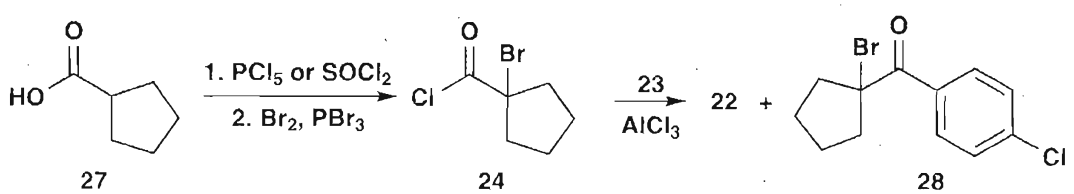
22

Answer 13.3: Friedel-Crafts disconnection **22a** suggests combining chlorobenzene **23** with the acid chloride **24**. Alternatively, acylation at carbon **22b** suggests combining the nitrile **25** with some organometallic derivative **26**.



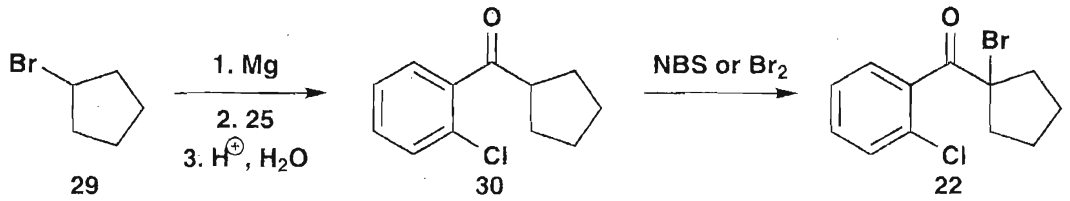
23 24 22a, b 25 26

There are advantages and disadvantages to both routes. The acid chloride **24** can be made by direct bromination of available cyclopentane carboxylic acid **27** and chlorine is *ortho, para*-directing. But, the *para* compound **28** may well be the main product.



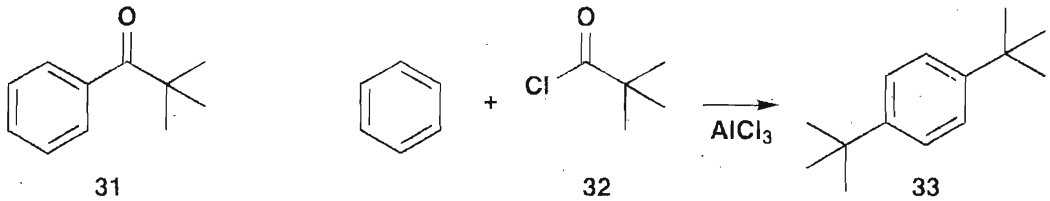
27 24 28

The *ortho*-chloronitrile **25** is also available but it is difficult to have an organometallic derivative **26** with a bromine atom on the same carbon as it would eliminate to form a carbene (chapter 30). However, the bromine can be introduced after the ketone is synthesised and this is the method that was adopted by Parke-Davis in the synthesis of the anaesthetic ketamine.[4]



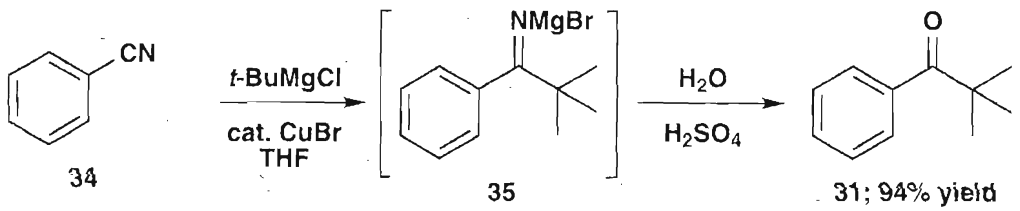
29 30 22

It may appear that the synthesis of the *t*-butyl ketone **31** is a trivial matter of a Friedel-Crafts reaction of **32** on benzene. Unfortunately the intermediate acylium ion decomposes with loss of CO and the main product is *para*-di-*t*-butyl benzene **33**.



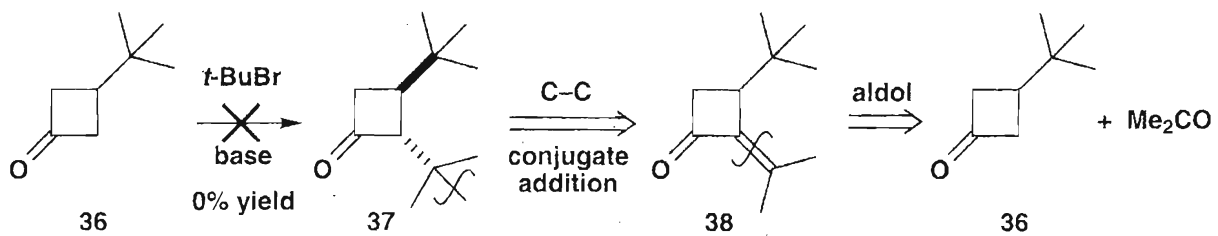
31 32 33

Sadly, the alternative route we have just been exploring fails also as neither *t*-BuLi nor *t*-BuMgCl adds to benzonitrile **34** in more than 8% yield. But if catalytic copper is added, just as if we were doing a conjugate addition, and the intermediate imine **35** hydrolysed in aqueous acid, 94% of **31** can be isolated.[5]



34 35 31; 94% yield

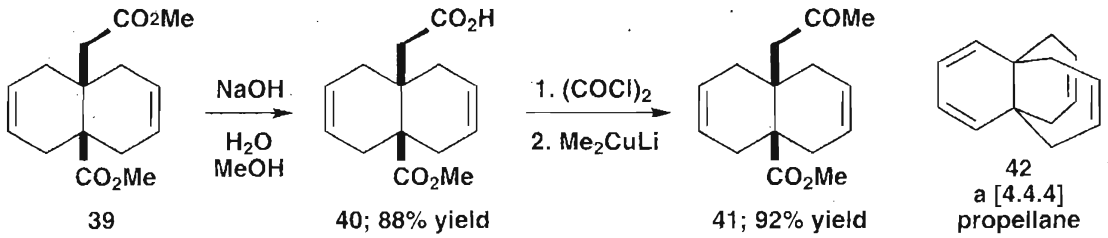
Another problem in the addition of a *t*-butyl group is solved by conjugate addition. As expected, attempted alkylation of an enolate of symmetrical ketone **36** fails to give any **37**, as S_N2 reactions fail with *t*-alkyl halides. But removal of just one methyl group reveals an enone **38** that can be made by an aldol reaction (chapters 19 and 20). The conjugate addition with MeMgI and Cu_2Cl_2 gives 100% of **37**. The *trans* compound is the only product[6] as expected from such large groups.



36 37 38 36

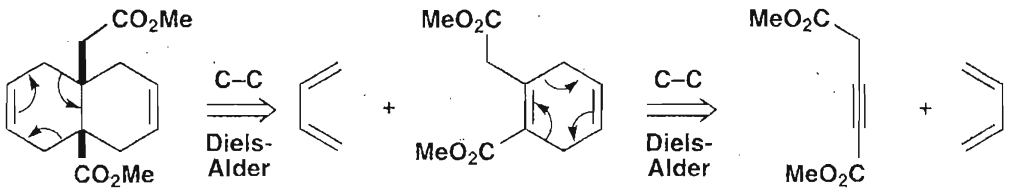
A Problem from the Chapter in the Textbook: In the textbook we challenged you to think about this. In his synthesis of the [4.4.4]'propellane' **42**, Paquette made the diester **39** easily but

wanted the *mono* methyl ketone **41**. Rather than add MeLi directly, he first hydrolysed one ester to the free acid **40** and then made the acid chloride with oxalyl chloride. Reaction with Me_2CuLi gave the ketone in excellent yield.[7] **Problem 13.4:** How was **39** made? Explain the hydrolysis of only one ester to give **41**.



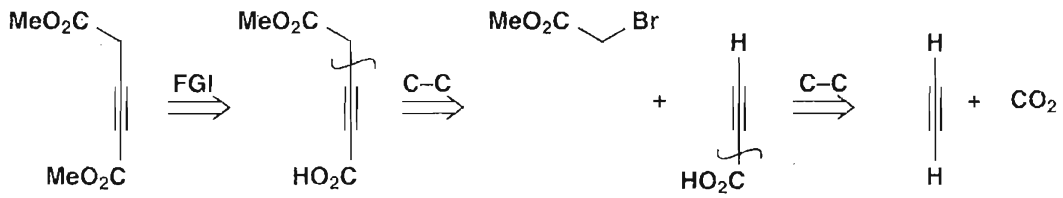
39 40; 88% yield 41; 92% yield

Answer 13.4: Diester **39** is an obvious Diels-Alder adduct and disconnects **39a** on either side to butadiene **43** and a new diester **44**. Repeating the Diels-Alder disconnection gives the alkyne **45** and another molecule of butadiene. No doubt the first Diels-Alder will give **44** but the second has a choice as there are two alkenes in **44**. But this is no problem as Diels-Alders require a conjugating electron-withdrawing group and only the alkene in the left hand ring has that.



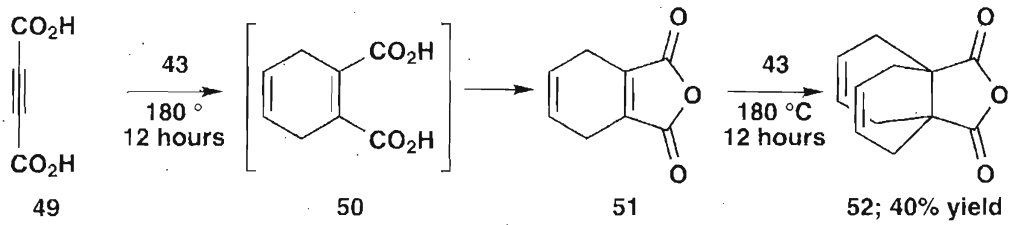
39a 43 44 45 43

We can make **45** using two C–C disconnections. It is easy to make metallic derivatives of acetylenes (chapter 16) so we can disconnect both C–C bonds at the ends of the triple bond. Acetylene would be treated with BuLi and then CO_2 to give **48**. Then treatment with BuLi again – two equivalents as one will be consumed by the CO_2H – and a suitable alkylating agent such as **47**. But none of this was carried out as it was known that acetylenes like **45** with only one activating group react only once with butadiene. The product would be **44** not **39**.

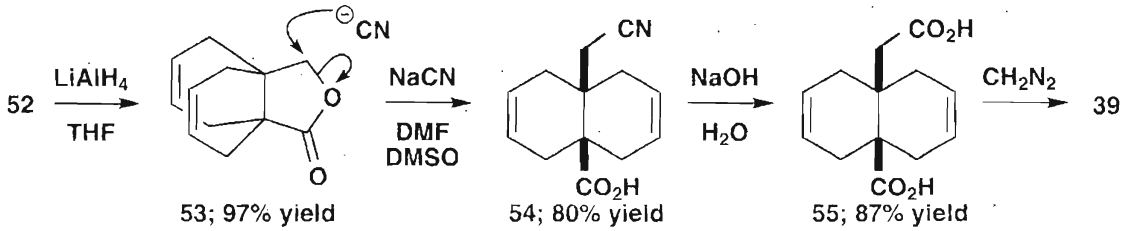


45 46 47 48

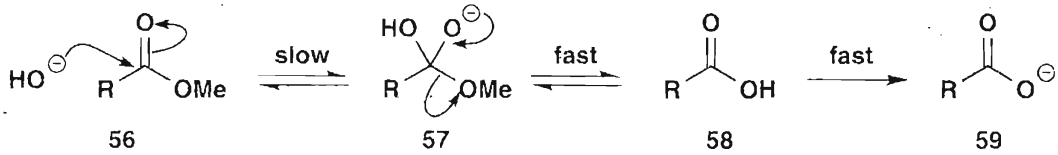
We need *double* activation on the triple bond and available acetylene dicarboxylic acid **49** is just right for this. The reaction goes twice but the product[8] is the cyclic anhydride **52**. As soon as one cycloaddition occurs, the two carboxylic acids in the product **50** are close together and at 180 °C the anhydride **51** is formed. This is even more activated towards a second cycloaddition so **52** is formed in one step. But **52** is not what is wanted so we must differentiate the two carbonyl groups.



Reduction with $LiAlH_4$ gives the lactone **53** and an S_N2 displacement of carboxylate with cyanide ion gives the chain-extended nitrile **54**, easily hydrolysed to the diacid **55** and hence, after esterification, the diester[9] **39**.



The rate-determining step in ester hydrolysis in base is the addition of hydroxide to the carbonyl group **56**. In this step, the flat ester **56** becomes tetrahedral **57** and this ionic intermediate is more heavily solvated by water and for both reasons becomes much larger. So the rate of ester hydrolysis depends on steric hindrance. The ester that does hydrolyse in **39** is in free space but the other is joined to a tertiary carbon atom and the product is **40**.



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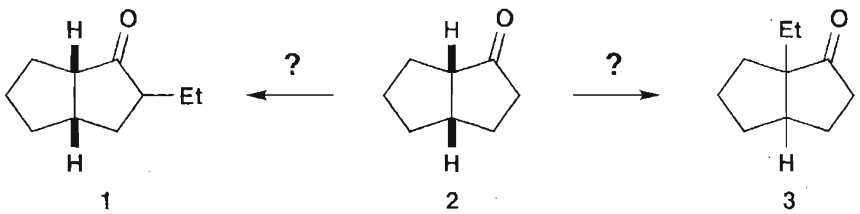
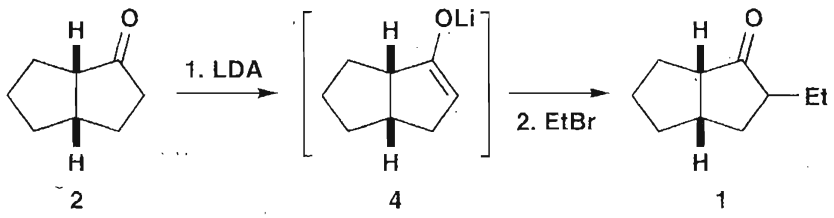
14 Strategy VI: Regioselectivity

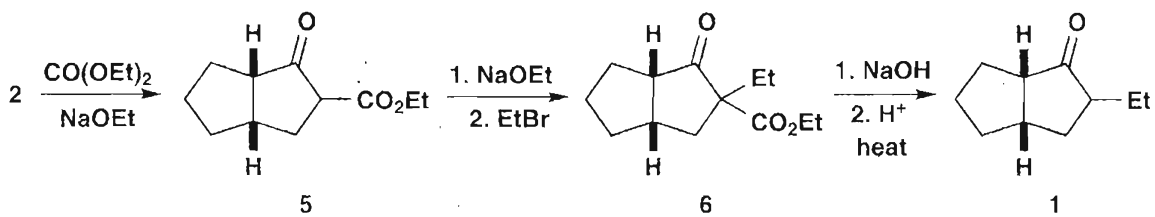
Problem 14.1: Suggest how the available ketone **2** might be converted into the two new ketones **1** and **3**. **Problem 14.2:** What will be the stereochemistry of **1** and **3** produced by your chosen methods? **Problem 14.3:** Will the products **1** and **3** be single enantiomers when formed by your chosen methods?



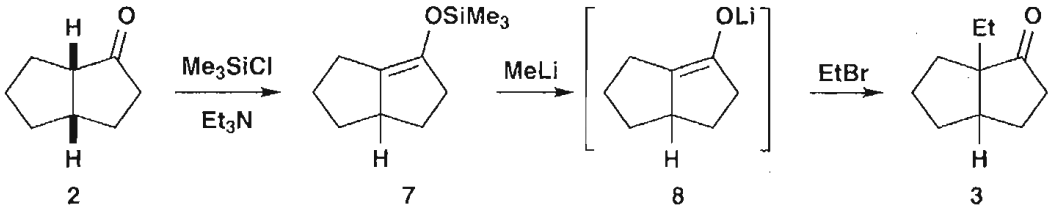
Answer 14.1: The disconnection in each case is of the ethyl group and strongly suggests the alkylation of some kind of enol(ate). Alkylation on the less substituted side to give **1** could be done via the lithium enolate **4**. But, as we pointed out in the textbook chapter, regioselectivity between primary and secondary centres is not wonderful.



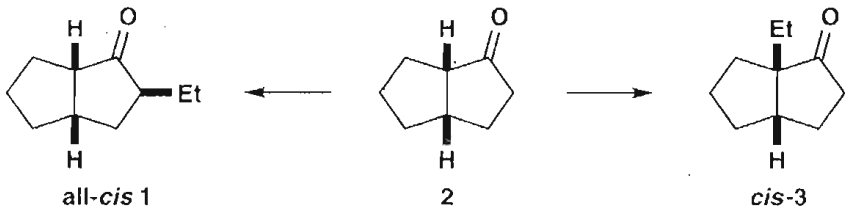
An alternative is to make the β-keto-ester **5** by reaction with diethyl carbonate under equilibrating conditions as this gives excellent selectivity in favour of **5**. Alkylation with ethoxide as base gives **6** exclusively and hydrolysis and decarboxylation of **6** gives **1**.



Reaction on the more substituted side will need the silyl enol ether **7** formed under equilibrating conditions. Reaction of **7** with EtBr and a Lewis acid might give **3** but such reactions with primary alkyl halides are usually poor. So it might be better to remove the silyl group with MeLi (releasing Me_4Si as the by-product) and alkylate[1] the lithium enolate **8**.

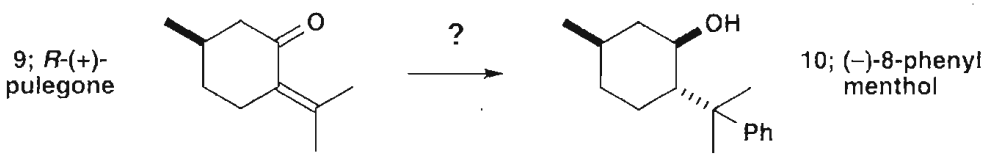


Answer 14.2: Two small rings fused together much prefer the *cis* ring junction as in **2**. This ketone has been made by old chemistry and every synthesis gave the *cis* compound.[2] So **1** will also have *cis* fused rings however we make it. The new substituent (ethyl) added to **4** will also prefer the outside (*exo* or convex) face and so that will go on the same side as the ring-junction hydrogen atoms. In the formation of **5** neither ring junction will change its stereochemistry and the β-keto-ester **5** will probably also have the CO_2Et group on the outside face. However, that doesn't matter as the stereochemistry is lost in the formation of the enolate from **5** and the decarboxylation of **6**. The stereochemistry of **1** is under thermodynamic control when derived from **6** and this too means that the CO_2Et group will be on the outside face. So, however we make **1**, it will have the same stereochemistry. The ring-junction stereochemistry is lost in the formation of **7** and **8** but will be restored to much the more stable *cis*-**3** when the ethyl group is added.



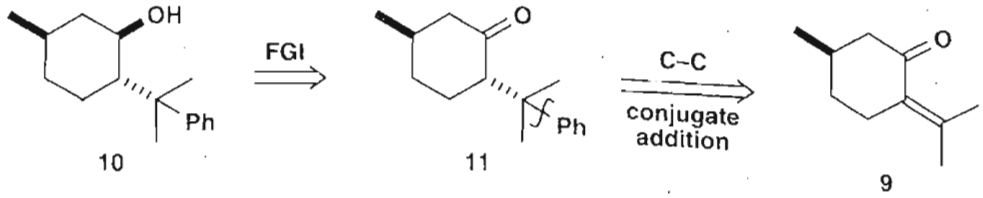
Answer 14.3: We don't know from the information given. If the sample of **2** we use is racemic, all products formed from it will also be racemic. If it is a single enantiomer, since one of the two centres remains intact in all the sequences we have proposed, the products all-*cis*-**1** and *cis*-**3** will also be single enantiomers. The chemistry we have described controls diastereo-selectivity but cannot create asymmetry as nothing asymmetric is used.

Pulegone **9** is a natural terpene and a good source for enantiomerically pure compounds. It has been used to make (–)-8-phenylmenthol **10** for use in asymmetric synthesis. **Problem 14.4:** Suggest how **9** could be converted into **10** as the main stereoisomer.

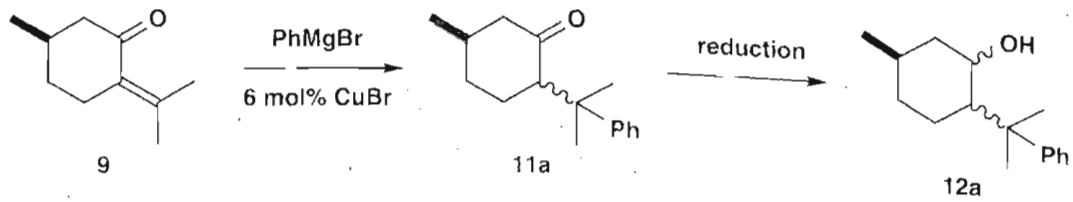


Answer 14.4: The stereochemical aspect is similar to that we have just discussed: one chiral centre (carrying the methyl group) remains unchanged in any synthesis so we do not have to worry about enantiomeric purity, just about diastereoselectivity. The only disconnection needed

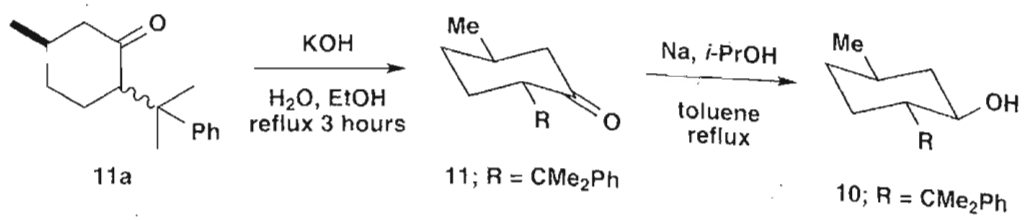
is of the phenyl group and that can surely be put in by conjugate addition. So the analysis becomes:



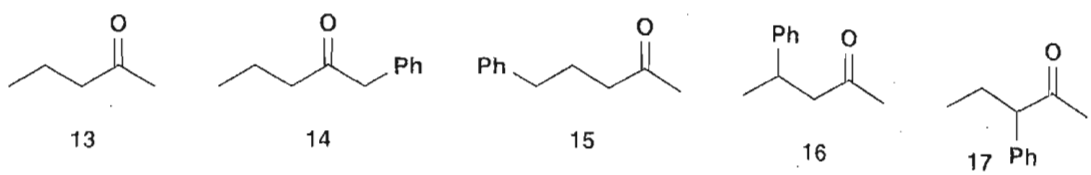
Conjugate addition will be achieved by the use of copper: a copper-catalysed Grignard addition gives good results. Any reduction of the ketone will give the alcohol **10** so the synthesis in outline is simple.[3]



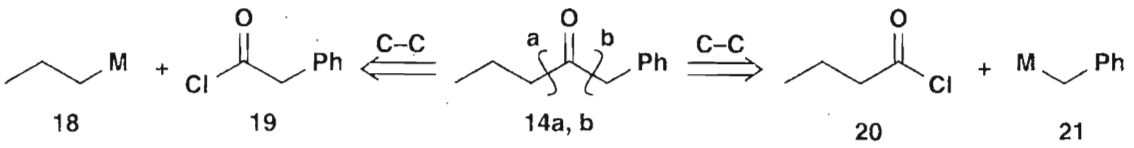
Now the question of stereochemistry must be addressed. Have you noticed that **10** is the all-equatorial product? This means that we should be able to equilibrate **11a** to **11** as the main product via the enol(ate) and this can be done by refluxing the mixture **11a** with KOH in aqueous ethanol. As much as 91% of **11** can be isolated. The final product **10** cannot be equilibrated so we need an equilibrating reduction method. This will not be a hydride reducing agent such as $LiAlH_4$, but sodium in *iso*propanol at reflux in toluene achieves full control over the final chiral centre. Reductions using alkali metals in alcohols are a good way to get the thermodynamic product as explained in chapter 12 of the textbook and chapter 33 of Clayden. The reducing agent (an electron) is very small.



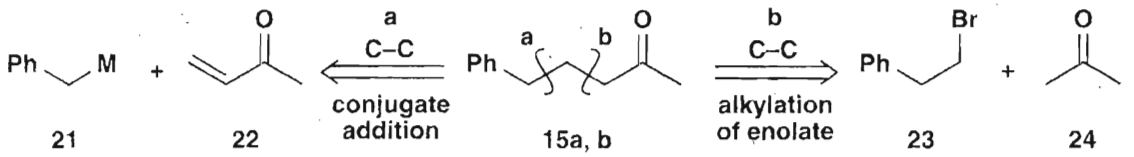
The four ketones **14** to **17** are all notionally derived from pentan-2-one **13** by the addition of a phenyl group. **Problem 14.5:** Suggest syntheses for these four ketones from readily available starting materials and discuss any regioselectivity. You may use **13** if you wish, but...



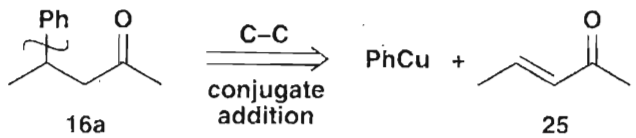
Answer 14.5: Phenyl groups cannot generally be added as electrophiles to enolates so the disconnection of a C–Ph bond to give **13** as starting material is going to be rare. There are many ways to make all these simple compounds and we shall describe only a few. The most obvious way to make **14** is by acylation of an organometallic derivative[4] **18** or **21**; M = metal. Copper derivatives made from the alkyl halides are the best and no regioselectivity is involved.



Two disconnections **15a** and **15b** suggest themselves for **15**. Copper catalysed conjugate addition of benzyl Grignard reagent **21** to butenone **22** or alkylation of acetone **24** with the alkyl halide **23**. The latter could be done with a lithium enolate, an enamine, or ethyl acetoacetate.



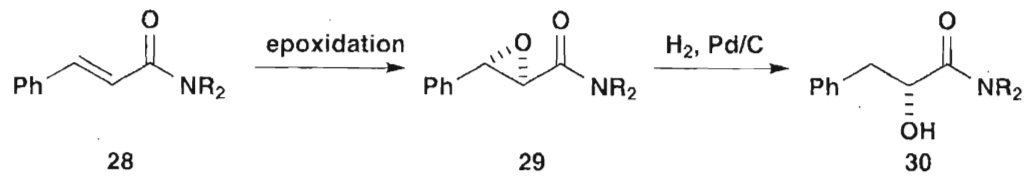
With **16** a C–Ph disconnection **16a** becomes a good idea as conjugate addition of some PhCu derivative to the enone **25** is the obvious method.



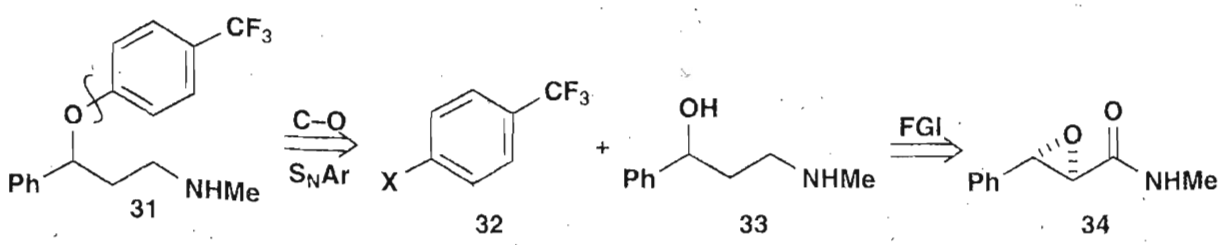
With our last example **17** alkylation of the more stable enolate **27** of the ketone **26** with ethyl bromide looks the simplest route. You may well have thought of other routes that are as good such as FGI to the alcohol and disconnection of a Grignard reagent. Though these four ketones are very simple, none is commercially available but all have been made, generally some time ago, often using the methods we have mentioned.[5]

Other Examples of Regioselectivity

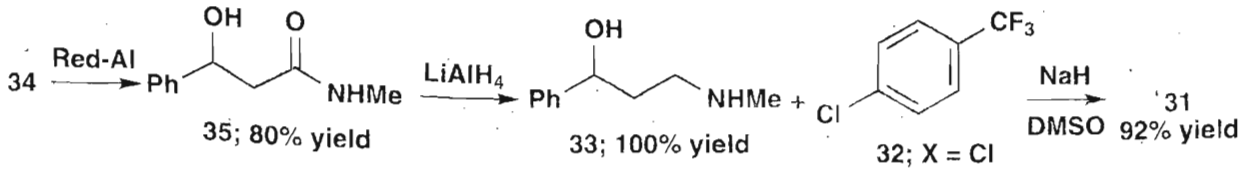
So far we have explored mostly C–C bond formation but there are many other kinds of regioselectivity. One published synthesis[6] of fluoxetine (Prozac™) uses the regioselective opening of an epoxide with a reducing agent. Before this work started, it was known that catalytic hydrogenation of epoxy-amides **28** gave isomer **30**, the wrong one for this work. The challenge was to get reduction at the other end of the epoxide.



Fluoxetine **31** comes from the alcohol **33** that could be derived from the epoxy-amide **34** if the regioselectivity problem could be solved. The answer was a reducing agent that complexed to the amide carbonyl group and delivered hydride to the nearer end of the epoxide.



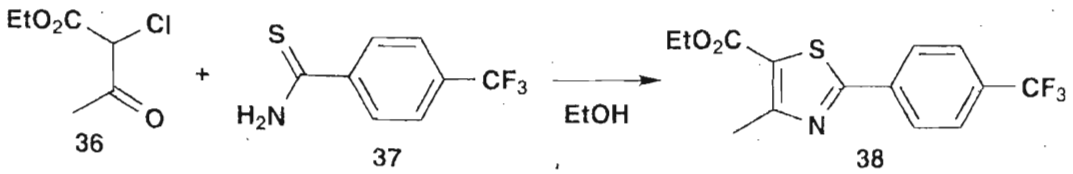
Red-Al, $NaAlH_2(OCH_2CH_2OMe)_2$, turned out to be the answer, giving 80% of the right regioisomer **35**. Reduction of the amide with $LiAlH_4$ gave a quantitative yield of **33** and the chloro compound **32**; X = Cl turned out to be the best for the final step. Note that the anion of the alcohol must be made with NaH to avoid substitution at nitrogen.



A Heterocyclic Example

The heterocyclic system **38** is the core of a group of drugs used to treat metabolic disorders. It can be made by simply combining the chloro-derivative of ethyl acetoacetate **36** and the thioamide **37**.

Problem 14.6: Comment on any selectivity shown in this reaction.



Answer 14.6: There is a great deal! We have a compound **36** with three electrophilic centres combining with a compound **37** with two nucleophilic centres. We might say that *chemo*selectivity is shown by **36** as the three electrophiles are separate functional groups. But a thioamide is one conjugated functional group so **37** shows *regio*selectivity. Sulfur (soft) prefers S_N2 reactions to additions to carbonyl groups so it displaces the chlorine atom in **36**. Nitrogen (harder) prefers additions to carbonyl groups to S_N2 reactions but it still has a choice and it prefers the more electrophilic ketone to the ester.[7] The need for regioselectivity is common in synthesis and you will meet many examples in the remaining chapters of the book.

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2. A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 1934, 946; A. C. Cope and W. R. Schmitz, *J. Am. Chem. Soc.*, 1950, **72**, 3056.
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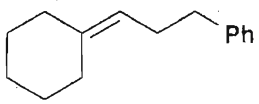
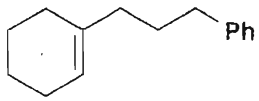
7. J. Guo, G. A. Erickson, R. N. Fitzgerald, R. T. Matsuoka, S. W. Rafferty, M. J. Sharp, B. R. Sickles and J. C. Wisowaty, *J. Org. Chem.*, 2006, **71**, 8302.

15 Alkene Synthesis

Problem 15.1: Suggest a synthesis for each of these two isomeric alkenes **1** and **2**.

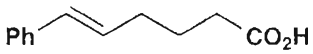


1

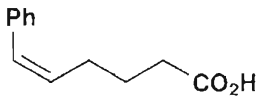


2

Problem 15.2: Suggest a synthesis for each of these alkenes **3** and **4**, isomeric in a different way.

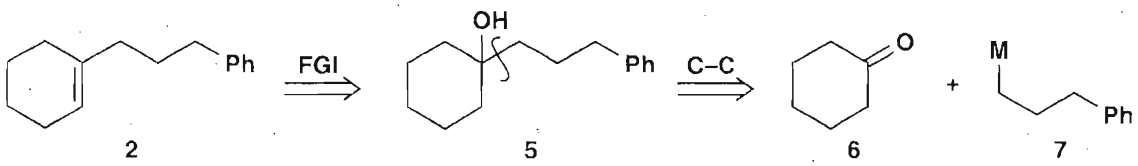


3



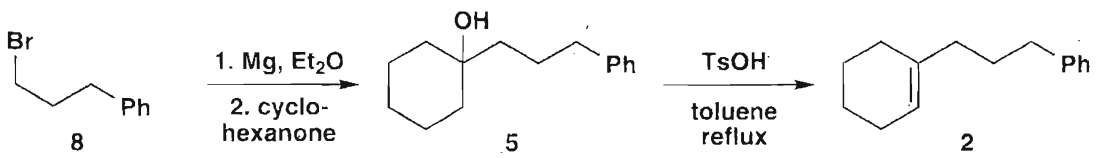
4

There are many solutions to these problems and yours may be as good as our proposals. **Answer 15.1:** Notice that neither alkene has any stereochemistry. The double bond is more stable inside the six-membered ring so a simple elimination on the alcohol **5** will make mainly **2**. Addition of some organometallic derivative **7** (organo-lithium or Grignard reagent) to cyclohexanone **6** will give the alcohol **5**.



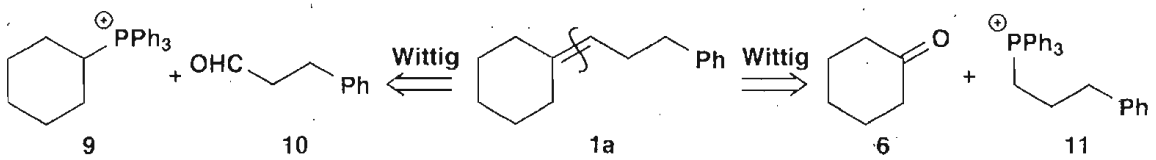
2 5 6 7

You could use many methods for the dehydration step. As **5** is a tertiary alcohol, an E1 reaction is preferred so an acid, such as TsOH in toluene, should do well.

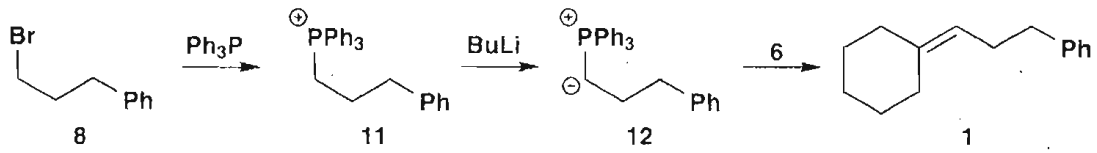


8 5 2

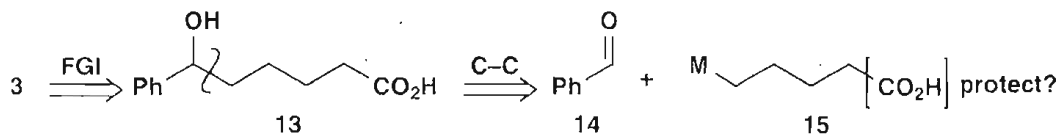
As **1** cannot be formed by dehydration, a Wittig disconnection **1a** is suggested and, as usual, there are two possibilities; we can put the phosphonium salt and the carbonyl group at either end.



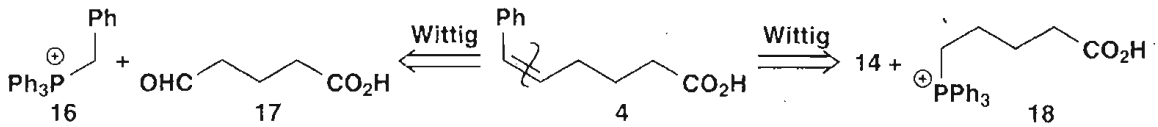
As we already have some halide **8** for the synthesis of **2**, we might as well use it here too: displacement of bromide by Ph_3P gives the phosphonium salt **11** and BuLi gives the unstabilised ylid **12**. Reaction with cyclohexanone should give only **1**.



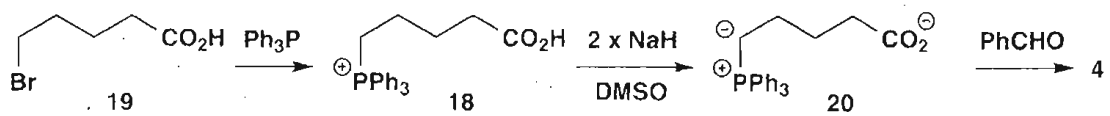
Answer 15.2: Again, there are many possibilities. Dehydration of the benzylic alcohol **13** would give only that alkene, mainly as the more stable *E*-isomer. The alcohol **13** could be prepared from benzaldehyde but the organometallic derivative required is **15** which would destroy itself unless the acid were protected in some way.



One simple way would be to make a salt of a haloacid before treatment with the metal. The *Z*-isomer **4** could be made from an acetylene by Lindlar reduction (chapter 16) but a Wittig reaction would also be good providing we choose the right reagents. The ylid from **16** would be stabilised by the phenyl group and would tend to give the *E*-isomer **3** but the ylid from **18** is not stabilised and should favour the *Z*-isomer **4**. Again, we shall have to remove the acidic proton from the CO_2H group before making the ylid.

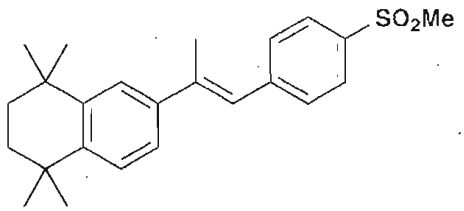


Treatment of the phosphonium salt **18** with two equivalents of NaH in DMSO removes first the CO_2H proton and then makes the ylid **20**. Reaction with benzaldehyde would give mainly *Z*-**4**. This ylid **20** has been widely used in prostaglandin synthesis.[1]



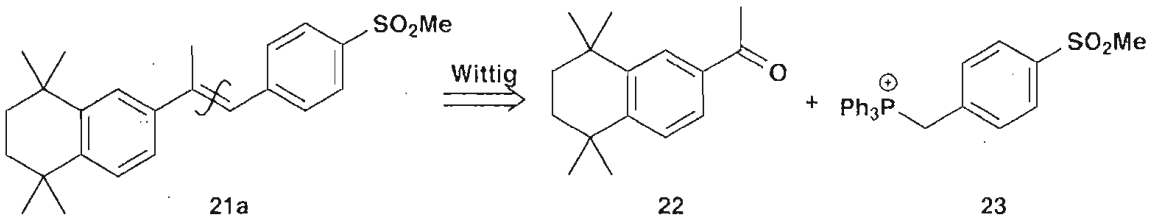
A Pharmaceutical Example

The rigidity of alkenes makes them attractive drug candidates where restricted conformation is needed, as in drugs for breast and skin cancer. One such drug is BASF's etarotene[2] **21** (also Roche's Ro15-1570). **Problem 15.3:** Suggest a synthesis of **21** from available starting materials.



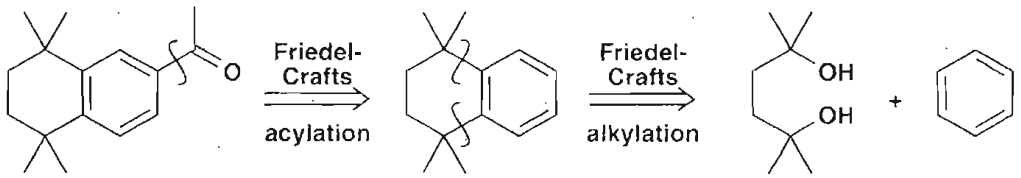
21
etarotene

Answer 15.3: It seems best to split the molecule in half with a Wittig disconnection **21a** and to put the phosphonium salt on the aryl sulfone half **23** as the ylid will then be stabilised by both the benzene ring and the very electron-withdrawing sulfone ensuring that the *E*-isomer **21** is the main product. The ketone **22** needs some more analysis – any suggestions?



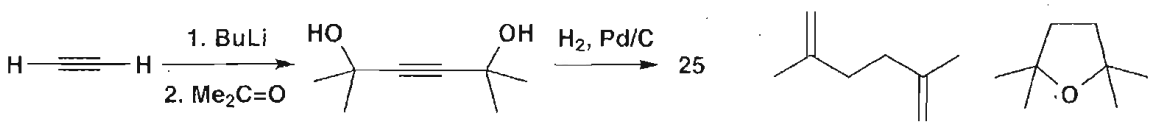
21a 22 23

Two Friedel-Crafts disconnections do the trick. The first is an acylation with the *t*-alkyl groups on the ring activating all four positions electronically but directing to the right positions by steric hindrance. Then a double alkylation, using perhaps the diol **25**, should give **24**.



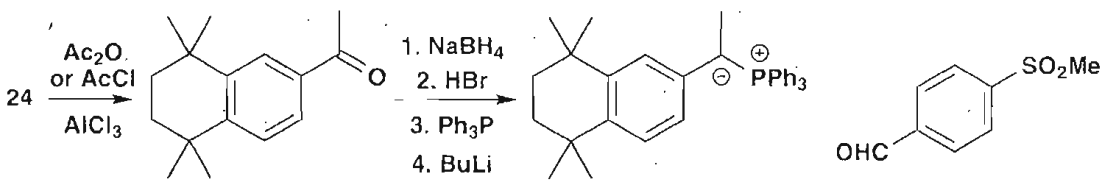
22 24 25

The diol **25** is very easy to make from acetylene by addition of two molecules of acetone (chapter 16) to give the diol **26**: catalytic hydrogenation then gives the saturated compound **25**. It turns out that the Friedel-Crafts double alkylation to give **24** is exceptionally easy. The diol **25**, the corresponding dichloride, the diene **27** or even the cyclic ether **28** all give a good yield with $AlCl_3$ as catalyst.[3]



26 27 28

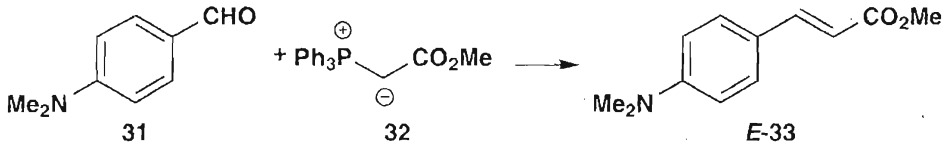
As it happens the chemists preferred[4] to do the Wittig reaction the other way round with the ylid **29** and the aldehyde **30**. It could be that the extra electrophilicity of this aldehyde over the conjugated ketone is a good thing.



22 29 30

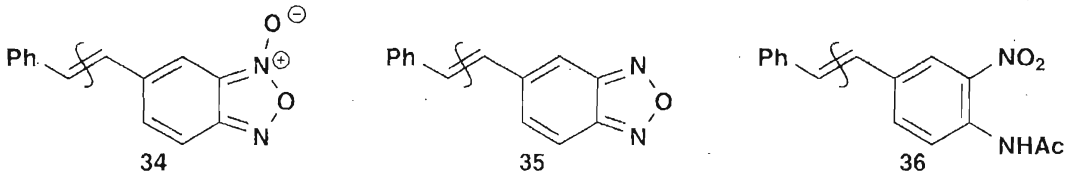
The Importance of Experimental Work

We normally do not consider how chemists have found the best conditions for a given reaction but, even with such a well-established method as the Wittig reaction, new developments are often produced. For example, the rather unreactive aldehyde **31** gives no **33** with the stabilised ylid **32** in CH_2Cl_2, a commonly used organic solvent. In the more polar solvent MeOH, the yield is 78% and the *E*:*Z* ratio is 75:25. But in water, even though the reagents are not completely soluble, the yield is 81% and the *E*:*Z* ratio is 90:10. Dramatic improvements occur with many aldehydes.[5]



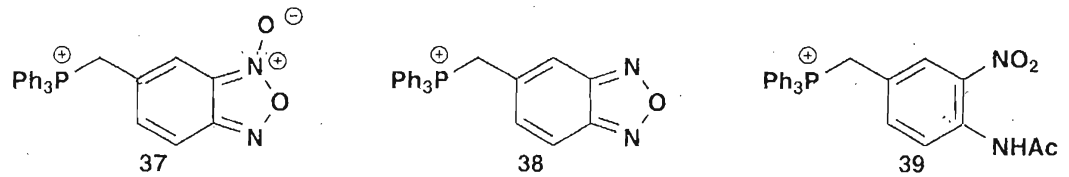
31 **32** ***E*-33**

Such considerations can be very important in the manufacture of drugs. The alkene **34**, used to treat Chargas disease in South America, could obviously be made by a Wittig reaction. The strange heterocycle at the right hand end of the molecule can be made from **35** or **36** giving a choice of three Wittig disconnections.



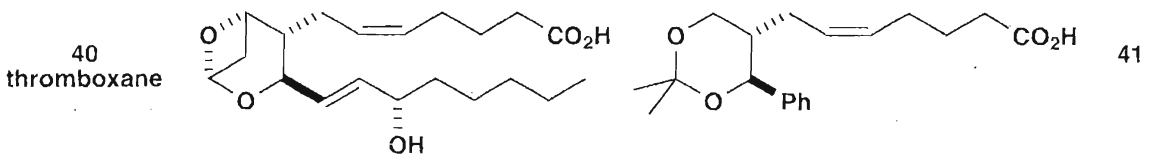
34 **35** **36**

In each case the Wittig reaction used benzaldehyde and the phosphonium salts **37**–**39**. In the original laboratory synthesis, **39** gave a good yield but the *E*:*Z* ratio was 1:1. In addition, **39** was difficult to make. The ylid from **38** gave low yields and it turned out that the most direct reaction of the ylid from **37** gave a reasonable yield (65%) and a good (3.8:1) *E*:*Z* ratio.[6] Most drugs are manufactured by a process very different from the original laboratory synthesis and this is developed by careful study of reagents and conditions.

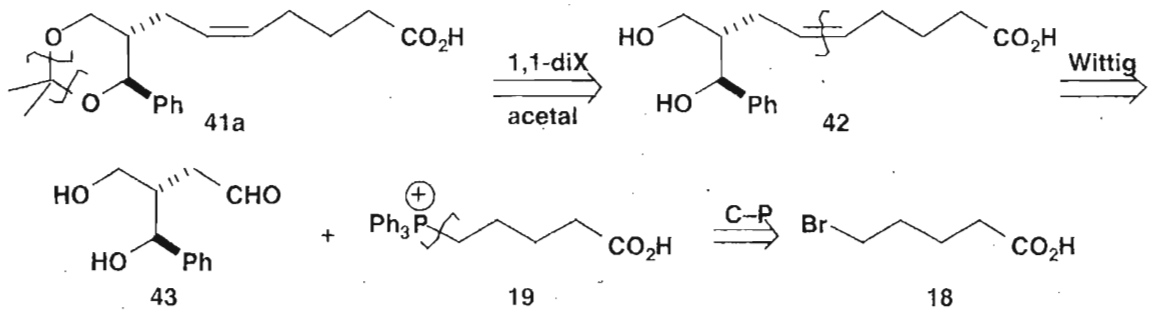


37 **38** **39**

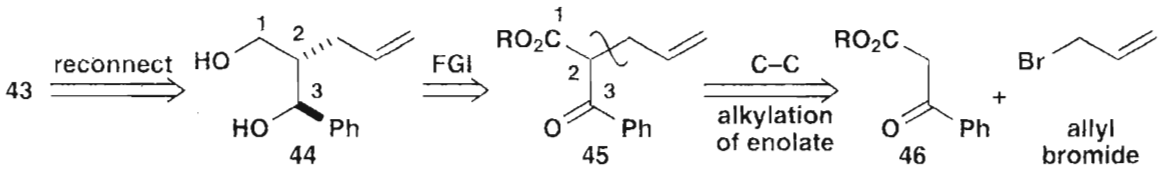
Analogues of the human blood clotting factor thromboxane **40**, such as **41**, might inhibit thromboxane synthesis and are of some potential in the treatment of heart disease **Problem 15.4:** Suggest a synthesis for **41**.



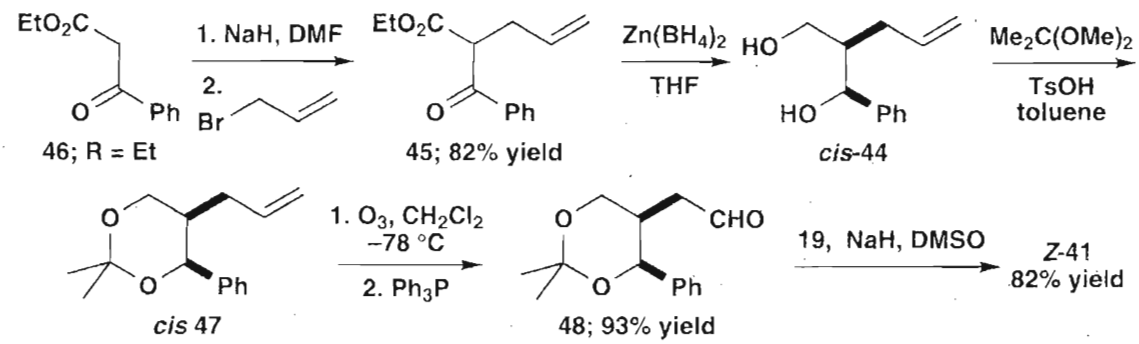
The removal of the acetal **41a** reveals the carbon skeleton and then a Wittig disconnection **42** takes us to the dihydroxy-aldehyde **43** and a strangely familiar phosphonium salt **19** already met at the start of this chapter.



The remaining question is how to make **43**. This compound would exist as a cyclic hemi-acetal or even a bicyclic acetal so we cannot allow all three functional groups to co-exist. One solution is to protect the aldehyde by the reconnection strategy (chapter 26) using oxidative cleavage of the alkene **44** to make the aldehyde. This reveals a 1,3-diCO relationship and invites FGI to the 1,3-dicarbonyl compound **45** and disconnection of the allyl group.

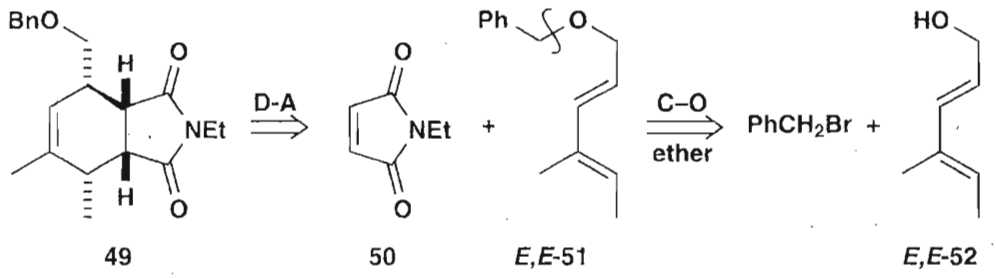


The synthesis[7] follows these lines: if **45** is reduced with $LiAlH_4$ the diol **44** is formed as a mixture of diastereoisomers (*cis* and *trans*). To the surprise of the chemists at AstraZeneca, *cis*-**44** proved more biologically active than *trans* and so they made *cis*-**44** with the chelating reducing agent[8] $Zn(BH_4)_2$. This was cyclised to the *cis*-acetal **47** and oxidised to give the aldehyde **48**. The Wittig reaction gave almost entirely the *Z*-alkene **41**. **Problem 15.5:** Comment on the stereoselectivity in this synthesis.

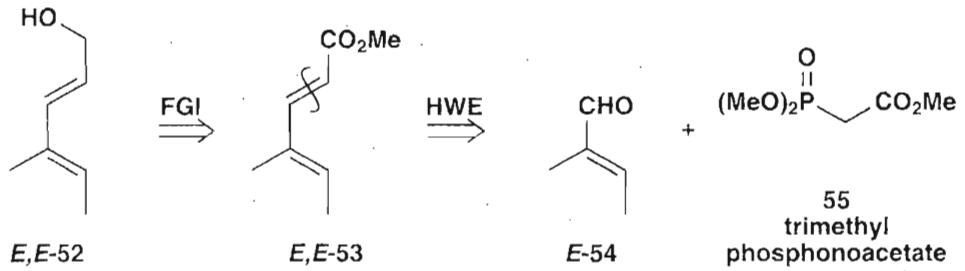


Answer 15.5: Some good, some bad. The stereochemistry of the alkene in **40** is very well controlled by the *Z*-selective Wittig reaction with the unstabilised ylid **20** but the diastereoselectivity does not look so good. In fact with $LiAlH_4$ it is non-existent: This problem was solved by the more selective reagent $Zn(BH_4)_2$ as explained in *Strategy and Control*.

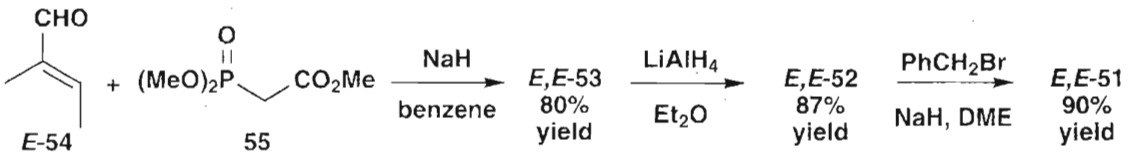
We promised in chapter 17 of the textbook to reveal the synthesis of the diene *E*,*E*-**51** used in Weinreb's synthesis of the cytochalasins.[9] Disconnection of the benzyl ether reveals the true TM: the diene alcohol *E*,*E*-**52**. **Problem 15.6:** Suggest a synthesis of *E*,*E*-**52**.



Answer 15.6: There are obviously many good answers so we just give the published method. Weinreb chose to change the alcohol into an ester **53** and use a HWE reaction to make the conjugated alkene. The required aldehyde **54** could be made by aldol chemistry but this is not necessary as it is available 'tiglic' aldehyde.



The synthesis is straightforward and every step is high yielding. Reduction with $LiAlH_4$ ensures no conjugate reduction occurs.[10]



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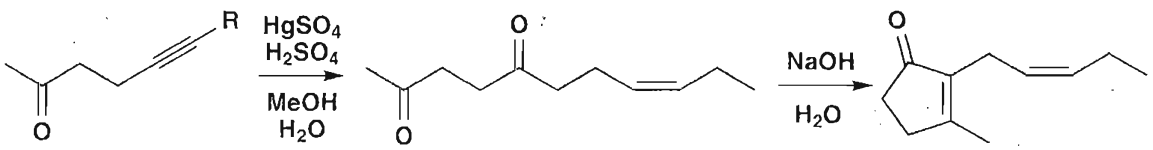
16 Strategy VII: Use of Acetylenes (Alkynes)

Examples from the Textbook Chapter

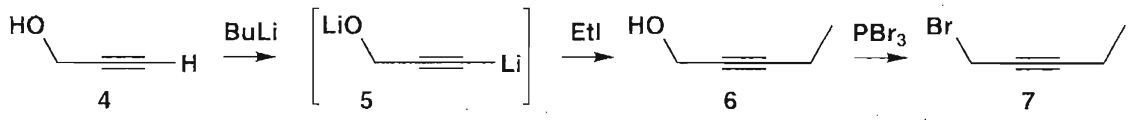
The Synthesis of cis-Jasmone

We discussed at length in the textbook chapter a synthesis of *cis*-jasmone **3** from an acetylene **1** by regioselective hydration to give **2** and cyclisation in base.[1] In fact acetylenes have been used in other ways to make *cis*-jasmone **3**.



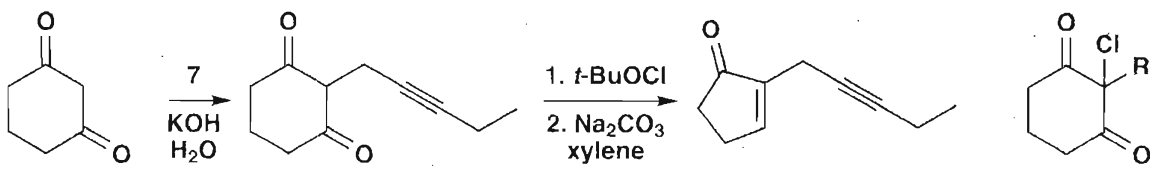
1 2 3; 75% yield from 1

We also described in the textbook the synthesis of the propargyl bromide **7** by standard acetylene chemistry. This compound can obviously be used to make the *cis*-allylic bromide by Lindlar reduction for use in a synthesis of *cis*-jasmone **3**.



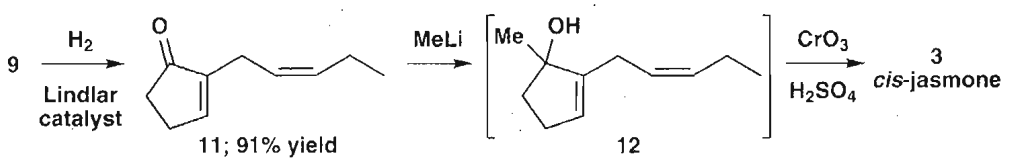
4 5 6 7

But the bromide **7** can also be used with the idea of doing the hydrogenation after the skeleton is assembled. In one ingenious synthesis,[2] cyclohexan-1,3-dione (that exists as an enol) is alkylated with **7** to give **8**. So far, so good but now chlorination to give **10** (not isolated) and reaction with sodium carbonate causes a ring contraction by the Favorskii rearrangement[3] to give the cyclopentenone **9** which looks a lot more like jasmone.

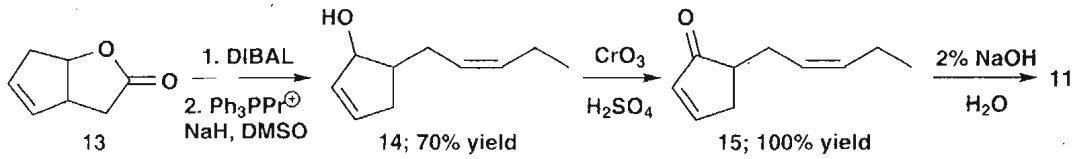


cyclohexan-1,3-dione 8; 82.5% yield 9; 74% yield 10

Hydrogenation put in the *cis* alkene **11** and all that remains is the addition of a methyl group. MeLi adds to the carbonyl group and then oxidation gives *cis*-jasmone.

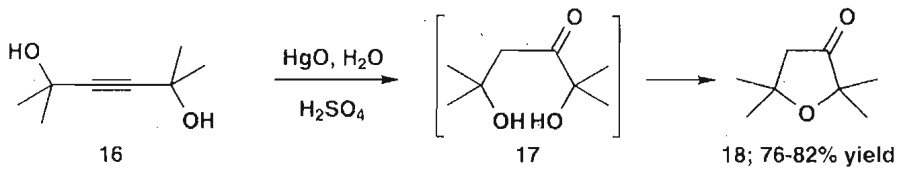


The same oxidation trick was needed in Grieco's Wittig-based synthesis[4] from the bicyclic lactone **13**. Reduction with DIBAL gives the hemiacetal that reacts with the ylid from triphenylpropylphosphonium bromide to give the Z-alkene **14**. Oxidation to the ketone **15** and equilibration with weak base via a sequence of enols gives **11**.

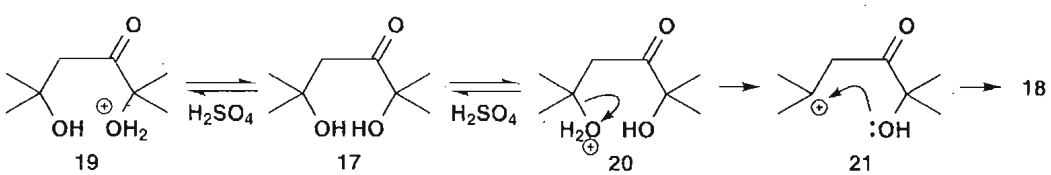


Synthesis of a Cyclic Ketone by Hydration of an Acetylene

We said, in the textbook chapter, 'Symmetrical acetylenes can also be hydrated to one ketone as the two possibilities are the same. An intriguing example is the hydration[5] of the diol **16** that presumably gives the ketone **17**. This is not isolated as, under the conditions of the reaction, formation of the cyclic ether **18** is faster than the hydration.' **Problem 16.1:** Suggest a mechanism for the cyclisation of **17** under the reaction conditions.



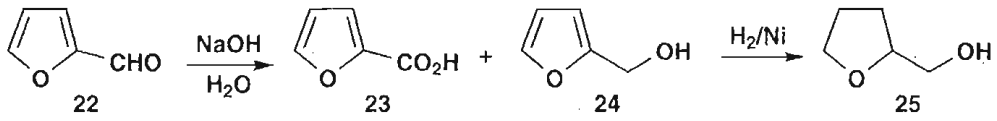
Answer 16.1: Either of the OH groups in **17** could be protonated to give **19** or **20**. But **19** will not lose a molecule of water as the resulting cation would be destabilised by the carbonyl group. Cation **21**, formed by loss of the other OH group **20**, is a stable *t*-alkyl cation and can cyclise readily to **18**.



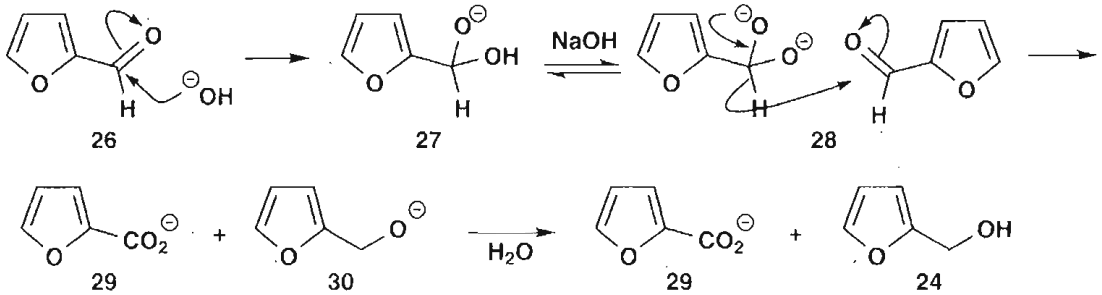
An Interesting Mechanism and a Useful Separation

Reactions that give a 50:50 mixture of two products are not usually highly valued. Yet the example we gave in the textbook chapter quotes 'Treatment of furfural with aqueous NaOH

disproportionates[6] the aldehyde **22** into equal amounts of the acid **23** and the alcohol **24**.' This route was used to make **25** and, eventually, an acetylene. **Problem 16.2:** Suggest a mechanism for the reaction of **22** with NaOH. Why is a reaction that gives a 50:50 mixture of products acceptable in this case?



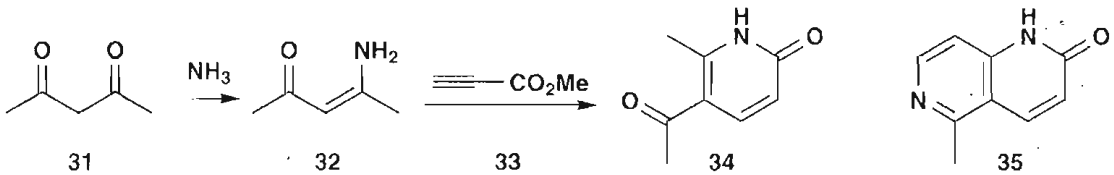
Answer 16.2: This is the Cannizzaro reaction.[7] It involves a hydride transfer from the dianion **28** giving, initially, the carboxylate anion **29** and the alkoxide **30**. Under the reaction conditions, the products are **29** and **24**.



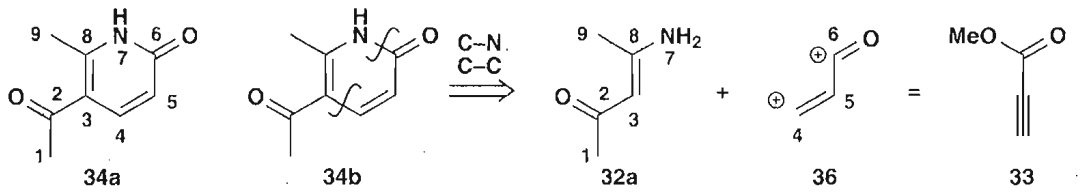
This mixture is very significant as the carboxylate anion **29** is soluble in water while the alcohol **24** is soluble in organic solvents. Extraction with ether removes the alcohol **24** and acidification of the aqueous solution precipitates the crystalline acid **23** and the separation is thus very easy. So, as the starting material, furfuraldehyde **22**, is exceptionally cheap, this method is acceptable.

Electrophilic Acetylenes

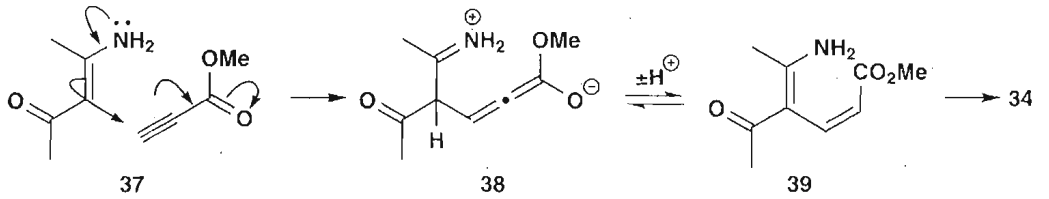
As is the case with alkenes, alkynes conjugated with carbonyl groups are electrophilic. One such compound **33** is used in the manufacture[8] of the cardiotonic medorinone **35**. The stable enamine **32** reacts with **33** to give the pyridone **34**. **Problem 16.3:** Draw a mechanism for the formation of **34** and identify the synthon(s) represented by **33**. *Hint*: You may find it helpful to number the atoms in **34** arbitrarily and work out where they come from in **32** and **33**.



Answer 16.3: We have arbitrarily chosen to number the atoms **34a** but any method will do. It is clear that the enamine with its two methyl groups must supply atoms C-1 to C-9 and the nitrogen atom tells us which way round it goes. So the synthon must be doubly electrophilic: at C-6 to acylate the nitrogen and at C-4 to make the new C–C bond. Both these atoms are naturally electrophilic in **33**.



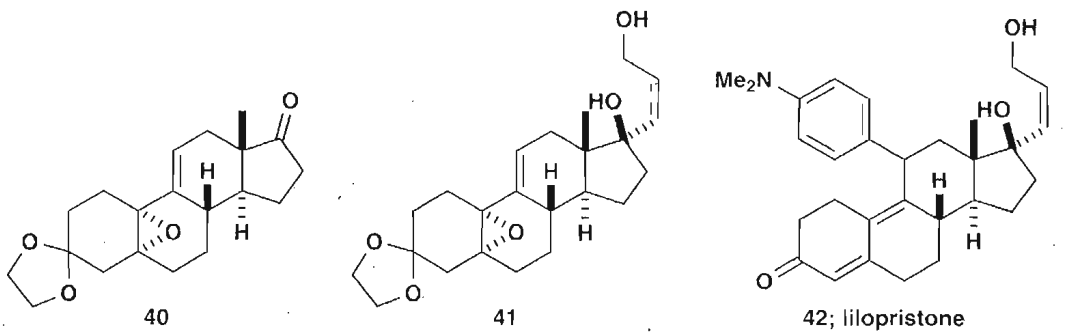
We don't know which bond is formed first so we shall arbitrarily go for the C–C bond. The nucleophilic enamine does conjugate addition to the electrophilic alkyne **37** and a proton exchange gives **39**. Amide formation between the amine and the ester gives the product **34**. If you had formed the amide first, you would have followed with the conjugate addition, and the reverse order is equally acceptable.



Whichever way you did the reaction, the second step, being a cyclisation, is an easy reaction. This is just as well as there is a stereochemical problem. Compound **39** is drawn with two alkenes of the specific geometry necessary for the cyclisation. The enamine is a tetrasubstituted alkene and there is little to choose between the stability of the two isomers. But the conjugated ester will much prefer the *E*-isomer to the *Z*-isomer **39**. The cyclisation happens because cyclisation of **39** is very fast, because the product **34** is aromatic (4π electrons from the two alkenes and the lone pair on N) and because rotation of conjugated alkenes is easier than that of simple alkenes.

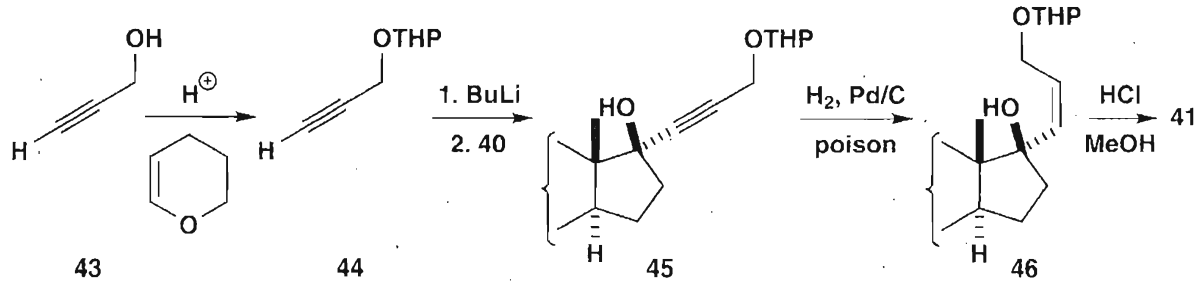
Alkynes in Synthesis

We have not featured steroids very much because they are such large structures but this chapter offers you the chance to try your hand at some steroid chemistry. The intermediate **41** is needed for the synthesis[9] of the Roussel UCLAF drug lilopristone **42** used in veterinary abortions. **Problem 16.4:** Suggest how the starting material **40** might be converted into the intermediate **41**.

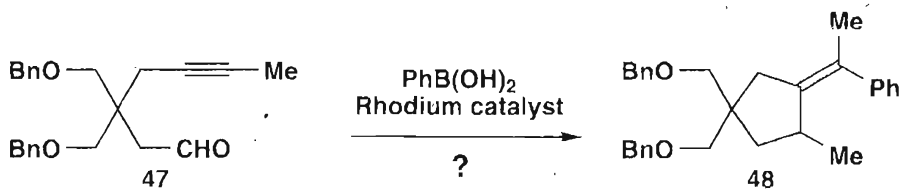


Answer 16.4: Addition of a functionalised acetylene to the ketone is the answer followed by reduction to give the *Z*-alkene **46**. Propargyl alcohol **43** was protected (chapter 9) as its THP derivative **44** and the acidic proton (explicitly drawn) removed with BuLi. Addition to the

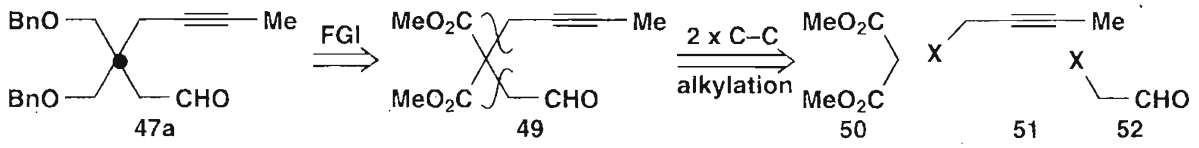
ketone **40** occurred from the bottom face opposite the axial methyl group to give **45**. Notice how we abbreviate the steroid by removing all the parts that do not react. Note that the lithiated alkyne prefers to add to the ketone rather than to the hindered epoxide. Now reduction and deprotection give **41**.



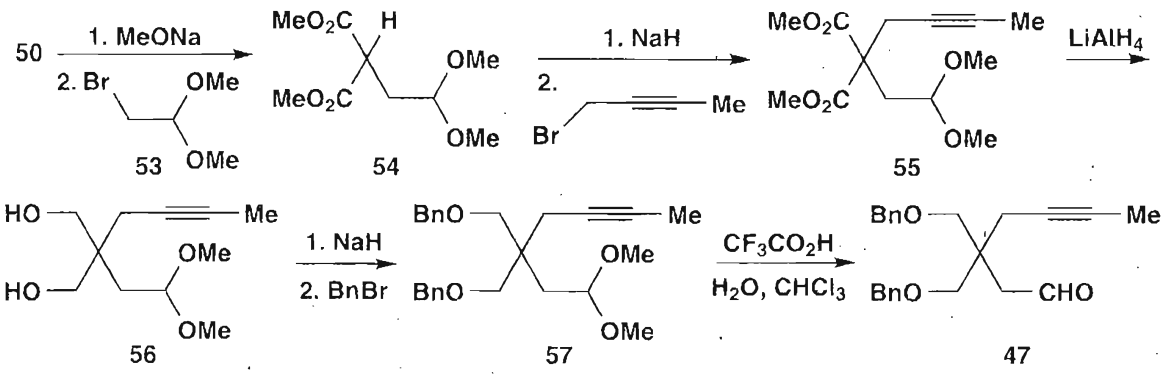
Alkynes may be needed to explore new reactions. Hayashi[10] needed compound **47** to investigate the possible Rh-catalysed cyclisation and arylation of an alkyne to give the cyclopentane **49**.
Problem 16.5: Suggest a synthesis of **47**.



Answer 16.5: The key to this problem lies in the quaternary centre (black blob in **47a**). No C–C bond can be disconnected easily in this structure but if we convert the two benzyl ethers into esters **49** the dialkylation of malonate **50** with **51** and **52** (X is a leaving group) looks very promising.



The aldehyde will have to be protected as we shall need to reduce the esters without reducing the aldehyde so the first alkylation was done with the acetal **53**. A second alkylation with propargyl bromide gave the complete skeleton **55** and it only remained to reduce, benzylate and deprotect **57** to give **47**.



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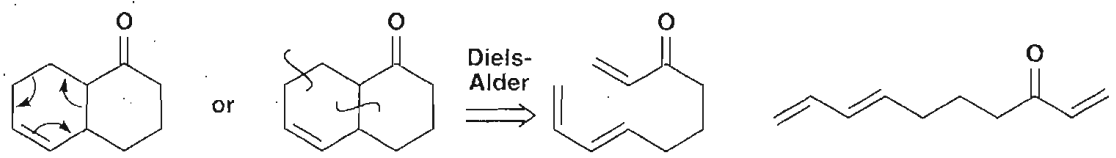
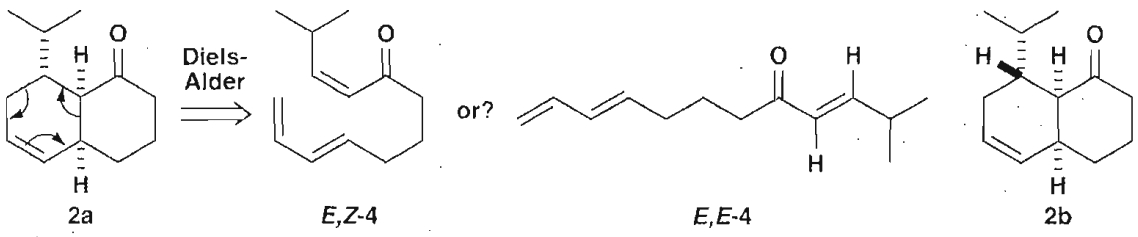
17 Two-Group C–C Disconnections I: Diels-Alder Reactions

Problem 17.1: What would be your starting materials for Diels-Alder reactions to make compounds **1** and **2**?

Answer 17.1: Compound **1** is shown without stereochemistry so only the disconnections **1b** are needed to reveal the starting material **3**. We suggested in the textbook that drawing the mechanism of the imaginary reverse reaction **3a** is the easiest way to find the disconnections, but either method gives **3** which is drawn more conventionally as **3a**.

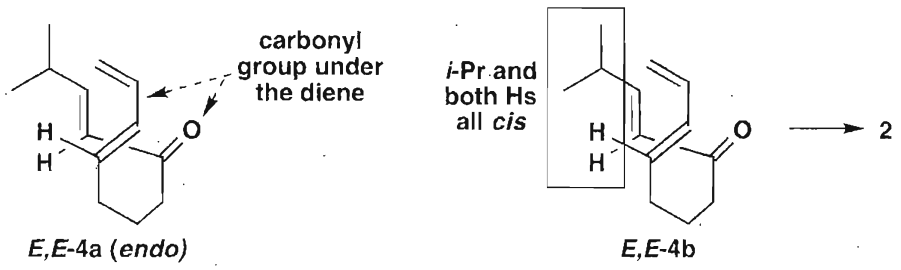


Compound **2** does have stereochemistry shown but the disconnections **2a** are the same. However, if we draw the starting material in the shape of **2** we have *E*,*Z*-**4** but we can see that this is wrong. The two marked Hs in *E*,*E*-**4** are *trans* to each other and this is also how they are in the product **2b**. The Diels-Alder reaction stereospecifically transfers the geometry of the dienophile into the stereochemistry of the product.

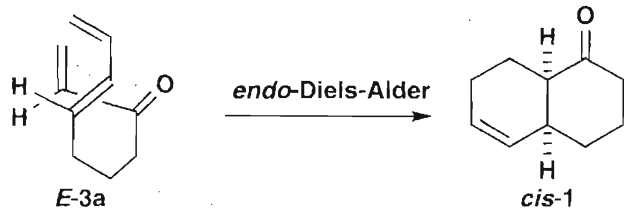


But what about the third centre? This is an *endo:exo* question and must be deduced from a 3D diagram. Our attempt is *E*,*E*-**4a** but, as long as your diagram reveals that the *i*-Pr and both

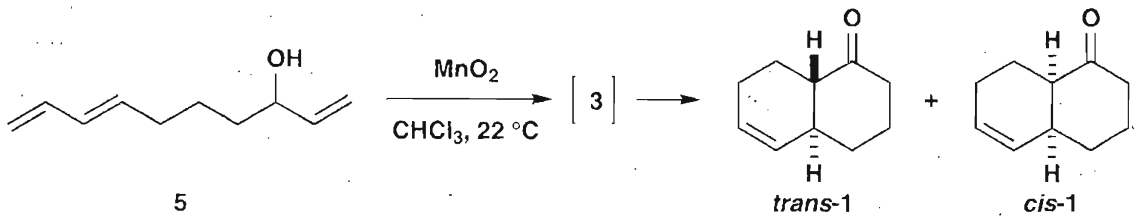
Hs are *cis* to each other, as in *E*,*E*-**4b**, you will discover that the *endo* transition state is required for the formation of **2**.



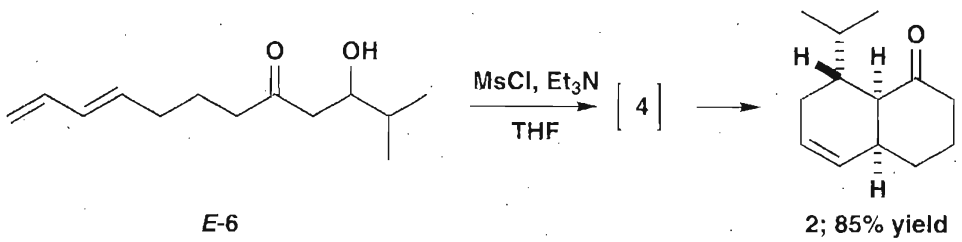
The same diagram, but without the *iso*-propyl group *E*-**3a**, gives the ring junction in **1** as *cis* also. We expect both ring junctions to be stereoselectively *cis* from the usual *endo*-selectivity. However, the attraction of the reagents by orbital interaction across space does not apply to intramolecular Diels-Alder reactions, and steric hindrance may lead to *exo*-selectivity. We need to do the experiments to discover what happens.



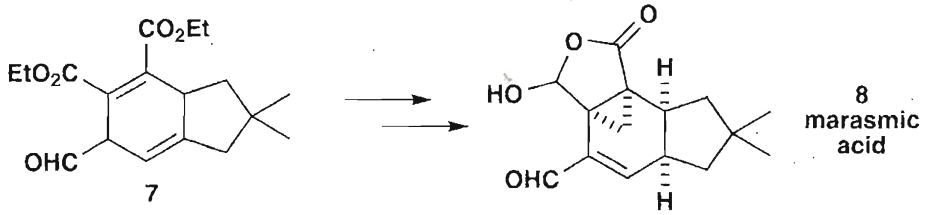
Fortunately the experiments have already been done.[1] Neither **3** nor **4** could be isolated as the intramolecular Diels-Alder reactions were so fast. The alcohol **5** was prepared and on oxidation with MnO_2 (a good reagent for oxidising allylic alcohols) in chloroform at 22 °C the adducts *cis*- and *trans*-**1** were formed directly. With ordinary MnO_2, the reaction needed 5 days and a 90:10 ratio of *trans*:*cis*-**1** resulted. But with activated MnO_2, only 4 hours were needed and a 5:95 ratio of *trans*:*cis*-**1** resulted.[2] The *trans* compound is more stable and is the thermodynamic product while the shorter reaction time gave the kinetically preferred *endo*-product *cis*-**1**.



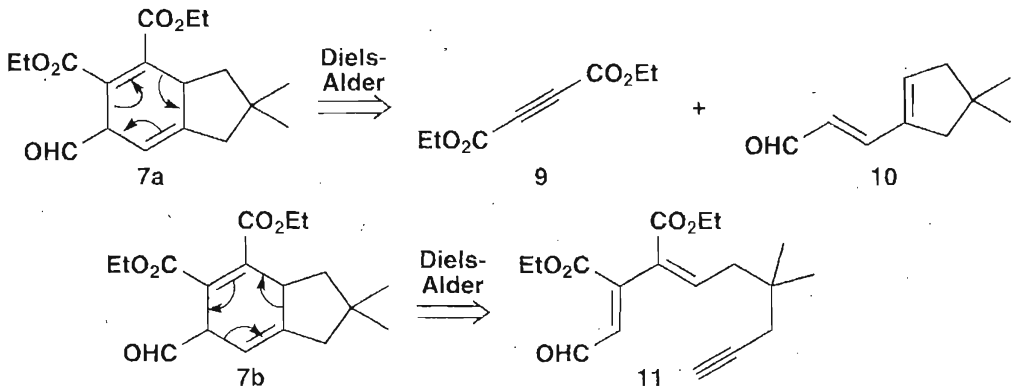
The precursor for **4** was the aldol product *E*-**6** (chapters 19 and 20) so elimination was necessary to give the enone **4**. Any method, such as MsCl and Et_3N, gave only the product **2** of the *endo*-selective Diels-Alder reaction.



Compound **7** was needed by Woodward[3] for his synthesis of marasmic acid **8**. **Problem 17.2:** How might **7** be made?

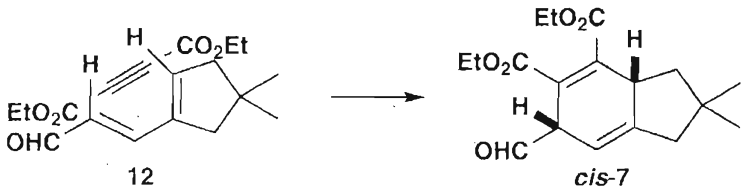


Answer 17.2: This target molecule has two alkenes in the six-membered ring so there are two Diels-Alder disconnections **7a** and **7b**. The first **7a** gives two simple starting materials **9** and **10** but the second **7b** gives one starting material **11** that looks difficult to make. Woodward preferred the first **7a** and we think you can see why. There is no regioselectivity problem as the dienophile is symmetrical.



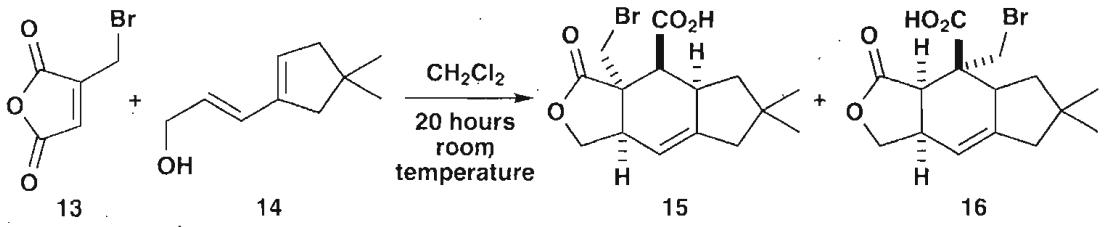
Problem 17.3: Assuming that *E*-**10** is used as the diene (as drawn), what will be the stereochemistry of the product **7**?

Answer 17.3: The dienophile is linear so there is no *endo/exo* question: the answer comes from the stereochemistry of the diene **10**. As the two marked Hs are on the same side as the molecules approach each other **12**, they are also on the same side in the product *cis*-**7**.

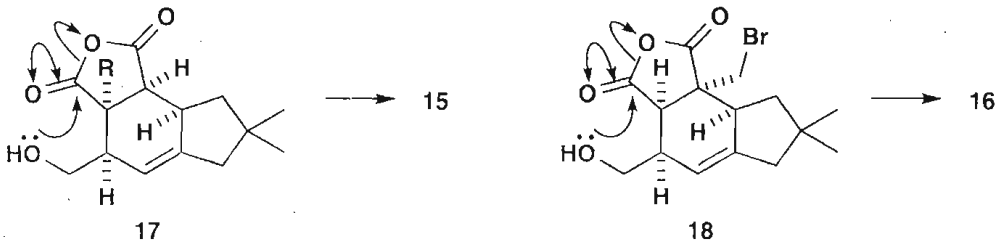


The Diels-Alder step was good but this synthesis as a whole was unsatisfactory as it proved difficult to add the three-membered ring needed for marasmic acid **8**. The final choice[4] for a satisfactory synthesis fell upon the less good Diels-Alder reaction between the substituted maleic anhydride **13** and the alcohol **14** from reduction of **10**. The two products were **15** and **16**.

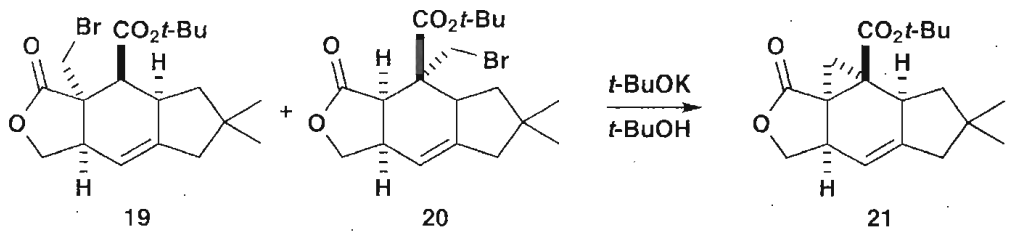
Problem 17.4: What was the structure of the initially formed Diels-Alder adducts? Comment on the selectivity.



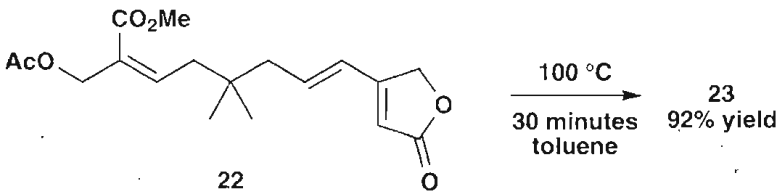
Answer 17.4: The most striking thing about these structures **15** and **16** is that both the anhydride and the OH group have disappeared. The appearance of a lactone suggests that the OH group has attacked one of the carbonyl groups of the anhydride. We can then argue backwards (a kind of mechanistic disconnection!) to the primary products of the Diels-Alder reaction **17** and **18**.



Now the stereoselectivity is perfect but the regioselectivity is not. Evidently the CH_2Br substituent on **13** is not enough to make a steric or electronic difference so both **17** and **18** are formed. Fortunately the *t*-butyl esters of both regio-isomers **19** and **20** cyclise in base to the same cyclopropane **21** in 44% overall yield from **14**. This begins to be recognisable as the core structure of marasmic acid **8**.

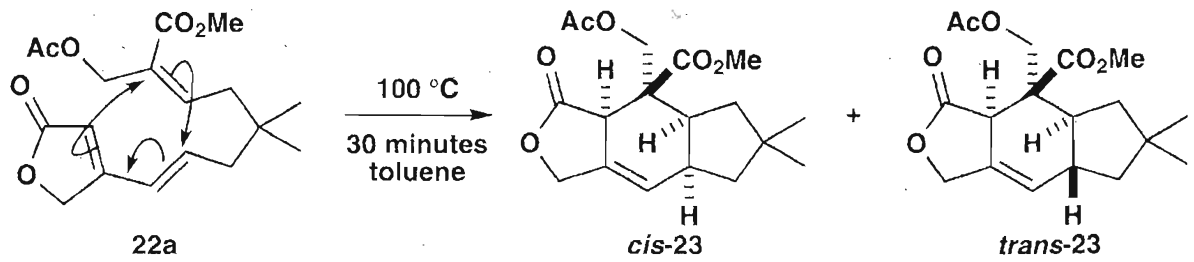


A third approach, based on an intramolecular Diels-Alder reaction, involved heating compound **22** at 100 °C for half an hour to give an excellent yield[5] of **23**. **Problem 17.5:** What is the structure of **23**?



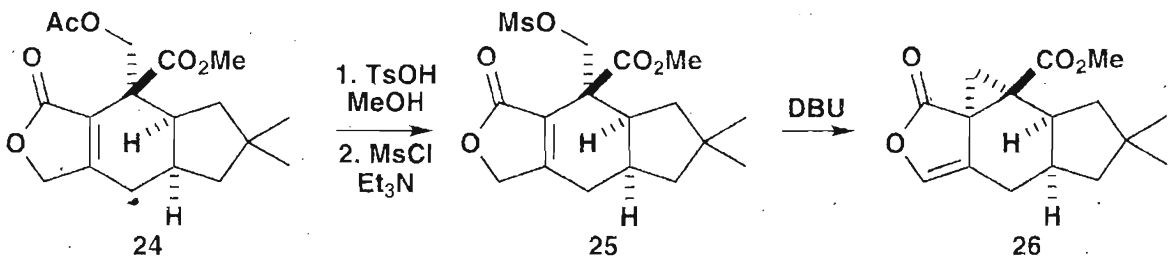
Answer 17.5: To discover the product, we need first to redraw the starting material in a conformation in which it can cyclise so that we can draw the mechanism **22a**. The product **23** is well on the way to marasmic acid: just compare **23** with **20**. You should have drawn structure *cis*-**23** to show the *endo* product but in fact a mixture of *cis*- and *trans*-**23** was formed. Our

diagram **22a** shows the regioselectivity but you would have to draw it in the style of **12** to see the stereochemistry. We leave this to you. As this is an intramolecular reaction, the *endo* product *cis*-**23** is not necessarily formed. The diene is deactivated by the lactone so this Diels-Alder reaction is probably successful only because it is intramolecular.



22a *cis*-**23** *trans*-**23**

The next few stages are interesting: the alkene is brought into conjugation **24** with *t*-BuOK, the OAc group turned into a good leaving group (mesylate **25**) and the three-membered ring **26** formed with an amine base. This intermediate resembles **21** very closely.



24 **25** **26**

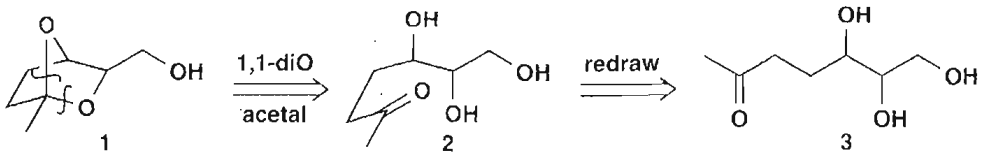
These three syntheses of marasmic acid illustrate an important aspect of the Diels-Alder reaction: its versatility. Here we have two inter- and one intramolecular reactions with rather different compounds, all leading to the same structure. This is one of the most important synthetic reactions at our disposal: all we need is a conjugated diene, an alkene, and a carbonyl group or two and we are in business.

References

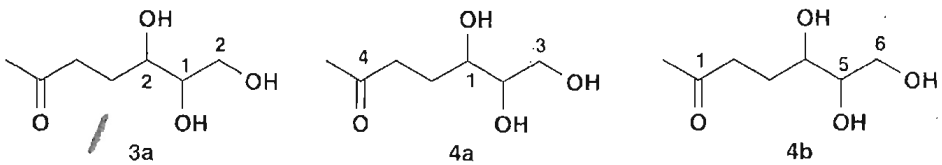
1. J.-L. Gras and M. Bertrand, *Tetrahedron Lett.*, 1979, 4549; D. F. Taber and B. P. Gunn, *J. Am. Chem. Soc.*, 1979, **101**, 3992.
2. A. J. Fatiadi, *Synthesis*, 1976, 65.
3. W. J. Greenlee and R. B. Woodward, *J. Am. Chem. Soc.*, 1976, **98**, 6075.
4. W. J. Greenlee and R. B. Woodward, *Tetrahedron*, 1980, **36**, 3367.
5. R. K. Boeckman and S. S. Ko, *J. Am. Chem. Soc.*, 1980, **102**, 7146.

18 Strategy VIII: Introduction to Carbonyl Condensations

In chapter 6 of this workbook, we analysed the synthesis of the bicyclic compound **1** and deduced that it might come from the open chain compound **3**. **Problem 18.1:** What relationships in the style presented in the textbook chapter 18, are present in this molecule?

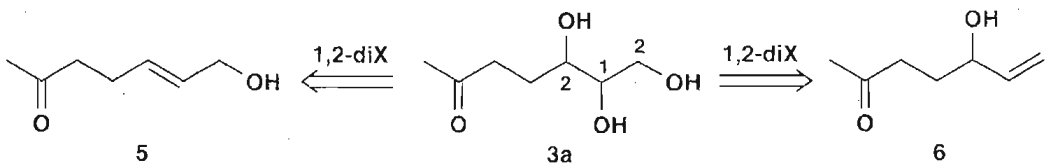


Answer 18.1: There are two obvious 1,2-diO relationships **3a**. There is a 1,3-diO and a 1,4-diO relationship from the same carbon atom **4a** and some more remote relationships from the ketone: a 1,5-diO and a 1,6-diO **4b**.

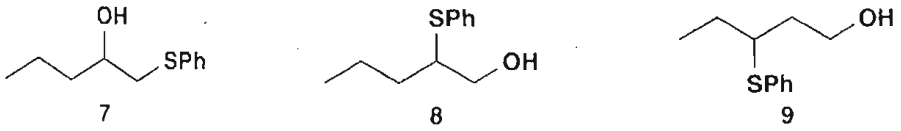


Problem 18.2: If we decided not to use a C–C disconnection to make either of the 1,2-diO relationships in **3a**, what other chemistry might we use instead?

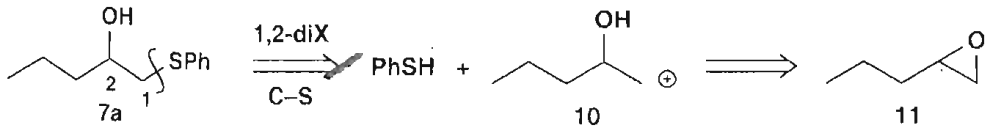
Answer 18.2: 1,2-Diols are easily made by dihydroxylation of alkenes or by epoxide formation followed by hydrolysis. Such disconnections on **3a** reveal two attractive starting materials **5** and **6**.



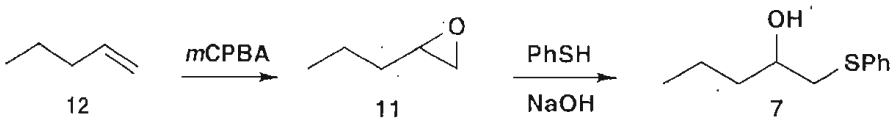
Synthon Revision: The synthons we used to make C–X bonds earlier in the book will now be needed for C–C bonds. **Problem 18.3:** Using C–S disconnections and drawing the synthons before choosing the reagents, suggest syntheses of these three isomeric compounds **7–9**.



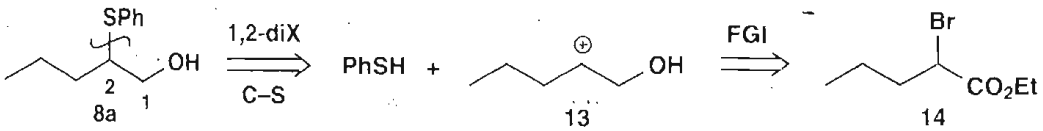
Answer 18.3: The routine is: (a) number the relationship, (b) choose the disconnection, (c) draw the synthons and (d) choose the reagents. With our first compound **7** this is easy: the 1,2-diX relationship disconnects **7a** to the synthon **10** and the obvious reagent is the epoxide **11**. As your experience grows, you may choose to omit stage (c).



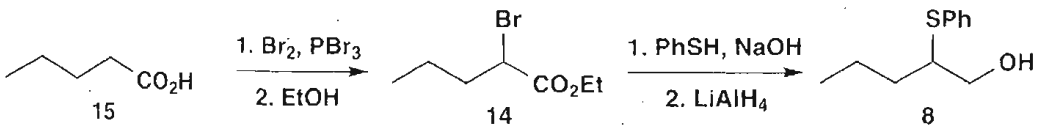
So the synthesis is to make the epoxide **11** and treat it with PhSH in basic solution so that the nucleophile is PhS^-.



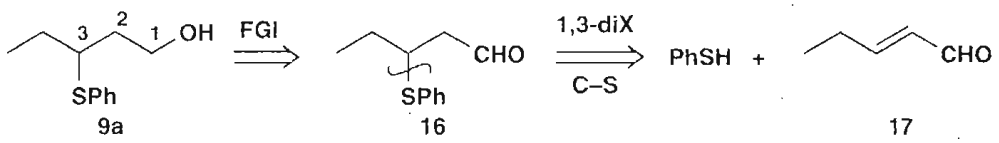
The second compound **8** also has a 1,2-diX relationship **8a** but we cannot make it from an epoxide as the regioselectivity is wrong. Instead we must change the oxidation level and use the bromoester as the electrophile. We prefer not to use the over-reactive bromoaldehydes.



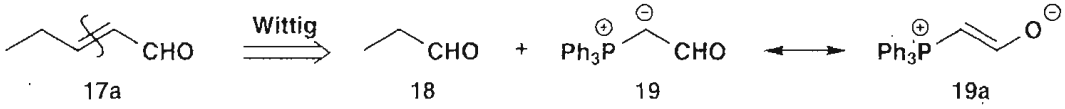
The synthesis involves making the α-bromoester **14** from the acid **15**, reacting it with the thiol, and reducing the ester with $LiAlH_4$.



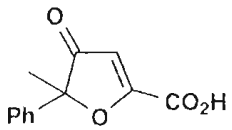
The third example **9** has a 1,3-diX relationship so we know at once that we need a carbonyl group for the conjugate addition (chapter 6). We hope very much that you did not disconnect **16** to a bromo compound: if you did, you should read chapter 6 in the textbook again. This time we can use an aldehyde as α,β-unsaturated aldehydes are easy to make and sulfur is very good at conjugate addition. Shortly in chapters 19 and 20 we shall see how to make compounds like **17** using the aldol reaction. But you have already met a method for making such alkenes. **Problem 18.4:** Suggest a suitable route.



Answer 18.4: The obvious route is a Wittig reaction (chapter 15) and this compound is an ideal Wittig product as the stabilised ylid **19** is available and would react well with the aldehyde **18** giving only *E*-**17**. This ylid **19** may look like a reagent that would destroy itself but drawing it as the enolate **19a** should show you that it is very stable. In chapter 20 you will discover that reactions of stabilised ylids with aldehydes are formally examples of the aldol reaction.

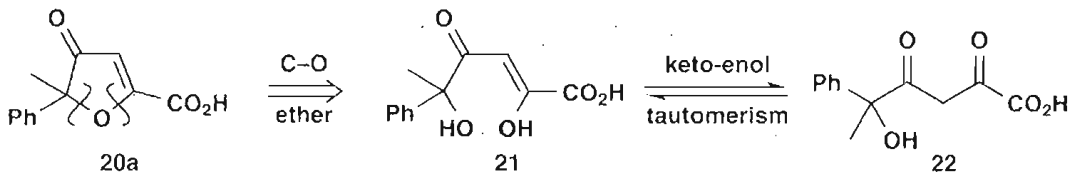


Looking for C–C disconnections by counting relationships between functionalised carbon atoms may have to wait until structural C–X bonds are disconnected. An example is the drug acifran **20**. **Problem 18.5:** Disconnect any structural C–X bonds to expose the carbon skeleton of acifran and state what relationships are present.

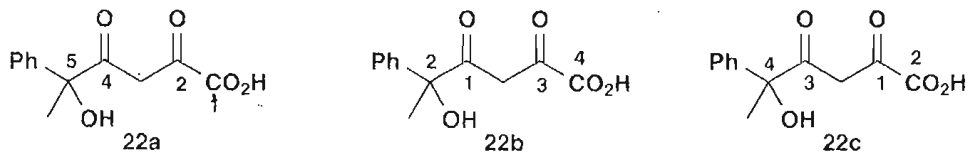


20
acifran
a lipid-lowering drug

Answer 18.5: Disconnecting the ether **20a** and writing the diol **21**, as recommended in chapter 4 of the textbook, reveals the carbon skeleton but **21** is an enol and tautomerises to the ketone **22**. So we need to look at the relationships in **22**.

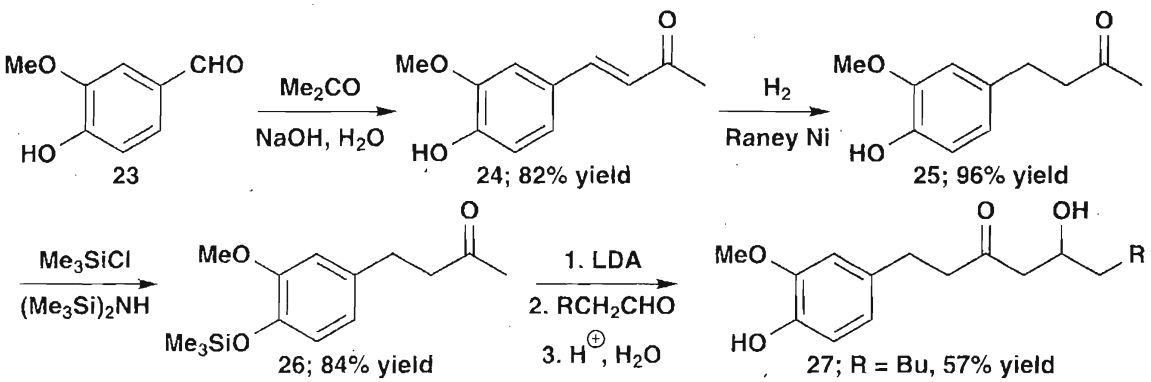


Starting at either end we have 1,2-, 1,4- and 1,5-diCO relationships **22a**. Looking at either ketone we can see 1,2-, 1,3- and 1,4-diCO relationships **22b** and **22c**. It is not obvious which of these will be helpful and in theory we could analyse all of them. But in chapter 23 you will find that the most helpful are the 1,3-diCO relationship between the two ketones and the 1,2-diCO relationship between the alcohol and its neighbouring ketone.

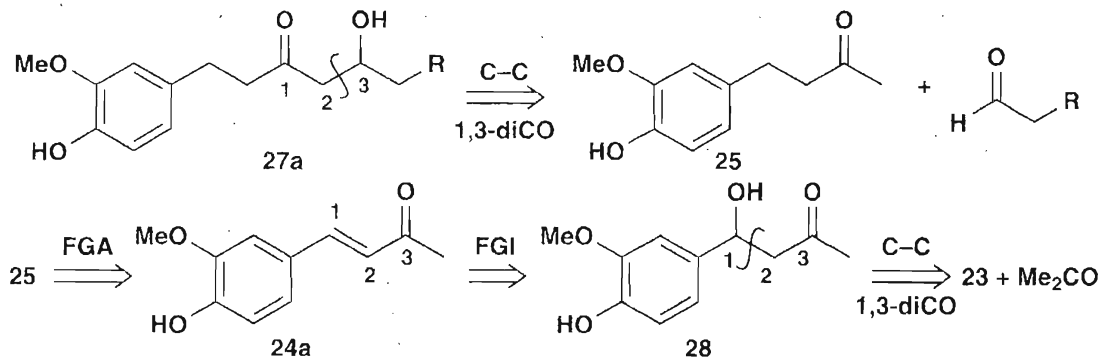


Now a rather different kind of exercise. The gingerols, the flavouring compounds in ginger, have the general structure **27** where R can be a number of different saturated linear alkyl chains. One synthesis[1] of gingerol is given in outline below. **Problem 18.6:** Without worrying about the

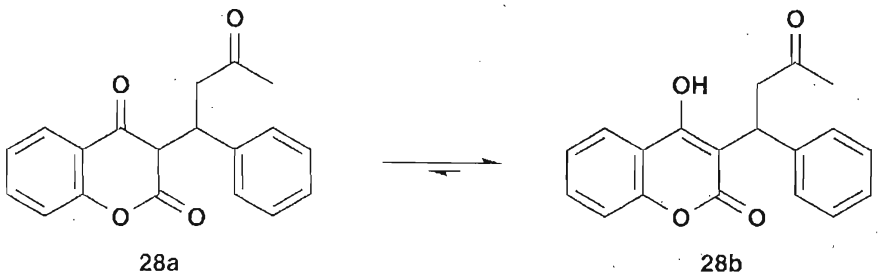
details of the chemistry, draw the disconnections and mark the 1,n-diCO relationships that are involved. There may be FGAs and FGIs as well.



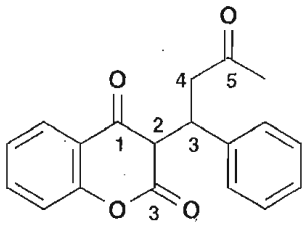
Answer 18.6: The first disconnection **27a** uses the obvious 1,3-diCO relationship and corresponds to the aldol reaction. Before we can do the next disconnection, we need to add the alkene by FGA **24a** and change the alkene into an OH so that we can use a second disconnection of the same kind **28**. If you drew this disconnection on **24** than you have done well as we recommend just that in chapter 20 of the textbook where you will meet this synthesis in detail. Notice that we have not put in the Me_3Si protecting group **26** in the analysis. The need for that would be discovered during the synthesis.



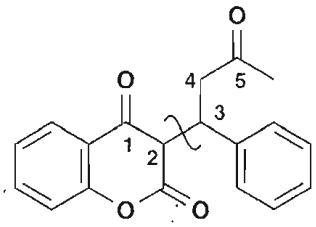
The exercises in this chapter aim to prepare you for the very important chapters ahead and we finish with one more having something in common with gingerol but with a significant difference. The widely used rat poison warfarin is a mixture of keto **28a** and enol **28b** forms. The enol predominates. **Problem 18.7:** Why does the enol form predominate? Using the keto form **28a**, identify the 1,n-diCO relationships. Which C–C bond would we like to disconnect most to achieve the greatest simplification?



Answer 18.7: The enol form **28b** is more stable because the heterocyclic ring is aromatic: it has 4π electrons from the two double bonds and 2π electrons from a lone pair on oxygen. There is a 1,3-diCO relationship between the two carbonyl groups in the ring and 1,5-diCO relationships between each of those carbonyls and the one on the side chain **28c**. The C–C bond we should most like to disconnect is the one joining the ring to the side chain as it is in the middle of the molecule and between two branchpoints **28d**. This means we want to use the 1,5-diCO relationship.

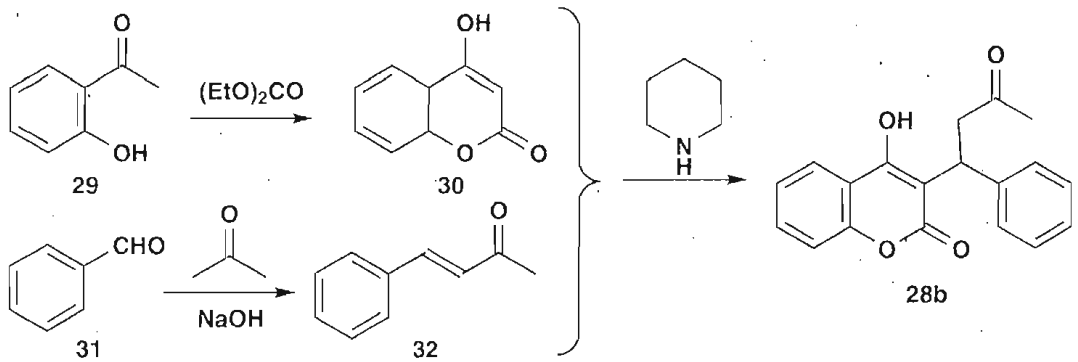


28c

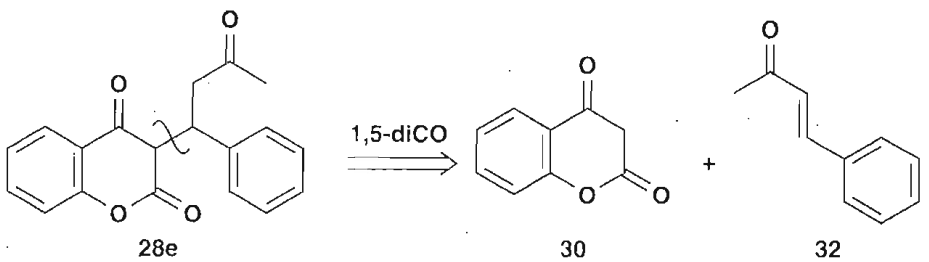


28d

Problem 18.8: Now that you have analysed the problem, you can look at the synthesis[2] and draw the corresponding disconnections. You should find that one of them is as shown in **28d**.

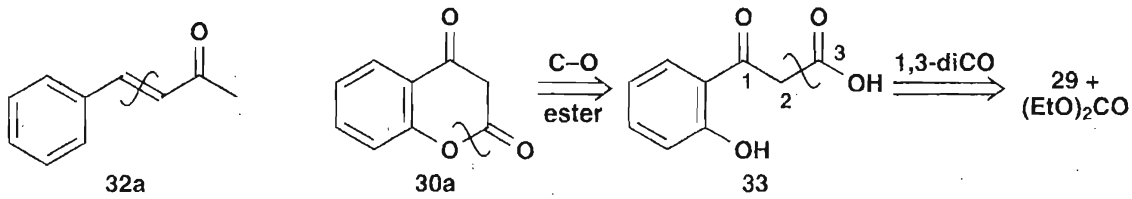


Answer 18.8: We can indeed make the key disconnection the first one **28e** as conjugate addition is required. This idea is developed in chapter 21. Note that the geometry of the alkene in **32** doesn't matter as it disappears in the conjugate addition.



Each of these compounds needs further disconnection: compound **32** is very similar to **24** and this time we shall disconnect without bothering to add the OH group. The starting materials are again ArCHO and acetone. Compound **30** is best approached by opening the ester first

30a to reveal a 1,3-diCO relationship and disconnection of the acid group leaves available ketone **29**.

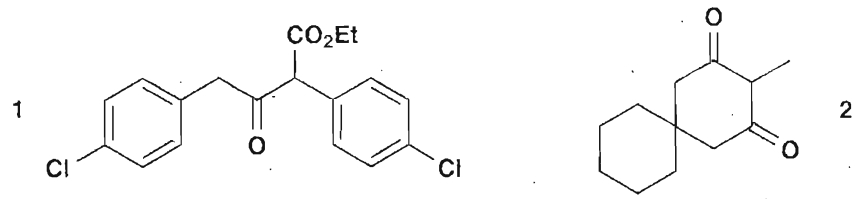


References

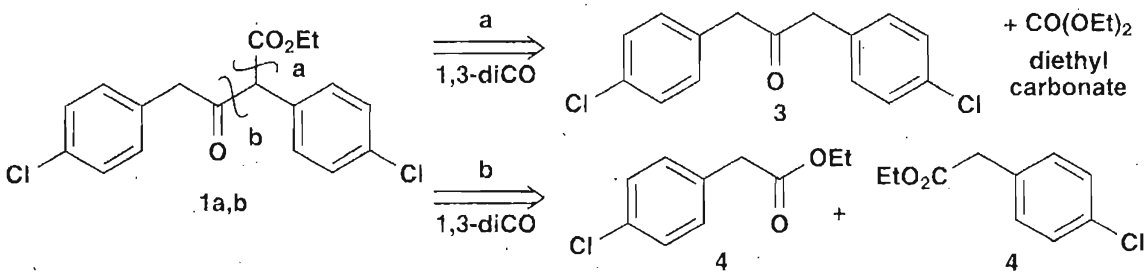
1. P. Deniff, I. Macleod and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1981, 82.
2. N. J. A. Gutteridge, *Chem. Soc. Rev.*, 1972, **1**, 381.

19 Two-Group C–C Disconnections II: 1,3-Difunctionalised Compounds

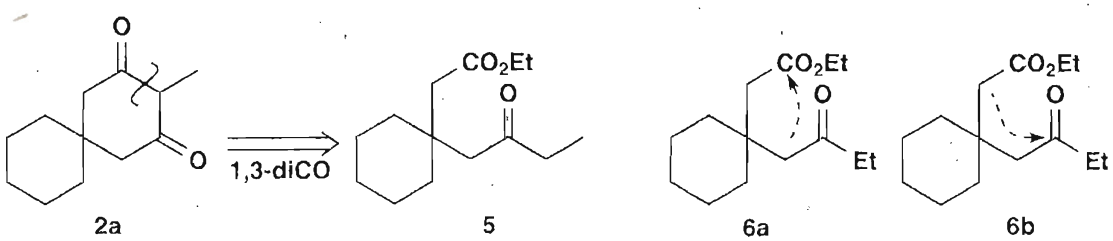
Do not despise these first three problems because of their simplicity. Skill at finding these disconnections is essential. **Problem 19.1:** Make disconnection(s) on these compounds and write the structures of the starting materials.



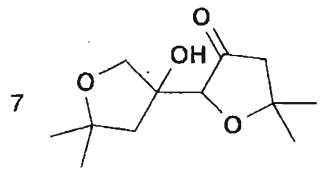
Answer 19.1: There are two 1,3-diCO disconnections for the keto-ester: **1a** and **1b**. The removal of one structural carbon atom **1a**, though it gives a symmetrical ketone **3**, is not so attractive as the disconnection in the centre of the molecule **1b** especially as this reveals two identical esters **4**. Condensation of **4** with base (*i*-PrMgBr was actually used) gives **1** in 93% yield.[1]



There is only one 1,3-diCO disconnection of symmetrical **2** revealing a new keto-ester **5**. It may appear that other cyclisations are possible but the alternatives shown by dotted arrows on **6a** and **6b** would give less stable four-membered rings. Treatment of **5** with NaOEt gives a quantitative yield[2] of **2**. Notice that there is one remaining proton between the two ketones in **2** so that the product will be formed as the stable enolate.



Now a slightly different combination of functional groups: **Problem 19.2:** again, make disconnection(s) on these molecules and draw the starting materials.



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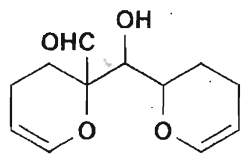
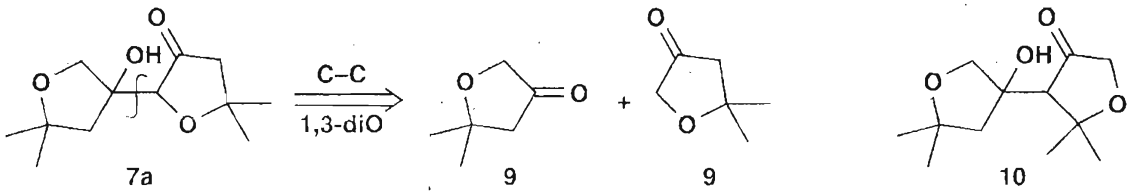


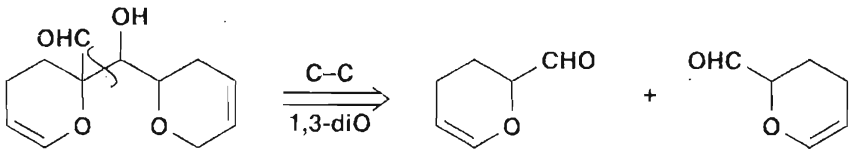
8

Answer 19.2: This time the target molecules are β-hydroxy carbonyl compounds rather than 1,3-dicarbonyl compounds, so the disconnection must be next to the hydroxyl groups on the carbonyl side if we wish to use the aldol reaction. This disconnection **7a** on **7** gives two molecules of the ketone **9**. The reaction of **9** with potassium in ether gives[3] only 50% of **7** presumably because alternatives such as **10** are also formed.



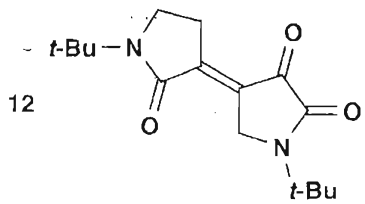
7a 9 9 10

Disconnection **8a** gives two molecules of the aldehyde **11**. Reaction of **11** with NaOH gives 76% of **8**. Here, as the starting material is an aldehyde, enolate formation can occur only in one place.[4]

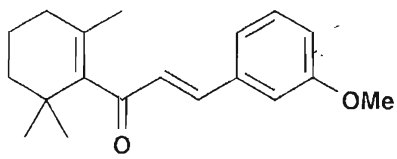


8a 11 11

The third type of target molecule made by simple carbonyl condensation is the α,β-unsaturated carbonyl compound. **Problem 19.3:** Disconnect **12** and **13** and draw the starting materials.

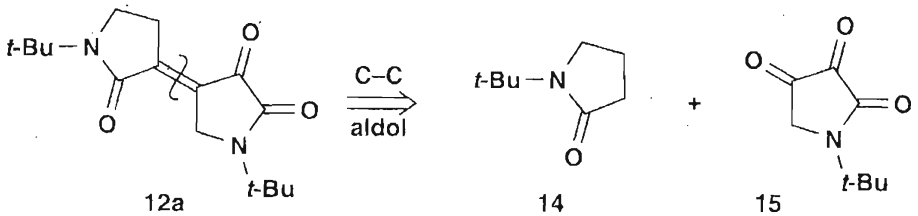


12



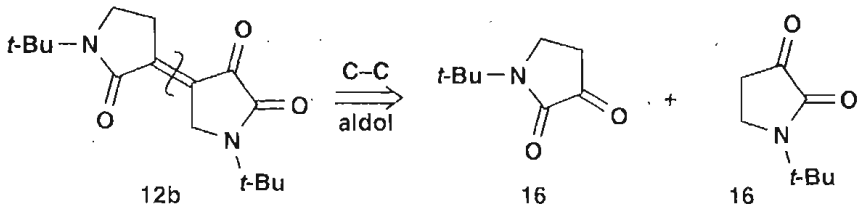
13

Answer 19.3: As there is only one alkene in **12**, that must be disconnected but there are two ways to do that. As the alkene is conjugated to a carbonyl group at both ends, either could be the carbonyl in the starting material. One possibility **12a** is the enolate from the simple amide **14** reacting with **15** as the electrophile. This is not very appealing as it would be difficult to make **15** and it is not obvious which ketone would be the electrophile.

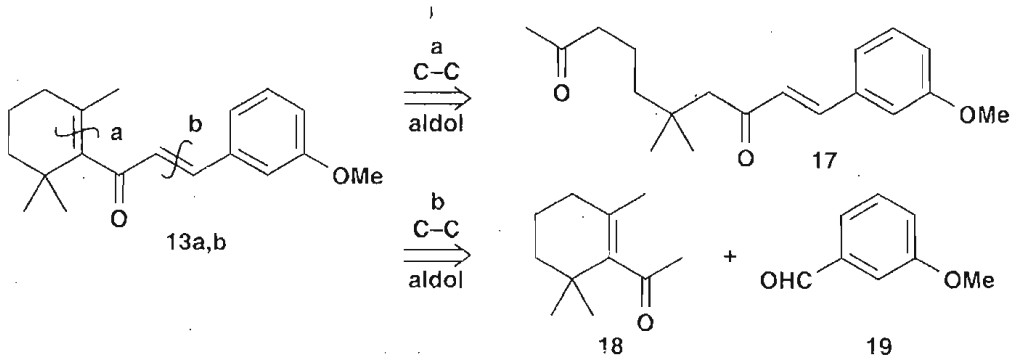


12a 14 15

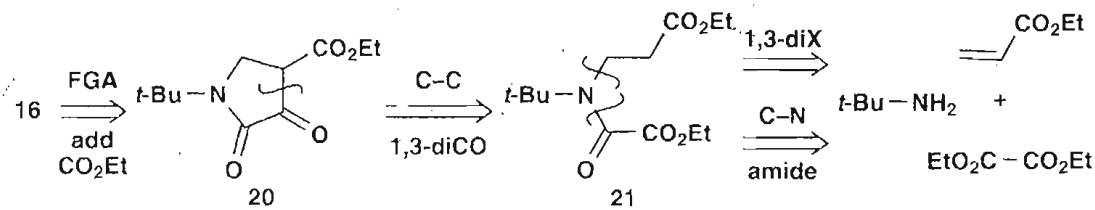
The other possibility **12b** is much better as the enolate provider and the electrophile are the same **16**. There is also no doubt that the ketone will be the electrophile rather than the amide. In fact[5] simply standing **16** in the fridge with catalytic pyridine gives 96% of **12**.



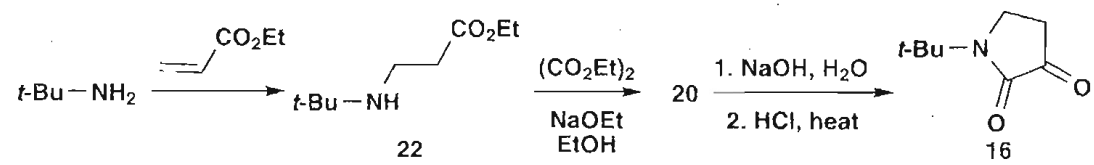
Compound **13** offers two different aldol disconnections as there are two alkenes each conjugated with the same ketone. One **13a** achieves little simplification and there is doubt as to which six-membered ring would be formed. The other **13b** splits the molecule more or less in half and reveals an available aromatic aldehyde **19** and a simply made enone. The aldehyde cannot enolise so there is no selectivity problem and heating a mixture of **18** and **19** in ethanol with KOH gave 60% of **13** used to make the natural product torreyol.[6]



One of the starting materials in the last problem **16** can also be made by 1,3-diCO chemistry. FGA of an ester group provides the 1,3-diCO relationship and disconnection **21** gives a simple amine, easily made from *t*-BuNH$_2$, ethyl acrylate and diethyl oxalate.

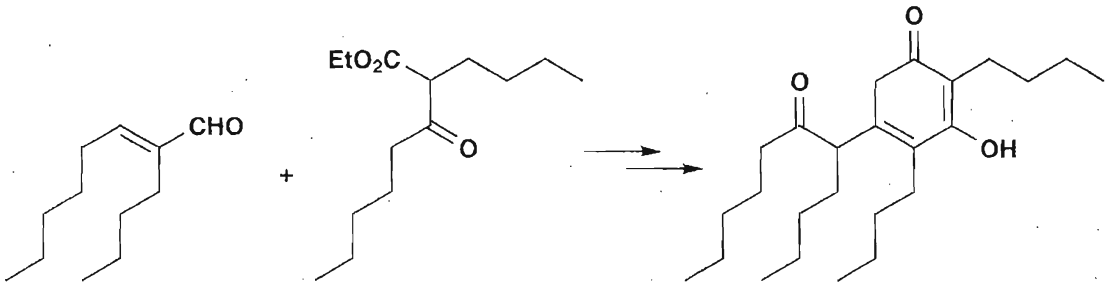


The published synthesis[5] adds the acrylate first to give **22** which is not isolated but treated with diethyl oxalate in base to give **20** directly. The cyclisation occurs under the conditions of the reaction. Hydrolysis and decarboxylation gives **16** in 57% overall yield from *t*-BuNH$_2$.



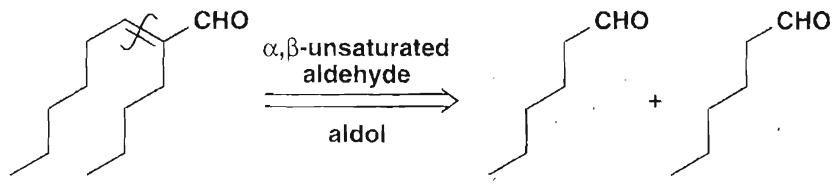
A Synthesis of the Enzyme Inhibitor Elasnin

Elasnin **25** has been synthesised[7] from starting materials **23** and **24**. It should be clear which parts of elasnin come from which starting material. But that is not your problem. **Problem 19.4**: Suggest syntheses of the two starting materials **23** and **24**.



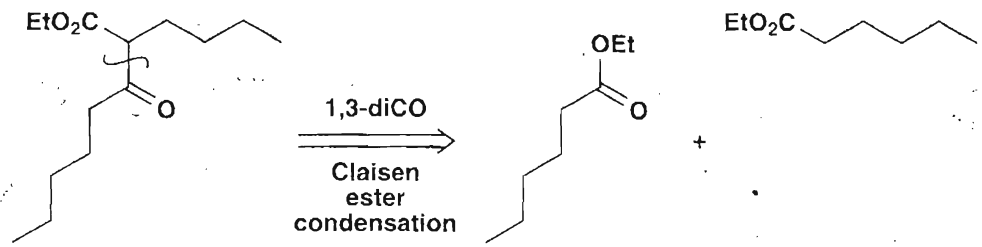
23 **24** **25; elasnin**

Answer 19.4: The enal **23** is a classic aldol product (an α,β-unsaturated carbonyl compound) and the aldol disconnection **23a** reveals that the starting materials are both hexanal **26**. Boric acid catalysed the condensation of **26** with itself and removal of water by distillation of xylene gives a 77% yield of **23**.



23a **26** **26**

The other starting material **24** is a 1,3-dicarbonyl compound and also ideal for aldol-style reaction except that we are using acylation. Disconnection **24a** reveals that we yet again have two identical starting materials: ethyl hexanoate **27**. Reaction of the ester **27** with NaH in THF gives a 90% yield of **24**. Sometimes syntheses turn out to be easier than expected. On other occasions . . .



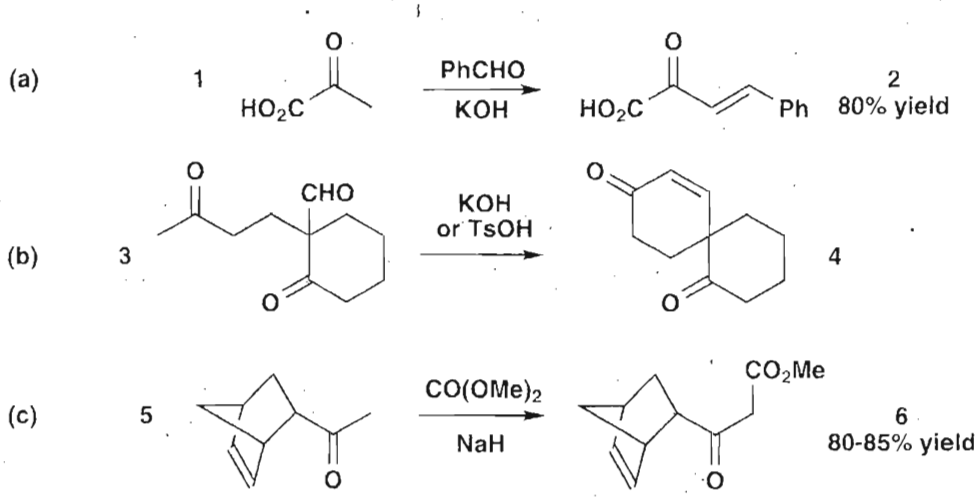
24a **27** **27**

References

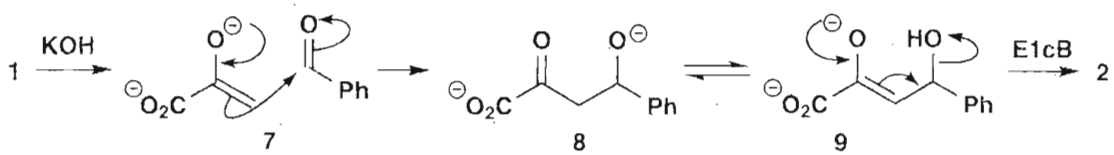
1. C. R. Hauser and B. E. Hudson, *Org. React.*, 1942, **1**, 266, see p. 291.
2. R. D. Desai, *J. Chem. Soc.*, 1932, 1079.
3. J. Colonge, R. Falcotet and R. Gaumont, *Bull. Soc. Chim. Fr.*, 1958, 211.
4. A. T. Nielsen and W. J. Houlihan, *Org. React.*, 1968, **16**, 1; see p. 88.
5. P. L. Southwick, E. P. Previc, J. Casanova and E. H. Carlson, *J. Org. Chem.*, 1956, **21**, 1087.
6. J. A. Barltrop and N. A. J. Rogers, *J. Chem. Soc.*, 1958, 2566.
7. J. R. Pfister, *Tetrahedron Lett.*, 1980, **21**, 1281.

20 Strategy IX: Control in Carbonyl Condensations

This chapter also starts with some apparently simple problems. Do not dismiss them as, at the least, they should confirm your understanding of the basic reasons for selectivity in carbonyl condensations. Remind yourself of the 'three questions' in the textbook chapter. **Problem 20.1:** Explain the formation of these products. In each case suggest an alternative product that might have been formed and explain why it isn't formed.

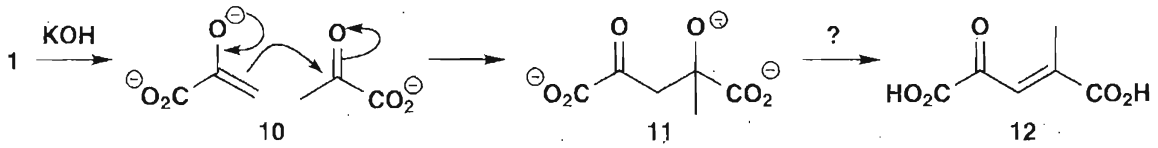


Answer 20.1: (a) Only the ketoacid **1** can form an enolate and it reacts with benzaldehyde as the electrophilic component **7** to give the dianion **8** in equilibrium with the new enolate that eliminates hydroxide by the E1cB mechanism **9** to give **2**.

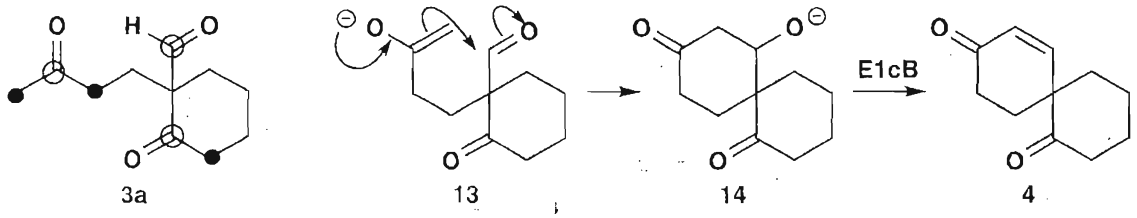


There is only one alternative product here: the self condensation of the ketoacid **10** to give, presumably, the enone **12**. So the only doubt is which of these two compounds **1** or PhCHO

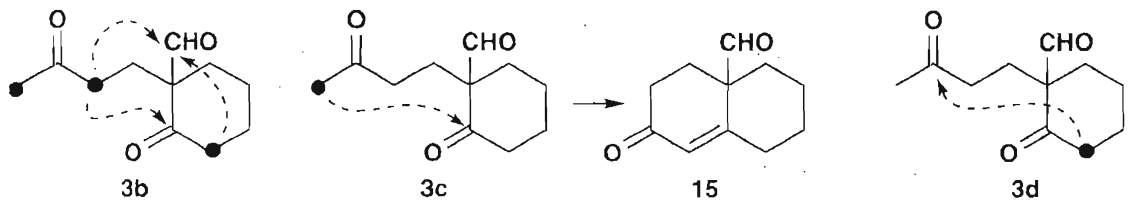
reacts as the electrophile. The aldehyde is the most electrophilic of the functional groups present. Furthermore the electrophile from **1** would *really* be the much less electrophilic anion of **1**.



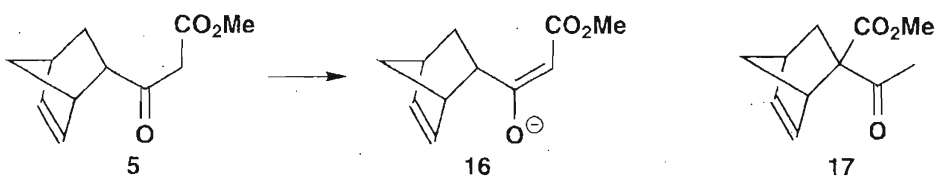
(b) There are three sites for enolisation (black blobs) and three electrophilic carbonyl groups (circles) **3a**. It is clear from the structure of the product **4** that the cyclisation must happen when the enolate on the methyl group attacks the aldehyde **13**.



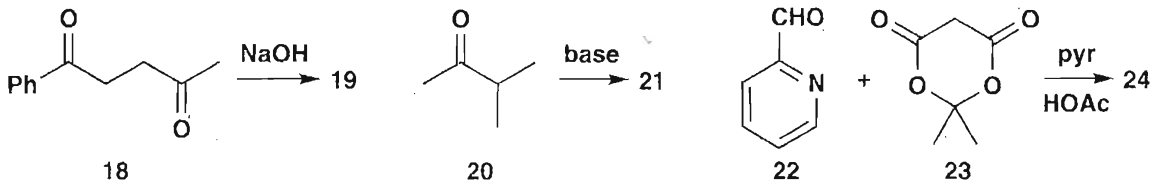
We can dismiss three of the alternatives **3b** immediately as they would form four-membered rings and under these equilibrating conditions such products would decompose back to starting material. Much the best alternative product **15** would be formed if the enolate on the methyl group attacked the ketone in the ring **3c**. We can deduce that the greater electrophilicity of the aldehyde makes **13** the better reaction. The final possibility **3d** would give a bridged compound that could not dehydrate and would revert to starting material. You might reasonably have drawn any of these alternative products. Note the control achieved[2] by an intramolecular reaction!



(c) This type of acylation was explained in the textbook: though there are two sites for enolate formation on the bicyclic ketone **5**, diethyl carbonate $CO(OEt)_2$ cannot be enolised. Reaction could occur at either site but compound **6** exists as the stable enolate **16** under the basic reaction conditions whereas the alternative **17** has no protons between the two carbonyl groups and will revert to starting materials. So both reactions may occur but the anion **16** is in a 'thermodynamic well'. It does not revert to starting materials as it would have to be protonated first and the reaction is in base. Self-condensation of **5** does not occur because carbonates are more electrophilic than ketones.[3]

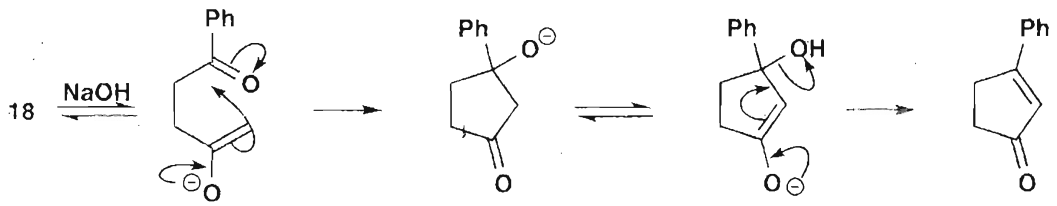


It is generally more difficult to predict products than to explain results but try your hand at these predictions using only the same principles. **Problem 20.2:** Suggest structures for the products of these reactions. In each case, one product is formed in high yield.



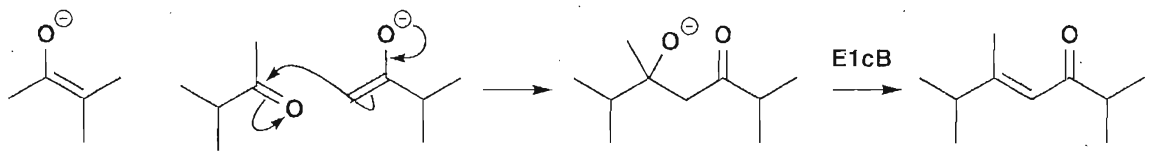
18 20 22 23

Answer 20.2: The first reaction is a cyclisation **25** to give the five-membered ring **26** as this will be faster than self-condensation of two molecules. The product[4] is the enone **19** from E1cB elimination **27** but if you drew the hydroxy-ketone from protonation of **26**, that is also an acceptable answer.



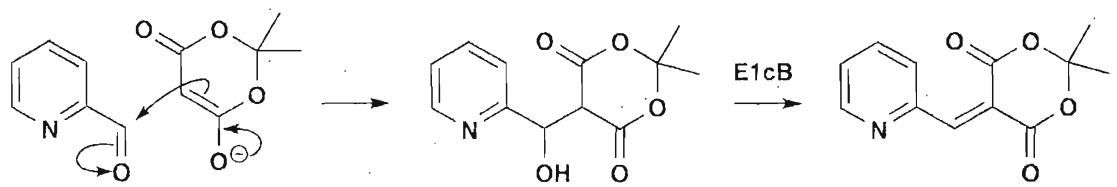
25 26 27 19

The reaction of **20** with base must be a self-condensation and the only question is which side of the ketone forms the enolate? Though enolate **28** is all right, it is condensation **29** of the less substituted enolate with **20** that leads to the product **21** as **30** can dehydrate to give a stable enone whereas the alternative adduct cannot.[1] Draw the structure of this alternative if you don't see why. Again this compound may form but it will revert to starting materials.



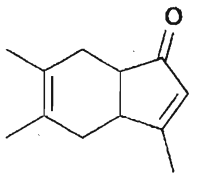
28 29 30 21

The cross-condensation of **22** and **23** is easy to explain if you answer the questions: which compound enolises? Only **23** can. Which compound is the electrophile? The aldehyde **22** is much more electrophilic than **23**. So we get[5] **24**. In fact **23** is a famous compound for forming stable enolates known as Meldrum's acid.



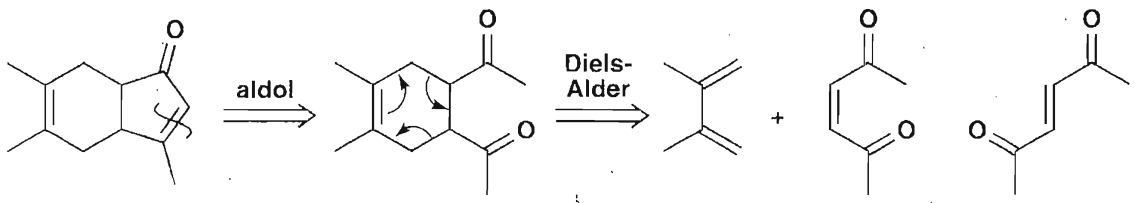
31 32 24, 76% yield

It's time for a straightforward synthesis question: **Problem 20.3:** Suggest a synthesis for target molecule **33**.



target molecule 33

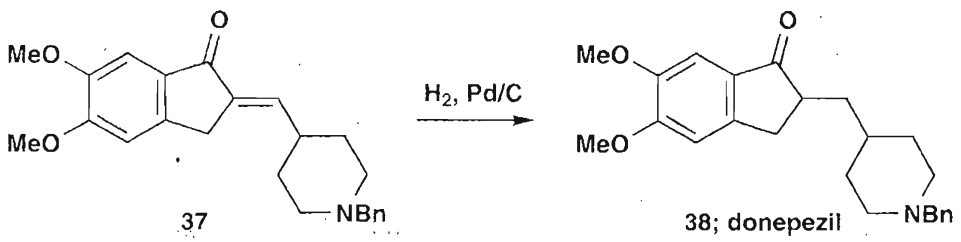
Answer 20.3: This compound has two alkenes but only one is conjugated with a carbonyl group so we must disconnect that one **33a** with an aldol reaction in mind. The intermediate we discover is an obvious Diels-Alder adduct of a diene **35** and an ene-dione **36**. Stereochemistry is not mentioned in the problem but it will be difficult to make *Z*-**36** and *E*-**36** was probably used. The compounds were made in just that way with the cyclisation of **34** to **33** being accomplished with NaOMe in methanol.[6]



33a 34 35 *Z*-36 *E*-36

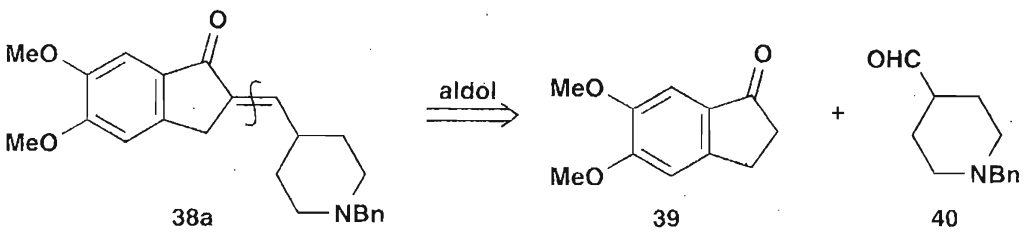
Three Examples

Three examples follow of the use of these methods in medicinal chemistry. The first is easy. **Problem 20.4:** Suggest a synthesis of an intermediate **37** in the synthesis of donepezil **38** a drug proposed for the treatment of Alzheimer's disease.[7]



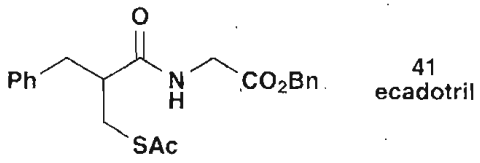
37 38; donepezil

Answer 20.4: The aldol disconnection is easy and in the middle of the molecule **38a** giving two much simpler starting materials **39** and **40**. We shall not follow this synthesis any further back but note that transformation of aldol products by many reactions widens the scope of the reaction greatly.



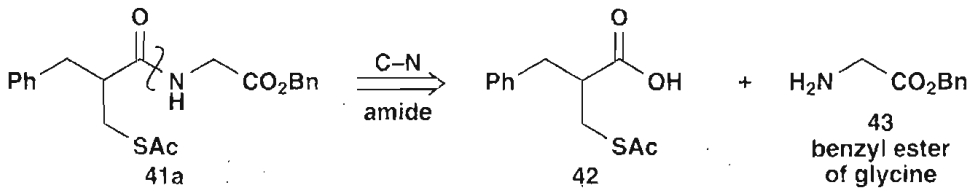
38a 39 40

In our second example conjugate addition is used after two aldol-style reactions, one a Mannich process and one a simpler aldol. **Problem 20.5:** With those hints to guide you, suggest a synthesis of ecadotril **41**, an ACE inhibitor used to control high blood pressure.[8]



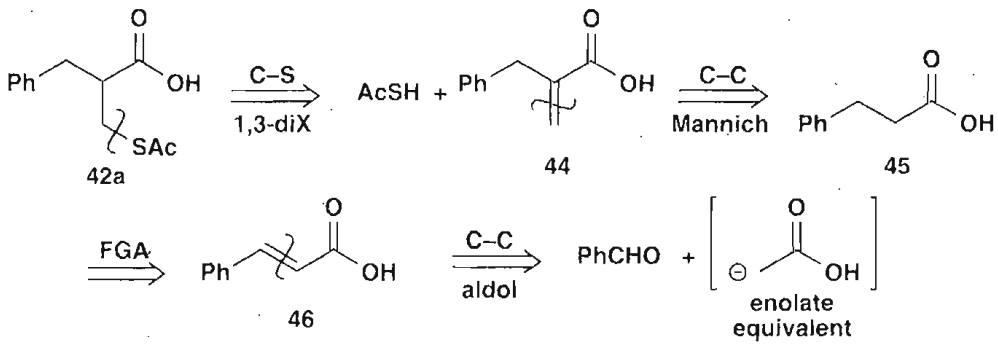
41
ecadotril

Answer 20.5: The obvious first disconnection is the structural C–N bond of the amide **41a**. The available benzyl ester of glycine **43** is revealed along with a carboxylic acid **42** that must be made. Any ideas?



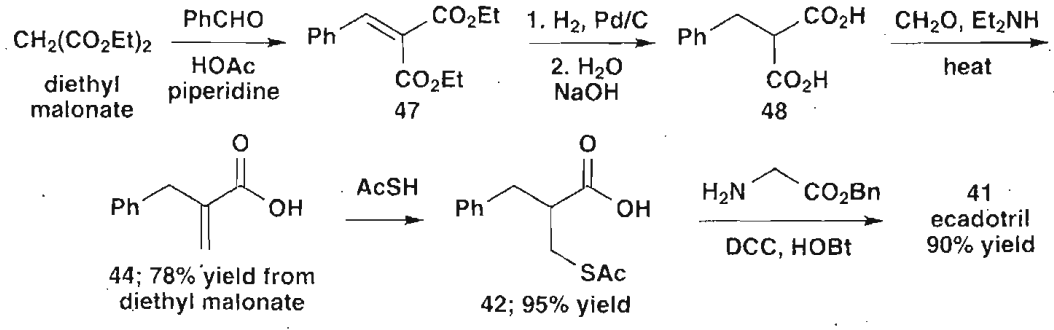
41a 42 43 benzyl ester of glycine

With the hint in the question that conjugate addition might be involved, the C–S disconnection **42a** is not hard to find and the unsaturated acid **45** looks an ideal candidate for a Mannich reaction. If we add an alkene (FGA), we get cinnamic acid **46** made by an aldol reaction.



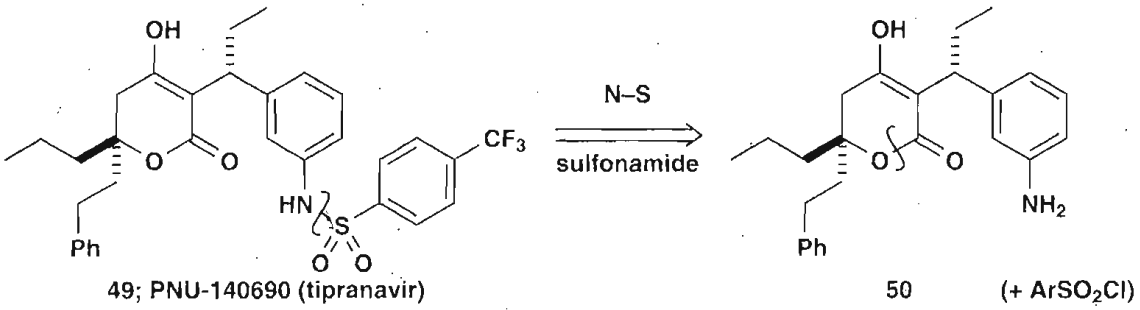
42a 44 45 46

This strategy was followed with some interesting variations in detail. The first step was a very favourable aldol ('Knoevenagel') condensation between diethyl malonate and benzaldehyde. The product **47** was hydrogenated and the esters hydrolysed but not decarboxylated to give the isolable malonic acid **48**. Direct Mannich reaction using Et_2NH as the amine and decarboxylation gave **44**. Conjugate addition worked well and the final step was a standard peptide coupling method to make the amide **41**.



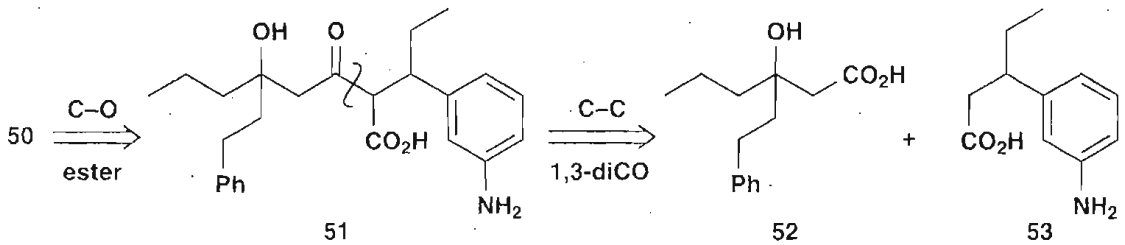
Our last example is Pharmacia and Upjohn's anti-HIV drug tipranavir[9] **49**. The key intermediate **50** is made from two starting materials coupled by an aldol reaction. Each starting material

is also made by an aldol reaction. We shall concentrate on making the skeleton and ignore the stereochemistry at this stage.



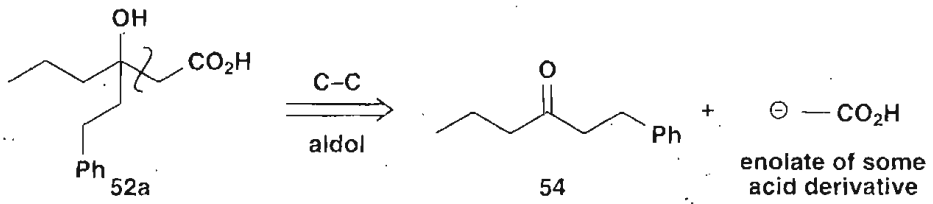
49; PNU-140690 (tipranavir) 50 (+ $ArSO_2Cl$)

Disconnecting the remaining structural C–X bond – the ester in the ring already marked on **50** – reveals the carbon skeleton **51** and disconnecting the 1,3-diCO relationship (also more or less in the middle of the molecule) reveals the two starting materials **52** and **53**. Both carbonyls are marked as acids but that may well not be the best choice in the synthesis.

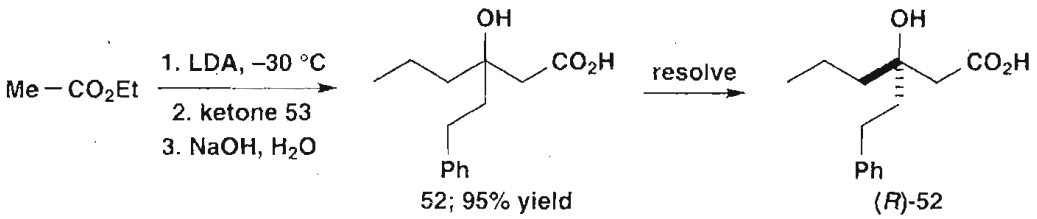


51 52 53

The first intermediate **52** contains an obvious aldol and disconnection **52a** shows that a specific enolate of the acid part will be needed as the ketone **54** can also form enolates.



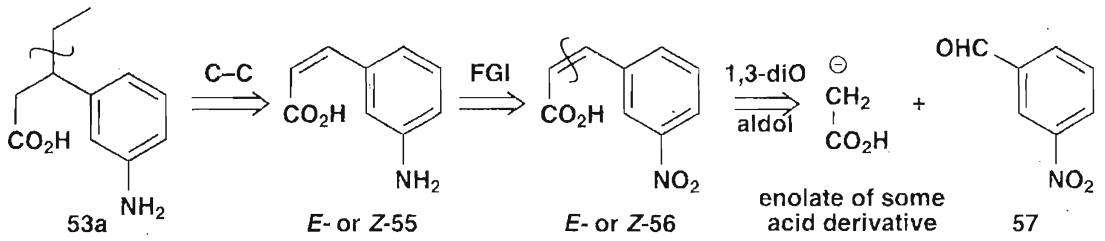
The workers at Pharmacia & Upjohn chose to use the lithium enolate of ethyl acetate for this reaction and hydrolysed the product to the free acid **52** in order to resolve it with norephedrine.[10]



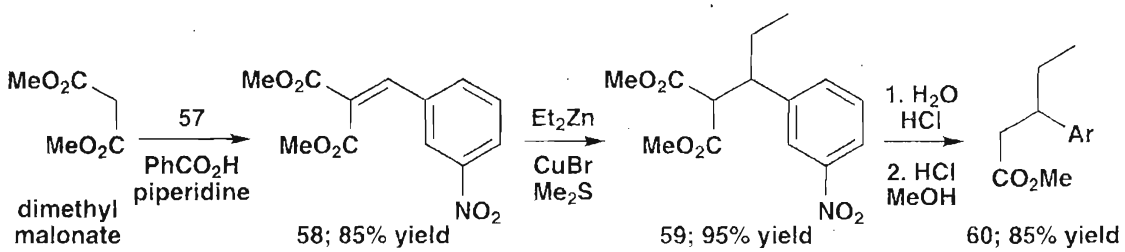
52; 95% yield (*R*)-52

The other starting material **53** has no 1,3-diCO relationship but removing the ethyl side chain **53a**, with the idea of conjugate addition, reveals just such an α,β-unsaturated carbonyl compound **55** as we have been discussing. The geometry of the alkene doesn't matter. We'd rather not

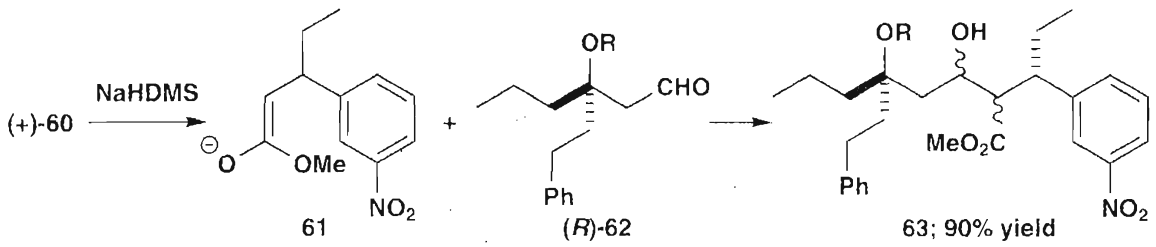
have an amine and a carboxylic acid in the same molecule so available *m*-nitrobenzaldehyde **57** was chosen for the reaction.



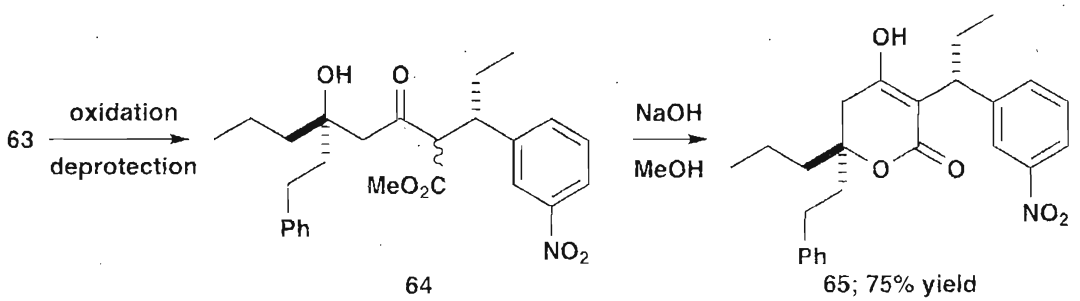
The 'aldol' reaction was carried out in Knoevenagel style with dimethyl malonate and the aldehyde **57**. Copper-catalysed addition (chapter 10) of diethyl zinc gave the malonate **59** which was converted into the ester **60**; Ar = 3-nitrophenyl that could be resolved[10] with a chiral column to give the right enantiomer.



The two halves were coupled in an aldol reaction between the sodium enolate **61** of **60** and a protected hydroxy-aldehyde **62** derived from **52** by protection and reduction.



The rest of the synthesis involves oxidation of the secondary alcohol to a ketone, deprotection to **64** and cyclisation to give **65** in excellent yield. You can now see why the lack of stereochemical control in the formation of **63** doesn't matter as both the undefined centres are lost in the cyclisation. The last step was reduction of the nitro group to an amine **50** and sulfonation to give **49**. This is a complicated molecule but it should show you that aldol and related reactions are important and versatile and have an important place at the centre of modern synthesis.



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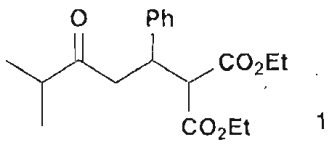
10. *Strategy and Control*, chapter 22.

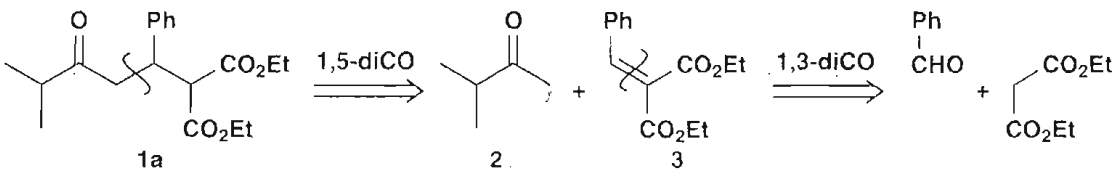
21 Two-Group C–C Disconnections III: 1,5-Difunctionalised Compounds Conjugate (Michael) Addition and Robinson Annelation

Two standard disconnections can be applied to unsymmetrical 1,5-dicarbonyl compounds. **Problem 21.1:** Carry out both disconnections on TM1 and suggest which is the better strategy.



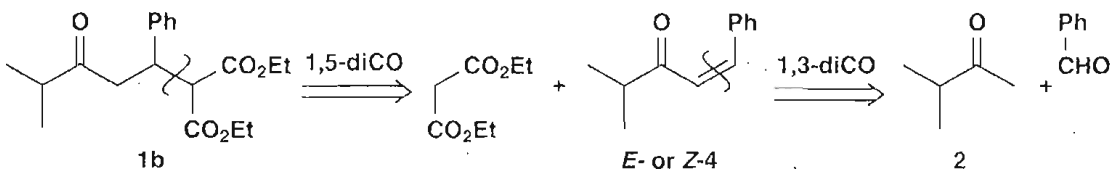
1

Answer 21.1: The first **1a** leads to a simple ketone **2** and an unsaturated ester **3** that can be disconnected in turn to benzaldehyde and malonate.



1a 2 3

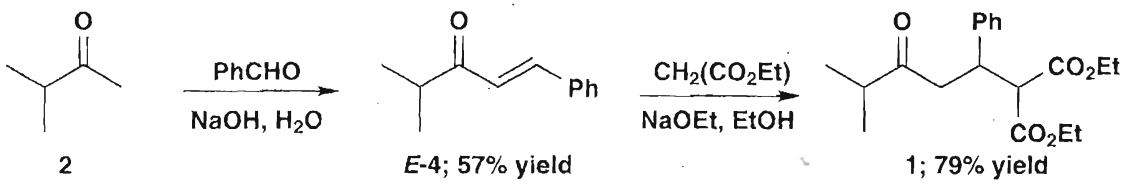
The second **1b** gives malonate and an enone **4** that can be disconnected to the same ketone **2** and benzaldehyde. Note that the geometry of the enone is unimportant as it disappears in the conjugate addition.



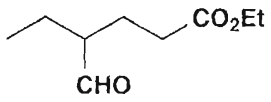
1b *E*- or *Z*-4 2

So the starting materials **2**, benzaldehyde and diethyl malonate, are the same for the two routes: only the order of events is different. Either route should work well. The published synthesis[1] uses strategy **1b** as no control is needed in the aldol reaction between benzaldehyde and the ketone **2**. Dehydration of the alternative aldol product would not be possible and the *E*-compound results. Malonate anions are very good at conjugate addition.

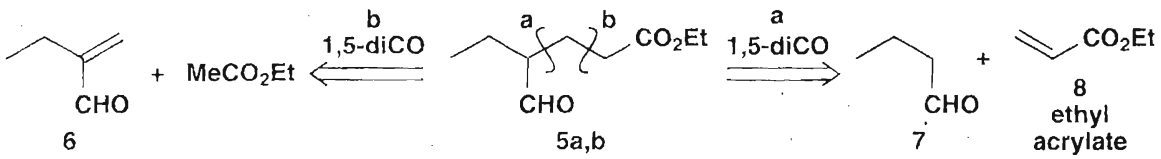
Workbook for Organic Synthesis: The Disconnection Approach, Second Edition Stuart Warren and Paul Wyatt



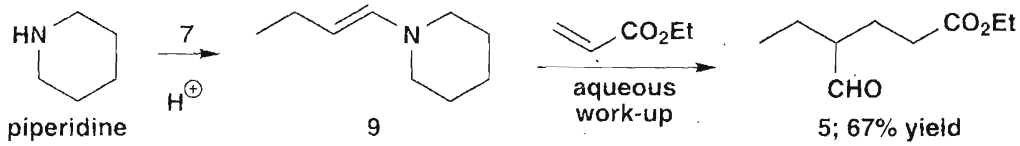
Problem 21.2: Suggest a synthesis for **5**.



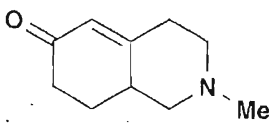
Answer 21.2: We much prefer disconnection **5a** as it is at the branchpoint and conjugated esters are good at Michael addition while conjugated aldehydes are not. We shall need a specific enol equivalent for the aldehyde to prevent self-condensation:



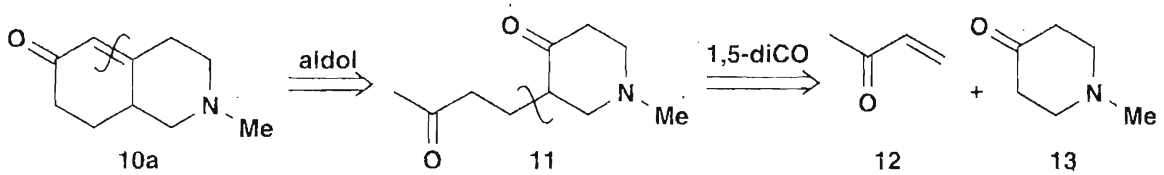
This was one of Stork's original applications of enamine chemistry and the piperidine enamine **9** reacts cleanly with ethyl acrylate to give **5** in one step.[2]



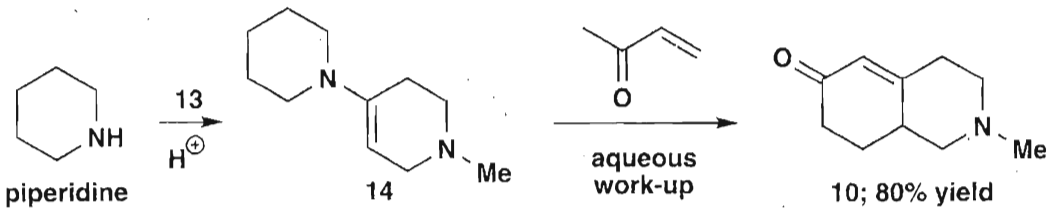
The combination of aldol reaction and conjugate addition was described in the textbook as very powerful. **Problem 21.3:** How might it be used to make this compound **10**?



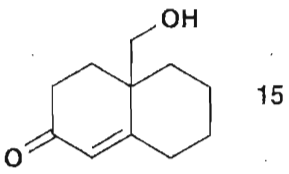
Answer 21.3: The disconnections are simple: aldol followed by conjugate addition. The starting materials are butenone (methyl vinyl ketone or MVK) **12** and the symmetrical heterocyclic ketone **13**. The synthesis of this compound **13** was discussed in chapter 19 of the textbook.



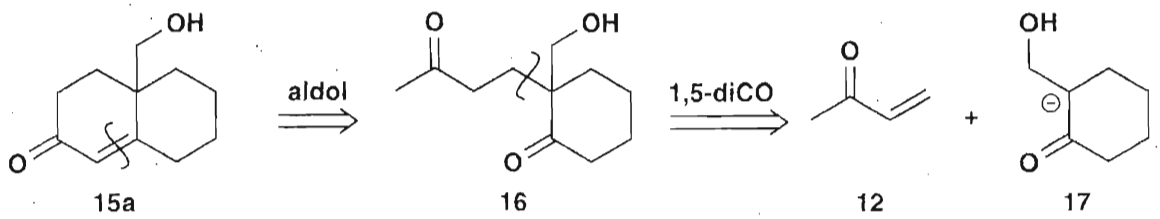
We need a specific enol equivalent of **13** to control the reaction as **12** can also enolise. You might have suggested adding a CO_2Et group but the published method[3] again uses a piperidine enamine.



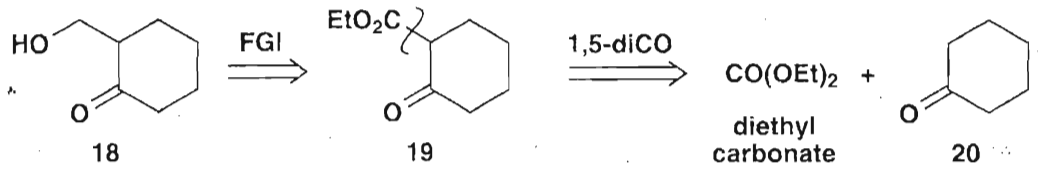
The cyclic enone **15** was used in a synthesis of the anti-cancer compound vernolepin.
Problem 21.3: Suggest a synthesis for **15**.



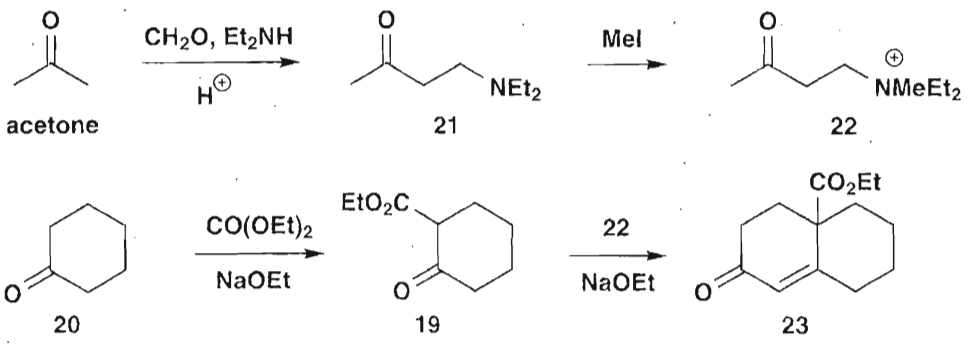
Answer 21.3: The same disconnections reveal the same enone **12** and a specific enolate **17** of an unsymmetrical ketone.



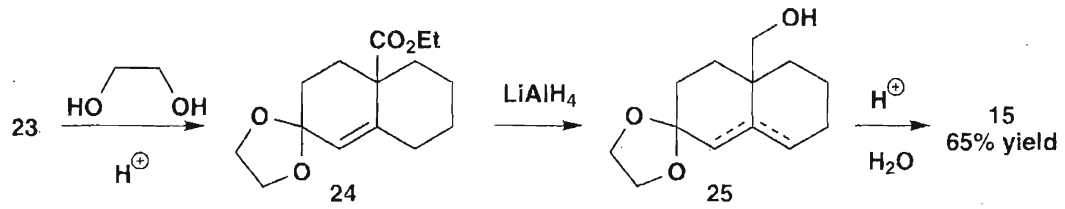
This is a tough problem with the OH group on the side chain but if we imagine making the alcohol by reduction of an ester, we have a much easier task. Now the enolate will be of a 1,3-dicarbonyl compound easily made from cyclohexanone **20** and diethyl carbonate.



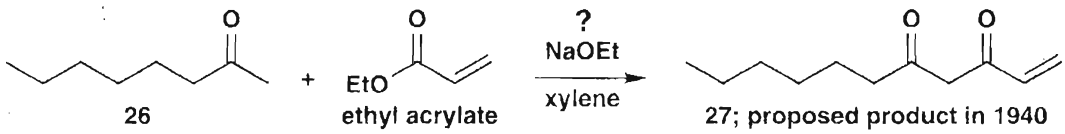
In the published synthesis[4] the enone **12** was replaced by a Mannich salt **22** made from acetone. This eliminates Me_2NEt to give **12** under the conditions of the reaction to give only a low concentration of **12** and hence avoid its self-condensation.



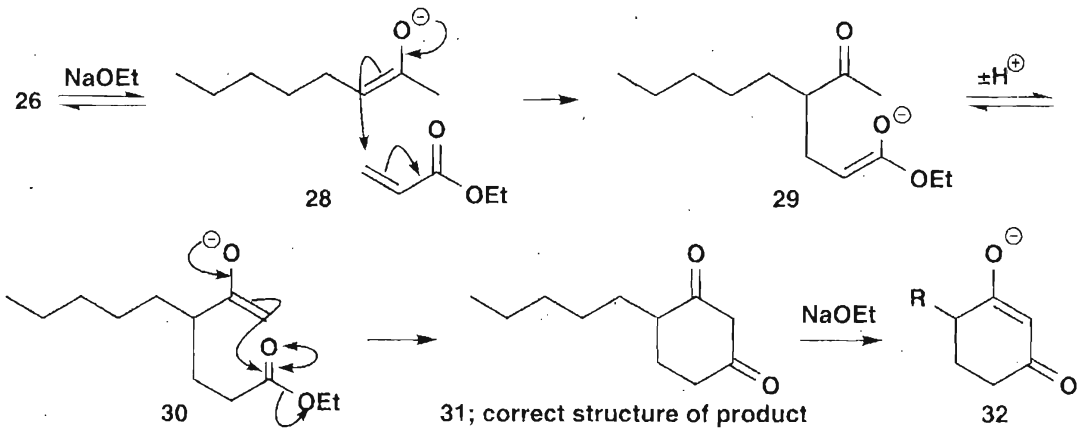
All that remains is to reduce the ester to the alcohol but that needs acetal protection **24** of the more easily reduced ketone. The alkene wanders about in the protected compound **25** but comes back into conjugation when the acetal is hydrolysed.



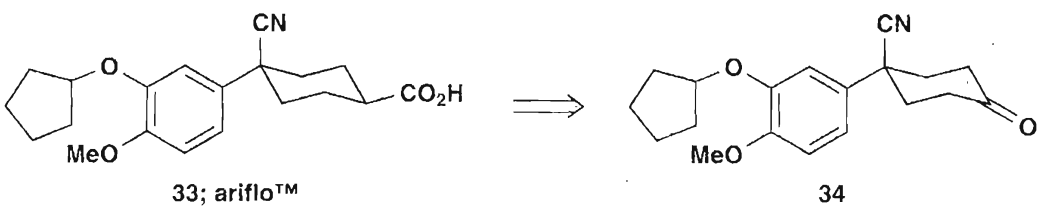
Now for a rather unusual type of problem. In 1940 the ketone **26** was combined with ethyl acrylate with NaOEt as catalyst and the product, identified by elemental analysis only, was proposed[5] as **27**. **Problem 21.4:** Suggest an alternative and more likely structure for this product: spectroscopy (not available in 1940) shows that there is no alkene.



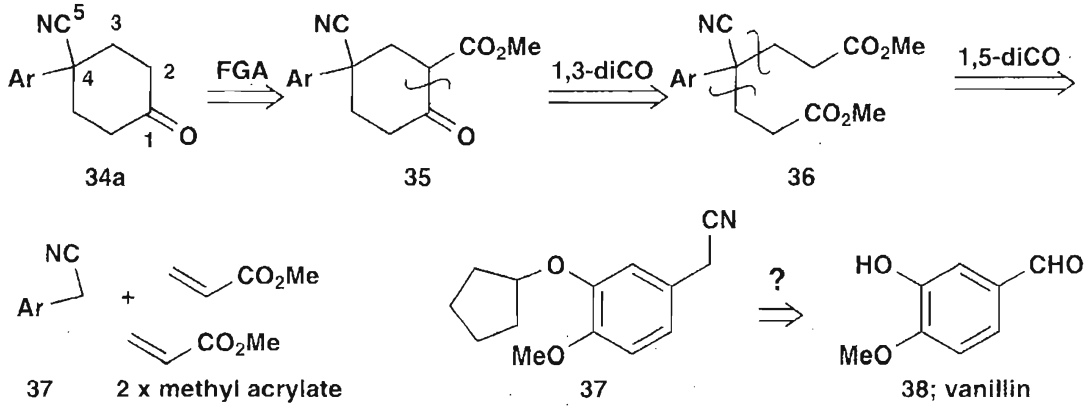
Answer 21.4: The proposed structure **27** is perfectly reasonable mechanistically but the evidence – all that matters – shows that it is not correct. The molecular formula dictates that, if there is no alkene, there must be a ring, and what really happens is conjugate addition of the more substituted enolate **28** to ethyl acrylate to give **29** and exchange of protons via EtOH to give the new enolate that can cyclise **30** to the true product,[6] the cyclohexanedione **31**. The base NaOEt is not strong enough to form only the kinetic enolate on the methyl group (you'd need LDA for that) so all the different enolates are in equilibrium and **31** is the thermodynamic product as it will exist in the reaction mixture as the stable enolate **32**.



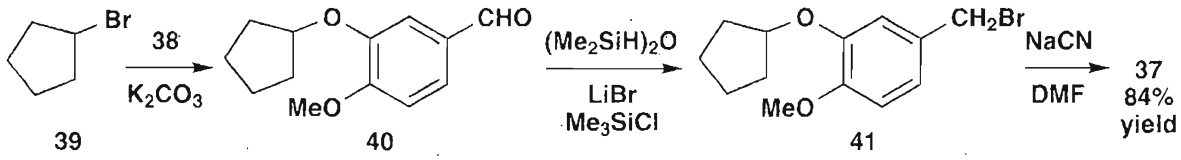
Now for a more serious example. GSK's phosphatase inhibitor ariflo™ **33** is made from the ketone **34**. **Problem 21.5:** Suggest a synthesis for this ketone. *Hint*: Are you aware of the structure of vanillin? If not, look it up!



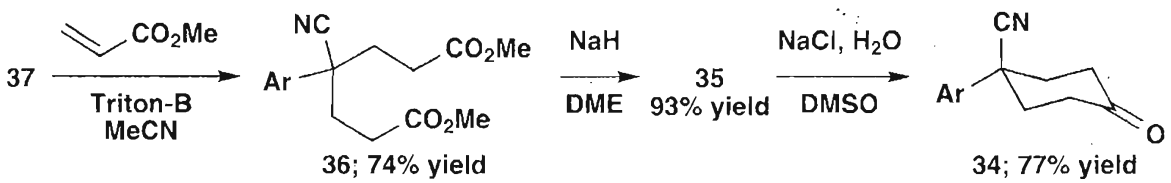
Answer 21.5: Drawing **34** in a simpler form **34a** we note a 1,5-relationship between the ketone and the nitrile. To take advantage of this we need to use a strategy met in chapter 19: FGA of an ester group so that we can disconnect a 1,3-diCO relationship **35** preparing the way for two 1,5-diCO disconnections at the branchpoint **36**. So we need two molecules of methyl acrylate and the nitrile **37** that can surely be derived from vanillin **38** by simple chemistry.



Alkylation of vanillin **38** (only a weak base was needed for the alkylation of a phenol) gave the ether **40** which was converted into the benzylic bromide **41** by a process the chemists[7] at SKB call 'reductive bromination'. The reducing agent is the hydrosiloxane $(Me_2SiH)_2O$ and bromide provides the nucleophile for, perhaps, an S_N1 displacement. A normal S_N2 reaction with cyanide ion gives **37**.



The rest of the synthesis was as conceived by the plan. Triton-B (*N*-benzyltrimethyl ammonium hydroxide) was used as the base for the double Michael addition and the diester **36** was cyclised and decarboxylated.



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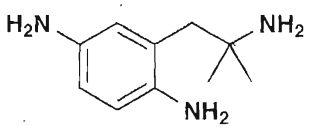
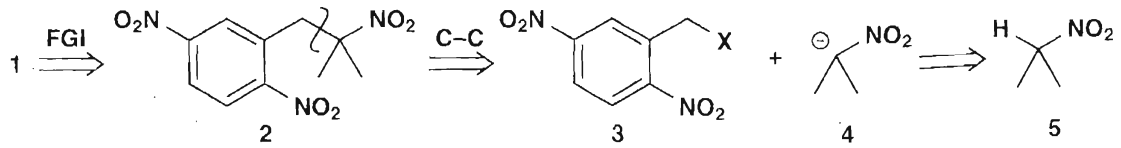
22 Strategy X: Aliphatic Nitro Compounds in Synthesis

A common use for aliphatic and aromatic nitro-compounds is in the synthesis of amines. **Problem 22.1:** Suggest how this triamine might be made.

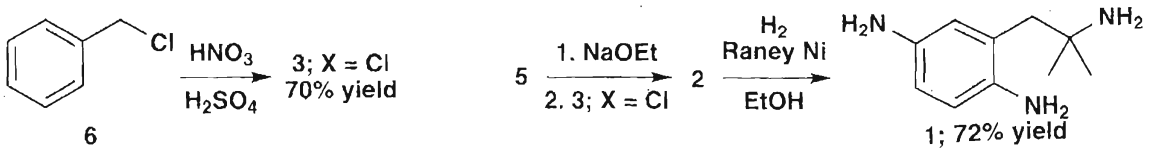


1

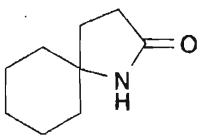
Answer 22.1: All three amino groups in **1** might be made by reduction of nitro groups. Disconnection of **2** suggests alkylation of a nitroalkane anion **4** (derived from available 2-nitropropane **5**) with the benzylic derivative **3**.



The chloro-compound **3**; X = Cl was chosen as the alkylating agent since available benzyl chloride is nitrated *ortho* and *para*. The anion **4** was created from **5** with NaOEt: alkylation and reduction then went well.[1]

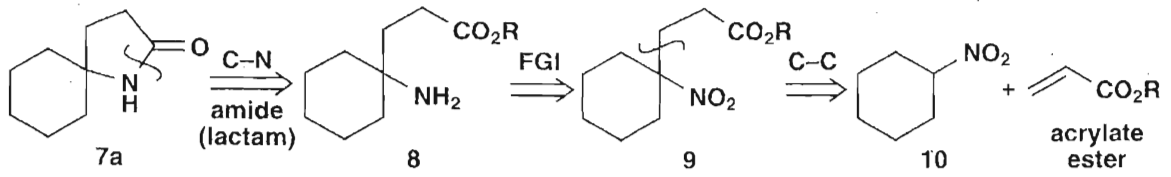


Problem 22.2: Suggest a synthesis for the spirolactam **7**, needed to check the structure of a rearrangement reaction.[2]

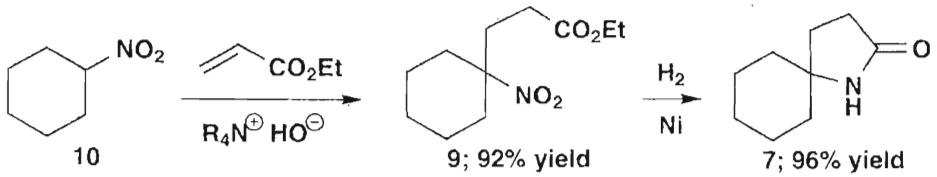


spiro-lactam
7

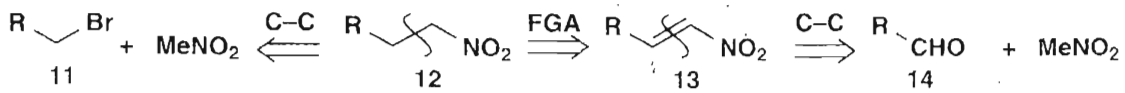
Answer 22.2: The obvious amide (lactam) disconnection **7a** reveals an amino ester **8** strongly suggesting FGI to the nitro-ester **9**. Disconnection of the C–C bond at the branchpoint can now use the excellent conjugate addition of nitroalkanes such as **10** to unsaturated carbonyl compounds such as an acrylate ester:



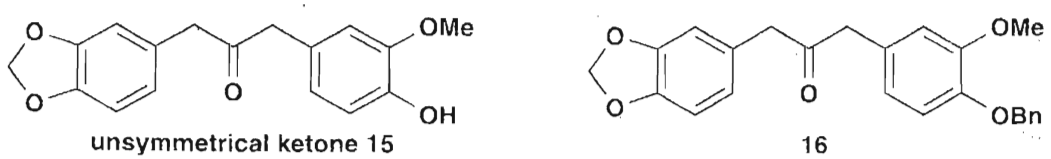
All three reactions go very well: the conjugate addition with ethyl acrylate and a tetra-alkyl ammonium hydroxide as base. Catalytic hydrogenation leads to spontaneous cyclisation[2] to the five-membered lactam **7**.



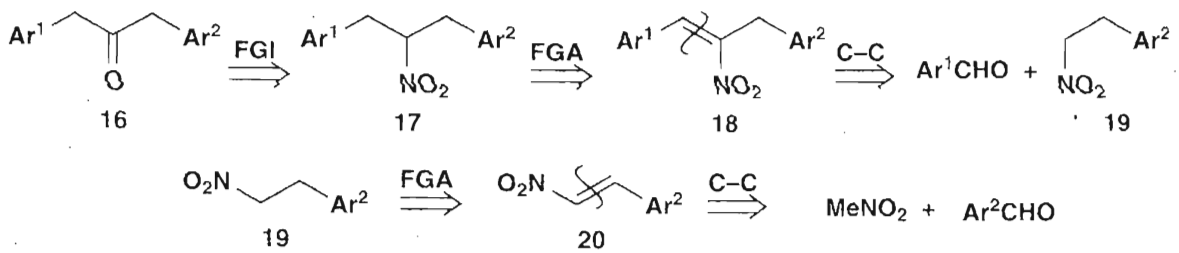
Other reducing agents such as sodium borohydride do not reduce the nitro group but do reduce nitroalkenes to nitroalkanes.[3] This means that many nitroalkanes **12** can be made by a 'nitro-aldol', otherwise known as the Henry reaction.[4] Nitromethane reacts with aldehydes to give **13** and then reduction of the alkene gives the nitroalkane. This can be easier and more reliable than alkylation with **11**.



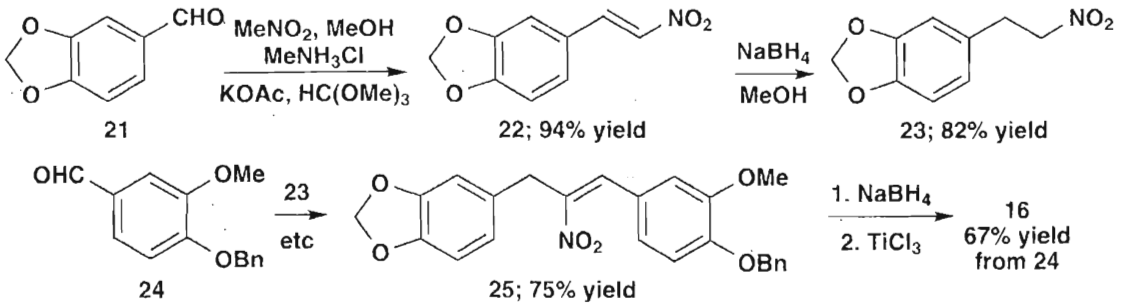
Since the reaction can be done twice (**12** can be combined with a different aldehyde) and the product converted into a ketone, by one of the methods discussed in the text, this sequence is an unusually simple synthesis of ketones. **Problem 22.3:** The unsymmetrical phenolic ketone **15** was needed to study selectivity in biomimetic phenol coupling. Suggest a synthesis of the protected ketone **16**.



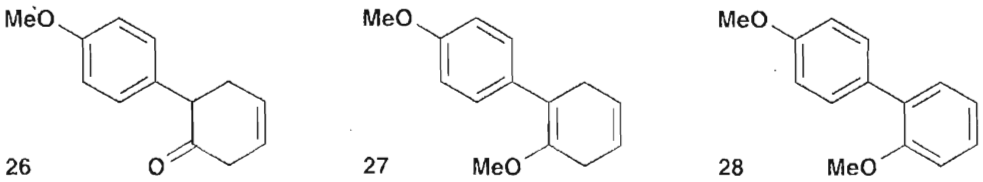
Answer 22.3: As it doesn't matter which group you disconnect first, after FGI to nitroalkane **17**, we shall call the groups Ar^1 and Ar^2 and say later which order was used in the published work. So we end up with nitromethane and two aromatic aldehydes as starting materials.



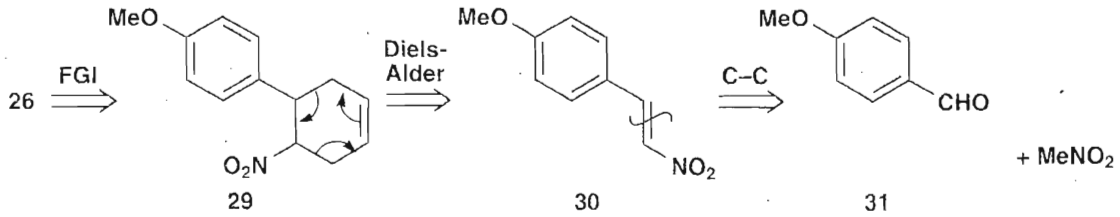
In the published synthesis, aldehyde **21** was first condensed with nitromethane and the product **22** reduced to the nitroalkane **23**. Condensation with the second aldehyde **24** gave the second nitroalkene **25**: reduction and hydrolysis gave the ketone **16**. Since nitro-compounds like **17** or **19** can alternatively be reduced to amines, this is a versatile route.[3]



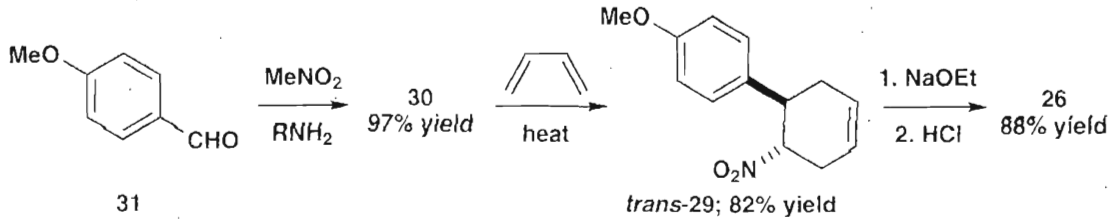
The unconjugated enone **26** was needed as a synthetic intermediate.[5] Our first thought might have been Birch reduction (chapter 36) until we see that the starting material would be **28** and one of two very similar rings would have to be reduced to give **27** and hence **26. Problem 22.4:** Suggest a synthesis of **26**.



If we first change the ketone into a nitro group, a Diels-Alder disconnection **29** gives a nitroalkene **30** and butadiene. The nitroalkene can be made from available aldehyde **31** and nitromethane by a nitro-aldol reaction, as we have just seen.

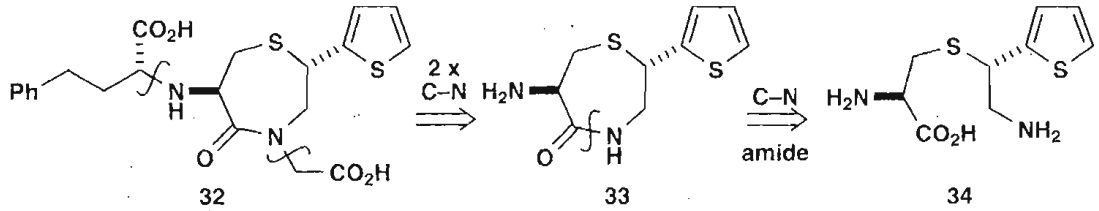


Various catalysts such as amines can be used[4] to make **30** and the Diels-Alder reaction gives a good yield of the *trans*-**29**, though the stereochemistry doesn't matter as it disappears in the hydrolysis of the nitro-compound to give **26**. In the published synthesis[5] acid hydrolysis of the 'enolate' of the nitro-compound **29** gave the best results.

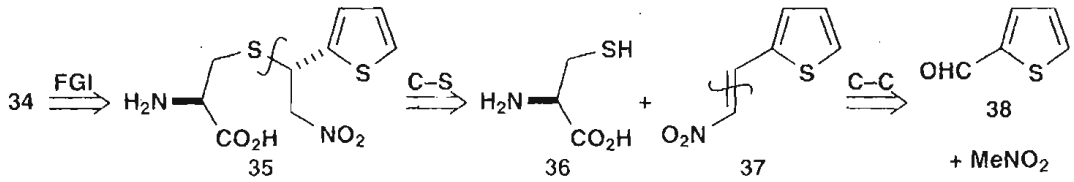


The Synthesis of an ACE Inhibitor

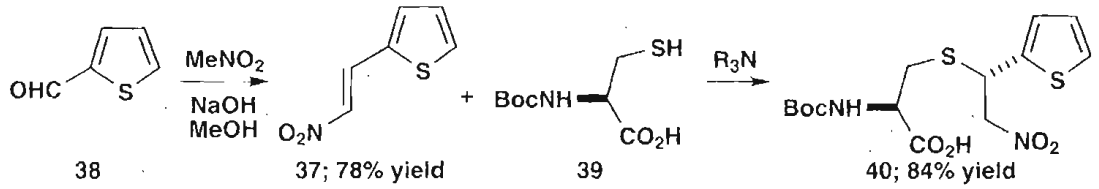
We conclude this chapter with an account of the synthesis of an angiotensin-converting enzyme inhibitor **32** used in the treatment of high blood pressure.[6] Some obvious disconnections of structural C–N bonds lead to the simplified heterocycle **33** and the open chain compound **34. Problem 22.4:** Suggest how a nitroalkane could be used in the synthesis of **34**. Do not concern yourself with the stereochemistry.



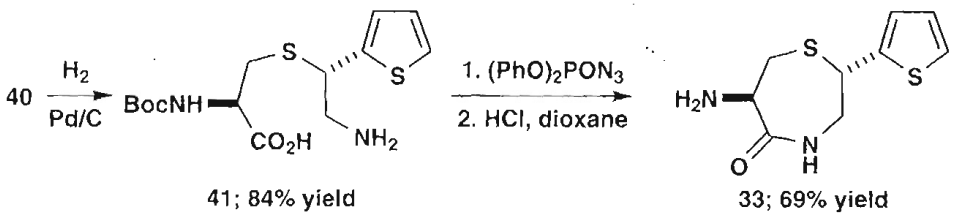
Answer 22.4: We still have structural C–X bonds in **34**: the two C–S bonds. There is nothing to be gained by changing the left hand amino group into a nitro group, but if we do FGI on the right hand amino group **35**, the sulfur can be added by conjugate addition of the thiol **36** to the nitroalkene **37**, easily made by a nitro-aldol reaction between available aldehyde **38** and nitromethane.



The nitro-aldol reaction needed only NaOH as catalyst[7] and the Boc-protected amino acid **39** added in good yield with *N*-methyl morpholine as catalyst.[6] In fact **39** was a single enantiomer and the product **40** was formed as a mixture of diastereoisomers which were separated.



Catalytic hydrogenation reduced the nitro group to the primary amine **41** which cyclised with the rather unusual reagent diphenylphosphoryl azide to give **33** after removal of the Boc group with acid. This sequence was used to make a variety of compounds of this general type from which **32** was selected for further development.



References

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2. R. K. Hill, *J. Org. Chem.*, 1957, **22**, 830.
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4. G. Jones, *Org. React.*, 1967, **15**, 204, see p. 495.
5. W. C. Wildman and R. B. Wildman, *J. Org. Chem.*, 1952, **17**, 581.
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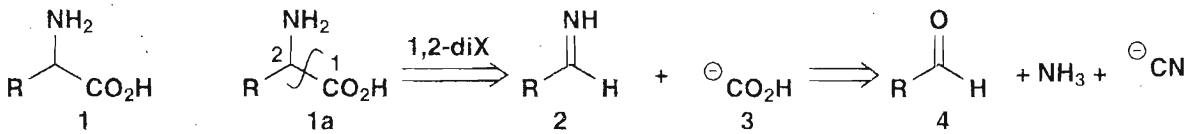
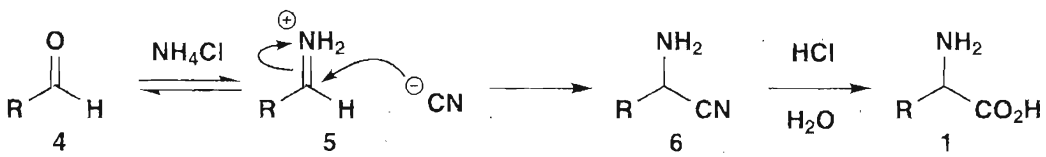
23 Two-Group Disconnections IV: 1,2-Difunctionalised Compounds

Acyl Anion Equivalents

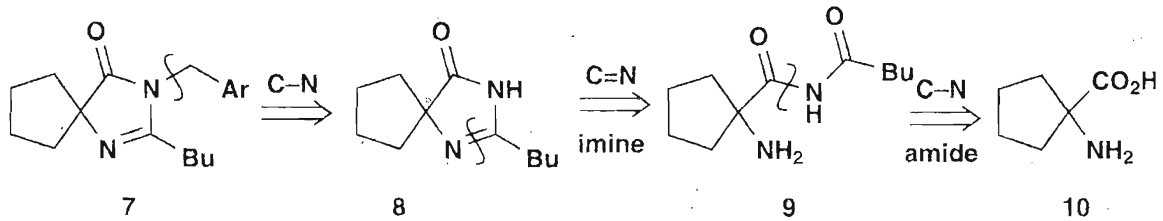
The Synthesis of Amino Acids: We listed available compounds with a 1,2-relationship in chapter 23 of the textbook and among these amino acids **1** are particularly valuable. That is, if they come from proteins. Other 'unnatural' amino acids have to be made. We also discussed cyanide ion as an acyl anion equivalent briefly in the textbook. One important application is the Strecker synthesis of amino acids. The 1,2-relationship suggests a disconnection between the two FGs **1a** requiring an unstable imine and a reagent for the carboxyl anion **3**. The Strecker synthesis combines an aldehyde **4** (or ketone), ammonia and cyanide in one reaction.



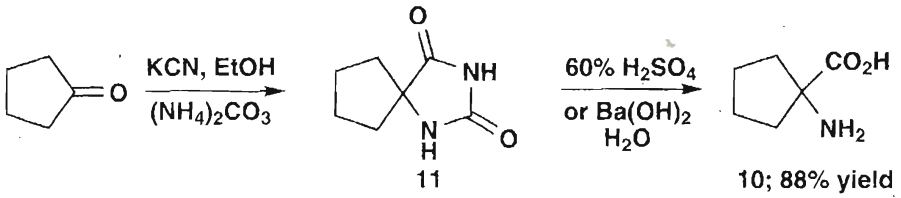
The ammonia, usually added as a salt, combines with the aldehyde to give an imine that is attacked by cyanide **5** to give an amino-nitrile **6**. A separate hydrolysis step is usually needed to convert this to the amino acid.



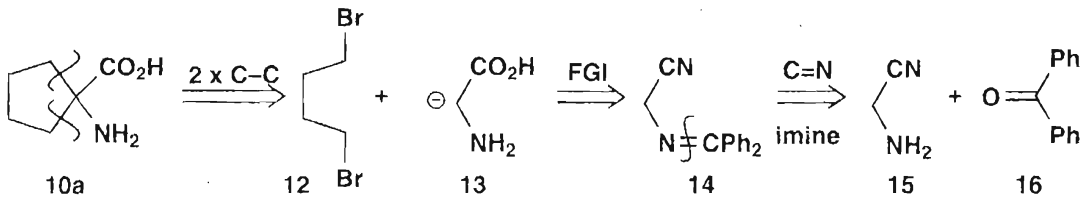
An example comes from Sanofi's series of ACE inhibitors **7** used to treat hypertension.[1] A series of C–N disconnections removing the side chain then disconnecting the imine **8** and the amide **9** reveals the unnatural amino acid **10**.



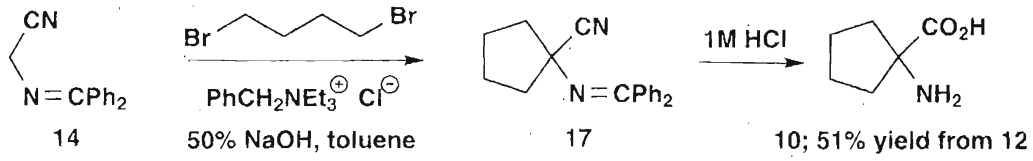
The synthesis starts with a Strecker reaction using ammonium carbonate.[2] The immediate product is the 'hydantoin' **11** that can be hydrolysed to **10** in acid or base.



Of course, other strategies can be used. One successful way is to disconnect both C–C bonds at the branchpoint **10a** with double alkylation of the synthon **13** in mind (the dianion might be needed). This synthon can be represented by the imino-nitrile **14**, prepared from the amino nitrile **15** and benzophenone **16**.

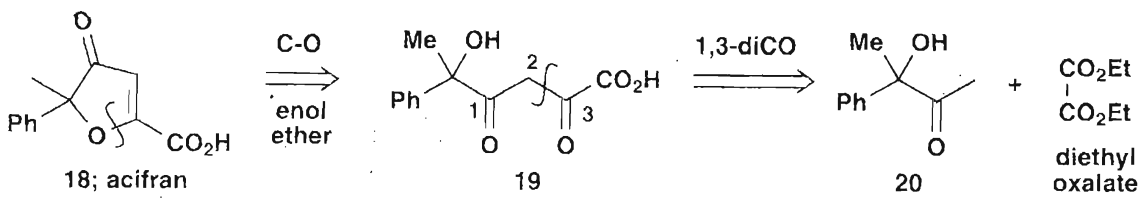


The double alkylation is best achieved[3] under phase-transfer conditions and the hydrolysis of both imine and nitrile requires only dilute HCl.

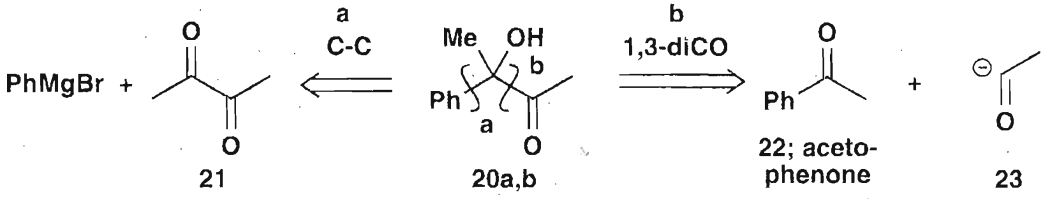


Acetylene and Dithian as Acyl Anion Equivalent

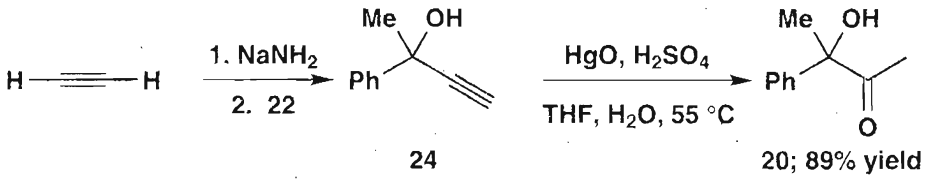
We can illustrate both these reagents with the same compound; Ayerst's lipid-lowering acifran **18**. Disconnecting the enol ether gives the open-chain **19** with plenty of functionality. We choose the 1,3-dicarbonyl disconnection **19** because it needs enolisable **20** and symmetrical, unenolisable but very electrophilic diethyl oxalate (chapter 20).



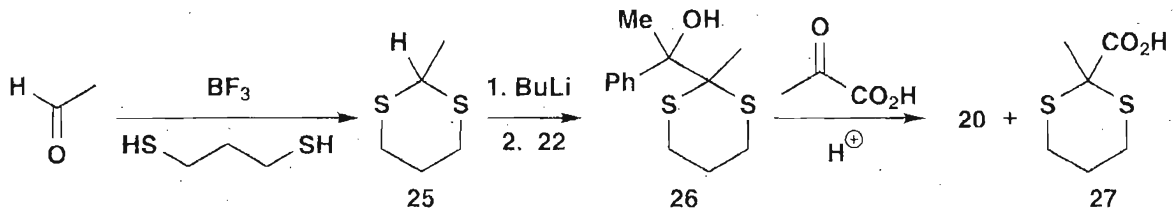
Now we have to make the hydroxyketone **20**. We don't normally consider one-group C–C disconnections such as **20a** but this one reveals a symmetrical reactive and available α-diketone **21**. In fact,[4] no Grignard reagent is needed as **21** is reactive enough to combine with benzene in a Friedel-Crafts style reaction under $AlCl_3$ catalysis, though the yield was only 48%. The alternative 1,2-diCO disconnection **20b** requires the addition of an acyl anion equivalent **23** to available acetophenone **22**.



In one synthesis[5] Ayerst used the sodium derivative of acetylene and hydrated it in acid with Hg(II) catalysis.

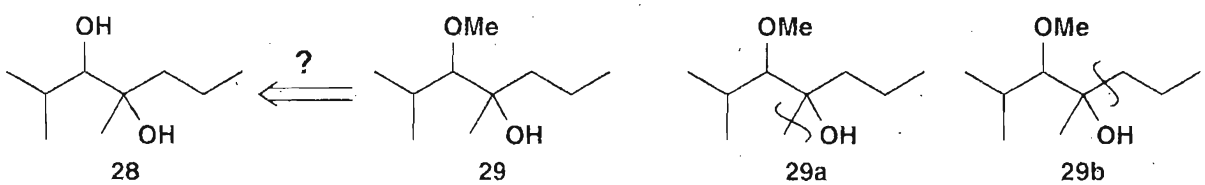


In another,[6] a dithian provided the reagent for **23**. Acetaldehyde reacts with propane dithiol with Lewis acid catalysis to give the dithian **25**. The lithium derivative of **25** adds to **22** to give **26** which was hydrolysed by acetal exchange with pyruvic acid so that the least stable carbonyl group was removed as the dithian **27**. This avoids the need for mercury in the hydrolysis. The synthesis of acifran is discussed in more detail in *Strategy and Control*, chapter 14.

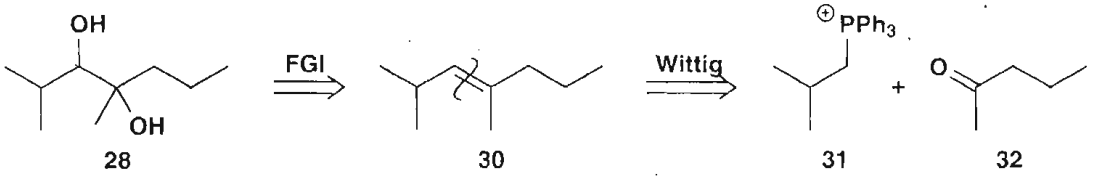


Some Problems

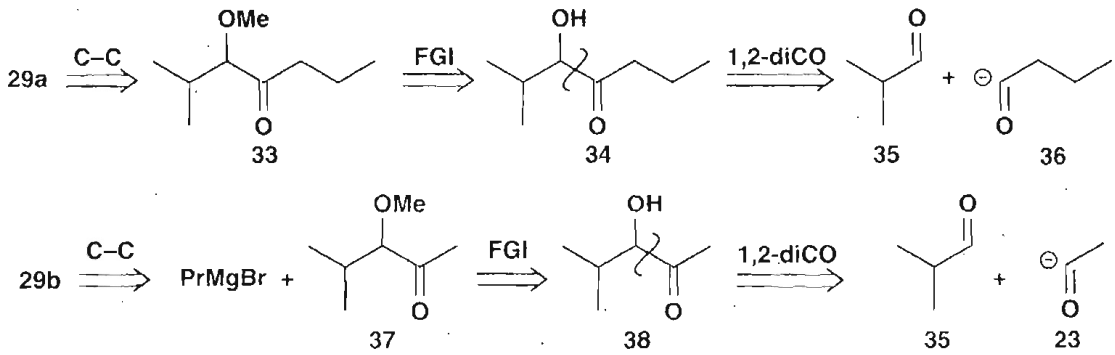
The half ether **29** of the diol **28** was needed for a study of stereochemistry. **Problem 23.1:** How might **28** be made? Assess the chance of making **29** by selective methylation of **28** and suggest how you might try it. **Problem 23.2:** Which do you prefer of the alternative disconnections **29a** or **29b**? Suggest how you might continue from your chosen precursor.



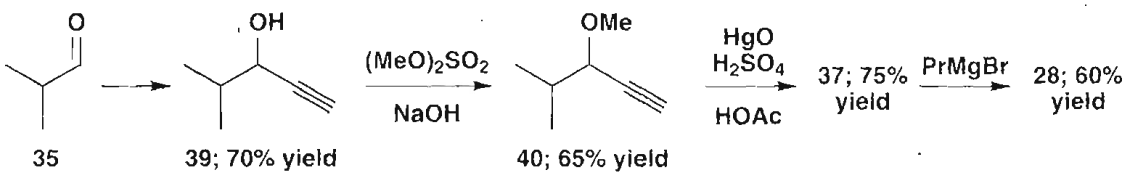
Answer 23.1: Of the many ways to make **28**, the most obvious is by dihydroxylation of the alkene **30** and that might perhaps be made by a Wittig reaction from a phosphonium salt such as **31** and a carbonyl compound. The chance of selective methylation of **28** is probably not very great as achieving chemoselectivity between the two alcohols might be difficult. Secondary alcohols are slightly more acidic that tertiary so you might try one equivalent of a base such as NaH and then a methylating agent such as MeI.



Answer 23.2: Both require the addition of a Grignard reagent (or organo-lithium) to an α-methoxy-ketone **33** or **37**, made from the hydroxy-ketones **34** or **38**. There is now no selectivity problem in the methylation. Further 1,2-diCO disconnection suggests addition of an acyl anion equivalent **36** or **23** to isobutyraldehyde **35**.

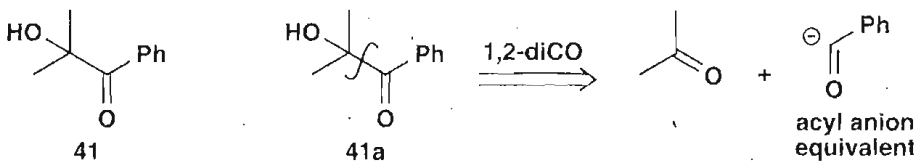


The published synthesis[7] uses acetylene for **23**, methylation with dimethyl sulfate, and mercury-catalysed hydration before addition of propyl Grignard reagent to give **29**. You might well have chosen other acyl anion equivalents such as **25**.

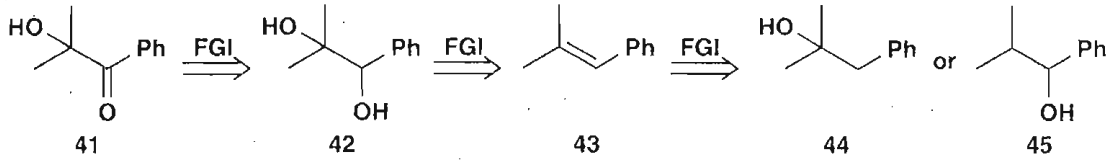


α-Functionalisation of Carbonyl Compounds

Problem 23.3: The simple α-hydroxy-ketone **41** can obviously be made by addition of an acyl anion equivalent to acetone. Suggest two alternative syntheses, one based on functionalisation of an alkene and the other on α-functionalisation of a carbonyl compound.

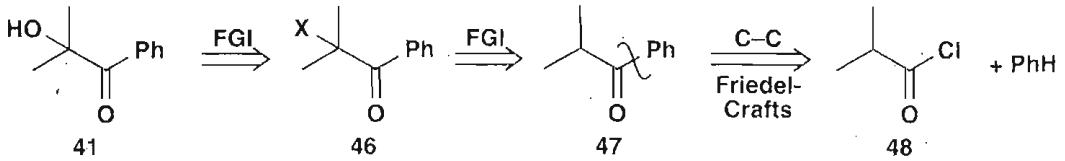


Answer 23.3: Functionalisation of an alkene is found by a series of FGIs, the alkene **43** being made easily by a Wittig reaction or by dehydration of either alcohol **44** or **45**. These are also easily made by the methods of chapter 10. The diol **42** will need to be oxidised but there is no selectivity problem as only the secondary alcohol can be oxidised.



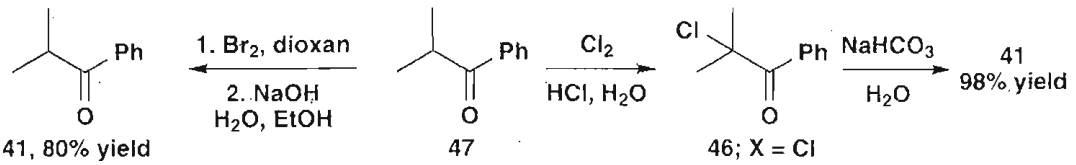
41 42 43 44 45

The approach based on α-functionalisation of a carbonyl compound is more interesting. Halogens are easy to add so FGI to **46** (X = Br or Cl) and then to the simple ketone **47** gives a simple route from benzene. In fact **47** is commercially available.



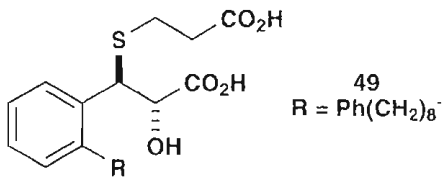
41 46 47 48

The only problem is the hydrolysis of **46** to the alcohol as neither S_N1 nor S_N2 looks very promising. It turns out that either **46**; X = Br or **46**; X = Cl can be used. The bromide was hydrolysed with aqueous NaOH without isolation[8] and the chloride needs only aqueous bicarbonate for three days at room temperature.[9]

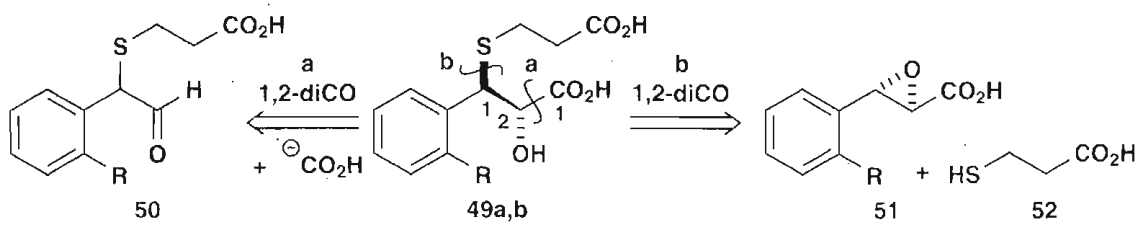


41, 80% yield 47 46; X = Cl

We conclude with an example with two 1,2-diX relationships – a leukotriene analogue that may be helpful in the treatment of bronchial asthma.[10] **Problem 23.4:** Suggest a synthesis of **49**.

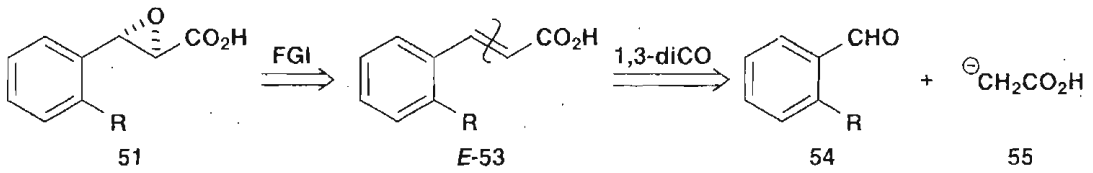


Answer 23.4: The two most obvious 1,2-disconnections are **49a** to the aldehyde **50** and some reagent such as cyanide for the carboxyl acyl anion. This removes only one carbon atom and we shall not pursue it. An alternative is the 1,2-diX disconnection **49b** of the C–S bond requiring the *trans* epoxide **51** and the available acid **52**.

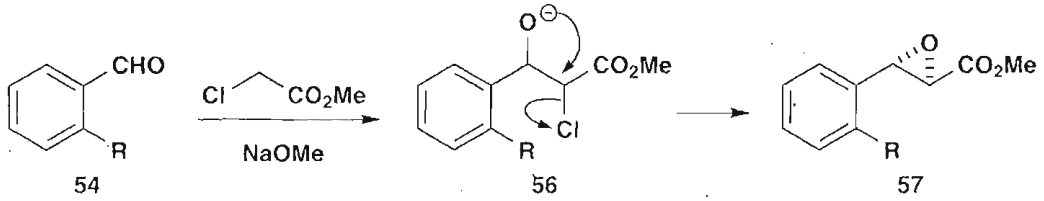


50 49a,b 51 52

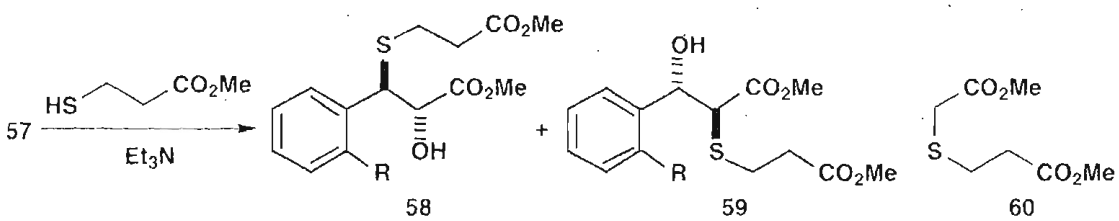
The epoxide **51** could be made from the alkene **53** in turn made by some aldol reaction between the aldehyde **54** and a reagent such as malonate for the synthon **55**.



In fact this was not the route chosen by the SKB chemists (now GSK) who preferred to use the Darzens reaction. The same aldehyde **54** was combined with methyl chloroacetate with methoxide as catalyst. Addition of the enolate from methyl chloroacetate to the aldehyde gave the intermediate **56** that cyclised under the conditions of the reaction to the *trans* epoxide **57**.



Now the methyl ester of **52** was added in base to the epoxide. Both ends of the epoxide are activated towards S_N2 reactions and in practice a 1:1 mixture was formed. This looks like disaster but treatment of the mixture with NaOMe in MeOH caused a retro-aldol reaction with **59** giving **54** and the stable enolate of **60**. Note that both regioisomers **58** and **59** are the *trans* isomers as the S_N2 reaction at either end must go with inversion. Hydrolysis of **58** (NaOH) gave **50**.



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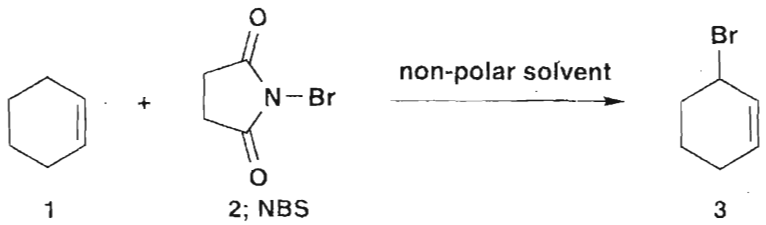
24 Strategy XI: Radical Reactions in Synthesis

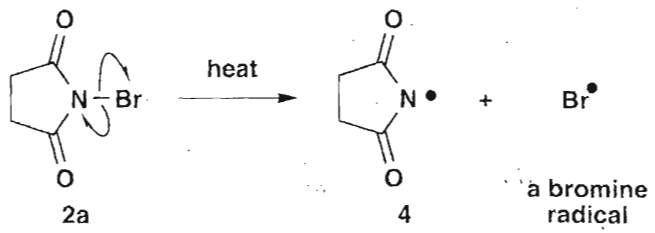
The Mechanism of Allylic Bromination with NBS

In the textbook we promised more details of this often misrepresented reaction. Alkenes such as cyclohexene **1** are brominated in the allylic position with NBS (*N*-bromo-succinimide) **2** to give the allylic bromide **3**. This is a radical reaction.



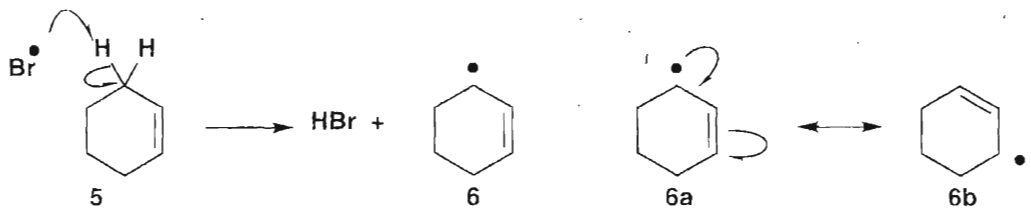
1 2; NBS 3

The first step is a homolytic cleavage **2a** of the weak N–Br bond. One product is the stable succinimide radical **4** but the other is the key player in the reaction: the bromine radical. This step that first produces radicals is known as *initiation*.



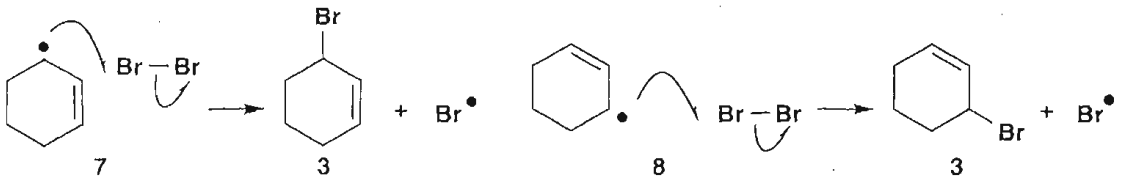
2a 4

The bromine radical now abstracts a hydrogen atom (not a proton but a hydrogen atom with one electron H•) from the allylic position **5** to give HBr and the allylic radical **6**. This is the most stable radical that can be formed as it is delocalised **6a**. The allylic C–H bonds are the weakest in **1**.



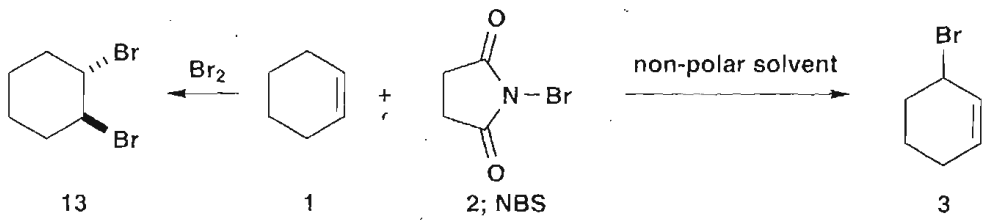
5 6 6a 6b

The next step is the reaction of the allylic radical with molecular bromine **7** giving the allylic bromide **3** and a new bromine radical. Of course we cannot tell which end of the symmetrical allylic radical **6** captures the bromine atom as the product from the alternative **8** is the same **3**. These last two steps are *propagation*: no radicals are created or destroyed and the final radical ($Br^{\bullet}$) is also the radical that starts the sequence. This is a radical chain reaction.

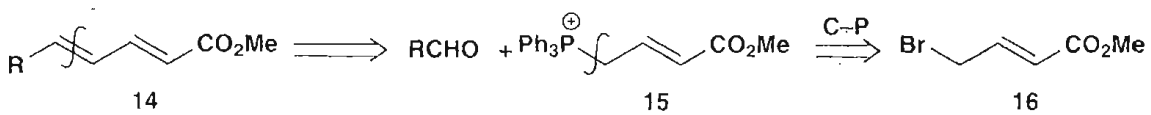


There is one mystery still to be solved: where do the bromine molecules come from? The answer is in a neglected product: HBr. This reacts with NBS in an ionic reaction **9** and **10** to produce molecular bromine and succinimide **12**. So the final products are the allylic bromide **3** and succinimide **12**.

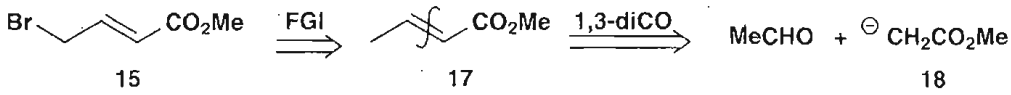
This last reaction is very important. If we simply mixed cyclohexene with bromine, we should get the well known electrophilic attack on the alkene to give the dibromide **13**. In the radical chain pathway only a small amount of bromine is formed from the small amount of HBr from **4** and therefore also the same amount as the allylic radical **5**. The bromine radical is more reactive than bromine molecules so hydrogen abstraction **4** is preferred to ionic addition of bromine. Be warned: in a polar solvent, NBS may produce much more bromine and the dibromide **12** may become the major product.



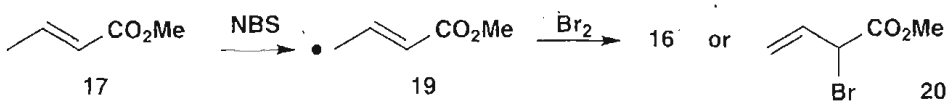
An application of this reaction comes in the synthesis of carotenoids of general structure **14**. As R is a large group, greatest simplification comes from disconnection of the inner alkene **14** using the phosphonium salt **15** and the appropriate aldehyde RCHO. Clearly **15** comes from the bromide **16. Problem 24.1:** How might radical chemistry be used to make **16**? What potential problem is there in this approach?



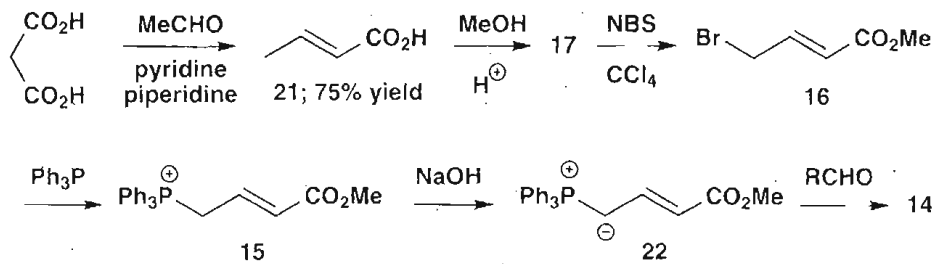
Answer 24.1: Since **16** is an allylic bromide we might be able to make it by allylic bromination of methyl crotonate **17** derived from acetaldehyde and some reagent for the synthon **18** such as a malonate or a Wittig reagent.



The potential problem is that after hydrogen abstraction from **17** the allylic radical **19** will be unsymmetrical and might react at either end with bromine. So the product might be **16** or **20**. It turns out that the alkene much prefers to be in conjugation with the carbonyl group and that **20** rearranges to **16** under the conditions of the reaction.

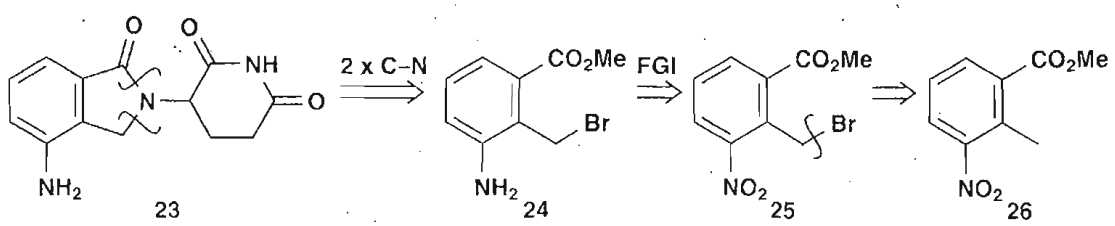


So the synthesis[1] involves a Knoevenagel aldol reaction, methylation, allylic bromination using CCl_4 as the non-polar solvent and a Wittig reaction.

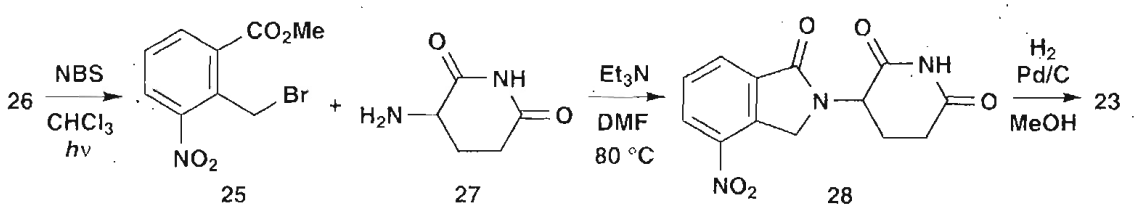


Application of NBS in Synthesis

Compound **23** was needed as a drug for the treatment of inflammatory bowel disease.[2] Disconnecting the heterocyclic amine revealed a simple benzene **24** derivable from the nitro compound **25** and hence from available **26**.

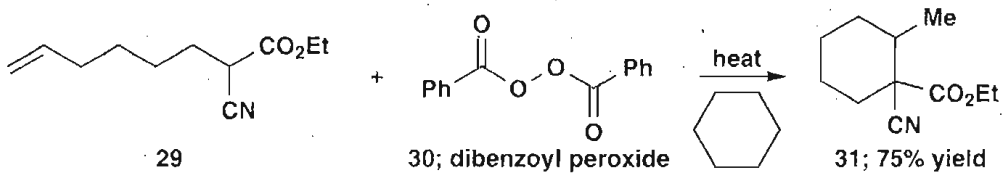


In the synthesis, the bromination was carried out with NBS in chloroform with activation by light. The coupling and cyclisation with the amine **27** required only weak base to absorb the HBr produced and it turned out to be better to reduce the nitro group at the end.

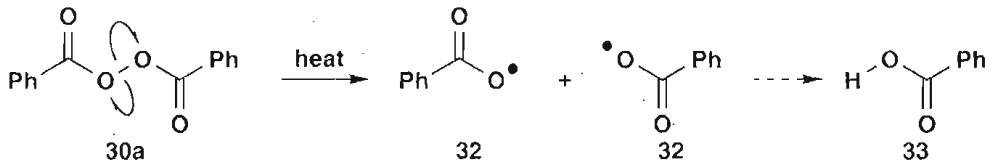


Carbon–Carbon Bond-Forming Reactions

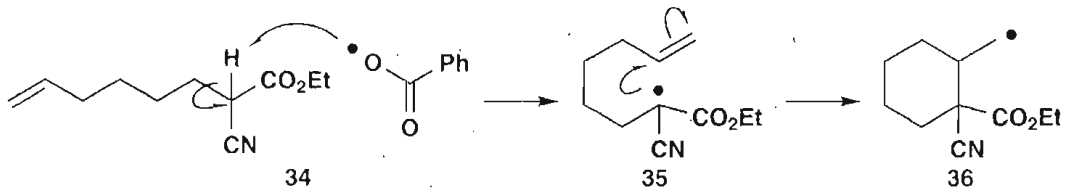
A remarkable variety of these reactions has now been discovered and we shall content ourselves with just two. In the first reaction, dibenzoylperoxide **30** catalyses the cyclisation of the unsaturated ester **29** in refluxing cyclohexane to give a good yield[3] of **31**. **Problem 24.2:** Suggest what might happen on heating dibenzoyl peroxide **30** and how that might lead to the reaction. *Hint:* What has been lost from **29** to allow the cyclisation to occur?



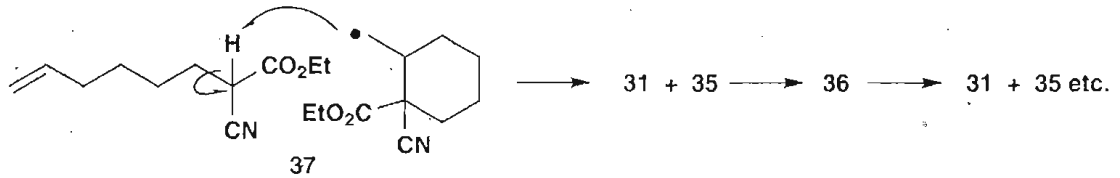
Answer 24.2: Just as with NBS, a weak σ-bond in **30** between electronegative elements is cleaved homolytically **30a** to generate two radicals though this time they are the same **32**.



Now the OH bond in **33** is very strong so the radical **32** abstracts a hydrogen atom **34** to give the most stable radical possible: the tertiary delocalised radical **35**. The combination of CN and CO_2Et is more stabilising than the simple alkene at the other end of the molecule. Cyclisation now gives a new and unstable radical **36**.

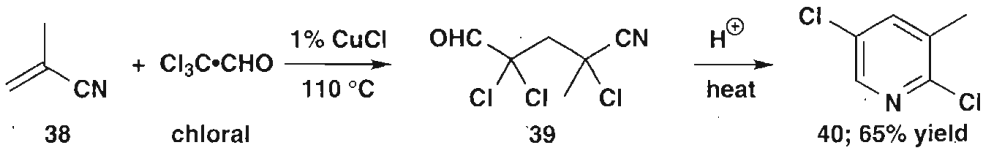


You might recall from the textbook chapter that good radical reactions are chain processes in which the last step creates another molecule of the key intermediate, in this case the stable radical **35**. The chain continues in this example when **36** abstracts the same hydrogen atom **37** to regenerate **35**. Radical **35** is stable because it is tertiary and conjugated with both CN and CO_2Et. Radical **36** is primary and has no stabilisation at all.

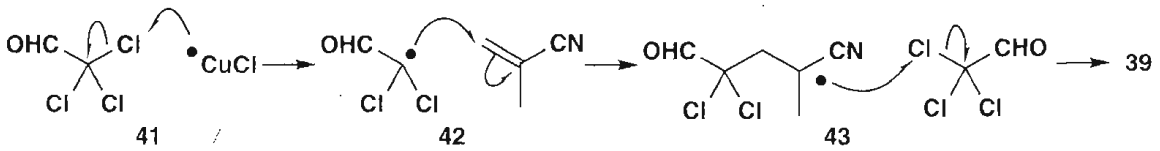


The second example is even more amazing. Combining the unsaturated nitrile **38** with chloral and catalytic amounts of Cu(I) gives an adduct[4] **39** that cyclises on heating to the substituted pyridine **40**. **Problem 24.3:** Suggest how the first step might occur. This is of course the radical

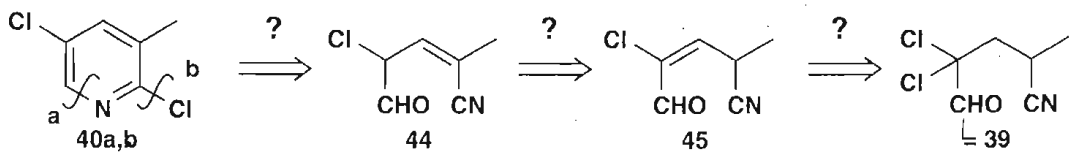
step and you may regard Cu(I) as a source of radicals, perhaps ClCu•. Remember to make the sequence a radical chain process as very little Cu(I) is needed.



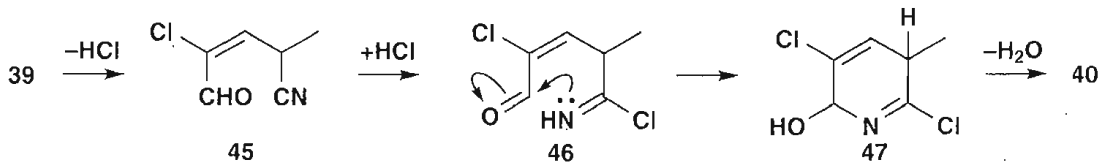
Answer 24.3: Drawing the initiator as ClCu•, chlorine abstraction is clearly indicated as one chlorine is lost in the product. In this step Cu(I) is oxidised to Cu(II). The new radical now adds in conjugate fashion to the nitrile **42** and the product completes the chain by removing a chlorine atom from another molecule of chloral **43. Problem 24.4:** Now can you suggest how the cyclisation occurs? This is an ionic reaction and you may like to try a disconnection approach so that you can work out which bonds are formed in the reaction.



Answer 24.4: There are many ways to get at the answer: we prefer to disconnect the enamine bond **40a** as the relative positions of the nitrogen atom and the methyl group reveal where the nitrile must be in the possible intermediate **39**. To write CN we also must remove a chlorine atom **40b**. Now we have a structure **44** that is starting to look like **39** and all we have to do is move the alkene **45** and add a chlorine atom back again.

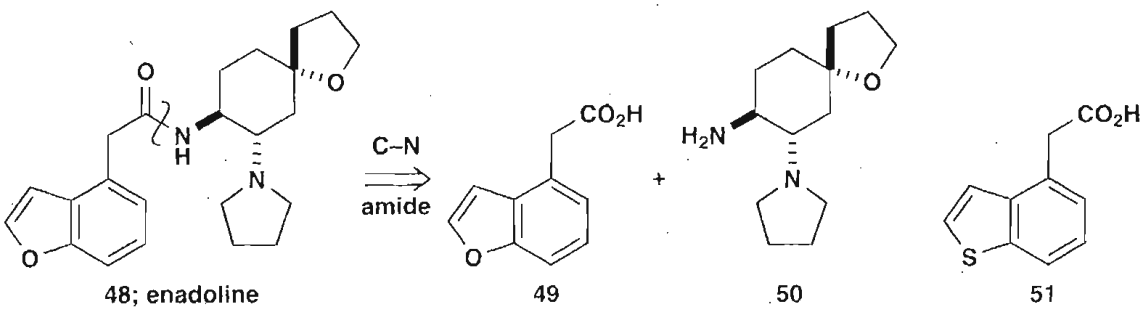


The details may not be correct but the mechanism might involve an elimination of HCl to give **45**, addition of HCl to the nitrile to give an intermediate that can cyclise **46** and a loss of water from **47** to give **40**.



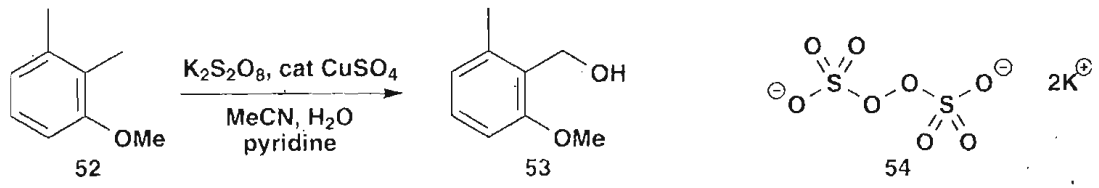
A Pharmaceutical Example

Parke-Davis have developed a series of selective analgesics[5] such as enadoline **48** that is clearly made from the complex chiral amine **50** and either the benzofuran **49** or the benzothiophene **51**. We shall be concerned only with **49** and **51** as these compounds have been made both by radical and by ionic chemistry.



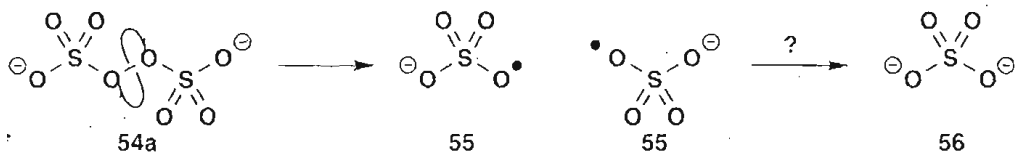
48; enadoline 49 50 51

The radical route starts with the oxidation of available **52** with potassium persulfate **54** to give the alcohol **53**. Note the impressive chemoselectivity: only the more hindered methyl group is oxidised.



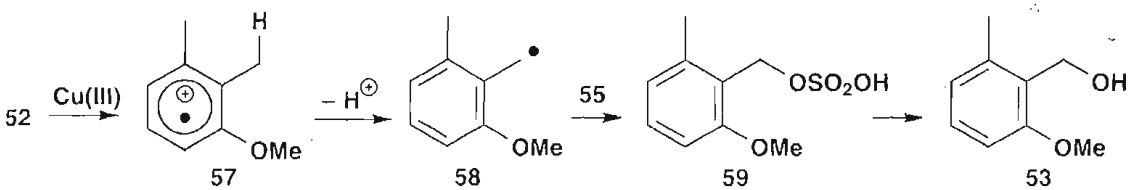
52 53 54

This must be an electronic rather than a steric effect.[6] Potassium persulfate breaks down in a familiar radical way **54a** into two radicals **55**. But these are not simple radicals: they are radical anions and would much prefer to be simple sulfate anions **56**.



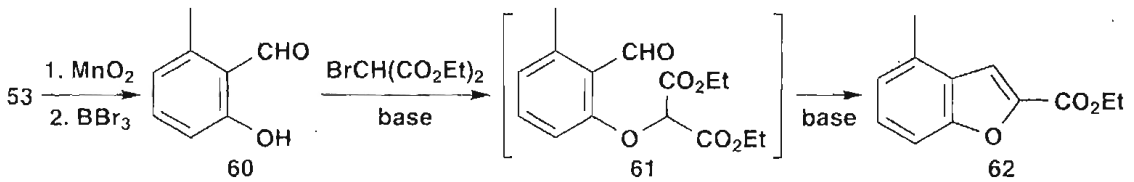
54a 55 55 56

They therefore capture an electron from Cu(II) to give very reactive Cu(III) which removes an electron from the aromatic ring. The radical cation **57** loses a proton (not a hydrogen atom!) to give the more stable radical, that is the one delocalised onto the OMe group **58**. This captures another **55** and the sulfate produced **59** hydrolyses to **53**.



57 58 59 53

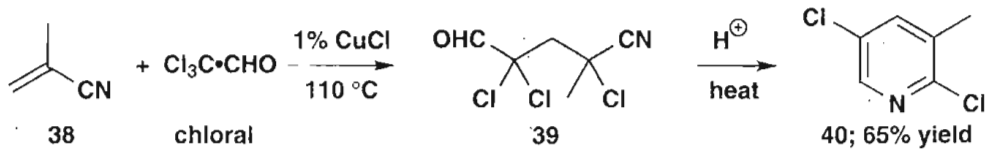
Allylic oxidation with MnO_2 gives the aldehyde **60** that reacts with bromo-malonate to give the benzofuran **62**, presumably via **61**, by an aldol reaction followed by decarboxylation.



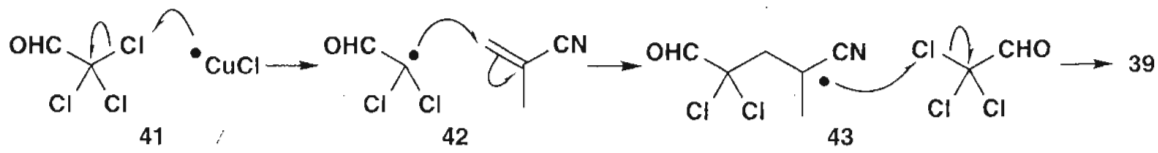
60 61 62

Now the other methyl group must be functionalised and NBS is fine for that. Hydrolysis of both the ester and the benzylic bromide in **63** gives **64** and decarboxylation gives the alcohol **65**.

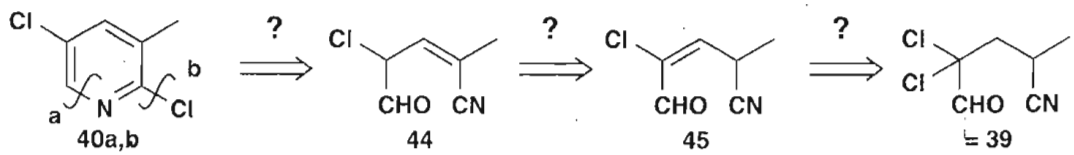
step and you may regard Cu(I) as a source of radicals, perhaps ClCu•. Remember to make the sequence a radical chain process as very little Cu(I) is needed.



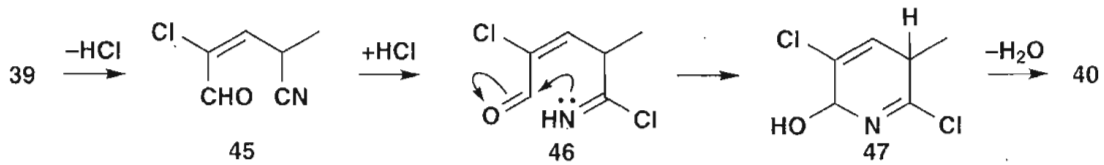
Answer 24.3: Drawing the initiator as ClCu•, chlorine abstraction is clearly indicated as one chlorine is lost in the product. In this step Cu(I) is oxidised to Cu(II). The new radical now adds in conjugate fashion to the nitrile **42** and the product completes the chain by removing a chlorine atom from another molecule of chloral **43. Problem 24.4:** Now can you suggest how the cyclisation occurs? This is an ionic reaction and you may like to try a disconnection approach so that you can work out which bonds are formed in the reaction.



Answer 24.4: There are many ways to get at the answer: we prefer to disconnect the enamine bond **40a** as the relative positions of the nitrogen atom and the methyl group reveal where the nitrile must be in the possible intermediate **39**. To write CN we also must remove a chlorine atom **40b**. Now we have a structure **44** that is starting to look like **39** and all we have to do is move the alkene **45** and add a chlorine atom back again.



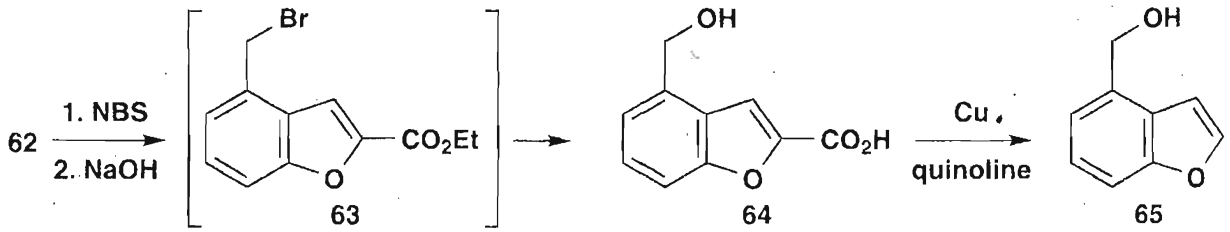
The details may not be correct but the mechanism might involve an elimination of HCl to give **45**, addition of HCl to the nitrile to give an intermediate that can cyclise **46** and a loss of water from **47** to give **40**.



A Pharmaceutical Example

Parke-Davis have developed a series of selective analgesics[5] such as enadoline **48** that is clearly made from the complex chiral amine **50** and either the benzofuran **49** or the benzothiophene **51**. We shall be concerned only with **49** and **51** as these compounds have been made both by radical and by ionic chemistry.

The rest of the synthesis is trivial.[7] More conventional syntheses of **49** and **51** without radical chemistry have also been completed.[8]



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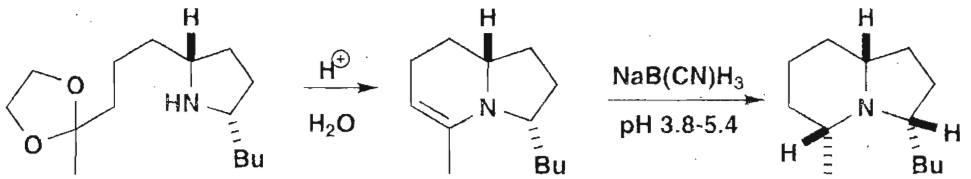
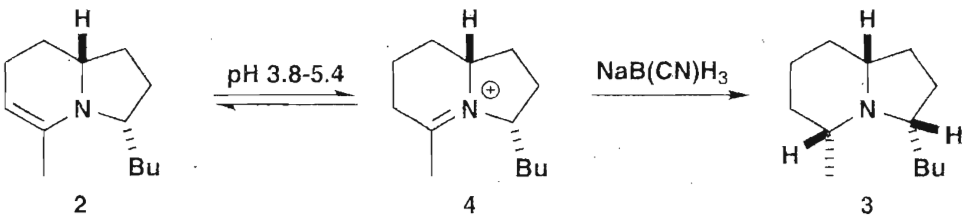
25 Two-Group Disconnections V: 1,4-Difunctionalised Compounds

A Problem from the Textbook: We revealed in chapter 25 of the textbook that compound **1** (**54** in the textbook) cyclised in acid to the enamine **2** and that this enamine was reduced to the saturated amine **3** by cyanoborohydride. **Problem 25.1:** Enamines are not usually reduced by nucleophilic reducing agents. How is this step successful?

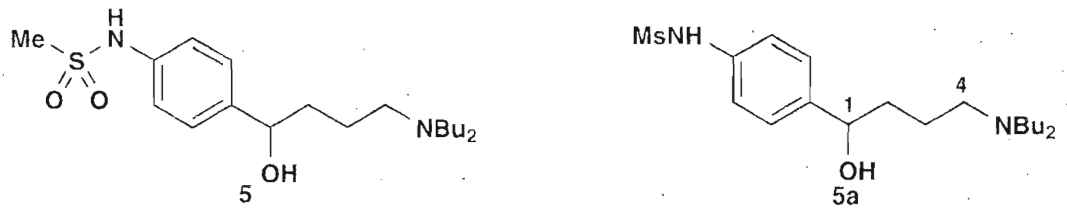


Answer 25.1: The slightly acidic conditions allow equilibration between the enamine **2** and the iminium salt **4** that is reduced by cyanoborohydride.[1]

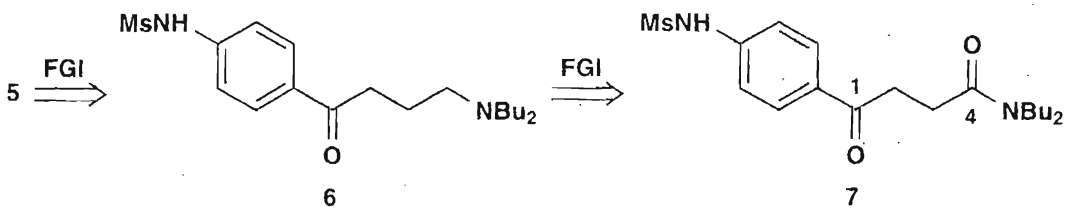


Buying the 1,4-diCO Relationship

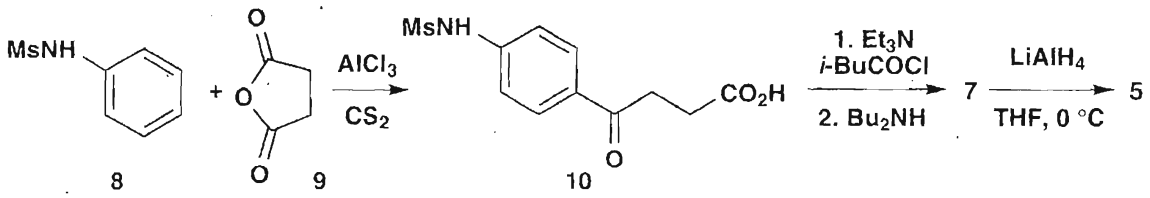
The Pharmacia & Upjohn drug **5**, loosely based on adrenalin, has a 1,4-diX relationship between the alcohol and the amine in the side chain. **Problem 25.2:** Suggest a synthesis of this compound using the hint that the 1,4-relationship **5a** is bought and not made.



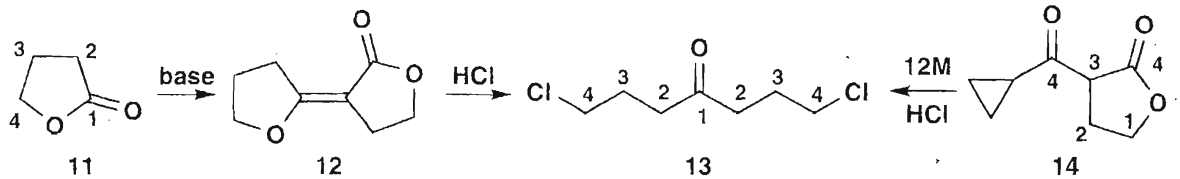
Answer 25.2: The alcohol suggests that the benzene ring has been joined to the side chain by a Friedel-Crafts reaction so we would change it into a ketone **6**. But the amine could also be made from an amide (chapter 8) and **7** gives us a compound with a 1,4-diCO relationship.



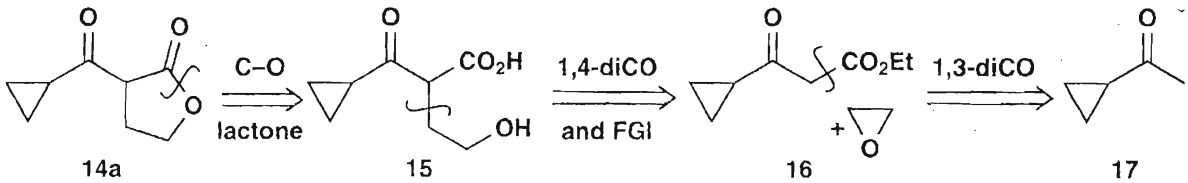
You might at this stage be reminded of succinic anhydride **9**, mentioned as an available starting material in the textbook chapters 5 and 25. An amide such as **8** is perfect for getting a Friedel-Crafts reaction in the *para* position and the two identical carbonyl groups in **9** are now automatically distinguished in **10**. Conversion of the acid into the acid chloride and then to the amide **7** is followed by reduction with $LiAlH_4$ that reduces both amide and ketone.[2]



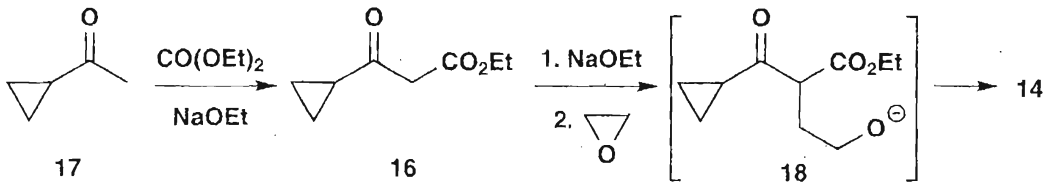
In the textbook we also made the dichloroketone **13** from the available starting material butyrolactone **11**. An alternative synthesis comes from a substituted butyrolactone **14**. **Problem 25.3:** Suggest a synthesis for **14**. *Hint:* This time the 1,4-diCO relationship can be made rather than bought.



Answer 25.3: Opening the lactone **14a** reveals a compound with two carbonyl groups and an alcohol **15**. Disconnection at the branchpoint allows the addition of ethylene oxide to a stable enolate from the 1,3-dicarbonyl compound **13** that can be made by regioselective acylation of **14**.

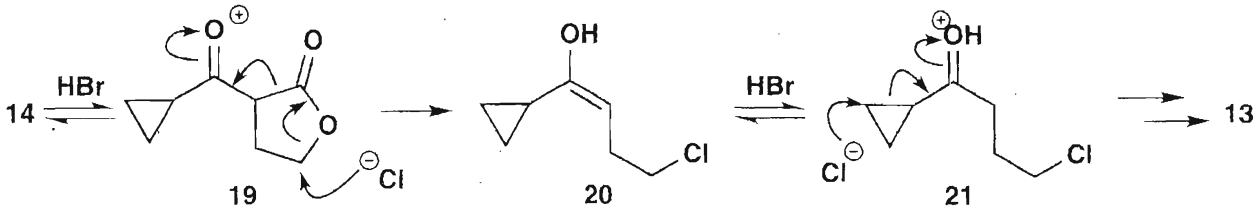


Reaction of **17** with diethyl carbonate and ethoxide gives the keto-ester **16** and reaction of its enolate with ethylene oxide gives the target molecule **14**, no doubt via the alkoxide **18** that cyclises spontaneously under the reaction conditions.



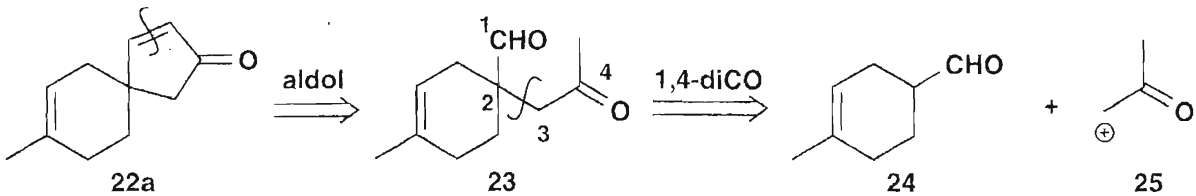
Problem 25.4: Suggest a mechanism for the transformation of **14** into **13**.

Answer 25.4: Protonation and loss of CO_2 **19** give the enol **20** and hence a protonated ketone that is attacked by chloride[3] with the opening of the strained three-membered ring **21** to give the enol of the product **13**. You may well have suggested routes that differ in detail but, as long as they have two nucleophilic attacks by chloride ion on a protonated intermediate and a decarboxylation, that is acceptable.

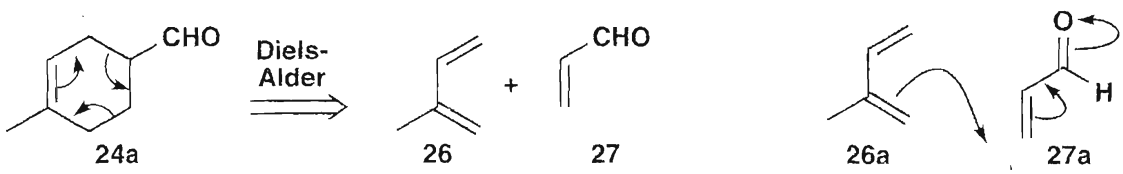


Problem 25.5: Suggest a synthesis of the spiroenone **22** that was needed for a synthesis of acorone.[4]

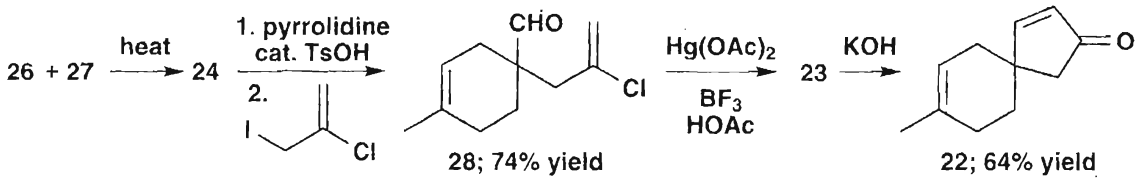
Answer 25.5: The obvious aldol disconnection **22a** reveals a 1,4-diCO compound that we should very much like to disconnect next to the branchpoint **23**. The sensible way to do this is to use the aldehyde **24** and a reagent for the a^2 synthon **25**.



The main reason that this is 'sensible' is that the aldehyde **24** is a Diels-Alder product revealed by drawing the mechanism of the imaginary reverse reaction **24a** (chapter 17). We must check that the starting materials **26** and **27** will give the right regiochemistry and we can do that by combining the more nucleophilic end of the diene **26a** and the more electrophilic end of the dienophile **27a**. Hence the Diels-Alder should have the right regioselectivity.

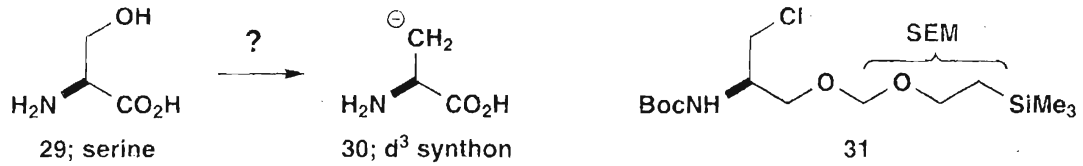


And it does. The obvious way to carry out the next step would be to combine the enamine of the aldehyde **21** with chloroacetone. The published synthesis[4] uses the pyrrolidine enamine of **24** but combines it with an allylic iodide to give **28** that needs mercury(II) and a Lewis acid to form **23**. There is no ambiguity in the cyclisation of **23** to **22** as the aldehyde cannot enolise.

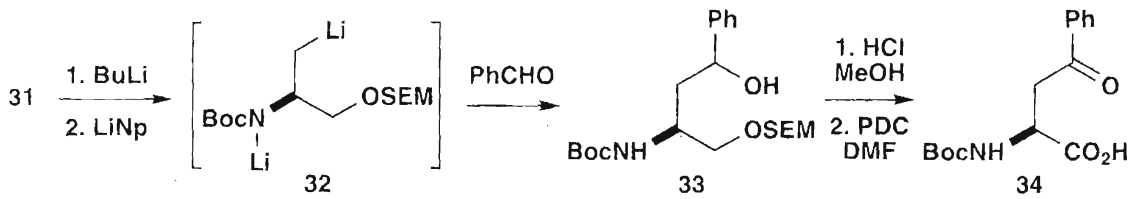


Troubles and Triumphs with Homoenolates

Perhaps the least favourite method for 1,4-diCO synthesis is the direct addition of a homoenolate (a d^3 reagent) to an electrophilic carbonyl compound. Recent work[5] illustrates problems and successes. The natural amino acid serine **29** is cheap and available as a single enantiomer. If the CH_2OH group could be turned into a *carbon* nucleophile, we should have a general reagent for amino acid synthesis corresponding to the synthon **30**. It turned out that all three functional groups of serine had to be altered: the carboxylic acid had to be reduced and protected, the amino group had to be protected and the OH group changed to a chloride **31**.



An example of its use is synthesis of the unusual keto-amino acid **34**. Two bases, BuLi and lithium naphthalenide give the dilithium derivative **32** that reacts with benzaldehyde to give **33**. Then HCl in MeOH removes the SEM group and oxidation converts both alcohols into carbonyl compounds **34**.

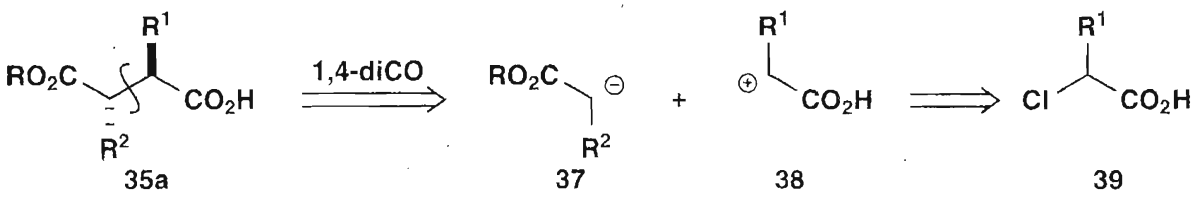


A General Synthesis of Partly Protected Succinic Acids

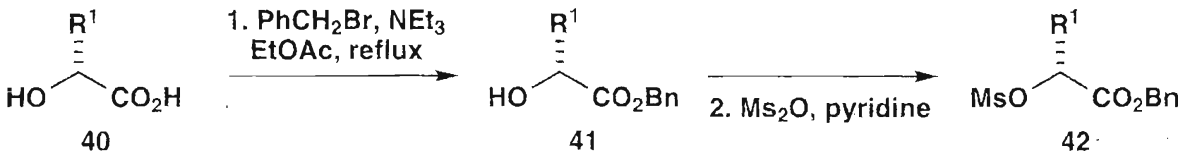
The substituted succinic acids **35** with one acid protected as an ester were needed at Roche to make compounds such as **36** as cartilage-protecting agents for the prevention of arthritis. We tell you these details partly out of interest and partly so that you can see that the simple chemistry you are seeing in these books is relevant to much larger molecules. **Problem 25.6:** Why is it necessary to have one acid protected? Which bond in **35** would you like to disconnect?

Answer 25.6: One acid must be turned into an amide so they need to be different. The bond we should like to disconnect is between the two branchpoints. **Problem 25.7:** How might that be achieved?

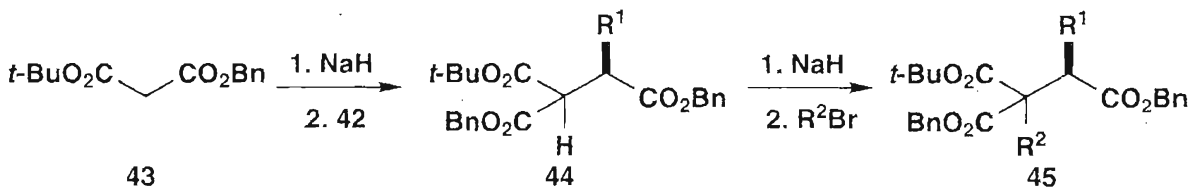
Answer 25.7: One acid (or ester) can supply a nucleophilic enolate **37** while the other will have to be a reagent for the a^2 synthon **38** such as an α-halo-acid **39**.



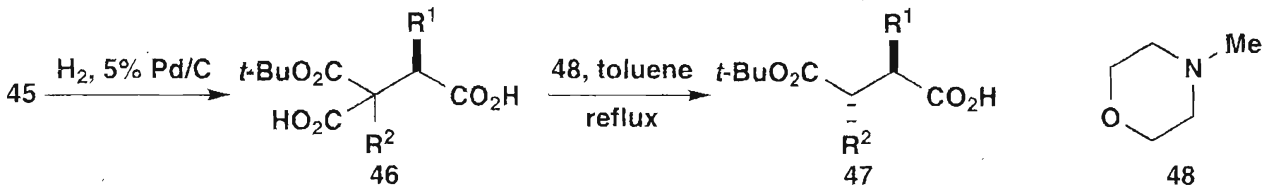
In fact, the workers at Roche chose to use an α-hydroxy-acid because such compounds are more available than α-halo-acids and many are available as single enantiomers. The acid was first protected as its benzyl ester **41**. Note the conditions for this step: Et_3N is strong enough to remove the carboxylic acid proton but not the alcohol proton and the anion of the carboxylic acid is more nucleophilic than the neutral alcohol (chapter 5). The alcohol was turned into a leaving group by mesylation **42**.



The enolate was supplied by a malonate ester **43** with two different ester groups. Alkylation with **42** must occur with inversion and gives **44** with the right stereochemistry. Now R^2 can be added by a second alkylation to give **45**.

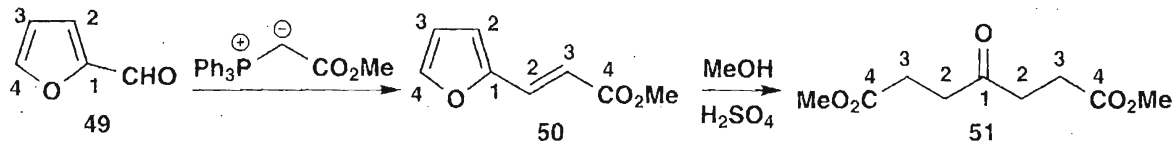


Hydrogenation removes both benzyl groups **46** and heating with *N*-methylmorpholine **48** decarboxylates the malonate to give **47** (= **35**; R = *t*-Bu). Using a malonate **43** for **37** has allowed alkylation with **42** without racemisation, has allowed us to keep just one of the three esters, and has allowed[6] epimerisation at the centre bearing R^2 during the decarboxylation in favour of the more stable *anti*-product **47**.



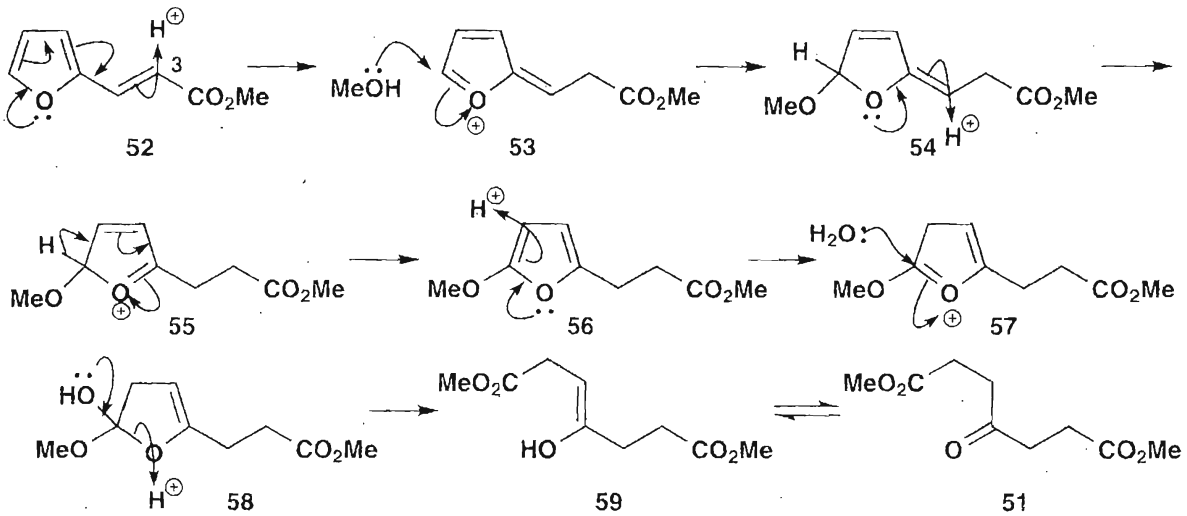
A Remarkable Reaction from the Textbook

In the textbook we promised to discuss the mechanism of the remarkable methanolysis of furan **50** into the keto-diester **51** with two 1,4-relationships.



49 50 51

At first sight it appears that a mistake has been made, but we'll take it step by step. The side chain (C-1 to C-4) must gain two protons so a good beginning is to protonate at C-3 using the furan oxygen atom **52**. Addition of MeOH at C-1 naturally follows and now a series of proton transfers **54** – **56** saturate the side chain and allow the addition of one molecule of water **57**. These latter stages could be written in various ways but the essence is the liberation of ester and enol of the ketone **59** as the furan is cleaved.



52 53 54 55 56 57 58 59 51

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5. M. N. Kenworthy, J. P. Kilburn and R. J. K. Taylor, *Org. Lett.*, 2004, **6**, 19.
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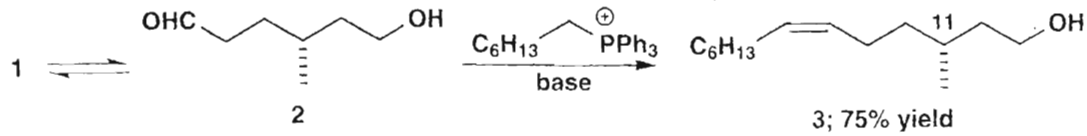
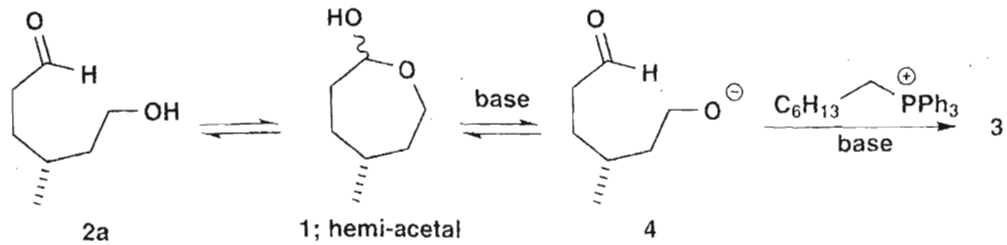
26 Strategy XII: Reconnection

A Problem from the Textbook: We revealed in chapter 26 in the textbook that: 'The aldehyde **2** is in equilibrium[1] with a cyclic compound **1** that also can be used in the Wittig reaction to give the same product **3**.' **Problem 26.1:** What might this cyclic compound **1** be?

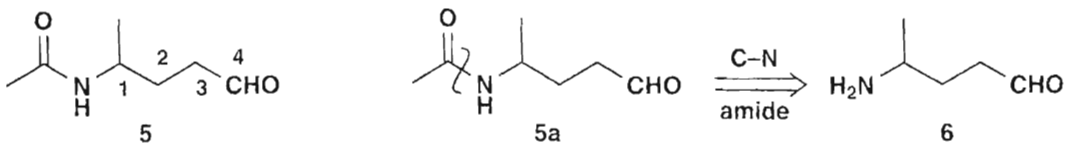


Answer 26.1: The hydroxyaldehyde **2** is in equilibrium with its hemi-acetal **1** as is more obvious from diagram **2a**. If it had been a five-membered hemiacetal, it would probably have existed entirely in that form but seven-membered rings are less stable. The hemi-acetal opens under the basic reaction conditions to give **4** thus freeing the aldehyde for the Wittig reaction.



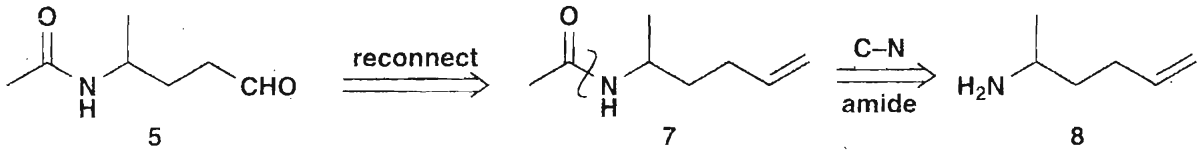
Synthesis of 1,2- and 1,4-diCO Compounds by Oxidative C=C Cleavage

The amido-aldehyde **5** has a 1,4-diX relationship. The obvious amide disconnection **5a** gives an amino aldehyde **6** that would instantly cyclise. **Problem 26.2:** With this in mind, suggest a synthesis of **5**.

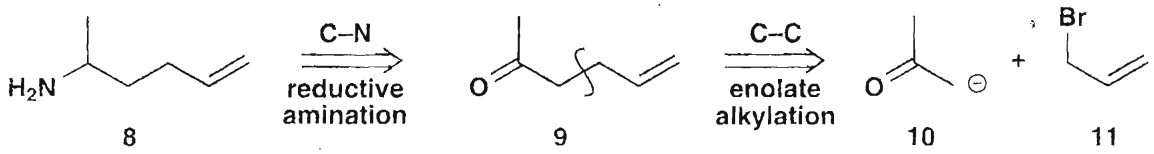


Workbook for Organic Synthesis: The Disconnection Approach, Second Edition, Stuart Warren and Paul Wyatt

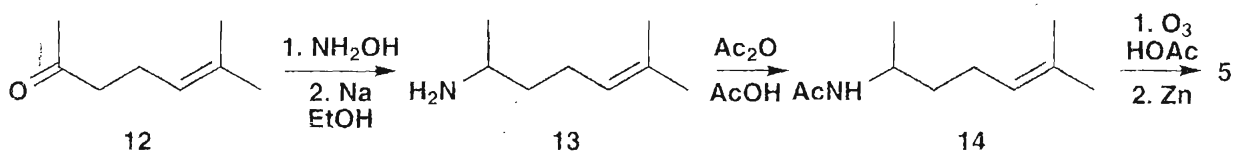
Answer 26.2: We want to reveal the aldehyde only after the amide is in position so reconnection to **7** gives a perfect solution.[2] The alkene will not react with the amine so the amide disconnection **7** to **8** now gives a reasonable solution.



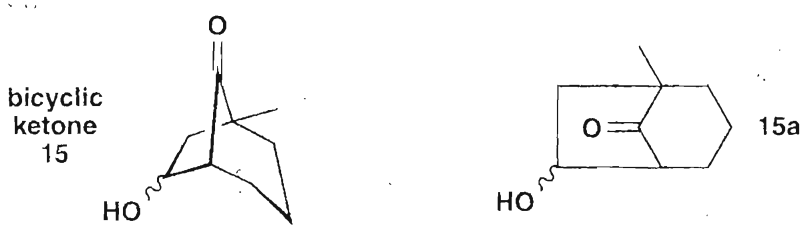
The branched amine in **8** could come from a ketone **9** by reductive amination and the ketone should be easy to make by alkylation. Some reagent for the enolate **10** of acetone and reactive allyl bromide **11** will do this.



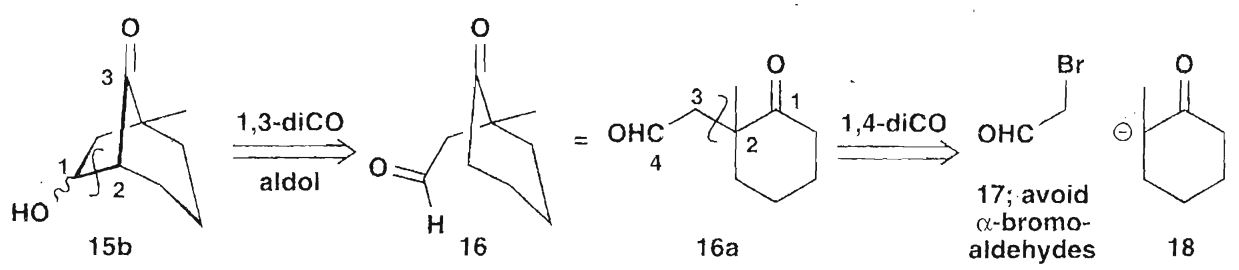
In fact the known ketone **12** (it is compound **62** in chapter 13 of the textbook) was already available so the chemists chose[2] to produce amine **13** by reductive amination and oxidise the amide **14** to give **5**. This is old work so reduction of the oxime of **12** with sodium in ethanol was used where we might prefer a more modern method (chapter 8). It is of course unimportant that there are two methyls instead of two hydrogens on the alkene as that just means that the by-product is acetone rather than formaldehyde.



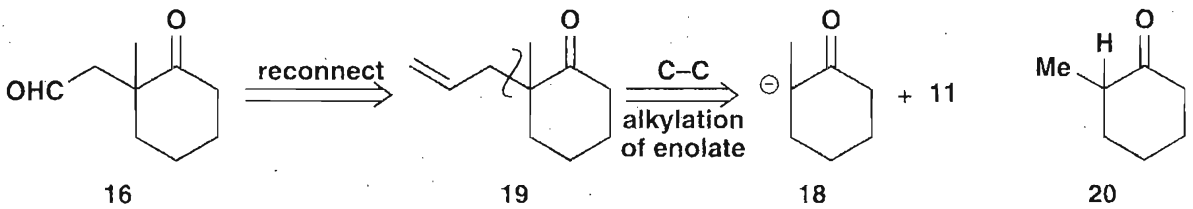
Problem 26.3: Suggest a synthesis of the bicyclic ketone **15**, often drawn less realistically as **15a**. Work on whichever diagram you prefer. You should examine the functional group relationships before considering any reconnection as a disconnection is needed first.



Answer 26.3: There is a 1,3-diCO relationship between the C=O and OH groups revealing that **15** is an aldol product from the keto-aldehyde **16**, now better drawn in a flat drawing **16a**. We now have a 1,4-diCO relationship and direct disconnection of the bond to the branchpoint would require a reagent for the synthon **18** and an α-bromoaldehyde **17** we should rather avoid.

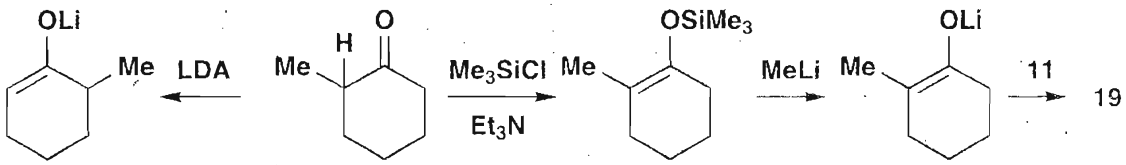


The solution is to use an allyl group, that is reconnection of **16** to **19**. Now alkylation of the same enolate **18** with allyl bromide **11** is easy. But we still need to control the regioselectivity of enolisation of the unsymmetrical ketone **20**. It is time to read chapter 14 of the textbook again.



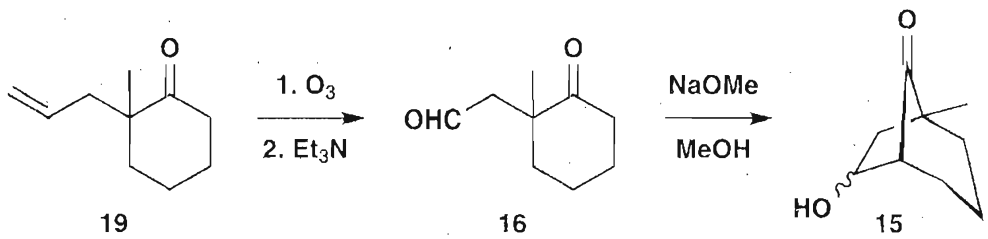
16 19 18 20

But if you do that, you will see that forming an enolate on the less substituted side is easy – just use LDA **21** – but not so easy on the other side. The answer is to make a silyl enol ether **22** under equilibrating conditions. Then addition of MeLi produces Me_4Si and releases the lithium enolate **23** which reacts with allyl bromide. This is rather complicated chemistry for this book and is developed further in *Strategy and Control*.



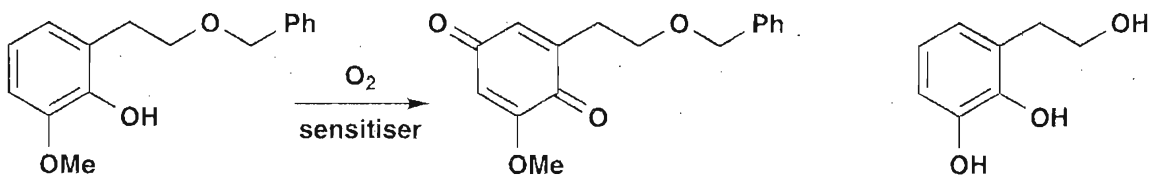
21 20 22 23

Then the allyl group in **19** was ozonised and worked up with Et_3N to ensure that no oxidation to the carboxylic acid occurred and that the aldehyde **16** was the product. Reaction with methoxide in methanol gave the required aldol product[3] **15**.



19 16 15

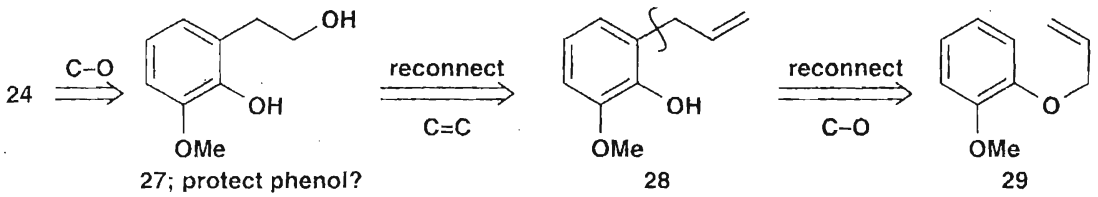
When Corey[4] wanted to synthesise the plant hormone gibberellic acid, he chose to use **24** as an intermediate. It was essential that only one OH group was free as the next step was the oxidation of **24** to the quinone **25**. Later, each of the protected OH groups needed to be freed selectively so they had to be protected differently. **Problem 26.4:** Suggest a synthesis of **24**. Selective protection of **26** is not a realistic strategy.



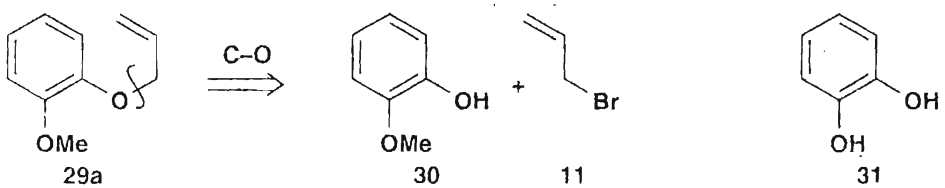
24 25 26

Hint: Did you consider another problem: how to get three substituents next to each other round a benzene ring? Or to put it another way: what would be a suitable starting material? The answer to both these questions is to use catechol (*ortho*-dihydroxybenzene) as starting material and use an OH group to direct the final side chain. You need to have read chapter 35 in the textbook to do this.

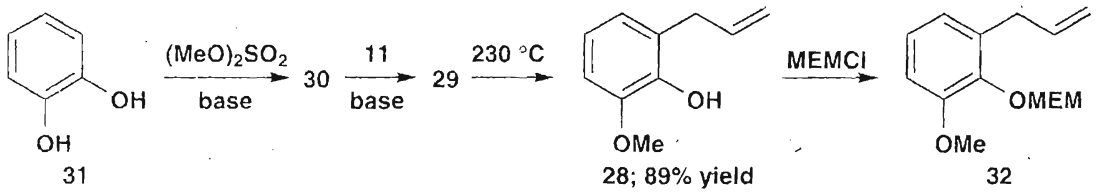
Answer 26.4: The benzyl group can obviously be added to the alcohol in **27**, though protection of the phenol may be necessary. We cannot easily add the side chain but if we reconnect to an allyl group **28**, the Claisen rearrangement should come to mind so we disconnect the C–C and reconnect the C–O bond to give **29** which is clearly derived from catechol.



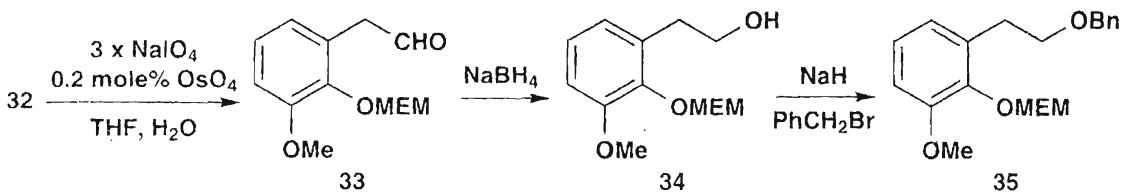
The allylic ether **29** is made from the phenol **30** and allyl bromide **11** and the only remaining question is how best to make **30** from catechol **31**.



You could probably make **30** from catechol **31** by methylation with dimethylsulfate in base but this is not necessary as it is available as guaiacol. Simple allylation comes next. Rearrangement by heating gave **28** in good yield. It is necessary to protect the phenol against oxidation so a MEM group [$MeO(CH_2)_2OCH_2$–] was added **32**.

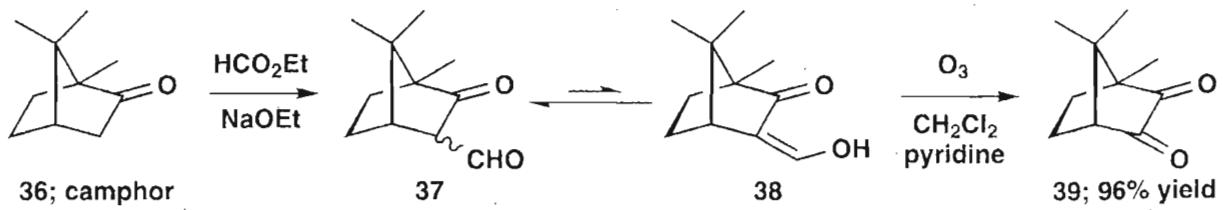


Note the conditions for the oxidative cleavage: only catalytic OsO_4 is needed with an excess of sodium periodiate. The product **33** was immediately reduced to **34** and the alcohol protected **35**. We now have the triol **26** with different protecting groups on each OH group. The MEM group was removed with CF_3CO_2H giving **24** in 74% yield from **28**.

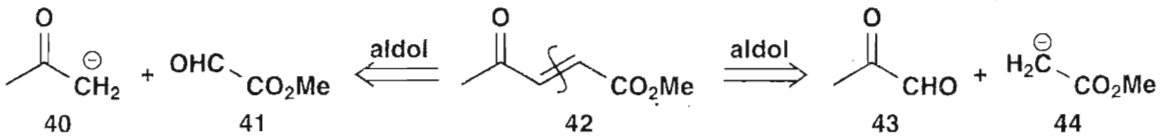


Oxidative Cleavage of Aldol Products

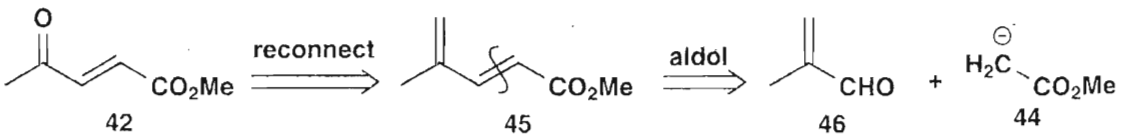
Even if the alkene is conjugated with a carbonyl group, as in an aldol product, it can be cleaved by oxidation. Ozone is an electrophile and prefers non-conjugated alkenes, but it has no choice in this oxidation of **38** to 'camphor quinone' **39** – not a quinone but an α-diketone. In the reaction with camphor **36**, many different carbonyl compounds could be used as the electrophile: here ethyl formate works particularly well. The initial product **37** is less stable than its enol **38** which is ozonised.[5]



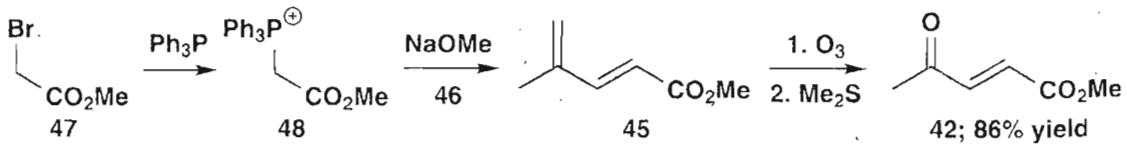
The simple ene-dione **42** looks as though it could be made by an aldol strategy. However, aldol disconnections give reasonable enolates **40** and **44** but unstable-looking α-dicarbonyl compounds **41** and **43** as electrophiles. Since **43** is rather like pyruvate, it may be possible to use it, but we should look for an alternative. **Problem 26.5:** Suggest a synthesis of **42** using a reconnection strategy.



Answer 26.5: Reconnecting the ketone in **42** to make it an alkene **45** allows a simple aldol disconnection to available methacrolein **46** and the enolate **44** of ethyl acetate. The aldehyde cannot enolise and is more electrophilic than the ester so things look good.

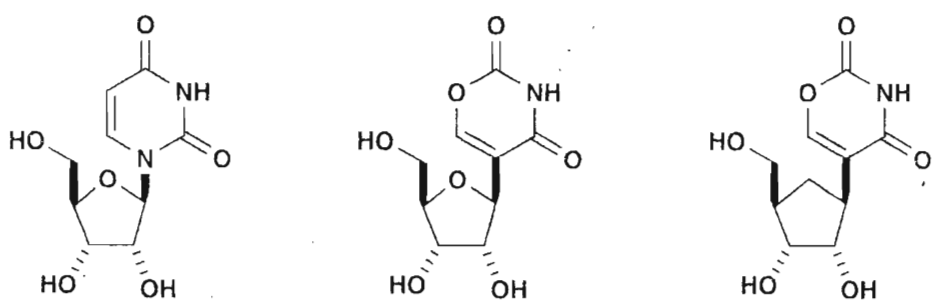


In fact a Wittig reaction was used[6] to make **45**, with the ylid from **48** playing the part of the enolate. Conjugate addition to **43** is probably a risk but using an ylid ensures that only direct addition leads to a Wittig product. If conjugate addition is reversible, which it may well be with this stable ylid, then everyone's a winner. The ozonolysis was regioselective in favour of the more nucleophilic alkene away from the carbonyl group.

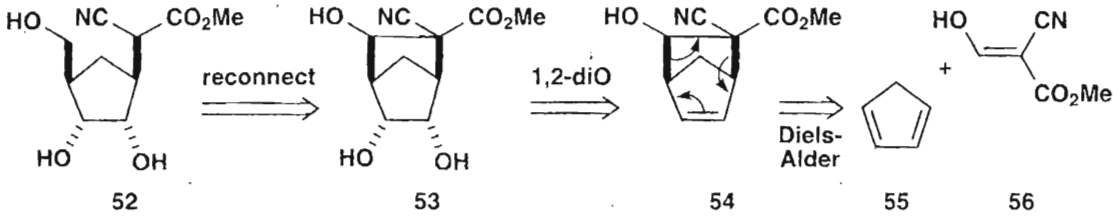


Cleavage of Aldol Products by Retro-Aldol Reaction

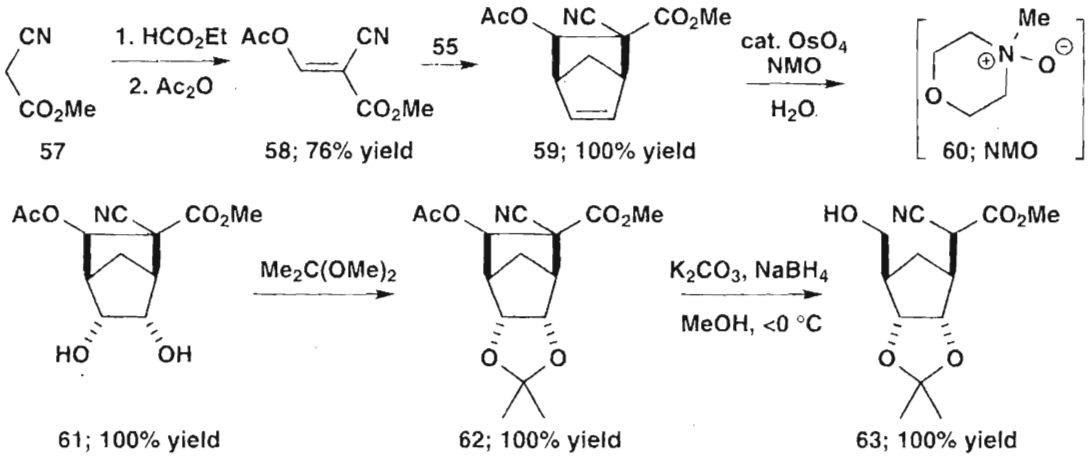
We have concentrated on oxidative cleavage but other cleavages are used and we shall give just one example: the synthesis of **51**. Antibiotics and anti-viral drugs are often invented by modifying the nucleosides from DNA or RNA. Uridine **49** is a natural nucleoside. Oxazinomycin **50** is an antibiotic: the heterocyclic ring has been changed. Chemists in Japan[7] wanted to make another modification by removing the oxygen atom from the sugar ring to give **51**.



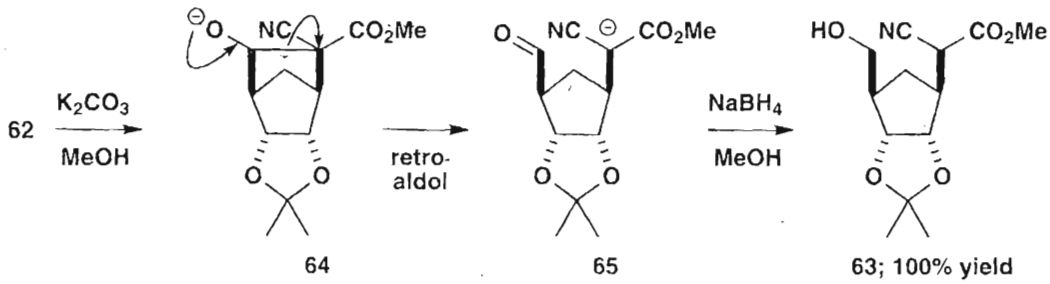
They decided to make **52** from which they could construct the heterocyclic ring. They argued that, if a single bond could be used to reconnect two atoms **53**, removal of the 1,2-diol would reveal an alkene **54** which could be made by a Diels-Alder between cyclopentadiene **55** and the unusual dienophile **56**.



Compound **56** may remind you of **38** and was made in the same way, though the enol form was trapped here by acetylation **58**. Diels-Alder reaction gave the cyclic alkene **59** then dihydroxylation using *N*-methylmorpholine-*N*-oxide (NMO **60**) as the stoichiometric oxidant gave the diol **61**, protected as the acetal **62**.



The retro-aldol required MeOH and a weak base for transesterification to the anion **64** that fragmented to the aldehyde **65** which is reduced *in situ* to **63**. Other reactions too can be turned backwards to make useful products.



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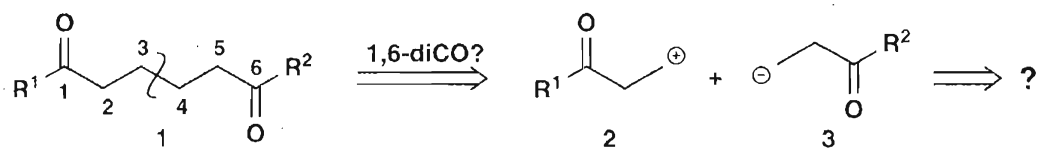
1. D. Pempo, J. Viala, J. -L. Parrain and M. Santelli, *Tetrahedron: Asymmetry*, 1996, **7**, 1951.
2. B. Helferich and W. Dommer, *Ber.*, 1920, **53**, 2004.
3. E. W. Colvin and S. Cameron, *J. Chem. Soc., Chem. Commun.*, 1986, 1084.
4. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck and J. -L. Gras, *J. Am. Chem. Soc.*, 1978, **100**, 8031.
5. D. Yang and S. W. Pelletier, *Chem. Commun.*, 1968, 1055.
6. P. L. Stotter and J. B. Eppner, *Tetrahedron Lett.*, 1973, 2417.
7. N. Katagiri, M. Tomura, T. Haneda and C. Kaneko, *J. Chem. Soc., Chem. Commun.*, 1987, 1422.

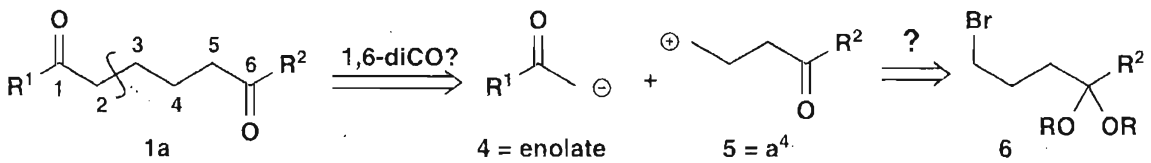
27 Two-Group C–C Disconnections VI: 1,6-diCarbonyl Compounds

Problems from the Textbook

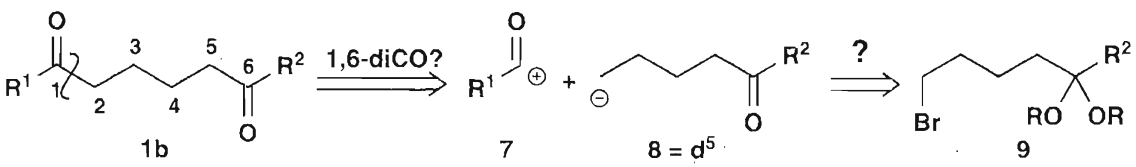
We introduced chapter 27 in the textbook with this comment: 'If we try to start in the same way as we have with the other chapters of this kind, with a generalised 1,6-dicarbonyl compound **1** and disconnect in the middle we might be relieved to see an a^3 synthon **2** easily recognised as an enone in real life, but the d^3 synthon **3**, with unnatural polarity, caused us problems in chapter 25 and now we should need a reagent for **3** that does conjugate addition. Though there are a few ways to do this, it has not been a popular strategy.' **Problem 27.1:** Draw some of the other possible disconnections and explain why they are difficult.



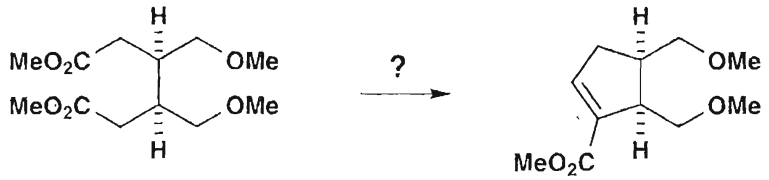
Answer 27.1: We might try disconnecting a different bond **1a** and again be pleased to see the enolate **4** but also be unhappy about the a^4 synthon **5**. We should probably have to use a protected alkyl halide so that we would not be using the ketone at all. Reversing the polarity of this disconnection only makes things worse.



Another possibility is **1b**: again we have a simple acylating agent **7** but a d^5 synthon **8** for which we could suggest little other than a protected alkyl halide **9** that would have to be turned into a Grignard reagent. There are more possibilities, but you get the idea.

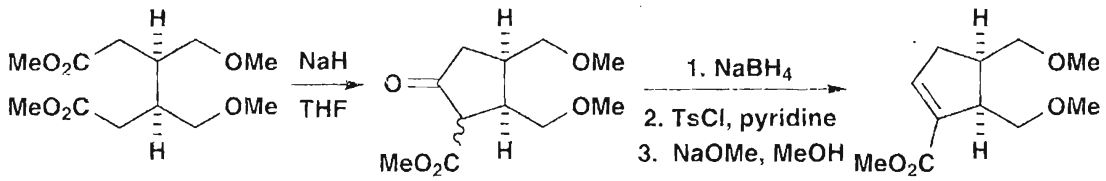


Later in the textbook we discussed the synthesis of compound **10**. In fact, what Heathcock wanted was the cyclopentene **11**. **Problem 27.2:** Suggest how this transformation might be carried out.



10 11

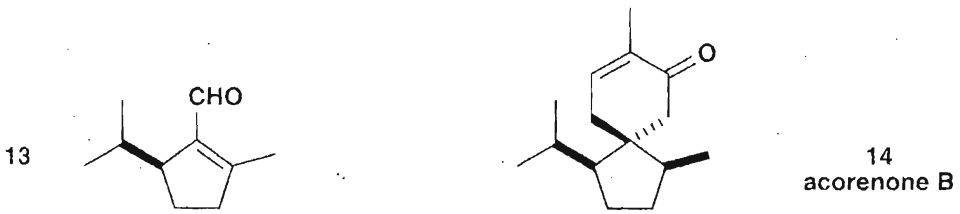
Answer 27.2: Since **10** is symmetrical, cyclisation by a Claisen ester condensation is bound to give **12** as it doesn't matter which ester forms the enolate.[1] The stereochemistry of the ester group in **12** is also irrelevant as it disappears on reduction and elimination.



10 12; 78% yield 11; 58% yield

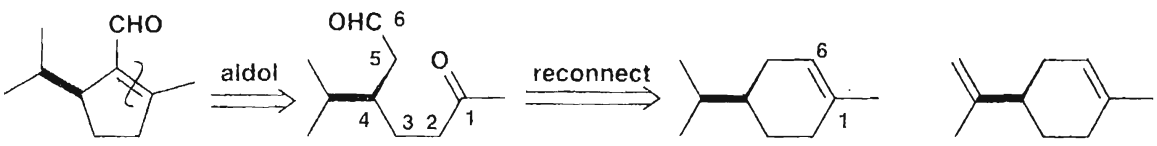
The Synthesis of Acorenone B

In chapter 25 of this workbook we mentioned the natural product acorone and now we come to an intermediate **13** in the synthesis[2] of the related acorenone **14**. **Problem 27.3:** Suggest what would be the ideal starting material to make this compound **13**.



14
acorenone B

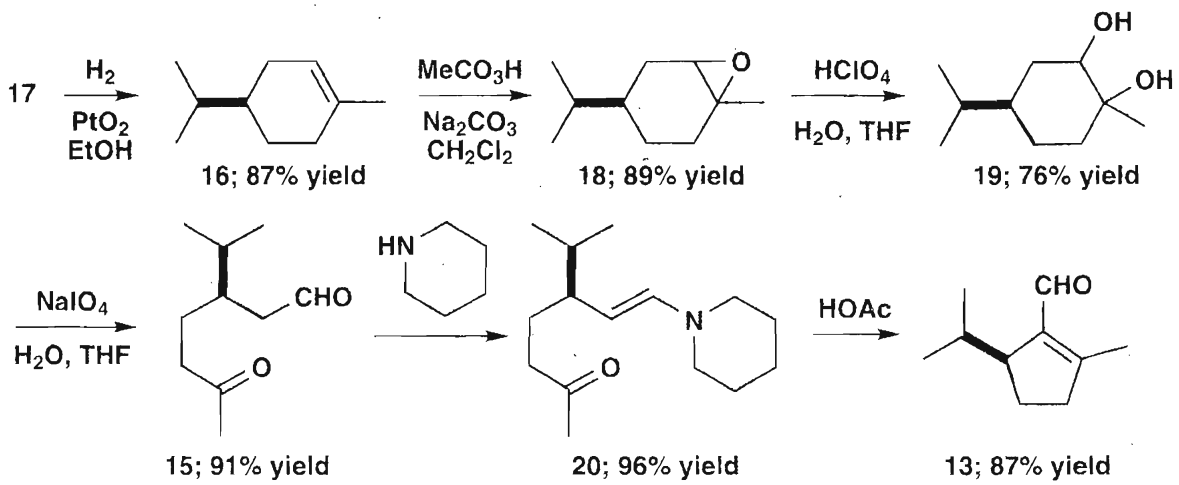
Answer 27.3: Making the aldol disconnection **13a** reveals a 1,6-dicarbonyl compound **15** that reconnects to the cyclohexene **16**. As it happens, there is an available terpene, the citrus flavour *R*-(+)-limonene **17**, that is almost exactly what we want.



13a 15 16 17; *R*-(+)-limonene

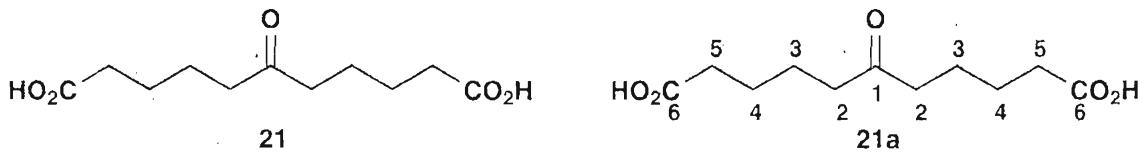
So the question is: can we hydrogenate just one of the two alkenes? The answer is 'yes' as White discovered after some trial and error. Hydrogenation over Adam's catalyst does the job in excellent yield. The oxidative cleavage was done by making the epoxide **18**, opening it with water to give the diol **19** and cleaving that with sodium periodate. You might expect that cyclisation to **13**

would occur easily in acid or base but a mixture of products was formed. Only when the enamine **20** was made and isolated and then treated with weak acid, was a good yield of **13** obtained.

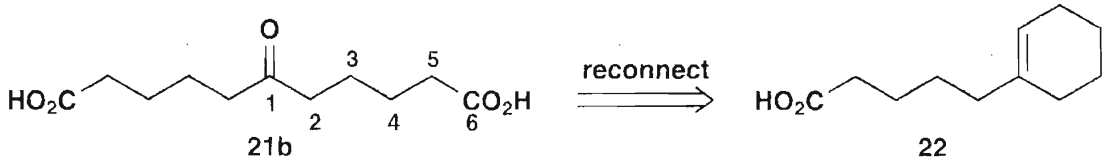


The Synthesis of a Symmetrical Keto-di-Acid

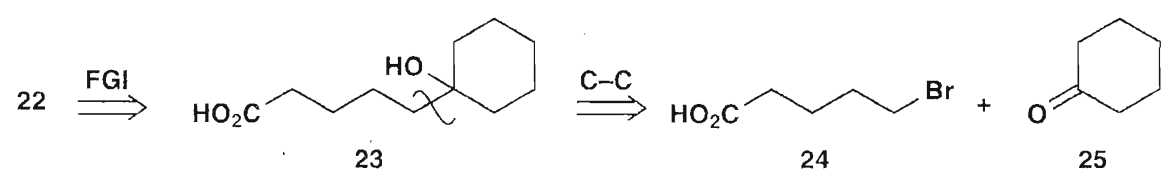
The symmetrical compound 6-keto-undecadienoic acid **21** has been synthesised by several different routes and we are going to explore these in a series of problems. There are obviously two identical 1,6-diCO relationships **21a**. **Problem 27.4:** What does the reconnection strategy suggest?



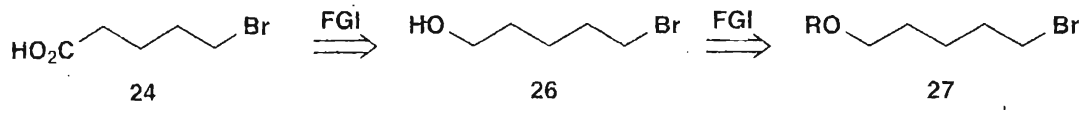
Answer 27.4: Reconnecting either of the 1,6-diCO relationships gives the same cyclohexene **22** with the other carboxylic acid on a side chain. None of the three standard strategies (Robinson annelation, Diels-Alder or reduction of an aromatic compound – chapter 36) seems much use. **Problem 27.5:** What do you suggest?



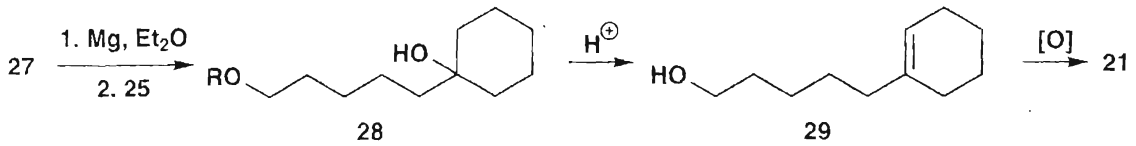
Answer 27.5: The simplest solution seems to be dehydration of the tertiary alcohol made by the addition of a Grignard reagent to cyclohexanone. However, we cannot use **24** itself as the carboxylic acid would destroy the Grignard reagent and we can't protect it as an ester as the Grignard reagent would cyclise. **Problem 27.6:** Any suggestions?



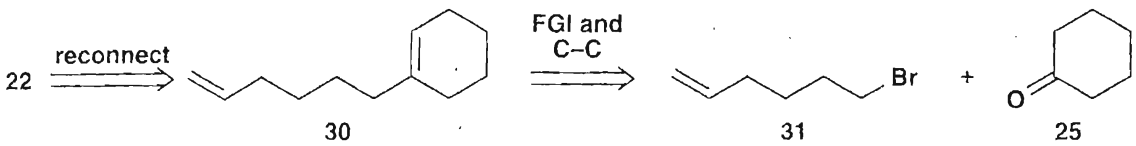
Answer 27.6: One possibility would be to use a protected alcohol **27** instead where R is perhaps THP.



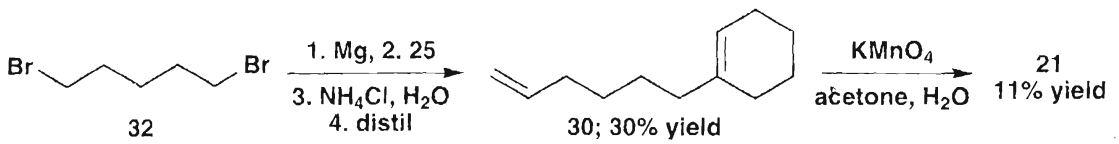
The Grignard could then be made from **27** and added to cyclohexanone, the tertiary alcohol in **28** dehydrated and the primary alcohol deprotected to give **29**. Oxidation of both the alkene and the alcohol should give **21**. As far as we know, this strategy has not yet been attempted. **Problem 27.7:** How could you push the reconnection strategy one stage further with intermediate **22**?



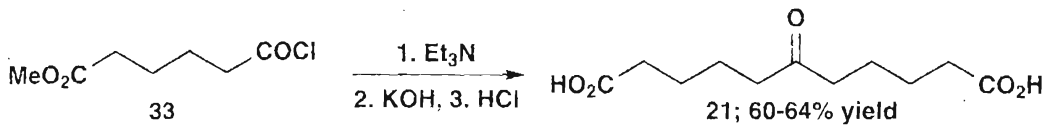
Answer 27.7: Reconnecting the carboxylic acid gives a diene **30** that could be made by addition of the stable Grignard from the halide **31** to cyclohexanone **25**.



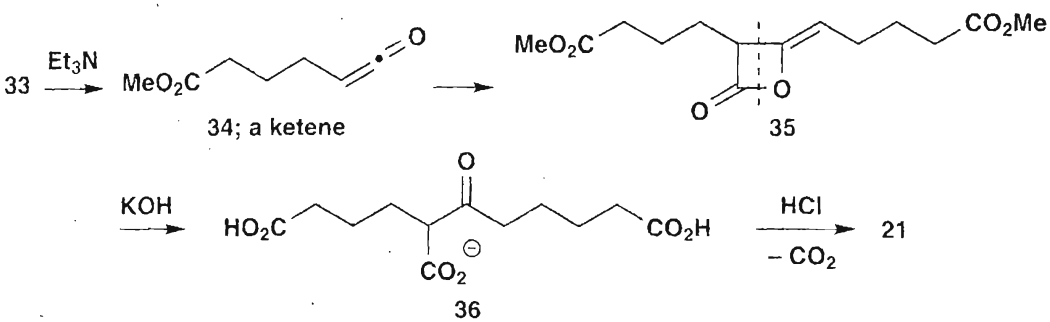
The bromide **31** is available but nobody seems to have added the corresponding Grignard to cyclohexanone. The diene **30** has been made but various attempts to make **21** by this route have all given low yields. This is all old work[3] but we give one example.



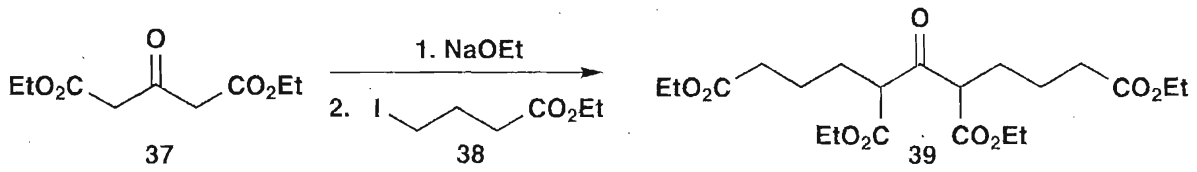
There is an *Organic Synthesis* procedure for this target molecule **21** that is curious, but works.[4] This is a very simple process and the key step is the dimerisation of **33** with Et_3N.



This is probably a ketene reaction (chapter 33) and may go through the dimer **35** that is hydrolysed by KOH to some anion(s) of **36** and then acid allows decarboxylation to give **21**.

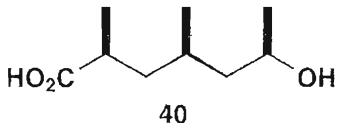


There are various other methods using ionic reactions rather than oxidative cleavage such as the double alkylation of acetone dicarboxylic ester **37** with the iodo-compound **38**. Hydrolysis and double decarboxylation[5] of **39** gives **21**.

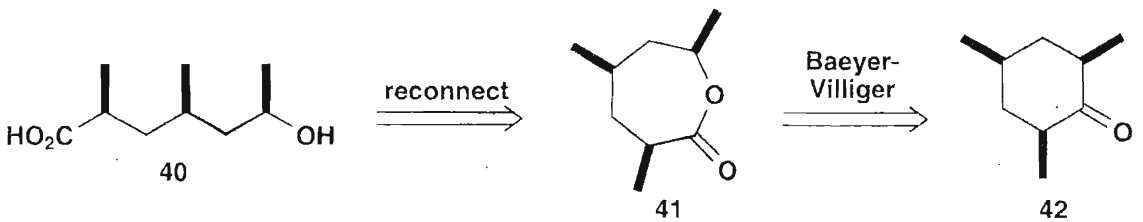


Oxidative Cleavage by the Baeyer-Villiger Rearrangement

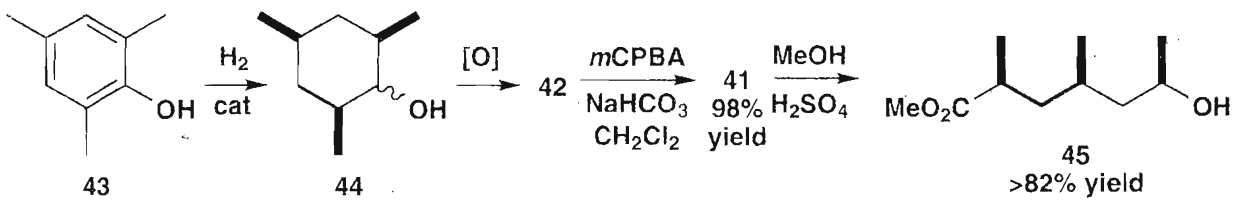
The Baeyer-Villiger rearrangement is mentioned in chapter 27 of the textbook and well reviewed[6] in *Organic Reactions*. **Problem 27.8:** Suggest a synthesis for this hydroxy-ester **40** needed to prove the stereochemistry of the aggregation pheromone of an acarid mite.[7]



Answer 27.8: Reconnecting to give the lactone **41** and removing the ester oxygen to reveal the starting material for the Baeyer-Villiger rearrangement reveals a symmetrical tri-methyl cyclohexanone **42**. Clearly it doesn't matter which alkyl group migrates.

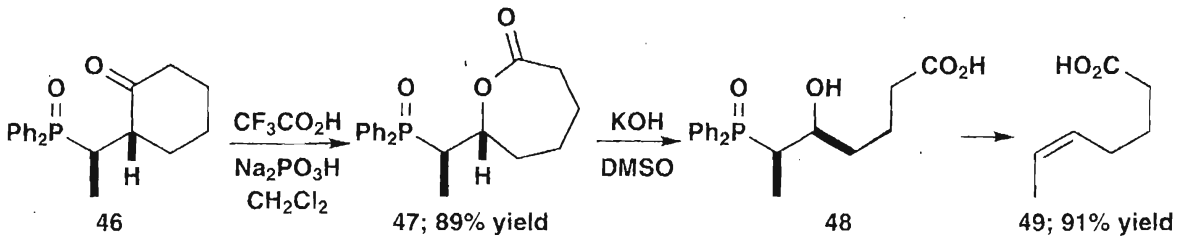


It turns out that hydrogenating 2,4,6-trimethyl phenol **43** gives (mostly) the all *syn* alcohol **44** that can be oxidised to the all *syn* ketone **42**. Now the Baeyer-Villiger reaction gives an excellent yield of the lactone **41**, which can be opened with methanol to give **45**, the methyl ester of **40**. It is important not only that the three methyl groups are *syn* in the ketone **41** but that the Baeyer-Villiger rearrangement goes with retention of configuration at the migrating group.



There may be a very special reason why the stereospecificity of migration is essential to a synthesis. The ketone **46** can be made as a single diastereoisomer and the Bayer-Villiger rearrangement goes in high yield with retention at the migrating group **47**. The 'special reason' here is that the two chiral centres in **47** can be transformed into the *Z* geometry of the unsaturated

acid **49**. Hydrolysis of the lactone **47** gives *Z*-**49** presumably via the Wittig-like intermediate **48** that eliminates $Ph_2PO_2^-$ stereospecifically.[8] This chemistry is detailed in *Strategy and Control*.



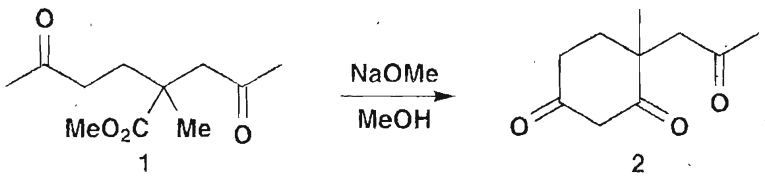
46 47; 89% yield 48 49; 91% yield

References

1. F. Plavac and C.H. Heathcock, *Tetrahedron Lett.*, 1979, 2115.
2. J. D. White, J. F. Ruppert, M. A. Avery, S. Torii and J. Nokami, *J. Am. Chem. Soc.*, 1981, **103**, 1813.
3. A. Kreuchunas, *J. Am. Chem. Soc.*, 1953, **75**, 4278.
4. L. Durham, D. J. McCleod and J. Cason, *Org. Synth. Coll.* **IV**, 555.
5. J. English, *J. Am. Chem. Soc.*, 1941, **63**, 941; N. J. Leonard and W. E. Goode, *J. Am. Chem. Soc.*, 1950, **72**, 5404.
6. G. R. Krow, *Org. React.*, 1993, **43**, 251.
7. K. Mori and S. Kuwahara, *Tetrahedron*, 1986, **42**, 5545.
8. D. Levin and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2155.

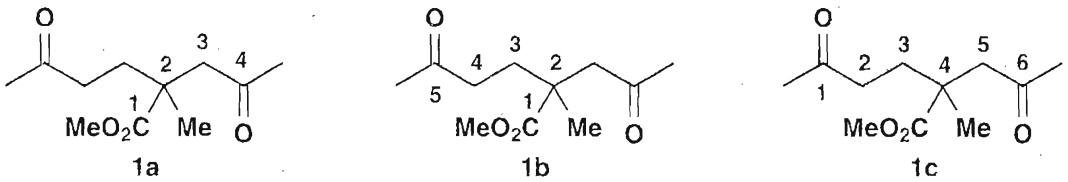
28 General Strategy B: Strategy of Carbonyl Disconnections

The triketone **2** can be made in moderate yield[1] by base-catalysed cyclisation of **1**. **Problem 28.1:** Count up the relationships in **1** and analyse possible approaches on the lines of the discussion at the start of chapter 28 in the textbook.

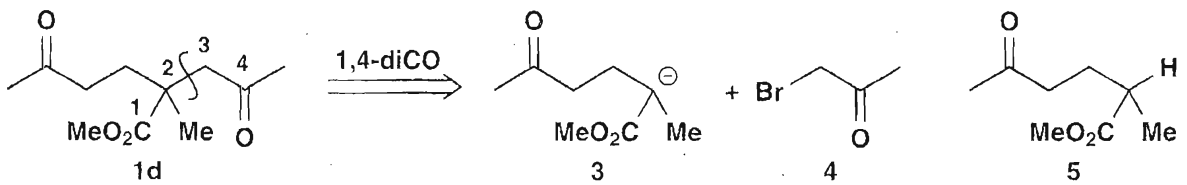


1 2

Answer 28.2: The diketo-ester **1** has 1,4-diCO **1a**, 1,5-diCO **1b** and 1,6-diCO **1c** relationships. We shall discuss each in turn.

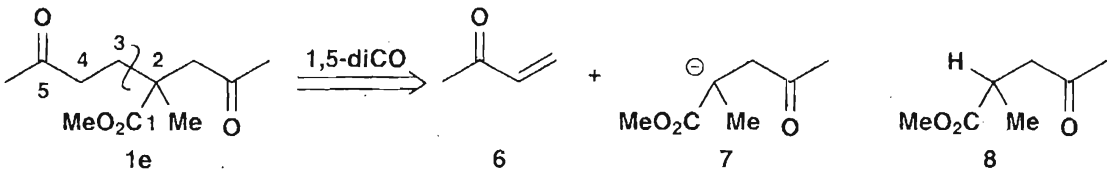


The most obvious 1,4-diCO disconnection is at the branchpoint **1d** and would need an ester enolate **3** to react with an a^2 reagent such as bromo-acetone **4**. The problem with this approach is how to make an enolate of the ester without doing something to the ketone. It is very likely that treatment of **5** with base would lead to cyclisation.

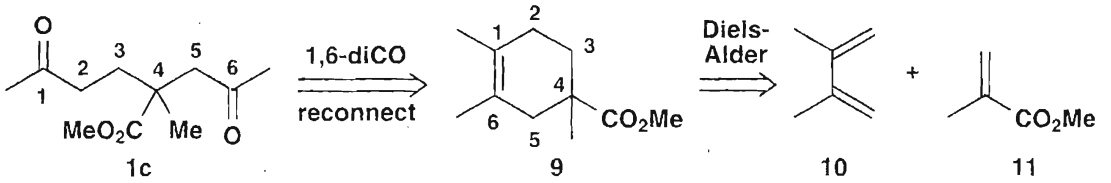


1d 3 4 5

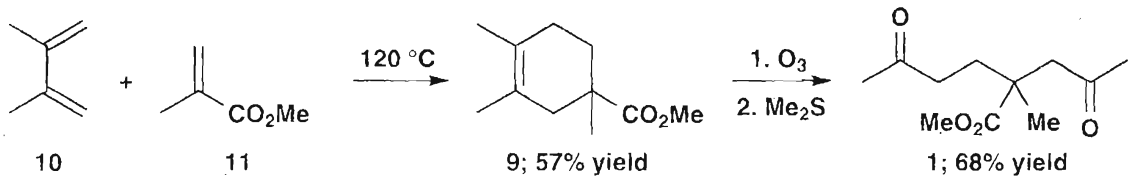
A 1,5-diCO disconnection **1e** can also be made at the branchpoint but a similar problem arises: the enolate **7** of the ester has to be made in the presence of the ketone so that conjugate addition to **6** occurs. Treatment of **8** with base would probably again lead to cyclisation. It is likely that protection of the ketone in **5** and **8** would be necessary before reagents for **3** or **7** could be used.



Reconnection of the 1,6-diCO relationship gives the cyclohexene **9** that is a perfect Diels-Alder product. The diene **10** is symmetrical and the dienophile **11** is activated by the ester group.

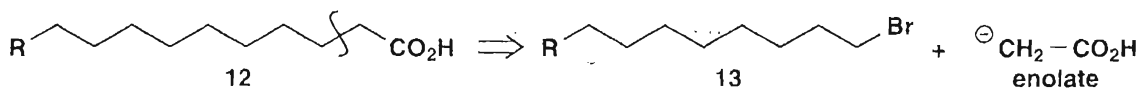


The compound was made by the Diels-Alder strategy. The alkene in **9** was ozonised with sulfide work-up to give the keto-diester **1** in reasonable yield.

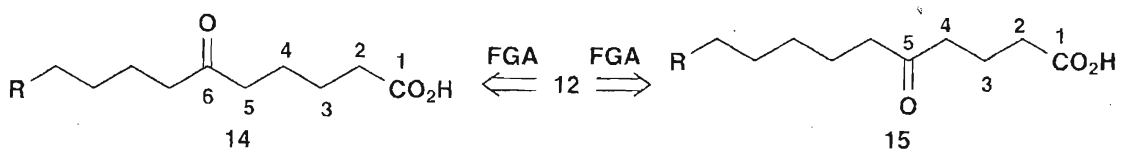


The Synthesis of Long Chain Fatty Acids

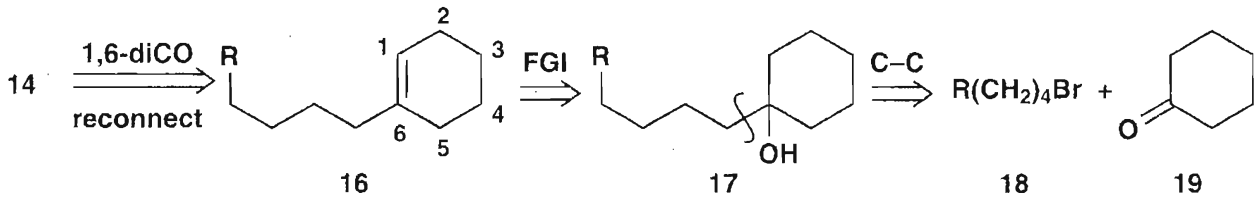
The problem of synthesising compounds like the fatty acid **12** is that there is only one functional group. Disconnections at one end remove only two carbon atoms as we should be using the alkylation of an enolate with an alkyl halide **13**. **Problem 28.2:** Consider adding a carbonyl group somewhere in the chain to allow useful disconnections nearer to the middle of the molecule. Where would you put it?



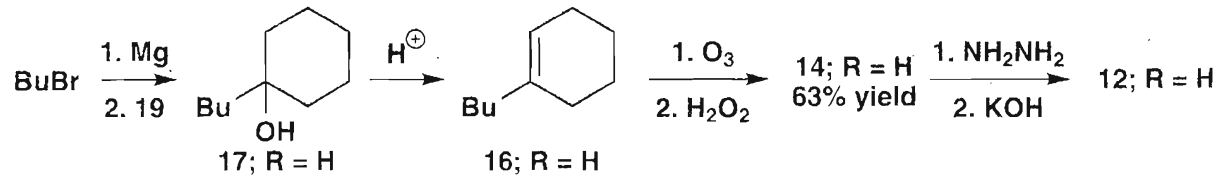
Answer 28.2: There are many possibilities but two are appealing. Creating a 1,6-diCO **14** or a 1,5-diCO **15** relationship allows us to use reactions we already know. How would you continue with **14**?



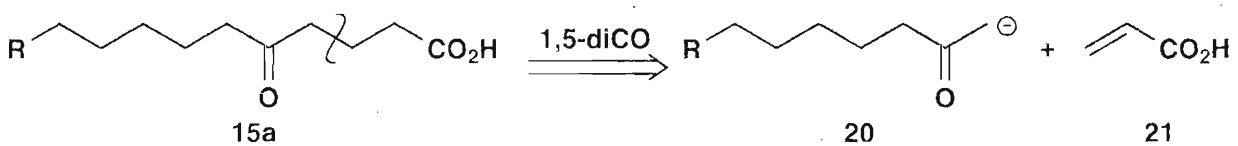
Reconnecting the 1,6-diO relationship gives us a cyclohexene **16** that could be made by dehydration of **17** which could come from cyclohexanone **19** and a Grignard reagent derived from an alkyl bromide **18**.



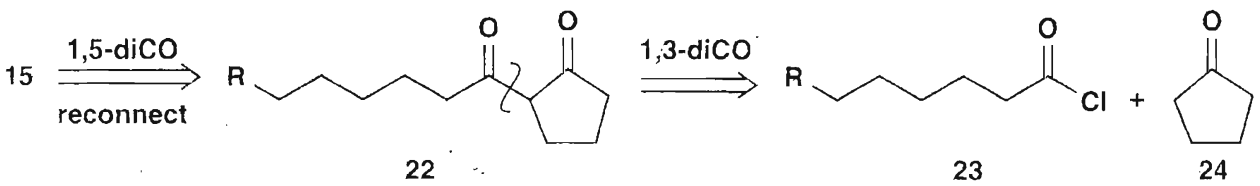
One such compound **12**; R = H has been made this way.[2] Dehydration of **17**; R = H in acid solution was followed by ozonolysis and oxidative work-up to give the acid. The Wolff-Kishner reduction[3] that uses hydrazine NH_2NH_2 removed the carbonyl group to give **12**.



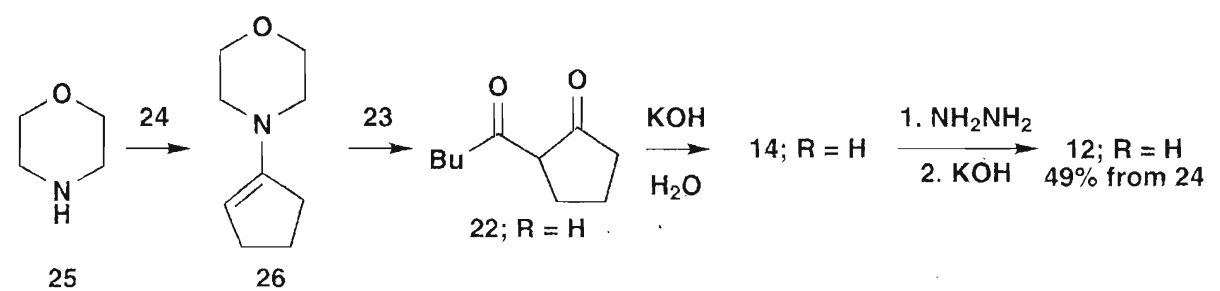
Now let us consider the other possibility. A reasonable suggestion would be to use a standard 1,5-diCO disconnection **15a** that gives the enolate **20** of a ketone and some derivative of acrylic acid **21**. This is fine but the disconnection is only one bond further in than that in **12**.



One ingenious solution was based on a reconnection to a *five*-membered ring **22** rather than the cyclohexene we might expect. This creates a 1,3-dicarbonyl relationship **22** that could come from some enol equivalent of cyclopentanone and the acid chloride **23**.

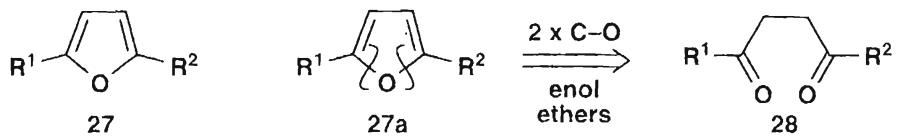


The same workers[2] used this route to make **12**: R = H. The morpholine enamine **26** was acylated and the cleavage of **22**; R = H accomplished with alkali to give **14**; R = H. Reduction with hydrazine gave **12**; R = H.

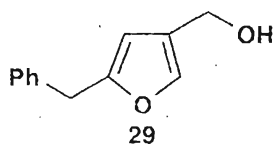


The Synthesis of a Furan

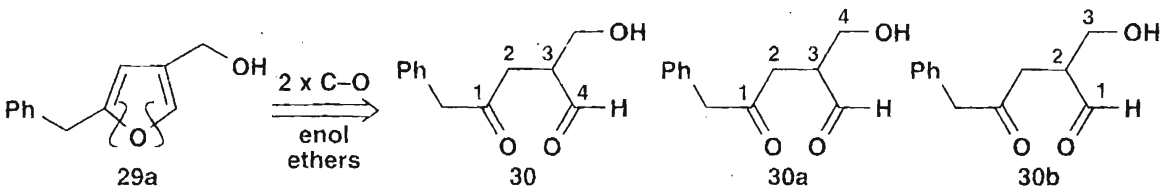
Furans **27** are cyclic *bis*-enol ethers stable only because they are aromatic – two electrons each from the alkenes and two from a lone pair on oxygen (chapter 39). Disconnection of both C–O bonds gives 1,4-diketones **28**. Treatment of **28** with acid usually leads to furan formation.



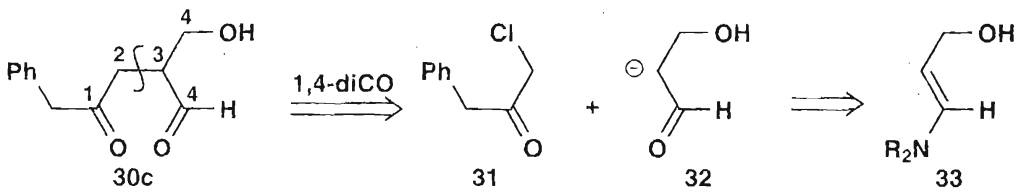
The ester of furan **29** with chrysanthemic acid is an exceptionally potent insecticide.[4] **Problem 28.3:** Carry out the double C–O disconnection on this furan and mark the various relationships in the resulting starting material.



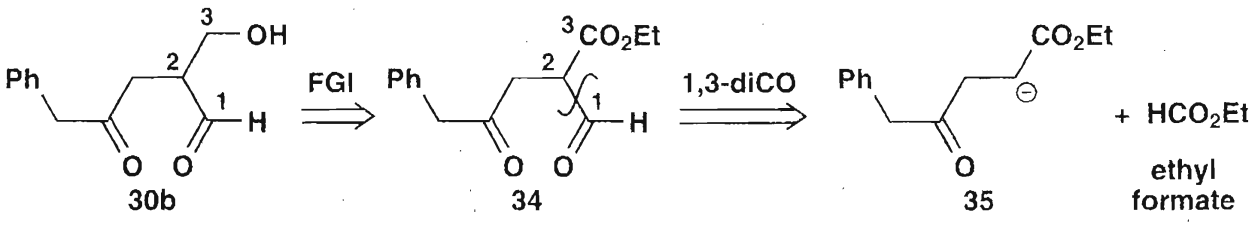
Answer 28.3: The disconnection is **29a** revealing **30** as the starting material. It has two 1,4-diCO relationships **30** and **30a** and one 1,3-diCO relationship **30**. **Problem 28.4:** Can you see a good disconnection for the 1,4-diCO relationships?



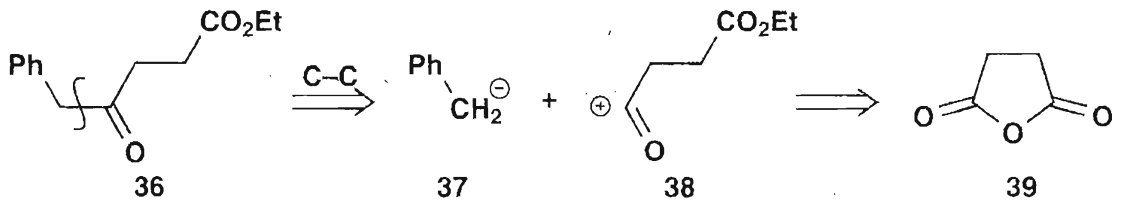
Answer 28.4: The best is next to the branchpoint **30c** requiring an enolate and an α-halo carbonyl compound. The most likely combination looks like **32** with some reagent, perhaps the enamine **33** for the enolate **32**. This does not look very promising. **Problem 28.5:** What can be done with the 1,3-diCO relationship?



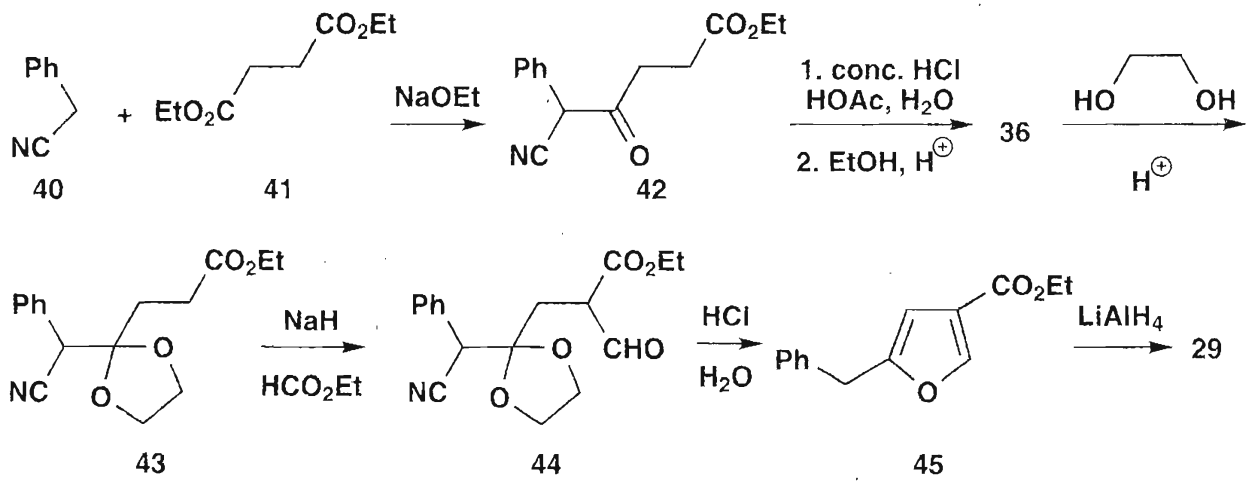
Answer 28.5: We must change the alcohol into a carbonyl derivative and it probably ought not to be an aldehyde as one reactive aldehyde is quite enough. An ester **34** seems the best choice. An alternative would be to disconnect the CH_2OH group with the Mannich reaction in mind but we shall not explore this. Now a 1,3-diCO disconnection **34** suggests an enolate **35** of a ketoester and ethyl formate. This enolate will be difficult to control and protection was used in the synthesis.



We must now face the 1,4-relationship and the best bet is to buy it in the form of succinic anhydride (chapter 25) and add it to some reagent for the benzyl anion.

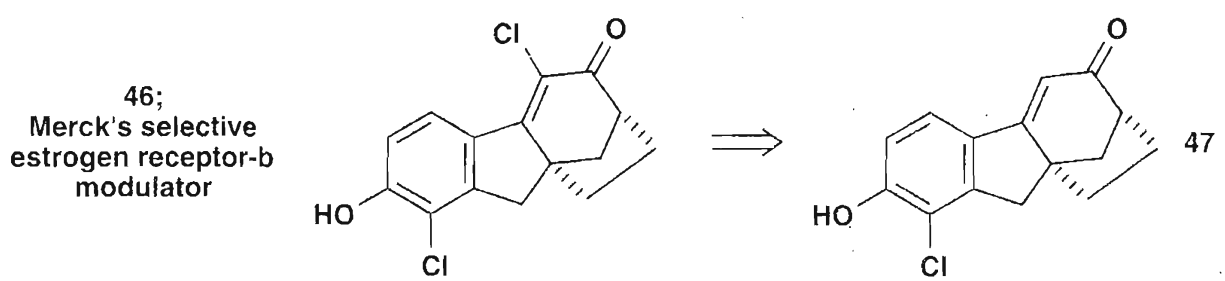


One synthesis[4] uses the nitrile **40** and diethyl succinate **42** as the reagents. It is necessary to protect the ketone as an acetal **43** before making the enolate of the ester. Hydrolysis of the acetal also forms the furan **45** and reduction gives **29**.



The Synthesis of a Modern Drug Candidate

We end with the synthesis of a Merck drug **46** for treatment of symptoms of menopause.[5] This may seem at first glance rather a simple compound. **Problem 28.6:** What difficulties do you see in designing a synthesis for **46**? You may ignore the apparent problem of chlorinating the enone. It is known that chlorination of **47** gives **46**.

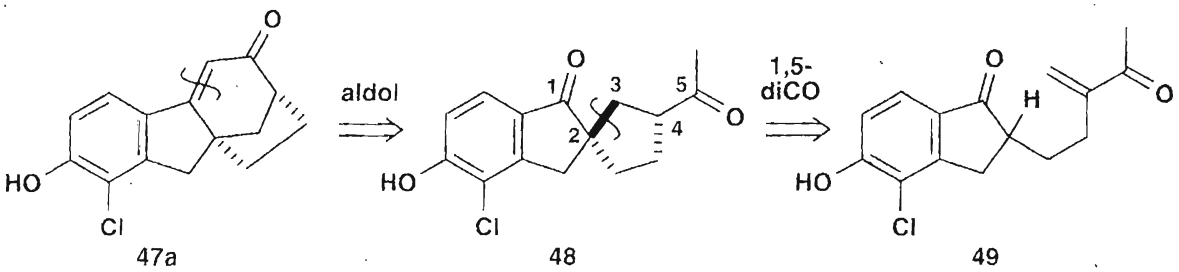


Answer 28.6: You may have picked out various things. Our list is:

The two-carbon bridge on the bottom face of the molecule.
Few functional groups in the skeleton – just one ketone and one alkene.
The quaternary centre – four C–C bonds to one C atom.
Selective chlorination of the aromatic ring.

Notice that the relative stereochemistry of the bridge is not a problem as the bridge can exist only as a *cis* unit. In the industrial synthesis they made the enantiomer shown but we shall be concerned with relative stereochemistry only.

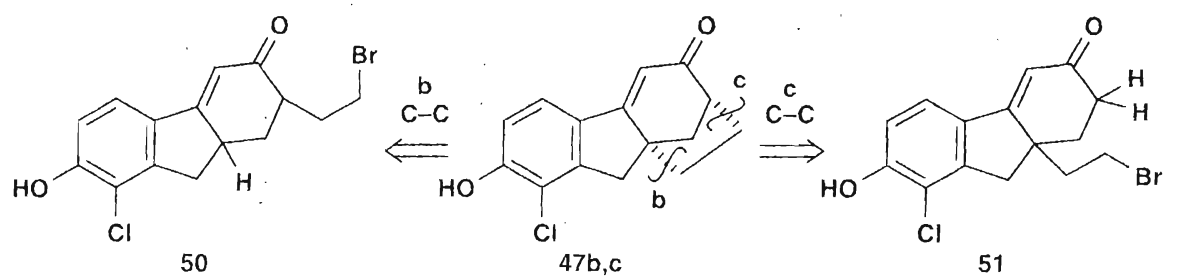
The only two-group disconnection available at the start is the aldol disconnection on the enone **47a**. This gives a spiro-diketone **48** with a 1,5-diCO relationship that can be disconnected only to **49** as we cannot have a double bond between C-2 and C-3. This looks pretty bad – the intermediate **48** has serious stereochemistry and the intramolecular Michael addition of **49** looks very awkward.



47a 48 49

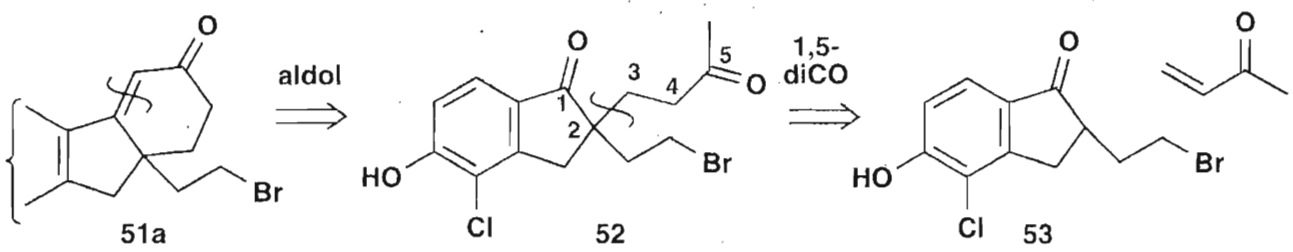
So we reject those strategies. The easiest way to avoid the stereochemical problem is to disconnect the bridge before we do the aldol disconnection. **Problem 28.7:** Which bond in the bridge would you like to disconnect (and why)?

Answer 28.7: Disconnecting the middle bond of the bridge is no good – there is no chemistry to do that and the stereochemistry would still be there in the starting material. So you have two choices: **47b** or **47c**. Both require the alkylation of an anion formed by removal of a marked H atom in **50** or **51**. Disconnection **47c** is better because there is only one acidic site. The marked H in compound **50** would give an extended enolate stabilised by the conjugated ketone but there is also a more acidic H next to the carbonyl group so the result of treating **50** with base is uncertain.

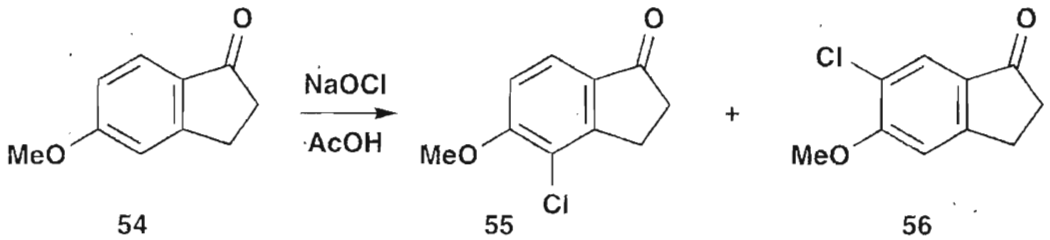


50 47b,c 51

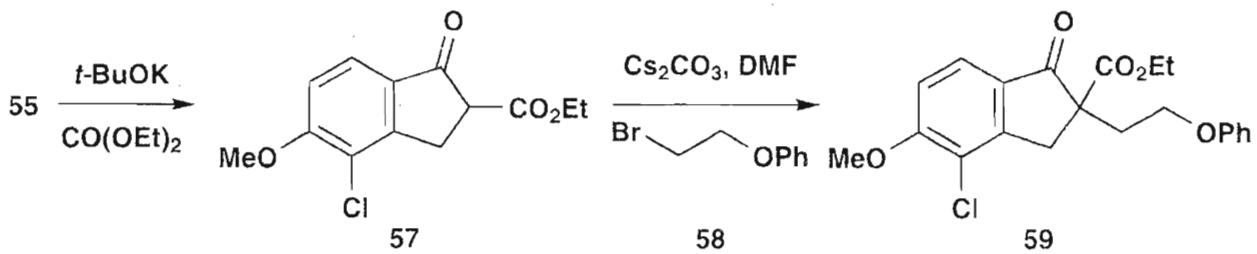
Let us continue with **51** by now making the aldol disconnection **51a** we wanted at the start. This reveals a 1,5-diCO compound **52** and disconnection at the branchpoint gives a much simpler ketone **53** and butenone. We have reinvented the Robinson annelation (chapters 21 and 36).



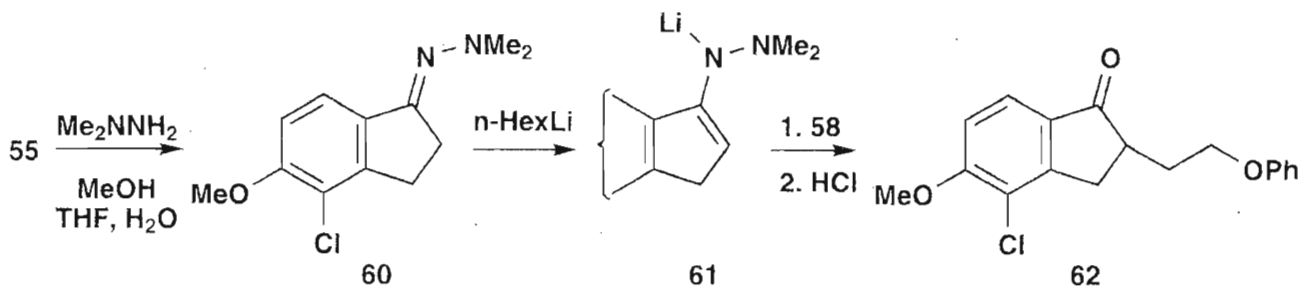
For most of this chemistry we cannot have a free phenol and, as 4-methoxy-indanone **54** is available, it makes sense to use that as a starting material. The first step is into the unknown: where is **54** chlorinated? On steric grounds, one might expect **56** to be the major product, but with cheap bleach (NaOCl) in acidic solution, the ratio is 85:15 in favour of **55**. Adding water to the mixture precipitates out the wanted isomer **55** in 74% yield.



The initial idea at Merck was to add an ester group to **55** to make **57** which is thus activated for alkylation with **58**. Though a reasonable yield of **59** was formed, it proved difficult to separate it from dialkylated by-products and another method was sought.

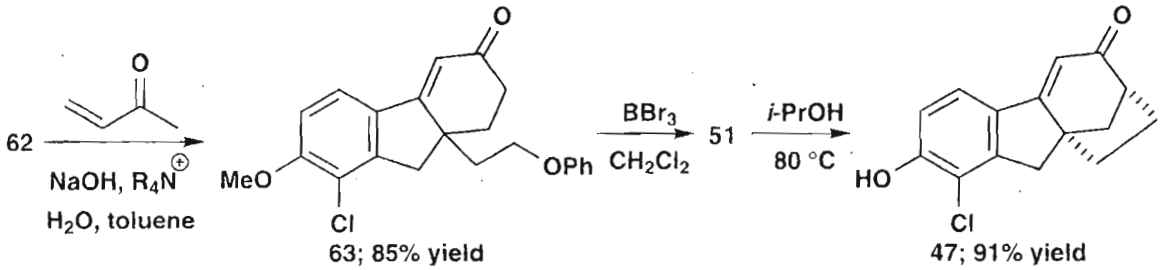


It turned out that the aza-enolate **61**, made from the stable hydrazone **60**, gave an excellent yield of **62** without the need of an activating group that would have to be removed later and without separation problems.



Now it is time for the Robinson annelation and they used NaOH for this with a phase-transfer catalyst. These tetra-alkyl ammonium salts help to transfer reagents between the aqueous phase and the organic phase. In the industrial synthesis this step was used to make a single enantiomer (more details in *Strategy and Control*). Treatment of the product **63** with the Lewis

acid BBr_3 removed the methyl group and converted the phenoxy group into a bromide **51**. The final cyclisation required only heating in *iso*propanol.

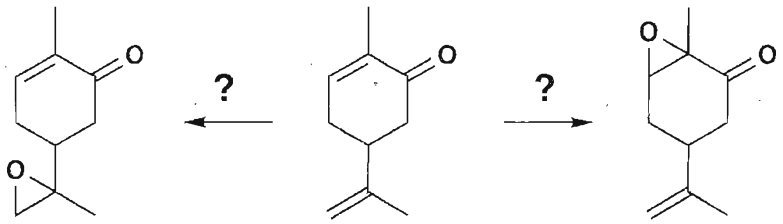


References

1. C. R. Owens and R. A. Raphael, *Unpublished Observations*.
2. S. Hünig and W. Lendle, *Chem. Ber.*, 1960, **93**, 913; D. G. M. Diaper, *Can. J. Chem.*, 1955, **33**, 1720.
3. *Vogel*, pp. 827, 831.
4. M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham and B. C. Pearson, *Nature (London)*, 1967, **213**, 493.
5. J.P. Scott, M. S. Ashwood, K. M. J. Brands, S. E. Brewer, C. J. Cowden, U.-H. Dolling, K. M. Emerson, A. D. Gibb, A. Goodyear, S. F. Oliver, G. W. Stewart and D. J. Wallace, *Org. Process Res. Dev.*, 2008, **12**, 723.

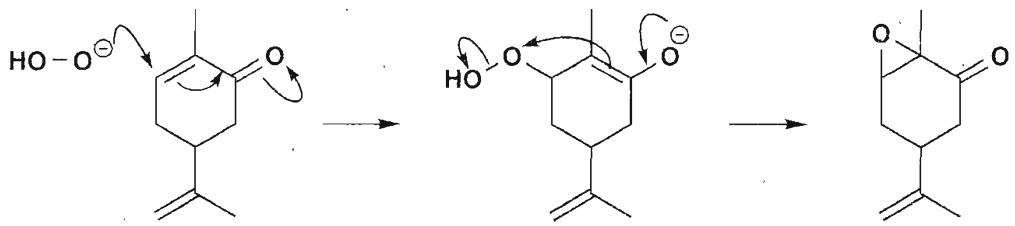
29 Strategy XIII: Introduction to Ring Synthesis: Saturated Heterocycles

Problem 29.1: How would you convert the natural product carvone **2** selectively into the epoxides **1** and **3**?



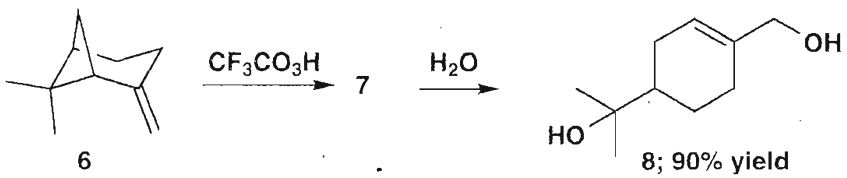
1 2 3

Answer 29.1: The two alkenes are distinct electronically. The external alkene is a normal nucleophilic alkene but the conjugated alkene is electrophilic. So we can choose which epoxide we want by choice of reagent.[1] The normal peroxyacid gives **1** but the nucleophilic reagent H_2O_2/NaOH gives **3**. Sodium hydroxide is more basic than H_2O_2 so the reagent is the hydroperoxide anion that does conjugate addition **4** on the enone. The intermediate cyclises by an unusual intramolecular S_N2 reaction at oxygen **5** to give **3**.



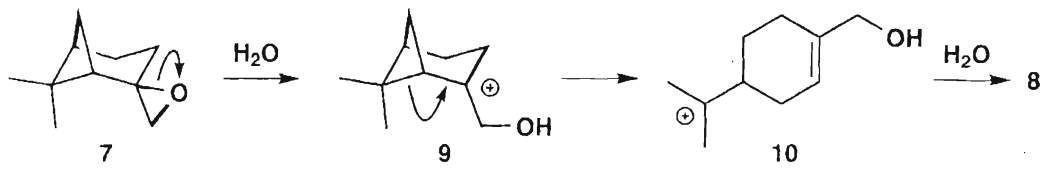
4 5 3; 92% yield

On treatment with a peroxyacid, **6** gives a compound **7** that reacts with water to give the diol **8** in excellent yield. **Problem 29.2:** What is the structure of **7**? Explain the formation of **8**.

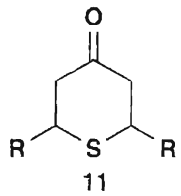


6 8; 90% yield

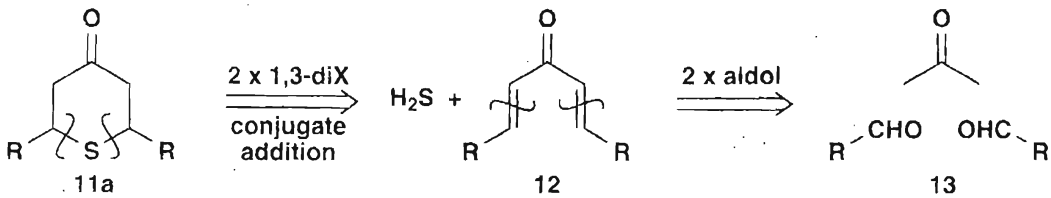
Answer 29.2: Intermediate **7** is of course the epoxide. If you mentioned stereochemistry, you should be proud of yourself as the epoxide forms on the top face of the molecule, away from the CMe_2 group. The epoxide opens in polar media to give the more stable carbocation **9**: fragmentation gives[2] the diol **8**.



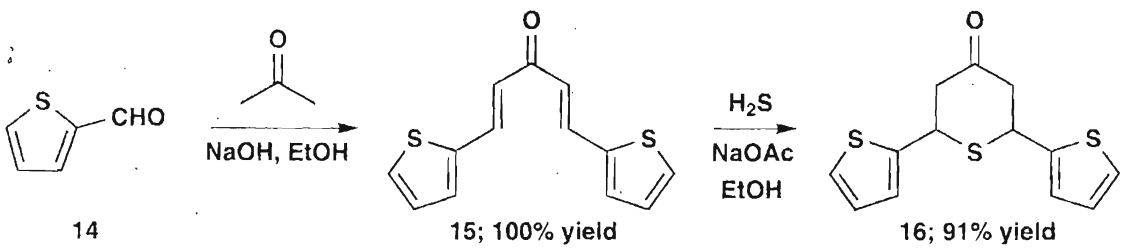
Problem 29.3: Moving on to a different heteroatom and ring size, how would you make compounds of the general structure **11**? We are looking for two different approaches. One successful retrosynthesis starts with C–X disconnections while the other has a C–C disconnection before any C–X disconnections.



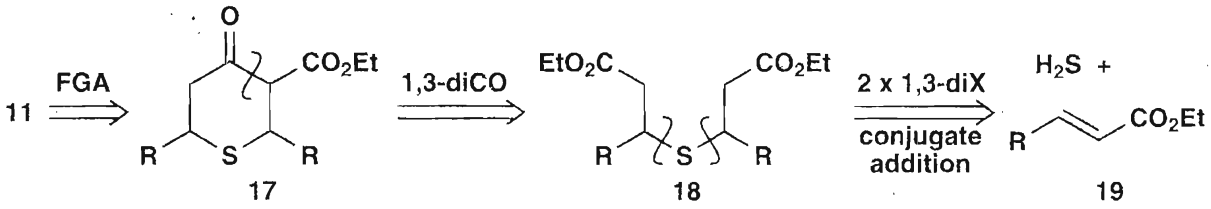
Answer 29.3: The most obvious strategy is to disconnect both structural C–S bonds. As they both have a 1,3-diX relationship with the carbonyl group, we can disconnect both **11a** and use H_2S in a double conjugate addition to the dienone **12**. If R = Ar, this could come from a double aldol[3] on acetone with RCHO **13**. Reaction with H_2S gives the heterocycle.[4]



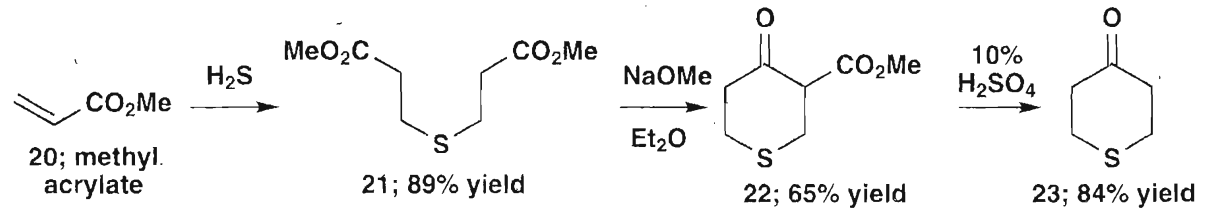
We choose an aromatic heterocyclic aldehyde **14** as an example. The condensation with acetone gives 100% yield of the dienone **15** and the reaction with H_2S, buffered with sodium acetate, gives a mixture of diastereoisomers of the heterocycle[4] **16**.



But ketones **12** with R = alkyl are not very stable so we move to the other strategy which we saw in chapter 19 for the corresponding nitrogen heterocycles. We first add an ester group so that we have a 1,3-diCO relationship **17** and disconnect that with a Claisen ester condensation in mind. Since the resulting diester **18** is symmetrical, we can again disconnect both C–S bonds and need H_2S with two molecules of the unsaturated ester **19**. Either *E*- or *Z*-**19** will do but *E*-**19** is easier to make.

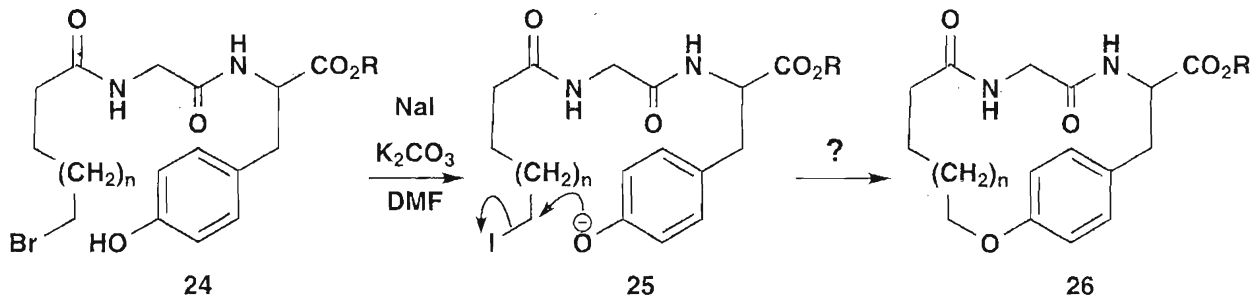


The synthesis[5] of the unsubstituted compound **23** is best done by this latter strategy. The double conjugate addition goes well and the cyclisation uses NaOMe to avoid problems with substitution at the ester groups. Hydrolysis and decarboxylation both occur in 10% aqueous sulfuric acid.

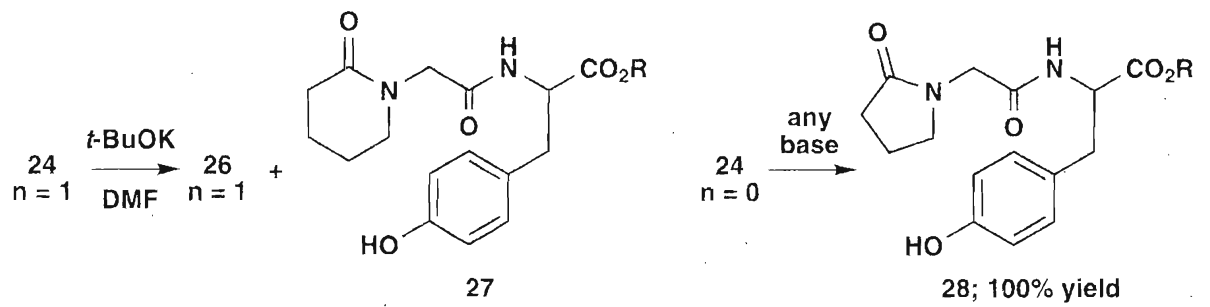


Cyclisation Reactions

In attempts to make cyclic peptide mimics, compounds such as **24** were cyclised[6] with NaI in base in the hope that the iodide would be displaced by the phenoxide anion **25** to give **26**.



When n = 7, the cyclic peptide mimic **26**, with a 22-membered ring, was indeed the product. When n = 1, no cyclisation occurred under these conditions but on treatment with *t*-BuOK in DMF, a 1:1 mixture of **26** and a different product **27** was formed. When n = 0, no **26** was formed but compound **28** was the sole product in 100% yield regardless of the base used. **Problem 29.4:** Comment on these results.

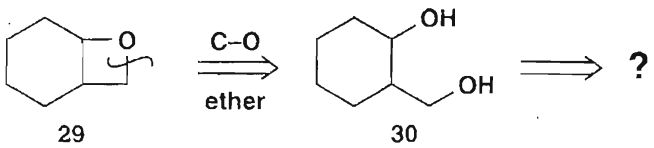


Answer 29.4: The question hangs on the relative ease of formation of the various ring sizes as the amide nitrogen offers an alternative, though much weaker, nucleophile. When n = > 1, the best reaction is **25** regardless of ring size as the alternatives (cyclic amides such as **27** or

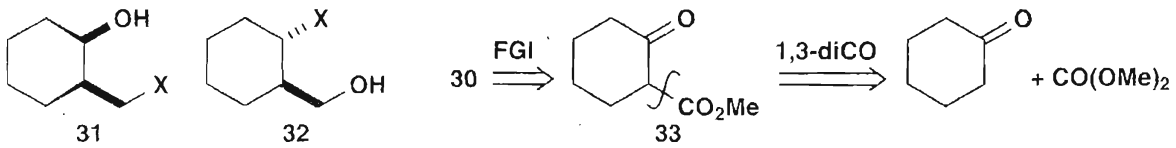
28) do not have a favourable ring size. When n = 1 the six-membered ring **27** is favourable enough to be formed along with the 16-membered ring in **26**; n = 1. When n = 0, the alternative very favourable five-membered ring **28** is much preferred over the 15-membered ring in **26**; n = 0.

Cyclisations to Form Oxetanes

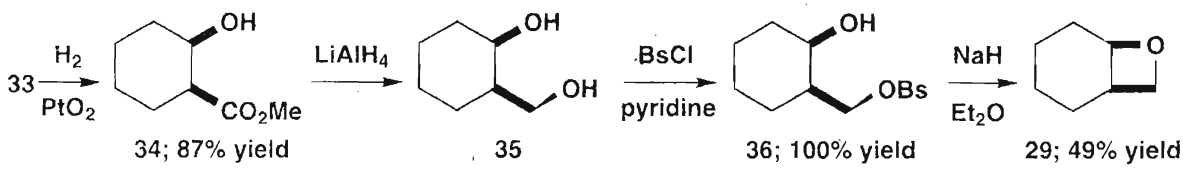
Four-membered rings are inherently difficult to make so we must make sure that everything is in our favour. A typical case would be the bicyclic oxetane **29**. Normal C–O disconnection gives the diol **30**. **Problem 29.5:** How would you make **30**? *Hint*: What is important but has not been shown on the diagrams?



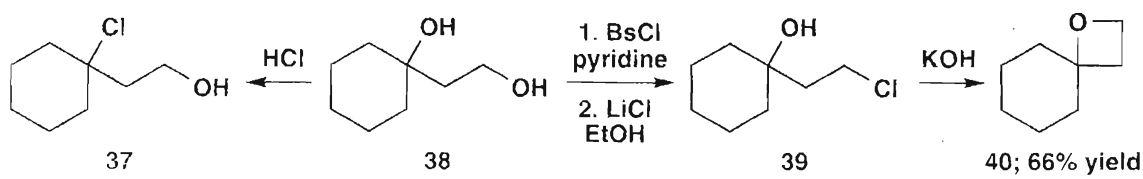
Answer 29.5: Stereochemistry! And that depends on which of the OH groups we make into a leaving group (X). Either will do but we need the *syn*-isomer **31** (no inversion) or the *anti*-isomer **32** (inversion during the S_N2 reaction). We might be able to make either from the 1,3-keto-ester **33** which we can easily make by acylation of cyclohexanone with dimethyl carbonate.



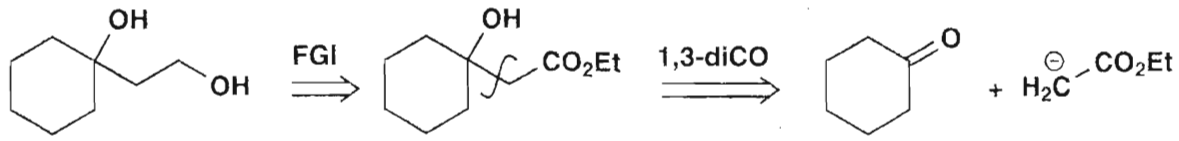
So, can we convert **33** into either the *syn* or the *anti*-diol **30**? It turns out[7] that hydrogenation over Adams catalyst (PtO_2) hydrogenates the ketone from the face opposite to the CO_2Me group. The oxetane can then be made if the primary alcohol is converted into a sulfonate leaving group – the *p*-bromobenzene sulfonate (OBs) was chosen.[8] Even then, the yield was only about 50%.



Is there a reason to make the primary (rather than the secondary) alcohol into a leaving group? There is indeed as is evident from attempts to make the spiro-oxetane **40** from the diol **38**. The chloride **37** could not be cyclised under any conditions but the chloride **39** gave a reasonable yield of **40**. **Problem 29.6:** Explain. How would you make **38**?



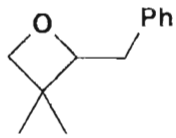
Answer 29.6: The tertiary chloride **37** could react only by the S_N1 mechanism and that is evidently not good enough. Elimination occurs instead. By contrast an S_N2 reaction at the primary chloride **39** is good because the anion of the alcohol participates in the cyclisation.[8] We cannot make **38** in the same way that we made **35** as only one of the alcohols can be changed into a carbonyl group. The ester **41** can be made from cyclohexanone and a suitable reagent for the enolate **42**.



38 41 42

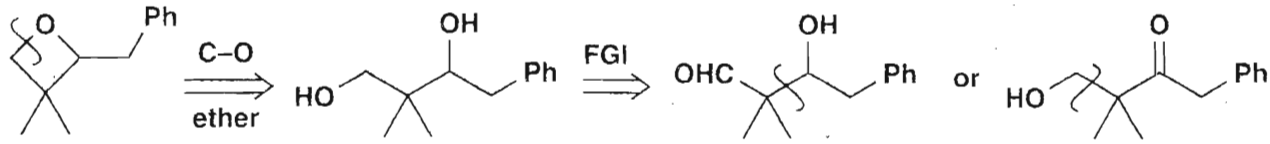
The standard reagent for **42** would be a lithium enolate or a Reformatsky reagent so that dehydration of **41** is avoided. Reduction with $LiAlH_4$ would then give the diol. Though this strategy is usual for this kind of diol, **38** was not actually made this way.

Now a synthetic example to illustrate more substituted oxetanes. **Problem 29.7:** How would you make oxetane **43**?



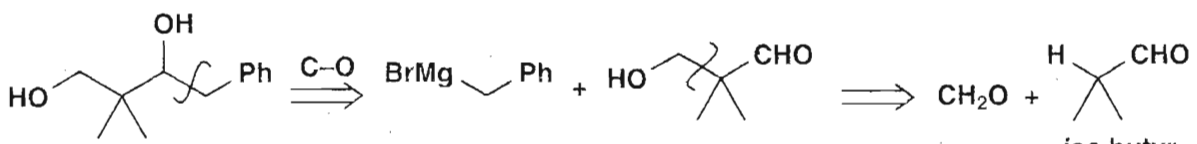
43

Answer 29.7: The usual disconnection **43a** gives diol **44** and we could change either OH into a carbonyl group to give **45** or **46** with the aldol disconnections drawn on them. The first **45** looks better as the disconnection is more central (**46** cuts off only one carbon atom) and an alternative to the aldol route might be the acylation of an enamine of *i*-PrCHO with $PhCH_2COCl$.



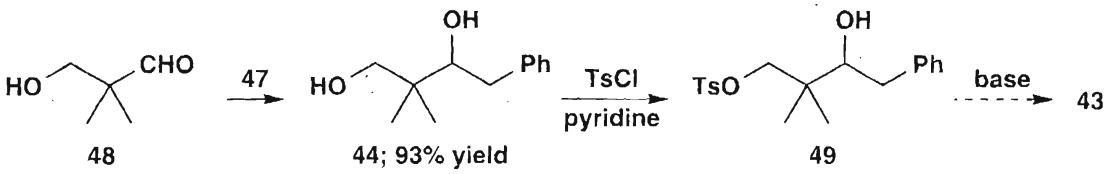
43a 44 45 46

But **44** was not made that way.[9] One-group C–C disconnection **44a** gave benzyl Grignard **47** and the hydroxy-aldehyde **48**. This route was chosen because **48** was a known compound and is easily made from formaldehyde and *iso*-butyraldehyde. It is not necessary to use the Mannich reaction as formaldehyde can react only once with this aldehyde. Sodium carbonate is used as the base to avoid a Cannizzaro reaction.[10]



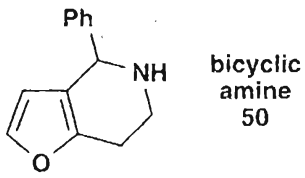
44a 47 48 *iso*-butyr-aldehyde

We have also deceived you in that the final step, the cyclisation of **44**, was not actually carried out by Hudrlik. But it is virtually certain that it would be successful.

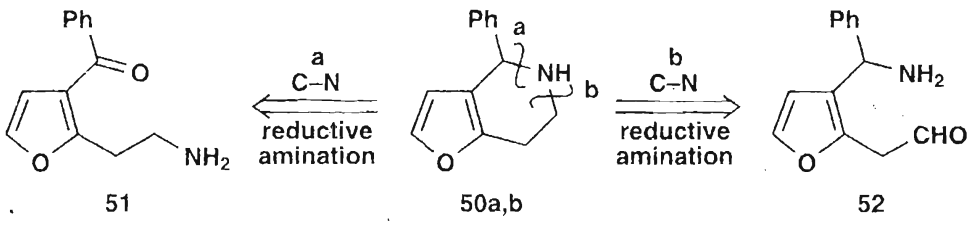


A Bicyclic Amine

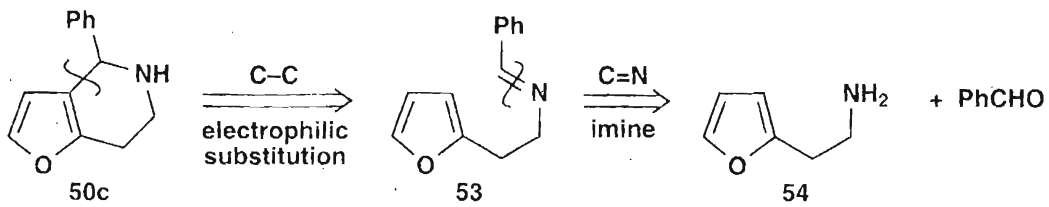
We end with a more straightforward problem involving a fused bicyclic compound with one aromatic and one non-aromatic ring. **Problem 29.8:** Suggest a synthesis for **50**.



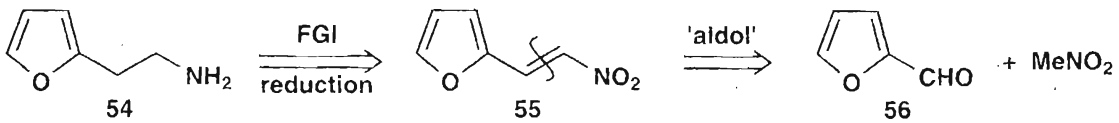
Answer 29.8: The most obvious first disconnections are **50a** or **50b** both with reductive amination in mind. There is no doubt that the reactions would work but both starting materials **51** and **52** have adjacent substituents on the furan ring and it might be difficult to use one substituent to introduce the other. Could we not make better use of the cyclisation?



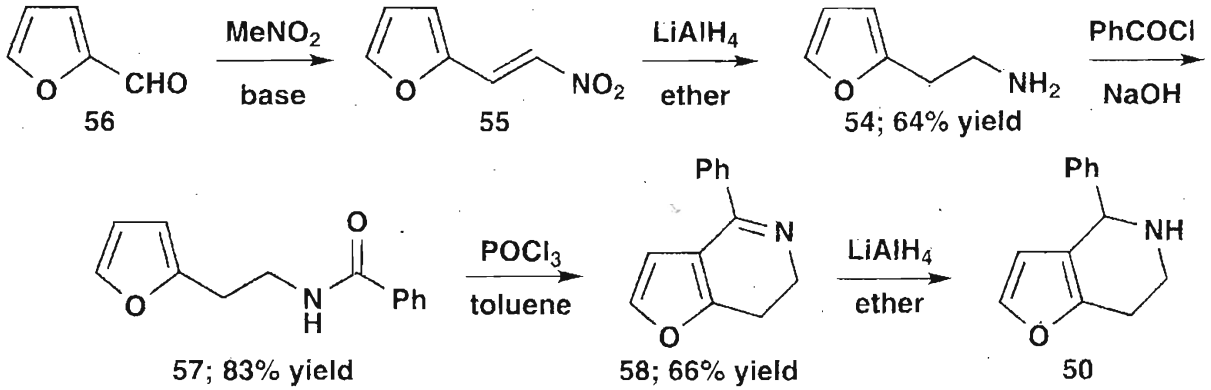
If we disconnect a C–C bond first **50c** we could use the imine **53** to deliver the electrophile to the right position: the difficult step would be cyclisation. This intermediate **53** is the imine between the primary amine **54** and benzaldehyde.



Now we must make the amine **54** and this could be done in many ways. Perhaps the simplest is some FGI giving the unsaturated nitro compound **55** with plenty of reduction in mind as this can be made from very cheap furan-2-aldehyde **56** and nitromethane.



In practice, the chemists[11] followed the first few steps as we have planned them but decided to cyclise the more easily made amide **57** and hence needed a reduction step at the end.



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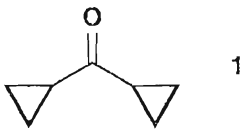
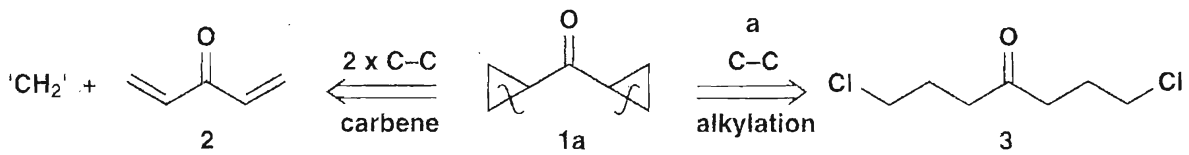
30 Three-Membered Rings

Problem 30.1: Suggest a synthesis for this ketone. You might consider (at least) two strategies.

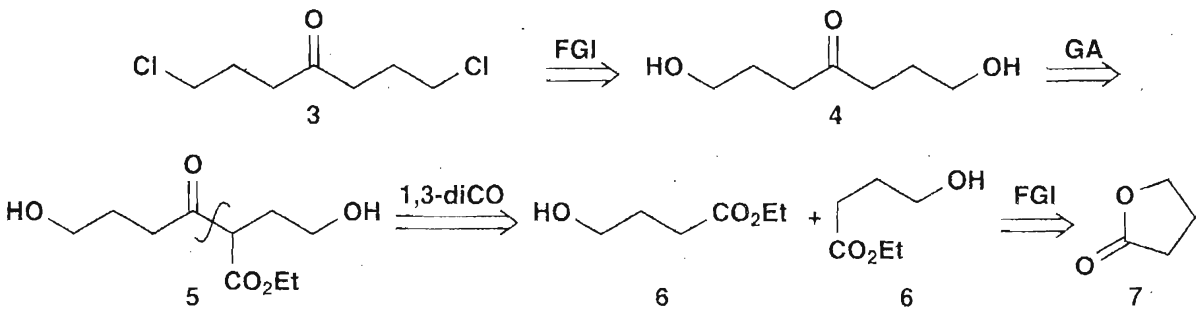


1

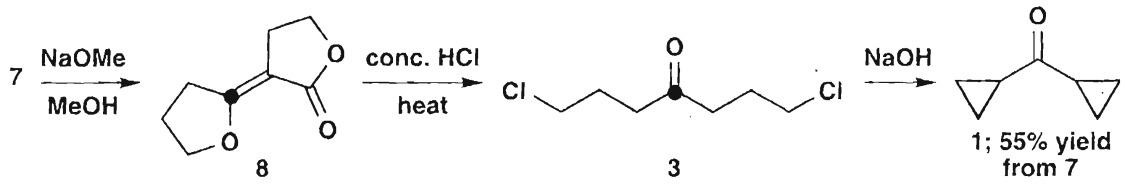
Answer 30.1: You might have considered a carbene approach involving adding two nucleophilic carbene equivalents such as sulfonium ylids to the dienone **2**. But you might then have reflected that we rejected unstable **2** as a synthetic intermediate in the last chapter. An alternative would be to make the three-membered rings by alkylation of the central ketone. The disconnections are of C–C bonds **1a** and the intermediate is thus something like **3**.



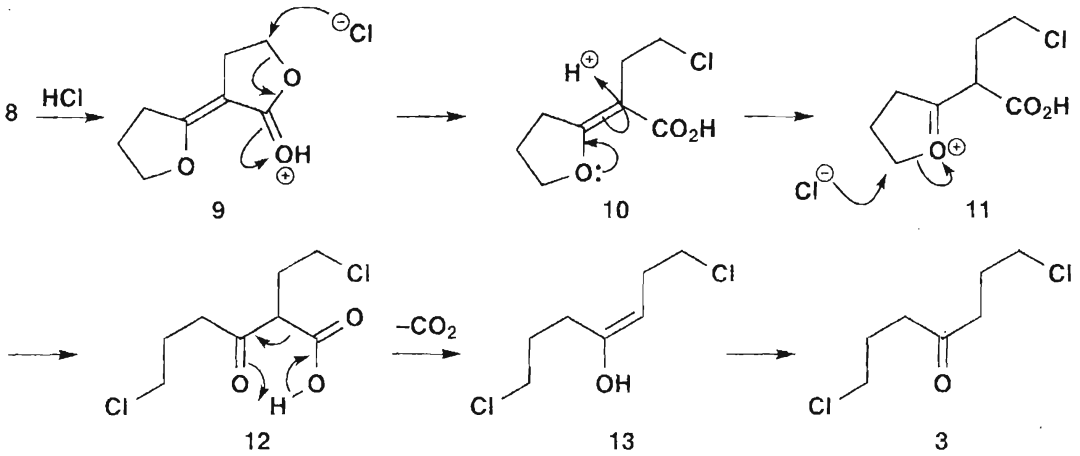
The dichloroketone **3** will come from the keto-diol **4** and we can use a strategy seen in the last chapter for this symmetrical ketone. After adding an ester group we can do a 1,3-diCO disconnection **5** revealing two molecules of **6** for which we can use available butyrolactone **7**.



The synthesis[1] can be carried out without isolating any intermediates. Condensation of the lactone in base actually gives the aldol product **8** rather than **5**. But this is all right as reaction with hot concentrated HCl gives **3** in one step.

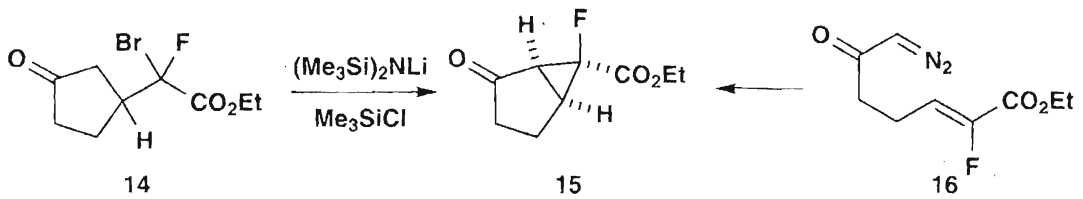


It may help to see that the carbon atom of the enol ether in **8**, marked with a black blob, becomes the ketone in **3**. Substitution of O by Cl **9**, enol ether protonation **10**, a second substitution by chloride **11** and decarboxylation **12** are all initiated by HCl to give the enol **13** of **3**.

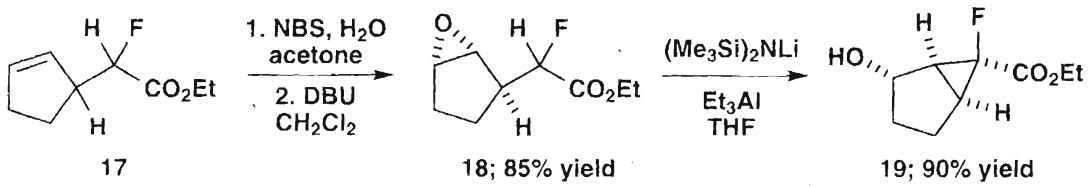


Cyclisation and Carbene Strategies Compared

The cyclopropane **15** is a key intermediate in the synthesis of a potential schizophrenia drug at Merck.[2] One laboratory route used the cyclisation of **14** in base and another the intramolecular capture of a carbene derived from the diazoketone **16**. Both were low-yielding and hazardous.

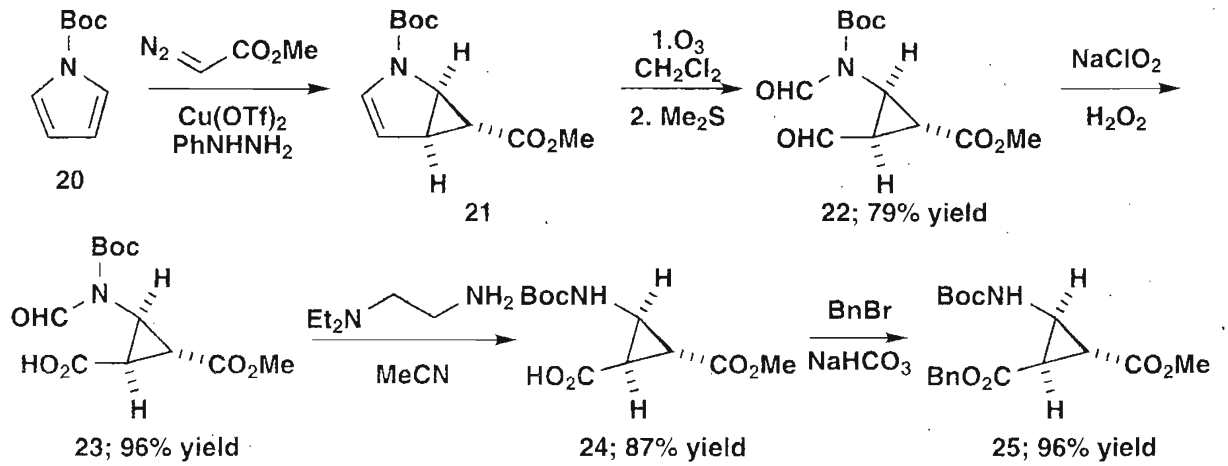


So the cyclopentene **17**, made by allylation of a fluoro-ester, was epoxidised with aqueous NBS to give an 8:1 ratio of **18** and the *cis* compound via the bromohydrins. Now intramolecular alkylation opens the epoxide to form the cyclopropane **19**, easily oxidised to **15**. You should not be surprised at the stereochemistry of the products. With 5/3 fused rings we have a classic folded compound and everything wants to be on the outside (*exo* or convex) face (chapter 38).

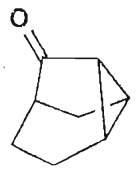


In another case, where rigid analogues of amino acids **25** were needed, the carbene strategy was better.[3] The decision to start with a pyrrole **20** is remarkable but they thought along the lines

of the reconnection strategy we have explored in chapters 26 and 27. The chemical reaction will be an oxidation of an alkene. But there is a clever variation here. The acid in **24** was reconnected to an alkene and the nitrogen atom was reconnected to the other end of the alkene. To make this a practical synthesis, the oxidation level of the acid in **24** was changed to an aldehyde and a formyl group introduced on the nitrogen **23**. The two aldehydes were then joined to make the alkene in **21**. This strategy was partly based on finding a simple starting material **20** and partly on using a five-membered ring to give control over stereochemistry. The amine used to convert **23** into **24** removes the *N*-formyl group.

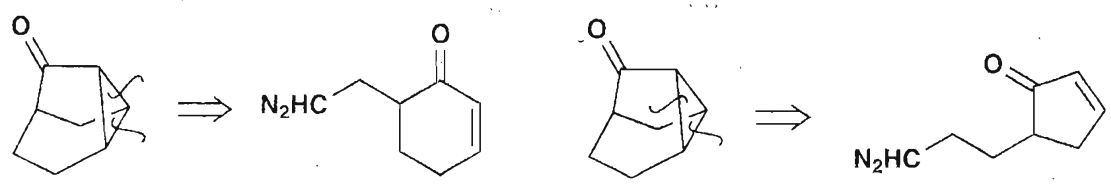


Problem 30.2: This tricyclic ketone **26** has been made by carbene insertion from a diazo-compound into an alkene. Try all three possible disconnections and say which you prefer.

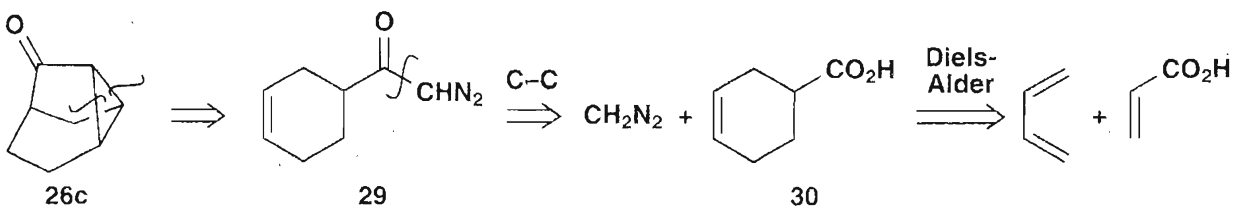


tricyclic ketone 26

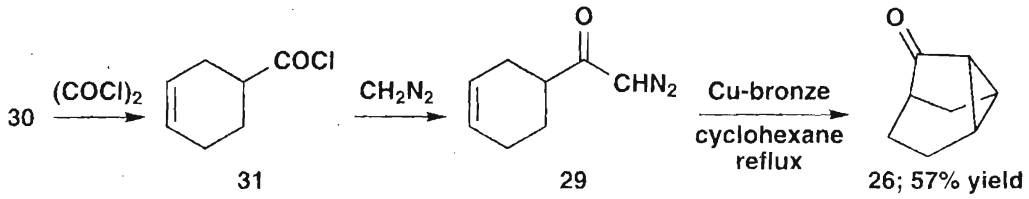
Answer 30.2: Two **26a** and **26b** are quite similar requiring a cyclic enone and a diazo group on a side chain **27** or **28**. We might have doubts about carbene insertion into a conjugated alkene, but such reactions are known, and we might prefer not to make the diazo compound by diazotising a primary amine, but these strategies could probably be made to work.



The third possibility **26c** is much the best as the alkene is not conjugated with a carbonyl group and the required diazoketone **29** can be made from an acid chloride and diazomethane. But the main reason is that the starting material **30** is the Diels-Alder adduct of butadiene and acrylic acid.

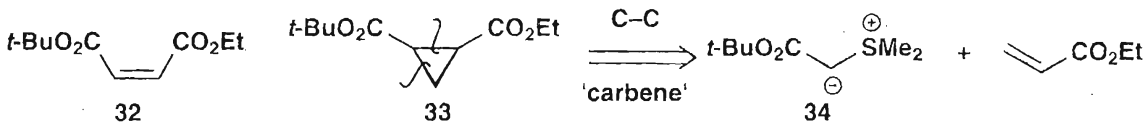


The synthesis[4] uses oxalyl chloride to make **25** and a copper-bronze catalyst to decompose the diazoketone to the carbene. None of the intermediates was isolated and the tricyclic ketone was formed in 57% yield from **30**.

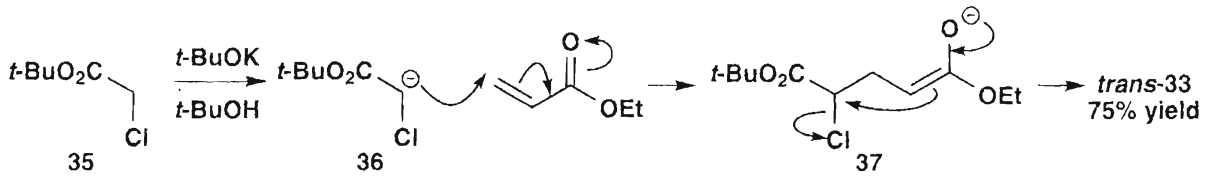


Cyclopropanes from Electrophilic Alkenes

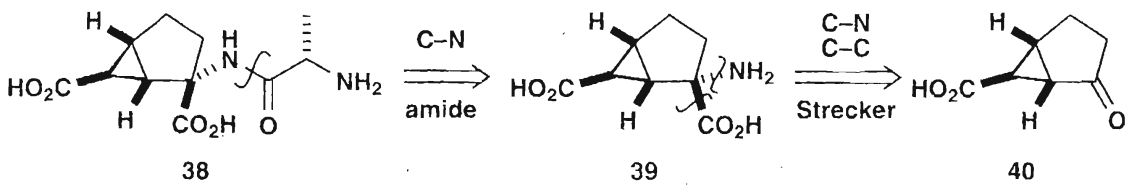
What strategy do you suggest for this (much simpler) cyclopropane **33**? Addition of diazomethane to **32** (*cis* or *trans*) is not likely to be good and the sulfur ylid strategy suggested in the textbook is likely to be much better.



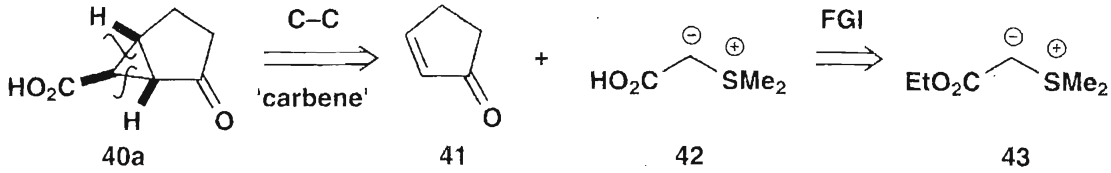
There is a simpler alternative: all we need is a nucleophile such as an enolate and a leaving group such as a halogen on the same atom **35** and we have a carbenoid. Conjugate addition of the enolate **36** to ethyl acrylate gives an intermediate that can cyclise **37** to give[5] the cyclopropane **33**. The stereochemistry is decided in the cyclisation step as the enolate is flat but *trans*-**33** is preferred. The mechanism resembles that of the Darzens reaction.



However, the sulfur ylid method has its uses. The Lilly compound for psychological disorders LY544344 **38** is obviously made from the simpler amino acid **39** by peptide coupling and **39** can be made by a Strecker reaction[6] on the bicyclic keto-acid **40**. **Problem 30.3:** Suggest a synthesis for **40**.

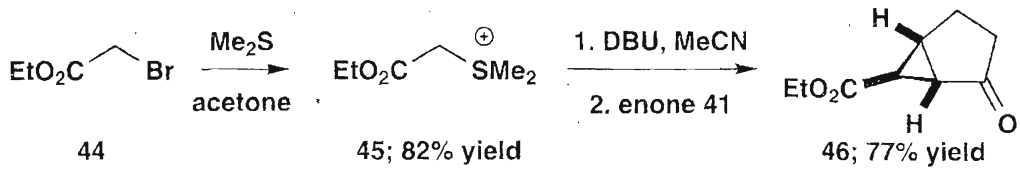


Answer 30.3: With the hint in the last paragraph, you might well have deduced that a sulfur ylid was used for the cyclopropanation. The best disconnection is **40a** as that gives us a simple enone **41**. The ylid **42** cannot be made because of the acidic proton but the ylid **43** of the ester is fine.



40a 41 42 43

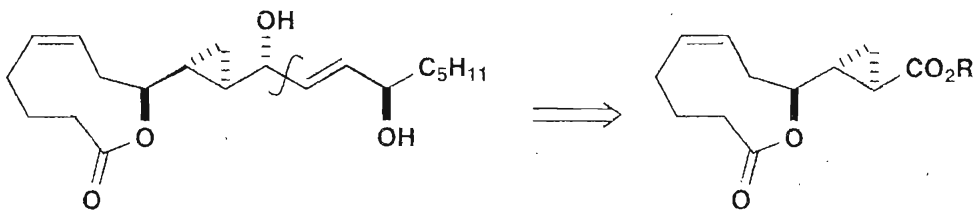
The sulfonium salt **45** was formed in acetone and the cyclopropanation carried out in acetonitrile with DBU as base. Though **46** could be hydrolysed to **39** it was better to carry out the Strecker reaction before hydrolysing the ester.[7] The stereochemistry of **46** comes from the cyclisation step. The 3/5 ring junction must be *cis* and the substituent CO_2Et much prefers the outside (*exo* or convex face) of the folded molecule.



44 45; 82% yield 46; 77% yield

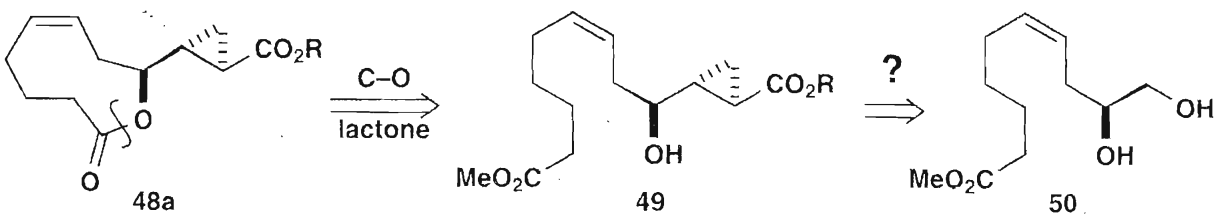
The Synthesis of Halicholactone

Halicholactone **47** is a lipoxygenase inhibitor from a sponge. It contains, according to Takemoto[8] 'a number of unusual structural features including a nine-membered lactone, *trans*-disubstituted cyclopropane ring, and bis-allylic alcohol'. We shall be concerned only with the cyclopropane. One synthesis[9] first made the nine-membered lactone **48**.



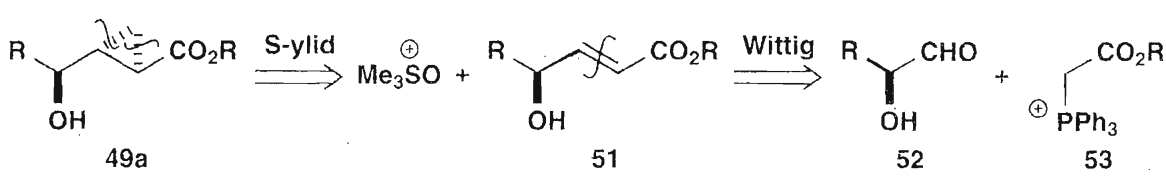
47; halicholactone 48

They did this because they knew how to make **50** from natural *S*-malic acid and how to cyclise the hydroxyester **49** to the lactone **48. Problem 30.4:** Suggest how they might convert **50** into **49**.



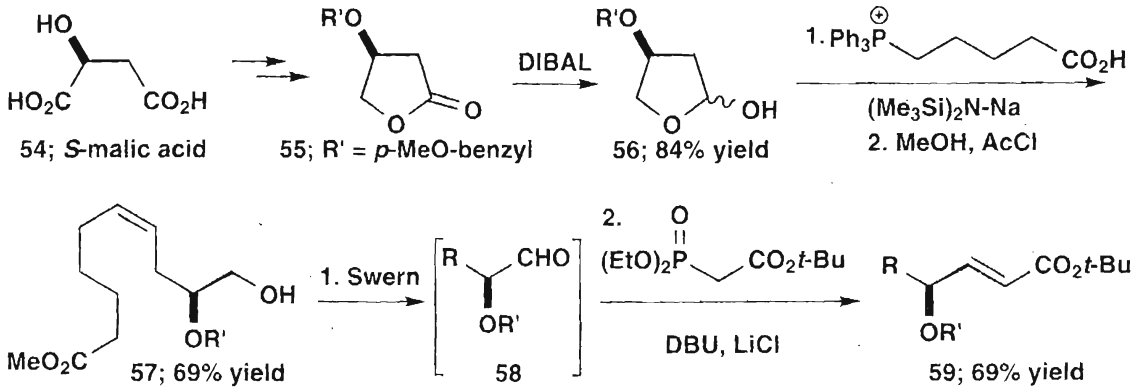
48a 49 50

Answer 30.4: There are many ways but a carbene method looks poor as there is an alkene in **49** that might also react. Instead Wills and his group went for the sulfur ylid method as only the conjugated alkene in the intermediate **51** will react. This alkene might be made by some sort of Wittig process from the aldehyde **52**.

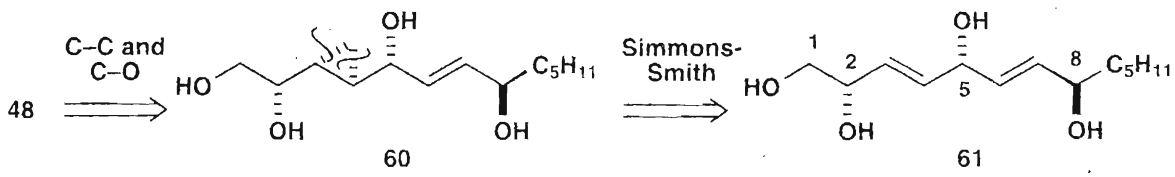


49a 51 52 53

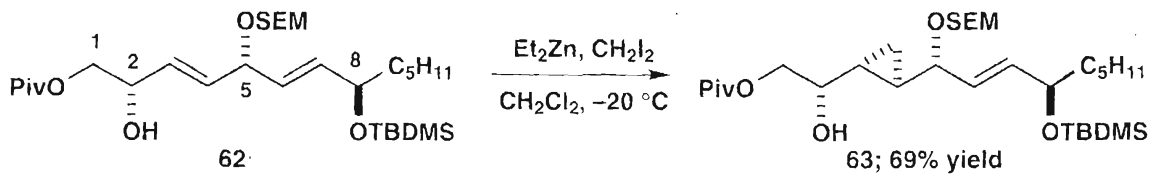
The secondary alcohol in **52** must be protected and they did this on the way from malic acid **54** to the lactol **56**. A Wittig reaction introduced the side-chain with the *cis*-alkene **57** and oxidation to the aldehyde **58** (not isolated) followed by a Horner-Wadsworth-Emmons olefination gave **59**. Finally, reaction with the sulfur ylid gave the cyclopropane as a 5:2 mixture of **49** and the other diastereoisomer.



By contrast, Takemoto's synthesis[8] used cyclopropanation by the Simmons-Smith method using a zinc carbenoid (see textbook chapter 30). This reaction is done on the skeleton that remains after removal of the whole left hand end **60**. We have not drawn the disconnections that take **48** to **60** but they must involve both C–C and C–O disconnections. **Problem 30.5:** What problems will arise with this approach? How might they be solved?



Answer 30.5: The Simmons-Smith on allylic alcohols is directed by the OH group and the problem is that we have two rather similar alkenes and *four* OH groups, three of them allylic. To get the right stereo- and regio-chemistry, it is essential that the cyclopropanation is directed by the OH on C-2. The OH on C-5 would give the right stereochemistry but might react with the other alkene. The only solution is to protect the other three OH groups **62**. The protecting groups are Piv = *t*-BuCO-, SEM = $Me_3SiCH_2CH_2OCH_2$- and TBDMS = *t*-$BuMe_2Si$-. The cyclopropanation gave **63** with no contamination by regio- or stereo-isomers.



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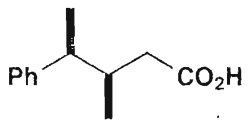
31 Strategy XIV: Rearrangements in Synthesis

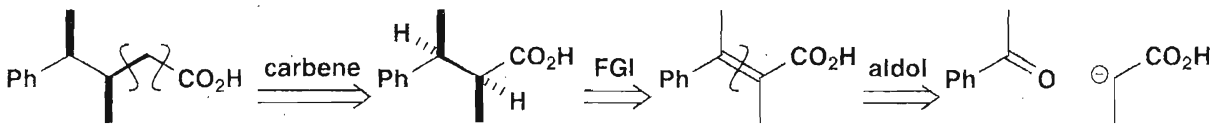
Diazoalkanes

Rearrangements are difficult to see retrosynthetically so we run through the chapter in the textbook with simple examples to help you recognise molecules that can be made by rearrangements. **Problem 31.1:** Suggest how this carboxylic acid **1** might be made using a diazoalkane.



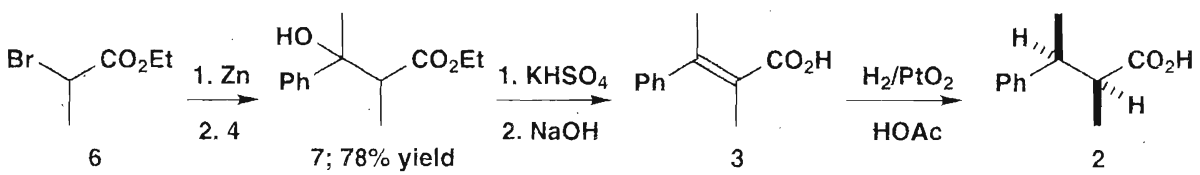
1

Answer 31.1: The CH_2 group between the carboxylic acid and the rest of the skeleton suggests a chain extension by the Arndt-Eistert procedure from **2**. Now the stereochemistry (easier to see that the Hs are on the same side if we draw them in) suggests hydrogenation of the conjugated acid **3** that could be made by an aldol reaction between acetophenone **4** and a reagent for the specific enolate **5**.

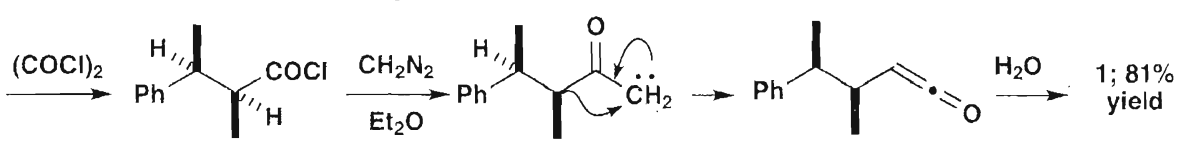


1a 2 3 4 5

Kloetzel[1] used a Reformatsky reagent (zinc enolate) for **5** and dehydrated the 'aldol' product with $KHSO_4$. Hydrogenation of **3** needed Adams catalyst and the rearrangement **9** to the ketene **10** went in excellent yield. It is important to recognise that the migration occurs with retention.



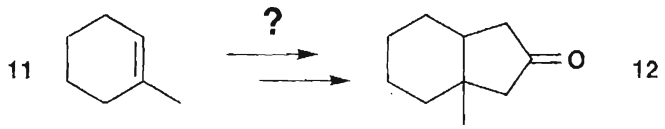
6 7; 78% yield 3 2



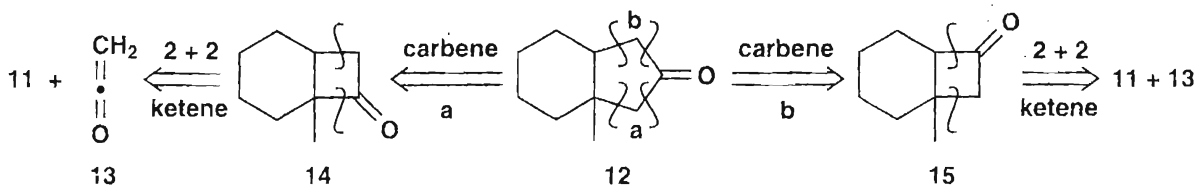
8 9 10

A Cyclopentannelation

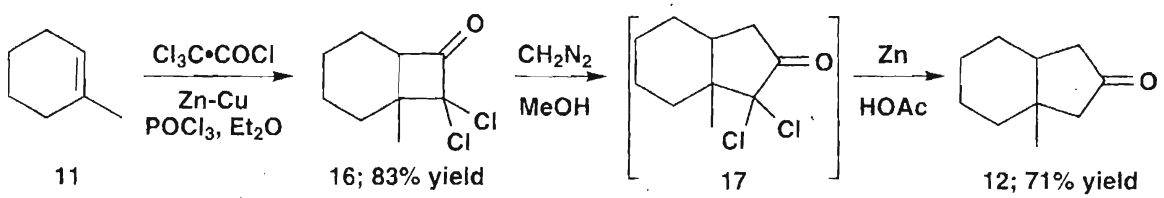
There are ways such as the Robinson annelation to add a six-membered ring to a molecule. **Problem 31.2:** But how would you add a five-membered ring to complete the transformation of **11** into **12**. *Hint:* If you have not yet read chapter 33, it may help you to do so now.



Answer 31.2: We know that rings can be made from smaller rings by ring expansion with diazoalkanes. So we could make **12** by ring expansion from either **14** or **15** and these cyclobutanones can be made (chapter 33) by 2 + 2 thermal cycloaddition of ketene to **11**. It may appear that each cyclobutanone could give two different cyclopentanones but migration of the tertiary centre in **14** or the secondary centre in **15** will be preferred over migration of the primary centre. But as the cycloaddition will go one way or the other, we do not have a choice.

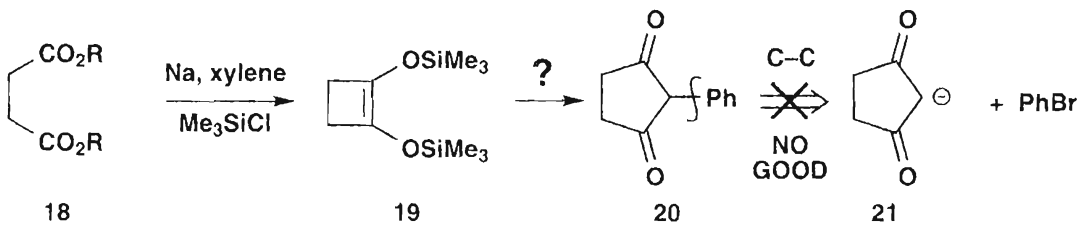


Dichloroketene was used in the synthesis[2] as it so much easier to prepare. Only one isomer **16** of the cyclobutanone **16** is formed and it rearranges with ring expansion to **17** which was dechlorinated without isolation to give **12**.



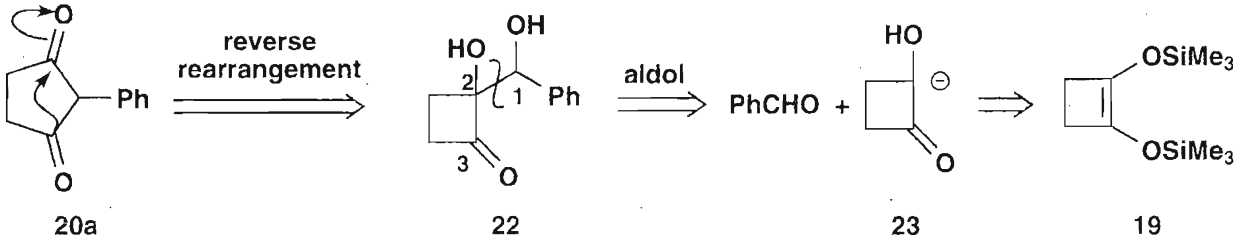
The Pinacol Rearrangement

The acyloin reaction (chapter 23) allows the easy synthesis of ene-diols such as **19** as their silyl ethers. **Problem 31.3:** How would you convert **19** into the cyclopentadione **20**? Why is the disconnection to the stable enolate **21** and PhBr no good?

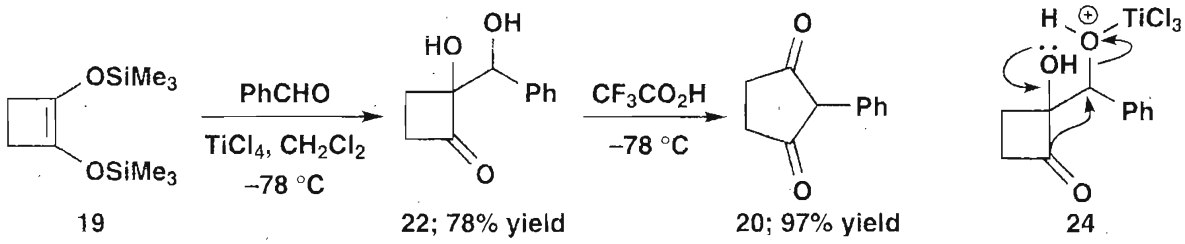


The heading of this section gives you the clue that we shall use a pinacol rearrangement. **Answer 31.3:** The easiest (though still not very easy) way to see the rearrangement is to reverse

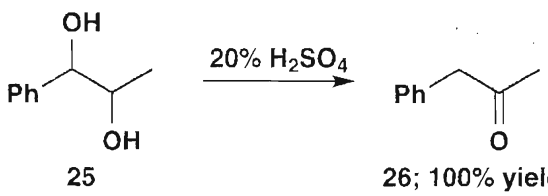
it **20a**. This gives the diol **22** that has a 1,3-diCO relationship and could be made by an aldol reaction between **19** and benzaldehyde. The disconnection **20** is no good because aryl bromides will not do S_N2 reactions.



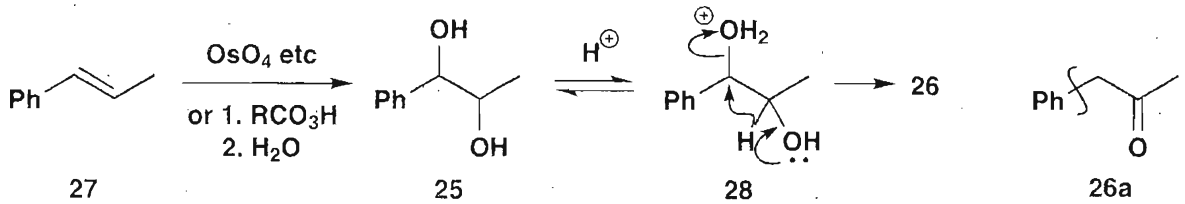
The aldol reaction was catalysed by Ti(IV) and the work-up removed the silyl groups. Rearrangement[3] with TFA (TriFluoroAcetic acid) gave an excellent yield of **20**. Notice that this (semi-)pinacol **22** is unsymmetrical and it is the secondary alcohol that leaves. This is partly because the secondary alcohol is also benzylic, partly because cyclobutyl cations are strained and partly because ring expansion of cyclobutanes **24** is very favourable.



Symmetrical pinacols with both alcohols secondary also rearrange using the leaving group that would give the more stable cation. **Problem 31.4:** How would you make **25**? Explain the reaction of **25** to make **26**. Why is it synthetically useful?

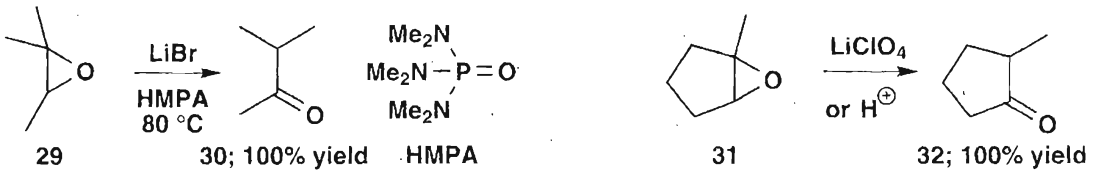


Answer 31.4: The simplest route is by dihydroxylation of the alkene **27** or epoxidation and hydrolysis. The benzylic OH leaves and the product is formed by hydrogen migration **28**. You might reasonably have suggested elimination of water to give the enol of **26**. The reaction is useful because the Friedel-Crafts disconnection **26a** of this class of ketones is no good as α-carbonyl cations are unstable. Such ketones are important anti-inflammatories.[4]

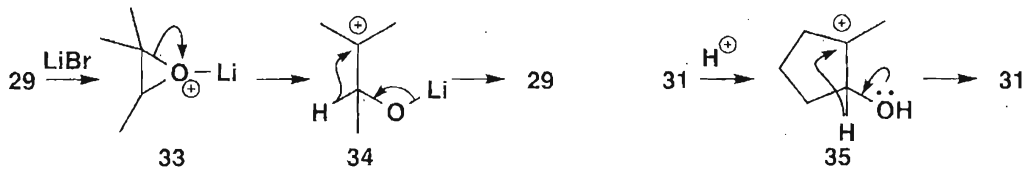


Rearrangements of Epoxides

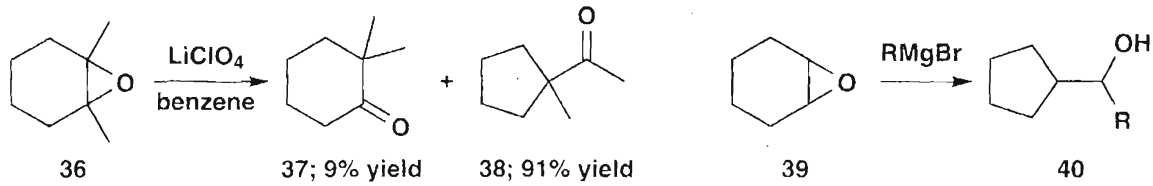
Unsymmetrical epoxides such as **29** or **31** rearrange in excellent yield.[5] **Problem 30.5:** Comment on the selectivity of the rearrangement.



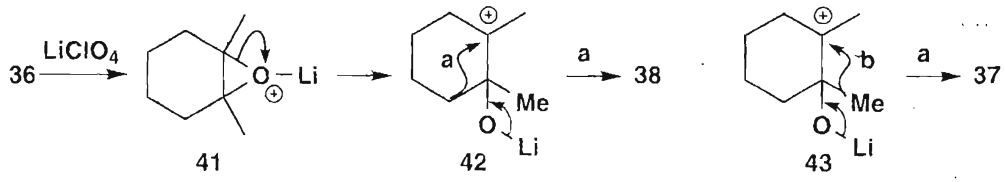
Answer 30.5: In both cases the tertiary alkyl cation is formed and hydrogen migration is preferred to methyl migration in **33** and to ring contraction in **35**.



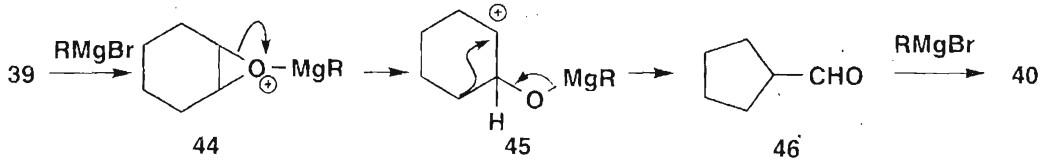
By contrast the symmetrical epoxide **36** gives a mixture[5] of ketones **37** and **38**. The less substituted cyclohexene oxide **39** gives rearranged product **40** on reaction with Grignard reagents.
Problem 31.6: Explain.



Answer 31.6: Epoxide **36** is symmetrical so it can open either way **41** to give a tertiary cation. The choice is then between methyl migration **43** and ring contraction **42**. Ring contraction wins. So we might deduce that hydrogen migration **35** beats methyl migration and ring contraction. But perhaps ring contraction in **35** doesn't happen as it would lead to a four-membered ring. Ring expansion of four-membered rings is often seen e.g. **16** to **17** or **22** to **20** but ring contraction to four-membered rings very rarely.

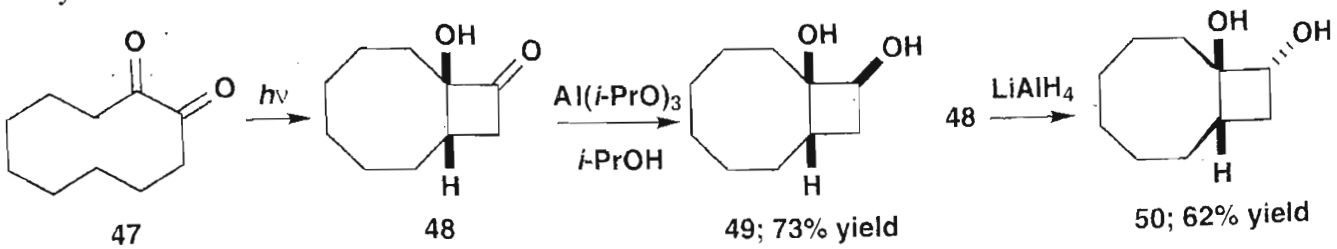


The formation of **40** clearly also requires ring contraction **45** to give the aldehyde **46** that is attacked by the Grignard reagent. Here ring contraction beats hydrogen migration. Perhaps the moral is not to be too confident in predicting rearrangements.



The Stereochemistry of Semi-Pinacol Rearrangements

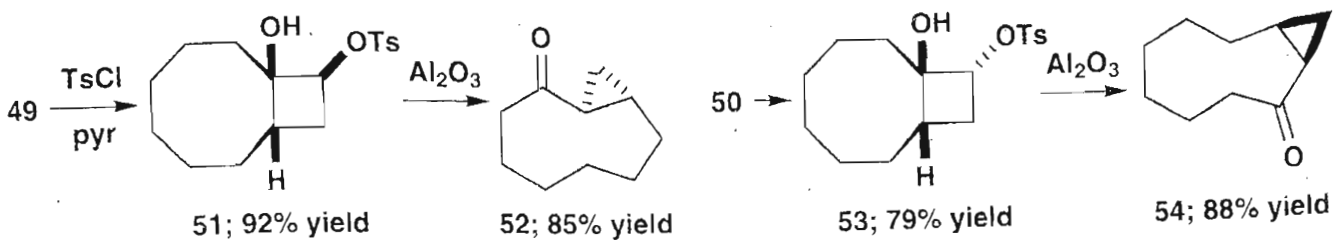
The pinacols **49** and **50** can be made[6] by stereoselective reduction of hydroxy-ketone **48**, available by a photochemical reaction on the α-diketone **47**. Though the eight-membered ring is large, it is floppy, and **48** behaves as a folded molecule. Kinetic control with $LiAlH_4$ adds hydride from the less hindered side but thermodynamic control with $Al(i\text{-}PrO)_3$ gives the more stable *exo*-alcohol **49**. Hydride is transferred from *iso*-propanol via an aluminium ate complex.[7]



47 48 49; 73% yield 50; 62% yield

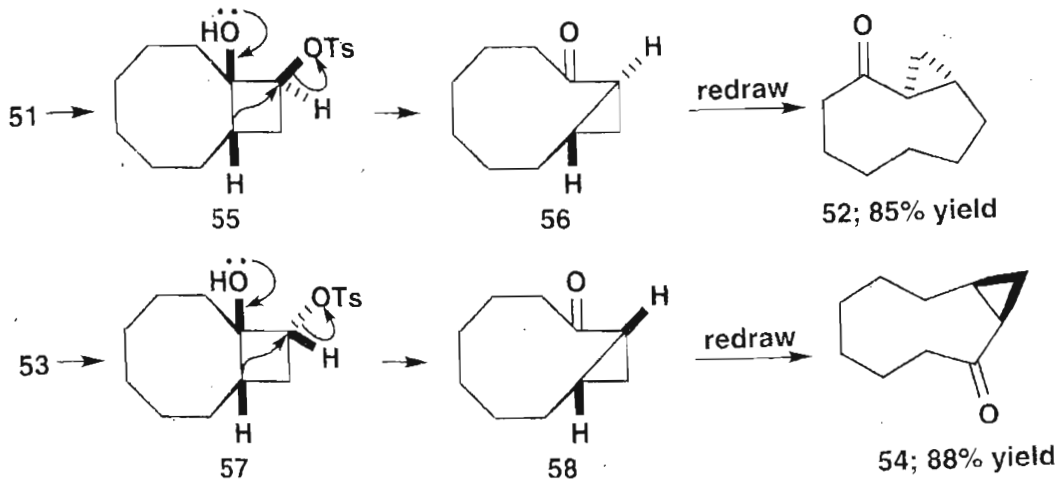
The secondary alcohols can be converted into good leaving groups (tosylates) and directed semi-pinacol rearrangement now leads to two closely related cyclopropyl ketones **52** and **54**.

Problem 31.7: What is the relationship between **52** and **54**? Explain these reactions.



51; 92% yield 52; 85% yield 53; 79% yield 54; 88% yield

Answer 31.7: The two cyclopropanes are diastereoisomers. The synthesis of **48** from achiral **47** means that all compounds are racemic so we are concerned only with relative stereochemistry. The rearrangement reaction is clearly stereospecific: each diastereoisomer of tosylate gives a single and different diastereoisomer of product. This is tricky to draw! Probably the only good way to see the stereochemistry clearly is to make models. Our suggestion is to draw the mechanism **55** or **57** without changing the shape of the starting material but marking the H that will be at the ring junction. Then draw the product in the same shape **56** or **58**. It is easy to see that **58** has a *cis* cyclopropane on the nine-membered ring but not so easy to see that we must redraw **56** so that the chain is in the plane of the paper **52**.

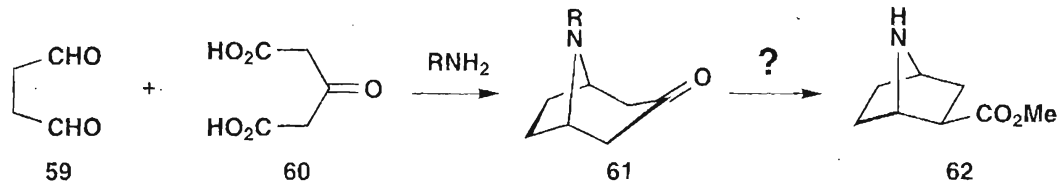


55 56 52; 85% yield

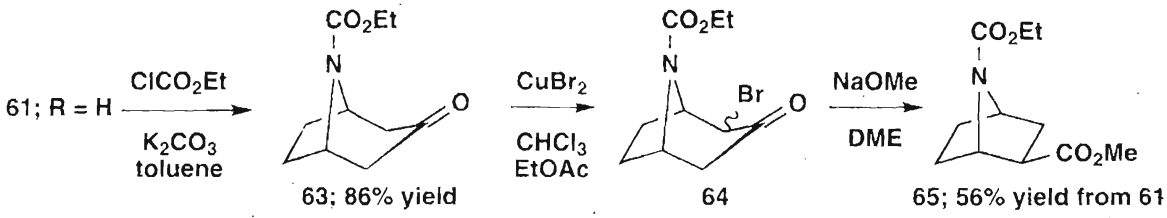
57 58 54; 88% yield

The Favorskii Rearrangement

We have mentioned the Robinson tropinone synthesis in several chapters of the textbook. It involves the condensation of a dialdehyde **59**, acetone dicarboxylic acid **60** and an amine to give a tropinone **61**. These tropinones are so easily made that it makes sense to try and form other ring systems from them. **Problem 31.8:** Suggest how tropinones might be converted into **62**.



The Favorskii rearrangement is perfect for this. You needed to brominate the tropinone and treat the bromoketone with methoxide. It turns out that a CO_2Et protecting group is needed on the nitrogen **63**. Bromination with bromine gives dibromination but $CuBr_2$ is more controlled. Treatment with methoxide gives the ester **65** from which the protecting group can easily be removed by hydrolysis and decarboxylation.[8]



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4. M. Tiffeneau, *Compt. Rend.*, 1935, **200**, 1217.
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7. *Vogel*, p. 519.
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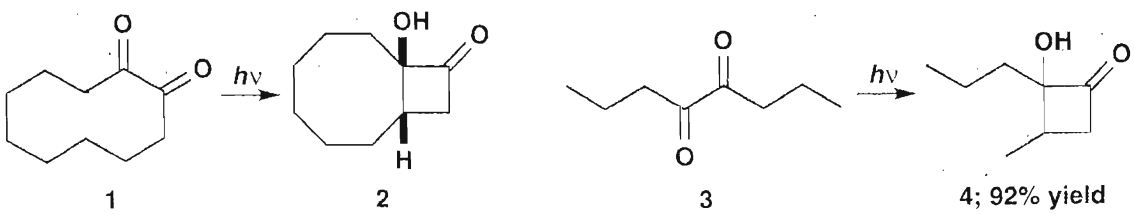
32 Four-Membered Rings: Photochemistry in Synthesis

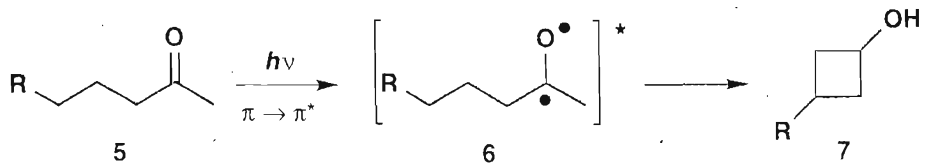
An Example from Chapter 31

In the last chapter we featured, but did not explain, a photochemical synthesis[1] of a four-membered ring **2** that was clearly not a 2 + 2 cycloaddition. In fact this is just an example of a general four-membered ring synthesis that works very efficiently[2] on simple α-diketones such as **3**.



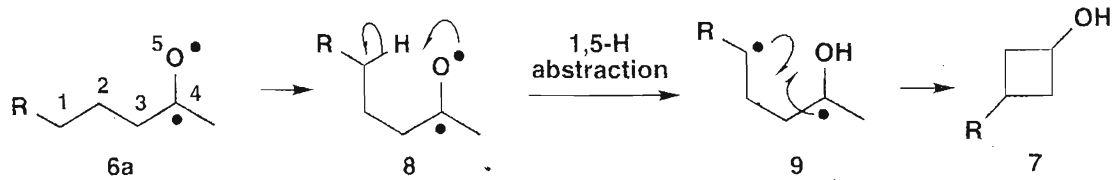
1 **2** **3** **4; 92% yield**

Even more generally, simple ketones such as **5** may give, usually in low yield, cyclobutanones such as **7**. A simple explanation is that the light is absorbed by the C=O π-bond and transfers one electron from π to π*. It is difficult to represent this well, but, as the π-bond is now weaker and the electrons are distributed more towards carbon, the diradical **6** is the best we can do. **Problem 32.1:** Can you draw a mechanism to get from **6** to **7**? *Hint:* Which atom in the chain has been altered and what is lost from it?



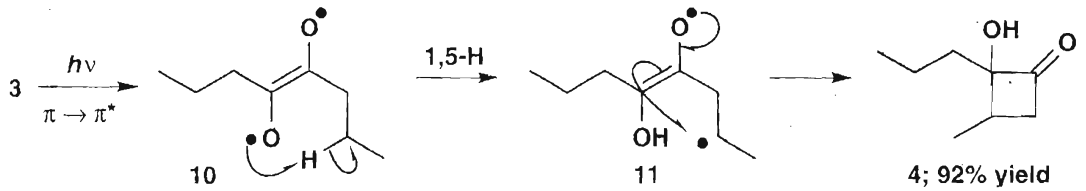
5 **6** **7**

Answer 32.1: A hydrogen atom must be abstracted from a carbon atom, marked C-1 in **6a**. This C-atom is 1,5-related to the oxygen radical and, as the O–H bond is stronger than the C–H bond, abstraction occurs **8** in the style of chapter 24. Finally the two carbon radicals cyclise **9** to give **7**. **Problem 32.2:** Suggest a mechanism for the photochemical cyclisation of **3** and say why you might expect it to be more efficient that the cyclisation of **6**.



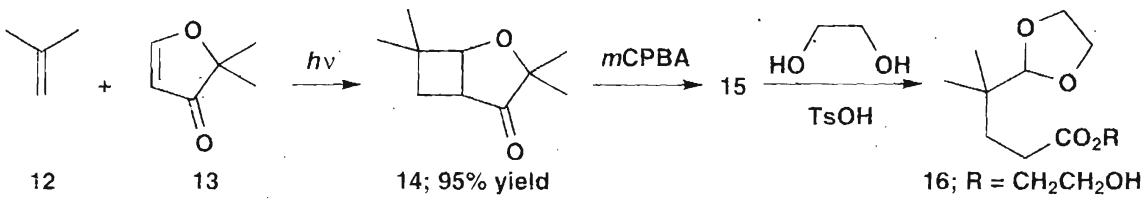
6a **8** **9** **7**

Answer 32.2: We now have a conjugated π-system that will absorb light more efficiently and at lower wavelength than a simple ketone. The diradical can be drawn in various ways with the odd electrons on carbon or oxygen as long as the 1,5-H abstraction **10** occurs from carbon to oxygen. We have drawn the cyclisation using an 'enolate radical' **11** but there are other ways to draw it. You will have noticed that both **1** and **3** are symmetrical molecules so that it doesn't matter which way the 1,5-H abstraction occurs.

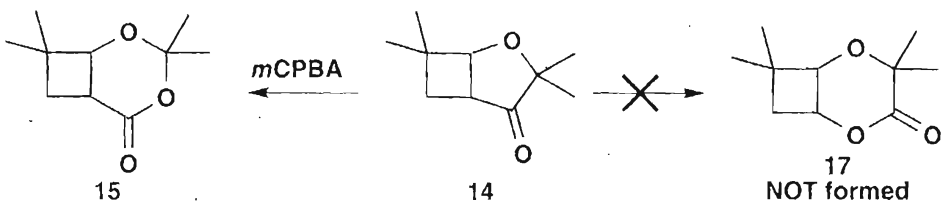


Development of Material from the Textbook

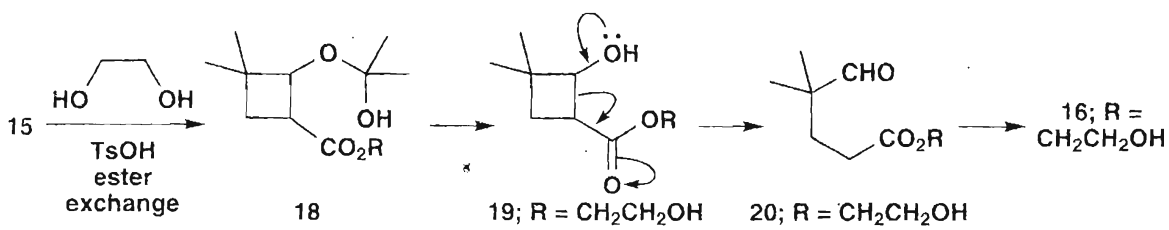
In the textbook chapter we revealed the excellent regiospecific photochemical cyclisation of **12** and **13** to give **14** but we did not reveal the application of this chemistry. The next two reactions were an oxidation with *m*CPBA and then a reaction with glycol in acid. **Problem 32.3:** Can you predict what the product **15** would be and how **16** is formed?



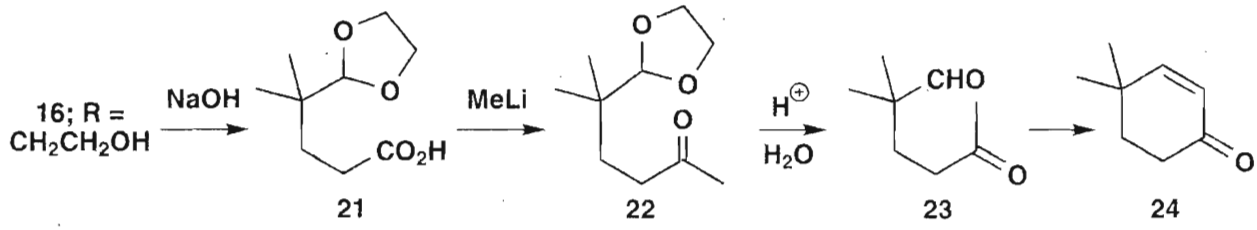
Answer 32.3: The first reaction is obviously a Baeyer-Villiger rearrangement (chapter 26) but which group migrates? You should have realised that the tertiary group would migrate to give the acetal **15** rather than the secondary group to give[3] **17**.



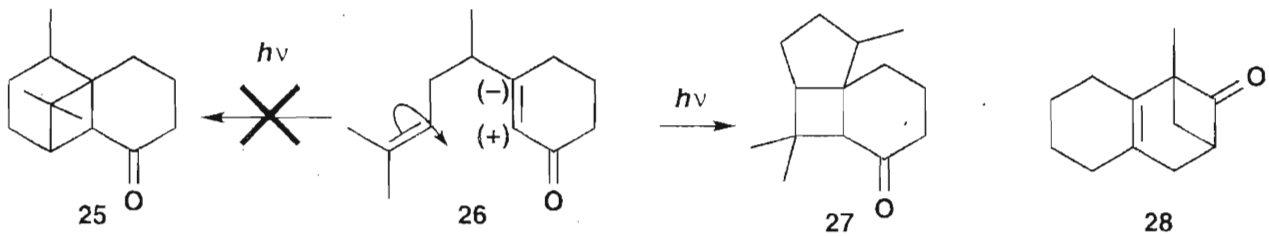
But the next step is something different. Ester exchange leads to **18** by attack of glycol on the lactone, releasing the unstable hemiacetal. Decomposition to the alcohol leads to fragmentation **19** with cleavage of the strained four-membered ring and formation of the aldehyde **20** that is immediately converted to the acetal **16** under the reaction conditions.



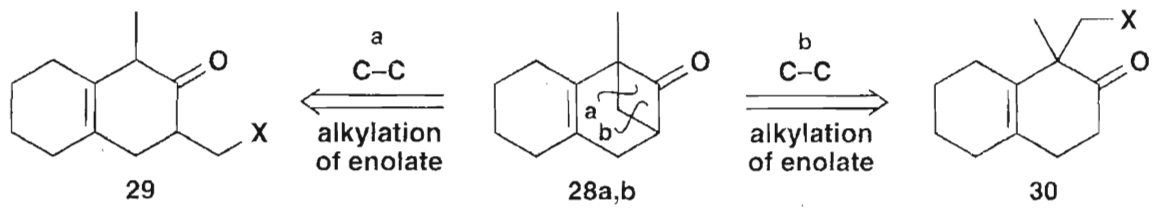
The point of all this was to make cyclohexenone **24** via ketone **22**. Hydrolysis of **22** gives the keto-aldehyde **23** that cyclised very easily in an intramolecular aldol reaction to give **24**.



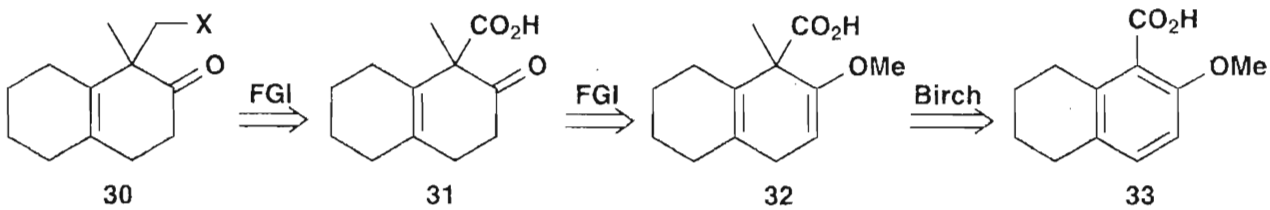
Later in the chapter we pointed out that photocycloaddition of **26** gave **27** rather than strained **25**. Notice that two new C–C bonds are formed at the expense of two weaker C=C bonds so there is some gain. Surprisingly, similarly strained compounds such as **28** can be made by ionic cyclisations. **Problem 32.4:** Suggest a precursor that might give **28** on treatment with base.



Answer 32.4: The only functional group is a ketone so alkylation of an enolate seems the best idea. There is a choice: disconnection **28a** gives **29** where X is a leaving group while **28b** gives **30**. The latter is much to be preferred as treatment of **29** with base would probably lead to elimination of HX rather than cyclisation. So how would you make **30**?

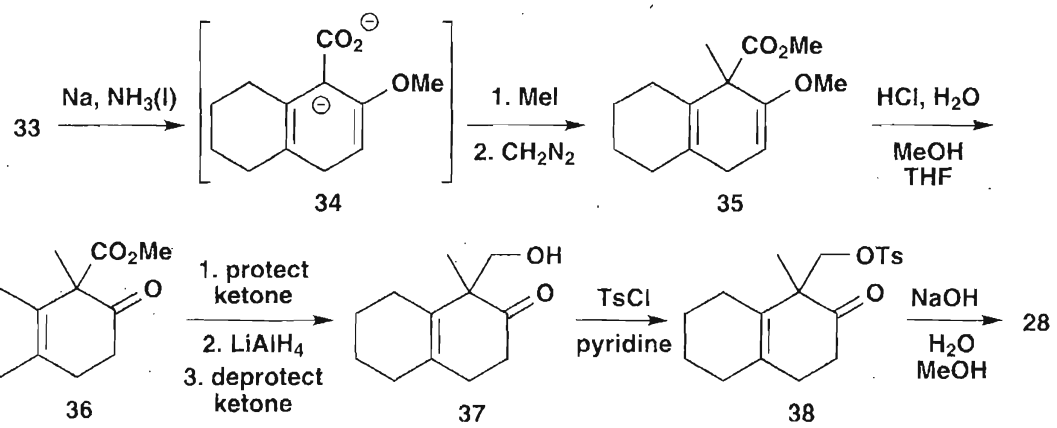


This is not straightforward, but if you have read chapter 36 you might have noticed that a Birch reduction route is ideal. The leaving group could come from a carboxylic acid **31** so Birch reduction of **33** followed by immediate methylation of the enolate anion of the carboxylate **34** should be all right.



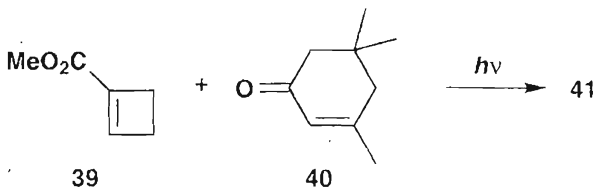
The synthesis[4] is summarised here. A tosyl group was chosen as the leaving group and the cyclisation to **26** occurred under surprisingly mild conditions. Note the selectivity shown by the two methylating agents: MeI reacts with the most nucleophilic species, here the carbon of

the enolate **34**. By contrast diazomethane CH_2N_2 needs protonation to make it reactive and the carboxylic acid, formed during the work-up of the first methylation, is ideal.

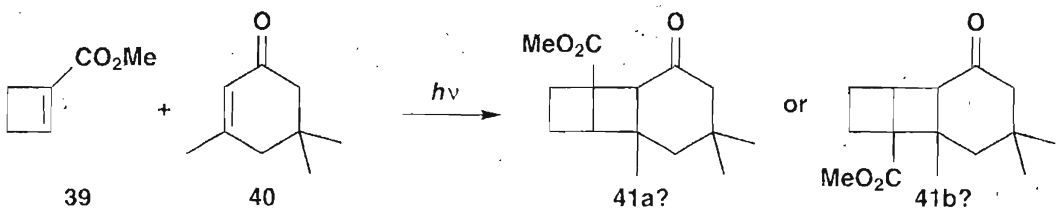


Photochemical Cycloadditions

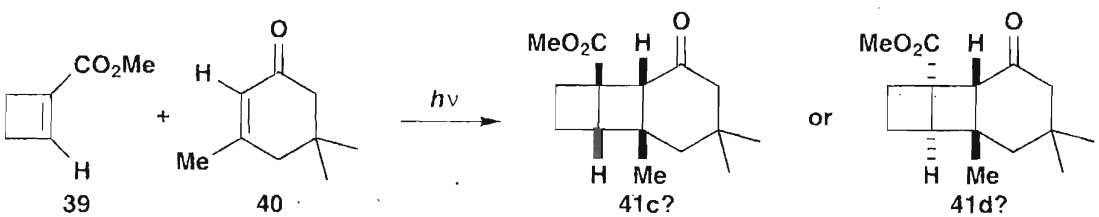
The two alkenes **39** and **40** combine on irradiation to give a single compound in 80% isolated yield.[5] Only one compound is activated, probably the enone **40** so the product **41** is a 1:1 adduct of **39** and **40**. **Problem 32.5:** What is the structure of the photoadduct **41**? *Hint:* More than one kind of selectivity is involved.



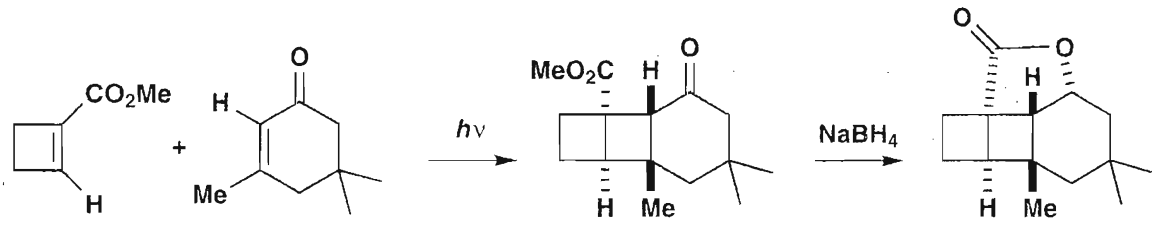
Answer 32.5: First the regioselectivity: redrawing the reagents so that they can add we find two possibilities **41a** or **41b**. We know from the textbook chapter that photochemical cycloadditions occur the 'wrong' way round so we choose **41a** formed when the two electrophilic ends of the alkenes form a bond.



Now what about the stereochemistry? We know that the 4/4 and 4/6 ring junctions must be *cis* and that the stereochemistry of the starting materials is preserved. Marking the Hs should help you to see this. So we have two possibilities: **41c** or **41d**.

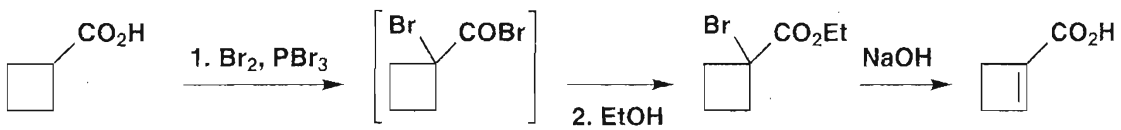


There is no '*endo*' rule controlling which of these is formed: the molecules can choose. They prefer to have the more stable arrangement **41d** with the end rings held apart. Note that all these molecules are racemic as the starting materials **39** and **40** are achiral. As it happens, the stereochemistry of **41** was known because reduction of the ketone with sodium borohydride gave the crystalline lactone **42** whose X-ray structure revealed all. The hydride transferred from aluminium prefers to come from the outside of the folded 4/6 fused rings.



39 **40** **41; 85% yield** **42; 65% yield**

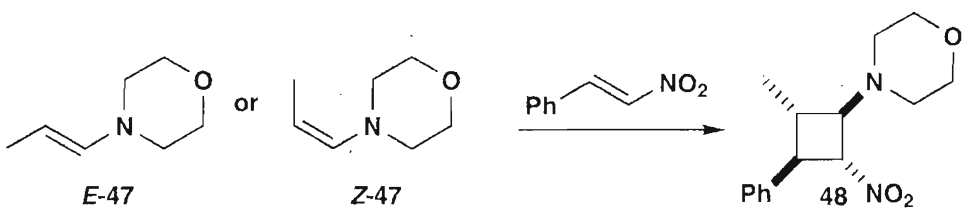
One starting material **39** is already a cyclobutene and it was made by the strategy of buying the difficult part of the molecule: the carboxylic acid **43** is commercially available. So bromination and work-up with ethanol gave **45** from which HBr could be eliminated to give cyclobutene carboxylic acid[6] **46**.



43 **44** **45** **46**

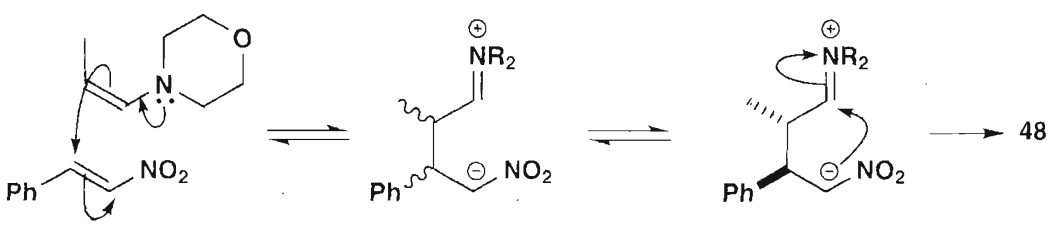
Four-Membered Rings by Ionic Reactions

Enamines such as **47** add to nitroalkenes to give four-membered rings **48** in good yield.[7]
Problem 32.6: Do you think that this is a concerted 2 + 2 cycloaddition, a stepwise radical reaction, or a stepwise ionic reaction given that either isomer *E*-**47** or *Z*-**47** gives the same regio- and stereoisomer of the adduct **48**?



E-47 *Z*-47 **48**

Answer 32.6: The loss of stereochemistry in the enamine suggests a stepwise mechanism and the combination of a strongly electrophilic nitroalkene and a nucleophilic enamine suggests an ionic mechanism. The regiochemistry agrees with an intermediate such as **50** and the stereochemistry suggests that only the *trans* intermediate can cyclise **51** and that the *cis* intermediate equilibrates via starting materials. The next chapter deals with another important way to make cyclobutanes.



49 **50** **51**

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1. J. V. Paukstelis and J.-L. Kao, *Tetrahedron Lett.*, 1970, 3691.
2. W. H. Urry and D. J. Trecker, *J. Am. Chem. Soc.*, 1962, **84**, 118.
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5. P. A. Wender and J. C. Lechleiter, *J. Am. Chem. Soc.*, 1977, **99**, 267.
6. W. G. Dauben and J. R. Wiseman, *J. Am. Chem. Soc.*, 1967, **89**, 3545.
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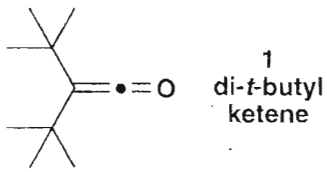
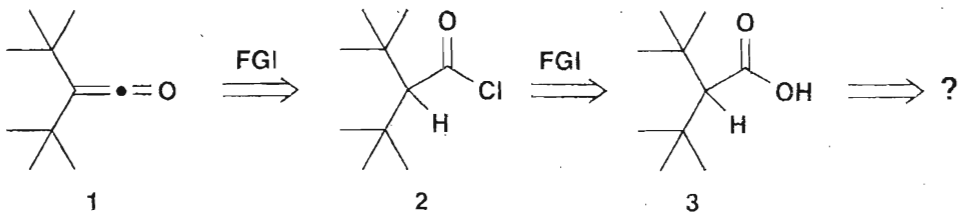
33 Strategy XV: The Use of Ketenes in Synthesis

Do Ketenes Exist?

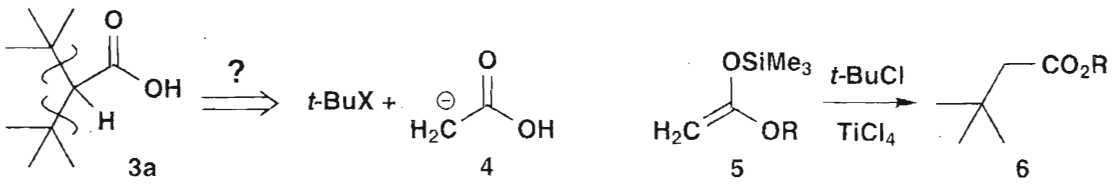
In spite of their high reactivity, some ketenes can be isolated and one at least can even be distilled. This is di-*t*-butylketene. **Problem 33.1:** What compound would you choose as an intermediate in the synthesis of **1**?



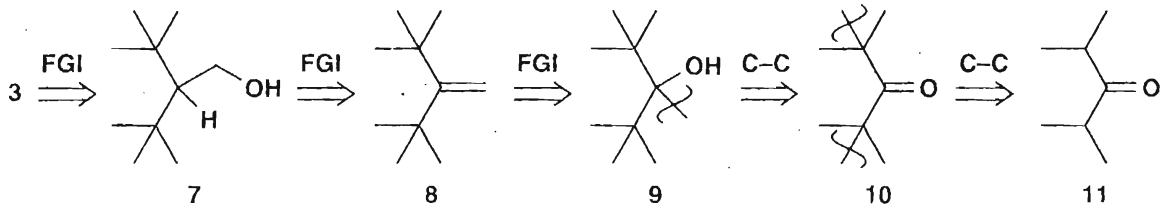
Answer 33.2: The obvious way to make **1** is by elimination of HCl from the acid chloride **2** and this means you must make the carboxylic acid **3**. **Problem 33.2:** Any ideas of how to do this?



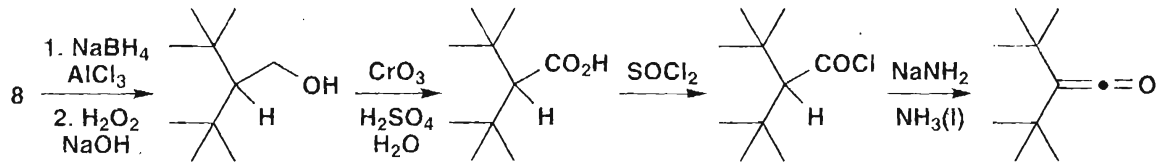
Answer 33.2: There are many possibilities but these do not include the alkylation of enolates of acetic acid derivatives **4** with *t*-butyl halides. The only such route that might work is the alkylation of silyl enol ethers **5** with *t*-BuCl and a Lewis acid. The half way stage would be **6**. This would have to be turned into a silyl ether and the alkylation reaction repeated. As far as we are aware, this has not been tried.



A reported synthesis[1] worked its way back from **3** through the alcohol **7** that might be made by hydroboration of an alkene **8** and hence from the isomeric alcohol **9**. The idea was to get back to the available ketone **11** that might be methylated twice before the addition of MeLi to give **9**.



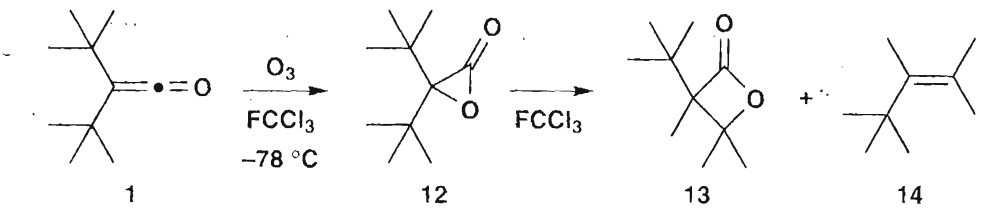
The double alkylation was done with $NaNH_2$ as base. Then MeLi was added to **10** to give **9**. Dehydration with $SOCl_2$ in pyridine gave the alkene **8**. The synthesis of the acid chloride **2** went as expected and elimination with $NaNH_2$ finally gave the stable ketene **1** that could be distilled. So some ketenes definitely exist.



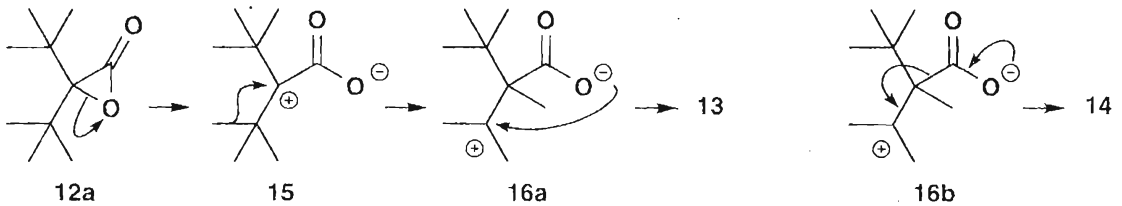
The Synthesis of α-Lactones

Unstable intermediates also include the α-lactones. Bartlett[2] wrote 'persuasive evidence exists that α-lactones occur as intermediates.' But he wanted to make one to be certain and found di-*t*-butylketene **1** the perfect starting material. Oxidation of **1** gave a solution of a compound with an NMR spectrum consistent with **12** that decomposed to a mixture of **13** and **14** on standing.

Problem 33.3: Are you convinced?

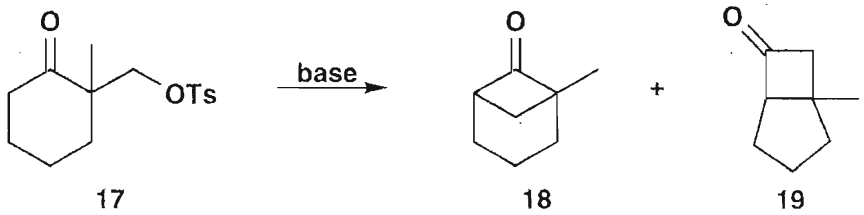


Answer 33.3: Well, we are! The very strained α-lactone would open in a polar solvent **12a** to the zwitterion **15** that would undergo methyl migration to give the stable tertiary cation **16** that could reclose **16a** to the lactone **13** or simply lose CO_2 **16b** to give the alkene **14**.



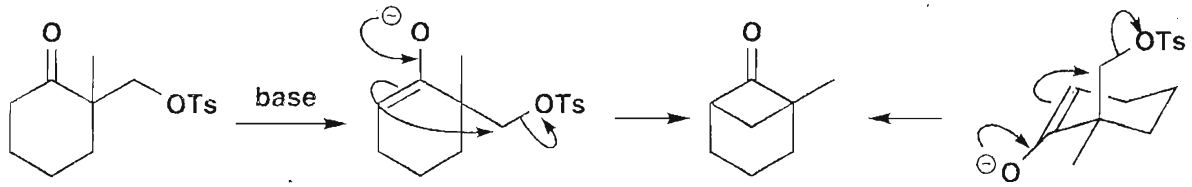
Ketenes as Intermediates

Treatment of the ketone **17** with base gives a mixture of cyclobutane products.[3] **Problem 33.4:** Propose mechanisms for the formation of these products.



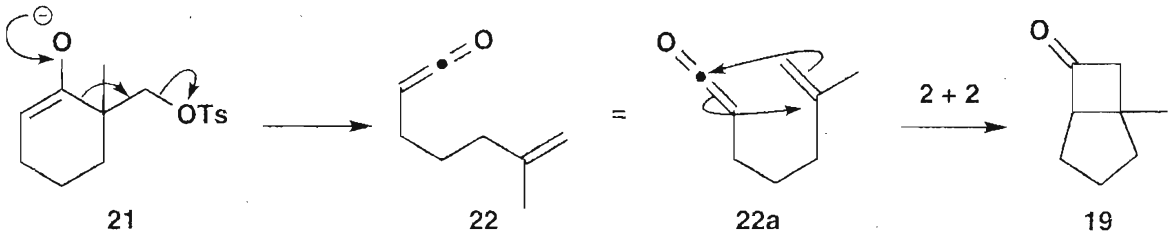
17 18 19

Answer 33.4: The formation of both products must surely start with enolate formation on the only possible side. There is then a simple route to **18** by alkylation with the tosylate **20**. The reaction looks rather awkward but it is better when the CH_2OTs group is drawn axially **20a**.



17 20 18 20a

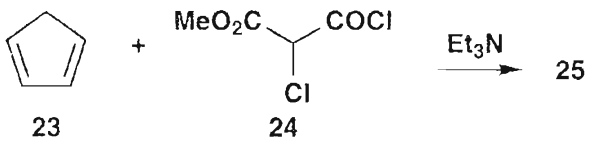
The other product **19** is more difficult but the clue is in the section heading. The enolate could fragment **21** to give the ketene **22**, better drawn **22a** which is more in the shape of **19** so that we can draw the [2 + 2] cycloaddition to give **19**. There is no agreement about this reaction but a ketene is at least one explanation.



21 22 22a 19

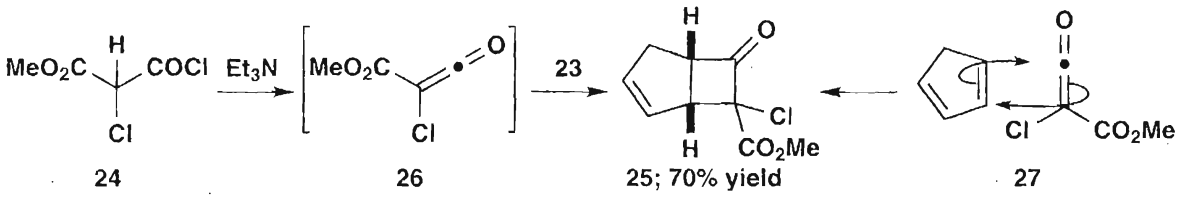
[2 + 2] Thermal Cycloadditions of Ketenes

Thermal cycloadditions of ketenes were discussed in the textbook chapter. **Problem 33.5:** Predict the structure of **25**.

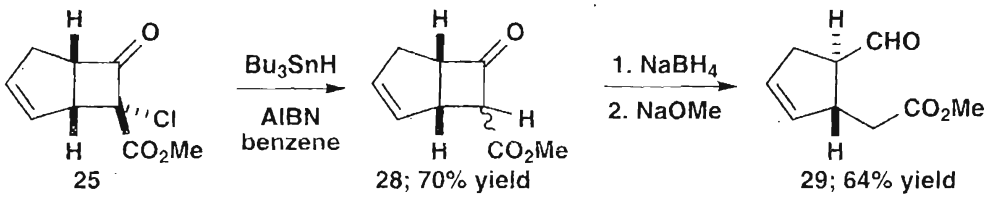


23 24

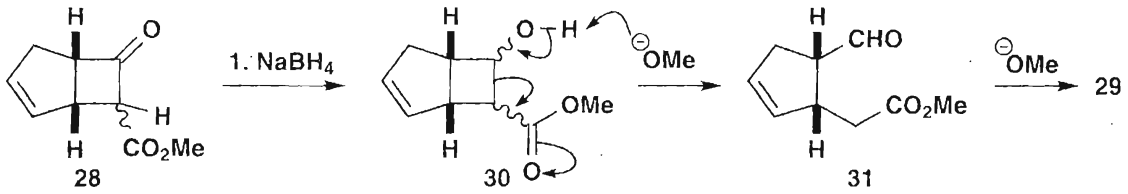
Answer 33.5: The amine eliminates HCl from **24** to give the ketene **26** that adds to one alkene of the cyclopentadiene to give **25**. The regioselectivity comes from the nucleophilic end of the diene attacking the electrophilic carbonyl group of the ketene **27**. But did you also predict the stereochemistry? One diastereomer of **25** is formed. Is it also one enantiomer?



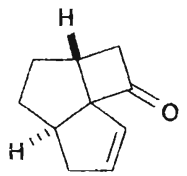
The larger ester group ends up on the outside (*exo*- or concave) face of the folded molecule. This compound **25** is not a single enantiomer: though **24** is chiral and could in theory be a single enantiomer, it would racemise quickly by equilibration with its enol. The ketene **26** is achiral as is the diene so no asymmetry could be transmitted. The chlorine was removed by treatment with Bu_3SnH (a radical reaction, see *Strategy and Control*) and the mixture of diastereoisomers **28** converted into **29**. **Problem 33.6:** Explain the reactions that convert **28** into **29**.



Answer 33.6: Borohydride reduces the ketone to the alcohol which is fragmented[4] by base **30** to give **31**, the *cis* isomer of **29**. The same base epimerises the aldehyde **31** by enolate formation to the more stable *trans* isomer **29**. This product was used in a synthesis of prostaglandins.

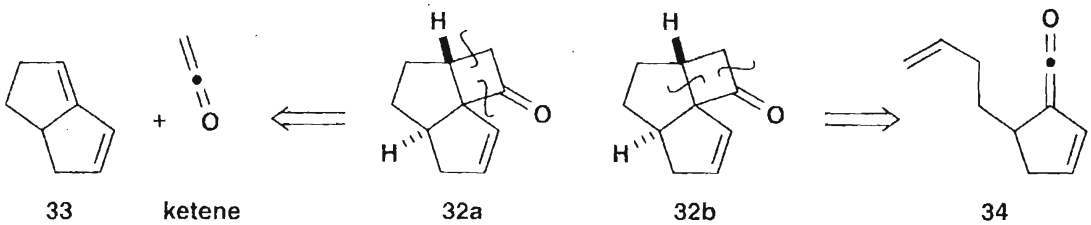


Ketene cycloadditions can produce complex structures in one step. **Problem 33.7:** Draw both disconnections corresponding to ketene [2 + 2] cycloadditions on this tricyclic ketone **32** and say which you prefer.

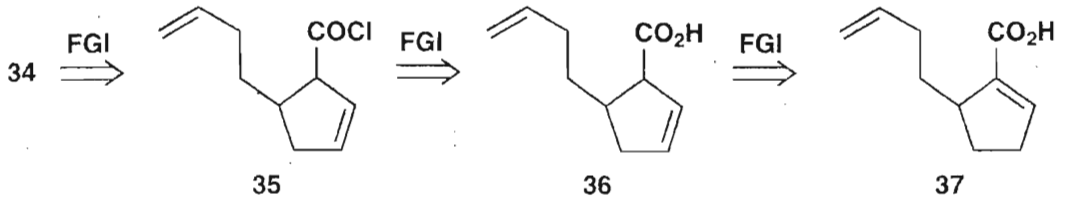


32
a tricyclic ketone

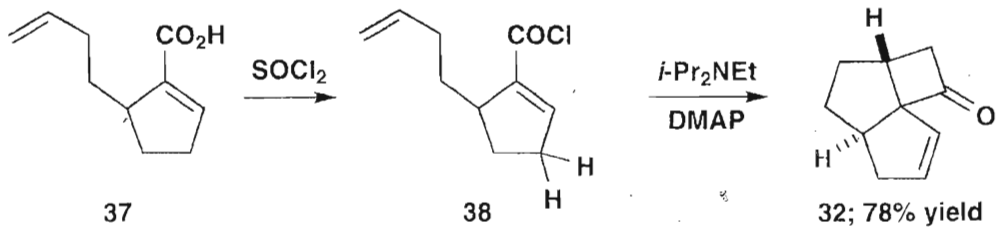
Answer 33.7: The two possibilities are **32a** and **32b**. The diene **33** could no doubt be made but the two alkenes are not the same and, in any case, the carbonyl group of ketene would not add to the middle of the diene so we reject that. We prefer **32b** that would need an intramolecular cycloaddition and would be constrained, so that the regiochemistry is controlled, to give **32**.



The starting material for ketene generation would be the acid chloride **35**, available from the acid **36**. In fact the conjugated acid **37** was preferred as it was easier to make.[5]

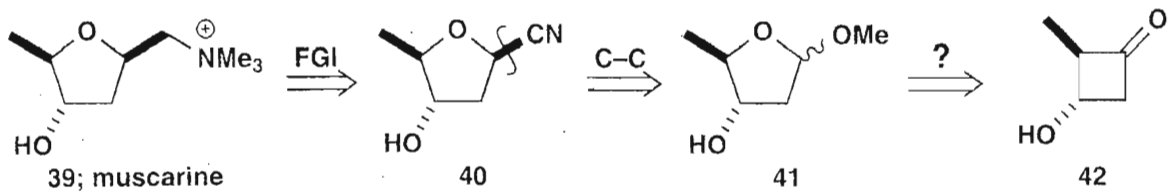


As the marked γ-hydrogens must be removed from **38**, and they are less acidic than the usual α-hydrogens, the stronger Hünig's base *i*-Pr_2NEt was used with catalytic DMAP to give **32** in good yield.

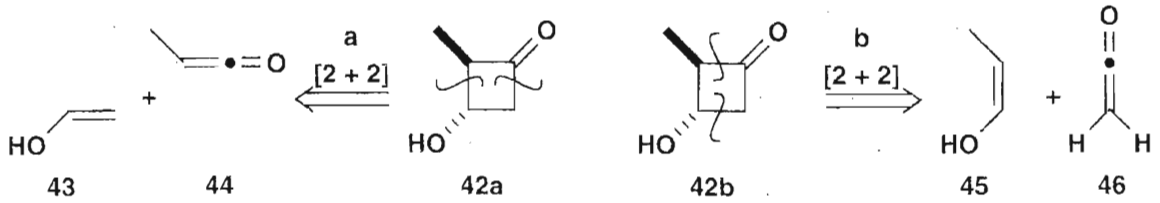


A Synthesis of Muscarine

Muscarine **39** is a toxin from the mushroom *Amanita muscaria*. The amine salt could be derived from the nitrile **40** and that could come from an S_N1 displacement on the acetal **41**. Pirrung and DeAmicis[6] believed that they had a way of making **41** by ring expansion from the cyclobutanone **42**. **Problem 33.8:** Suggest a synthesis of **42**.

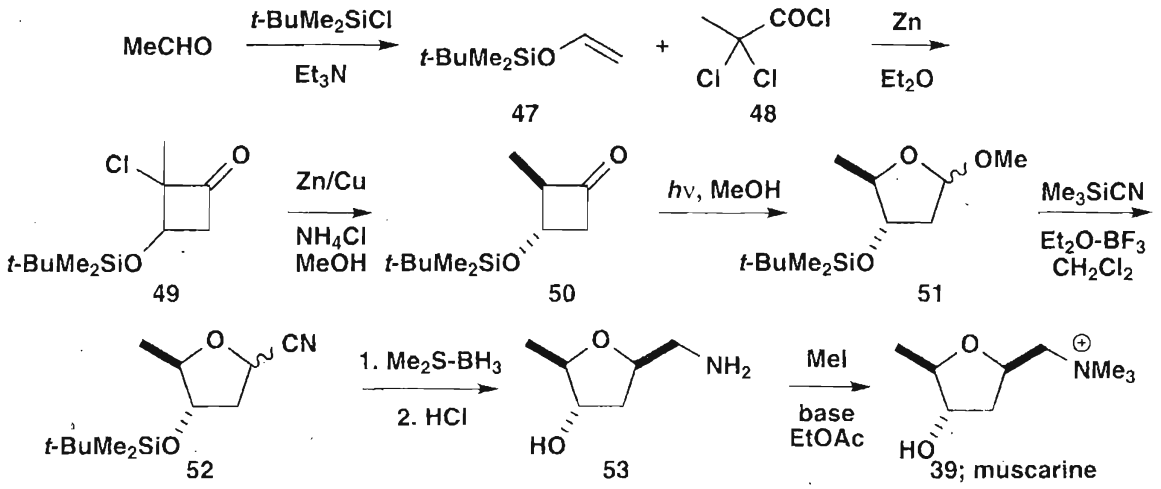


Answer 33.9: There is a problem with either disconnection **42a** or **42b**: the alkenes **43** and **45** are enols and would have to be stabilised by silylation. The stereochemistry from route **b** would come from the stereochemistry of the enol **45** and perhaps that was why they chose route **a** as we should expect the reagents to come together to give the more stable *trans* cyclobutanone without having to control reagent stereochemistry. Fortunately the regiochemistry of both approaches is fine: the nucleophilic end of the enol should attack the electrophilic carbonyl group of the ketene.



The synthesis is outlined below. They used the TBDMS group on the enol **47** and preferred to use zinc on the dichloro acid chloride **48** to make the ketene and then dechlorinate the adduct **49**

with more zinc. This gave a 3:1 mixture of the *trans* cyclobutanone **50** and the *cis* compound. Their new chemistry was a photochemical reaction with methanol that gave a mixture of epimers of **51**. Substitution with cyanide and Lewis acid catalysis gave a mixture of epimers of **52**. These were separated by chromatography and the *cis* isomer used to make muscarine. Ketenes have found many applications where the final product bears little resemblance to the key intermediate.



References

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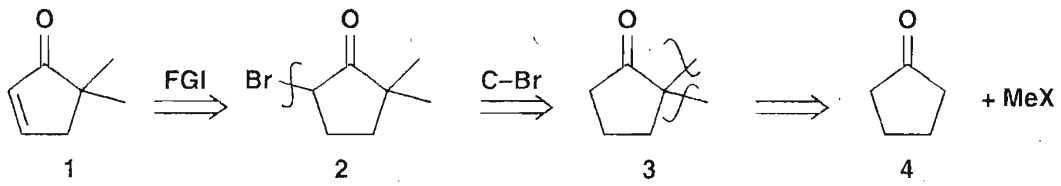
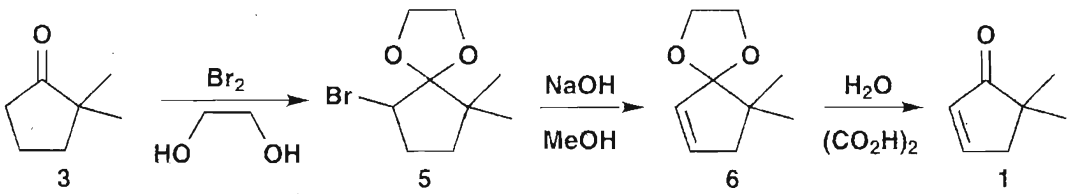
4. S. Goldstein, P. Vannes, C. Houge, A. M. Frisque-Hesbain, C. Wiaux-Zamar, L. Ghosez, G. Germain, J. P. DeClercq, M. Van Meerssche and J. M. Arriete, *J. Am. Chem. Soc.*, 1981, **103**, 4616.
5. S. J. Veenstra, A. De Mesmaecker and B. Ernst, *Tetrahedron Lett.*, 1988, **29**, 2303.
6. M. C. Pirrung and C. V. DeAmicis, *Tetrahedron Lett.*, 1988, **29**, 159.

34 Five-Membered Rings

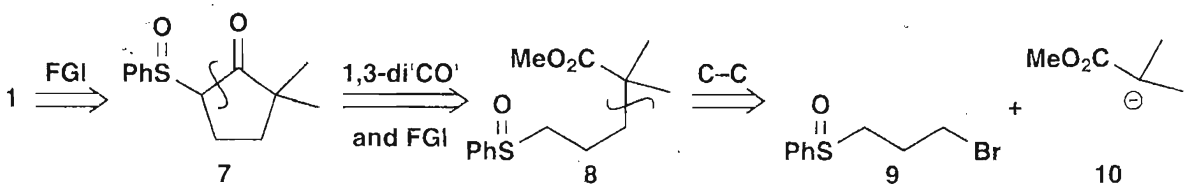
The cyclopentenone **1** was needed for some photochemical experiments.[1] One synthesis involved the bromination and dehydrobromination of the saturated ketone **3**. This ketone can be made[2] by selective methylation of cyclopentanone **4**.



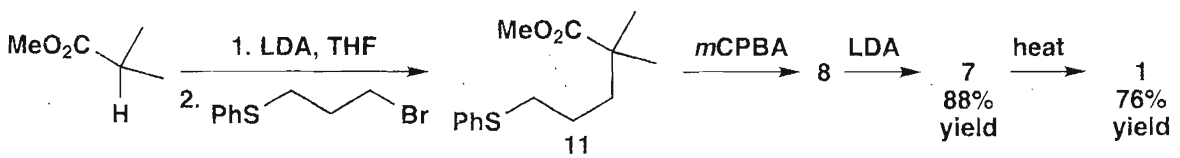
Bromination and debromination by the method of Garbisch[3] gave the ketal **5** in moderate yield and elimination is easier while the ketal is still in place to give **6** which is then hydrolysed as needed.



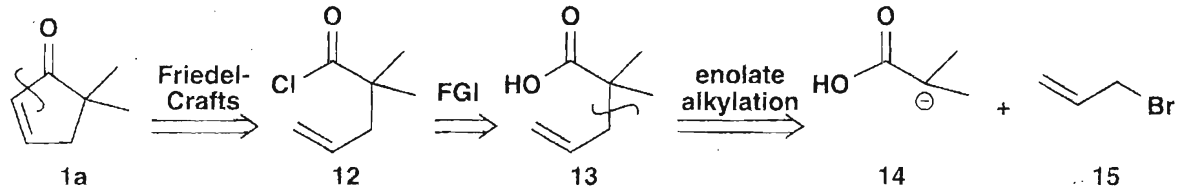
A better version of the same strategy[4] uses the sulfoxide **7** that can be made by acylation of the ester **8**, made in turn by alkylation of the enolate **10**.



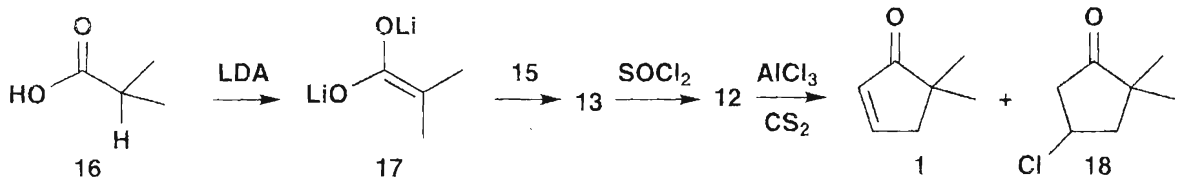
The synthesis used the lithium enolate of the ester and the sulfide rather than the sulfoxide version of **9**. The all-important cyclisation of the sulfoxide and elimination gave excellent yields.



In any case, 'preparation of **3** was sufficiently tedious, however, to render this route unsatisfactory.' The next route tried was an aliphatic Friedel-Crafts cyclisation of the acid chloride **12** derived from the unsaturated acid **13** which might be made by allylation of an equivalent of the enolate **14**.

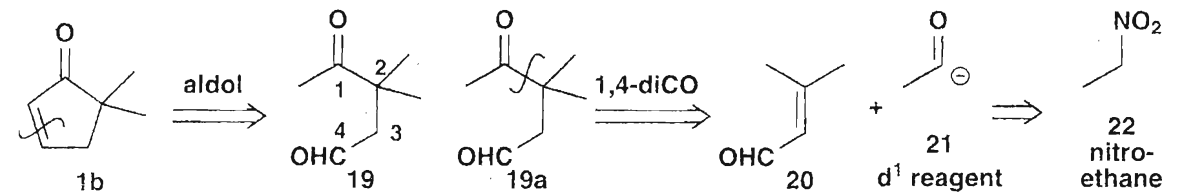


This synthesis used the lithium enolate **17** of the acid itself **16**. The acid **13** was converted into the crude acid chloride **12** and immediately cyclised to a mixture of **1** and the β-chloroketone **18** which can be eliminated more easily than can **2**. Carbon disulfide (CS_2) used to be used as a solvent but it is exceptionally flammable.

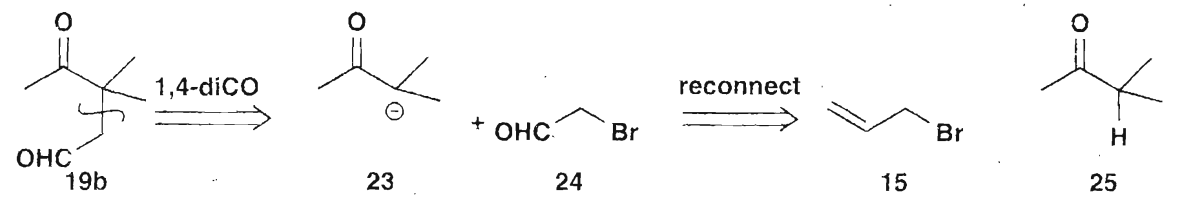


But neither of these routes is very good. They are long and the yields are not great. The planning uses only one-group disconnections. **Problem 34.1:** Can you do any better with two-group disconnections?

Answer 34.1: Almost certainly. The aldol disconnection **1b** reveals a 1,4-dicarbonyl compound **19** that might be made by any of the methods from chapter 25. The most promising disconnections are those next to the branchpoint such as **19a**. We need an acyl anion equivalent **21** that will do conjugate addition. The best one from chapter 25 is the nitroalkane **22** that might even be successful with the enal **20**.

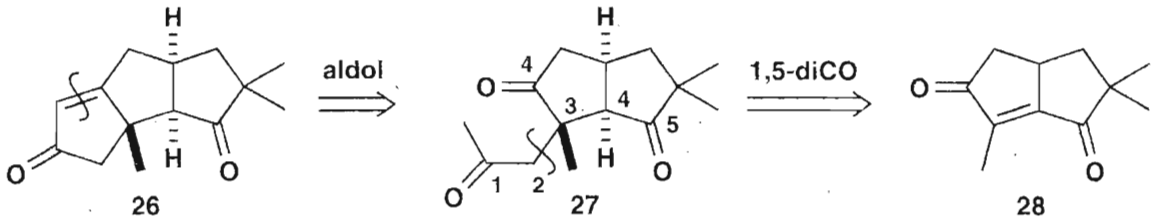


The alternative **19b** requires a specific enolate **23** of the ketone **25** in reaction with an α-bromo-aldehyde **24**, a type of molecule we suggested you should avoid. It would be better to adopt the reconnection strategy (chapter 26) and use allyl bromide **15**. But there is still the problem of making the enolate **23**. The first strategy **19a** looks better but neither has been tried as far as we are aware though many cyclopentenones have been made by similar methods.[5]

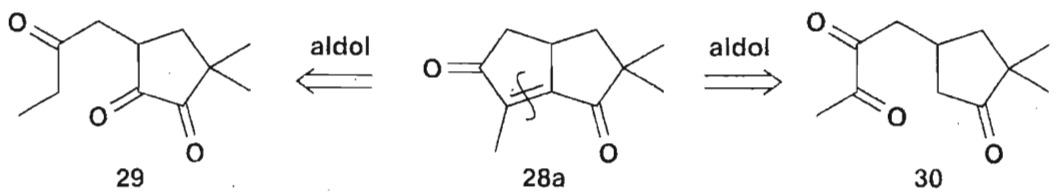


An Intermediate in the Synthesis of Coriolin

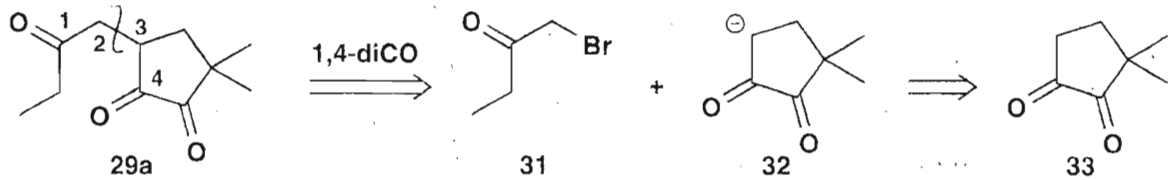
The coriolins are a group of natural products with anti-tumour activity based on the skeleton **26** with its three fused five-membered rings.[6] Aldol disconnection reveals a tricarbonyl compound **27** with 1,4- and 1,5-dicarbonyl relationships. Preferring the latter we come back to a much simpler bicyclic compound **28**, the subject of this section. **Problem 34.2:** Suggest an approach to **28**.



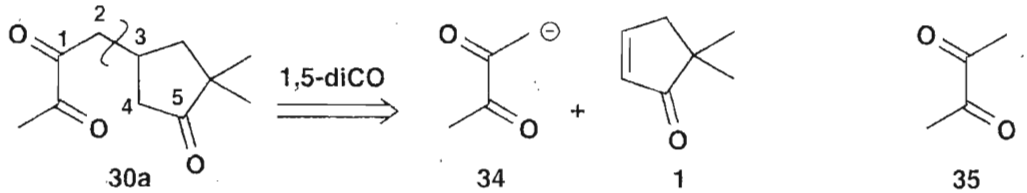
Answer 34.2: The aldol disconnection **28a** gives two possible starting materials **29** and **30**. Which do you prefer?



Further disconnection of the 1,4-diCO relationship on **29** at the branchpoint suggests an alkylation of the enolate **32** from the α-diketone **33** with the bromoketone **31**. This has the advantage that there is only one enolisable position in **33** and an enamine, say, might work well.

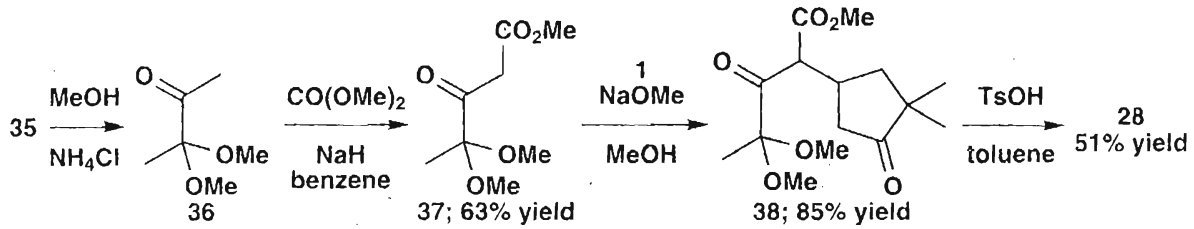


Triketone **30** has, by contrast, a 1,5-diCO relationship allowing disconnection **30a** at the branchpoint into an enolate **34** and a rather familiar compound **1** that we have just made. Further, the enolate is from available symmetrical butane-2,3-dione **35**. This was the route Danishefsky chose.



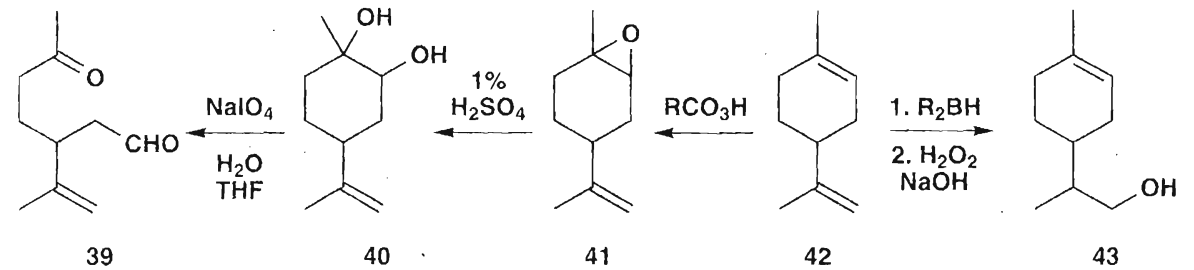
The α-diketone **35** had to be protected as the dimethyl acetal **36**. There is no trouble over this[7] as α-diketones are very reactive. Then the remaining ketone was activated with an ester group **37** so that it would be good at conjugate addition (chapter 21). Sodium methoxide catalysed the

Michael addition and the product **38** could be converted into **28** in one step under acid catalysis.[6] We shall go no further in this synthesis as adding the side chain to make **27** proved very difficult.

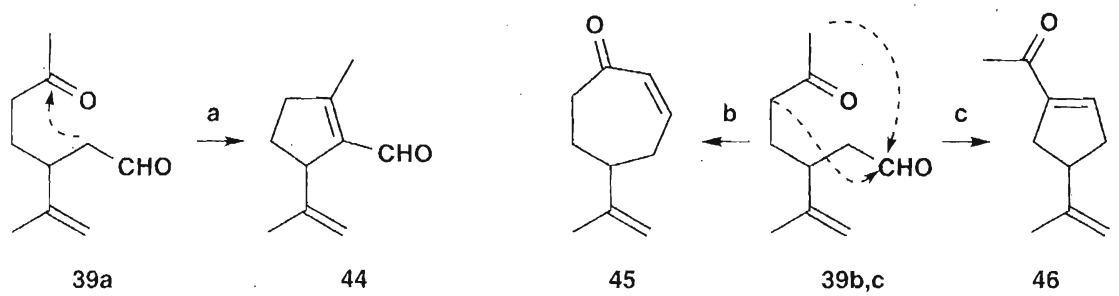


Asymmetric Synthesis from Terpenes

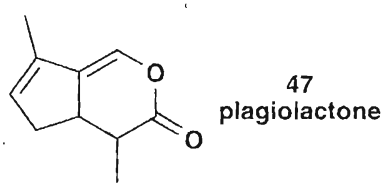
Terpenes are present in nature in great variety and form a valuable resource of enantiomerically pure starting materials but at first sight they are not much use for five-membered ring compounds as six-membered rings such as limonene **42** are much more common. Limonene is particularly valuable as the two alkenes have significantly different reactivities and both enantiomers are available. Epoxidation gives **41** but hydroboration with a bulky borane gives the alcohol **43**. The epoxide **41** can be hydrolysed to the diol **40** and the diol cleaved to the keto-aldehyde **39**. The epoxide **41** and the diol **40** are both *cis* but the only stereochemistry that matters is at the third chiral centre as only that survives in **39**. **Problem 34.3:** Predict the compound formed on treatment of **39** with base.



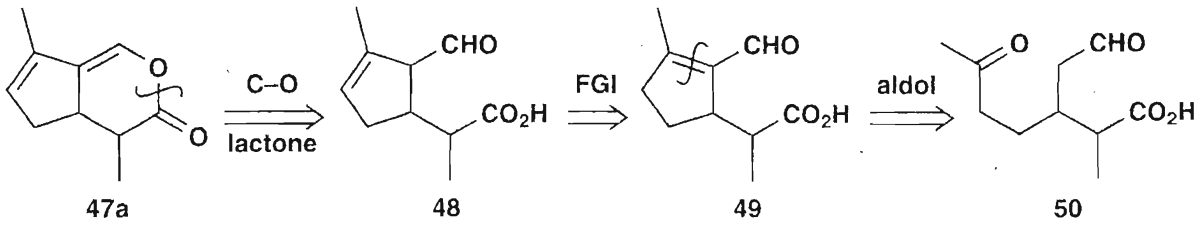
Answer 34.3: There are three possibilities: the enolate of the aldehyde could attack the ketone **39a** or either enolate of the ketone could attack the aldehyde **39b,c**. We can discount the slower cyclisation to the seven-membered ring but either answer **44** or **46** would be reasonable. In fact, which you get depends[8] on the conditions: KOH gives **46** while pyridine and acetic acid give **44**.



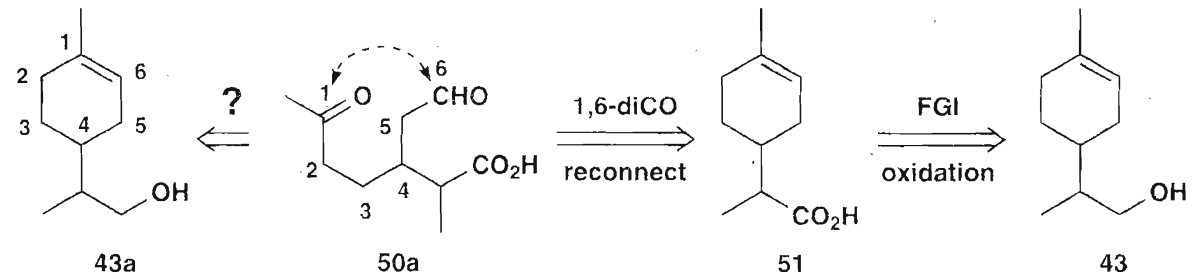
So six-membered cyclic terpenes can be used to make five-membered rings. **Problem 34.4:** How could you use **43** to make plagiolactone **47**?



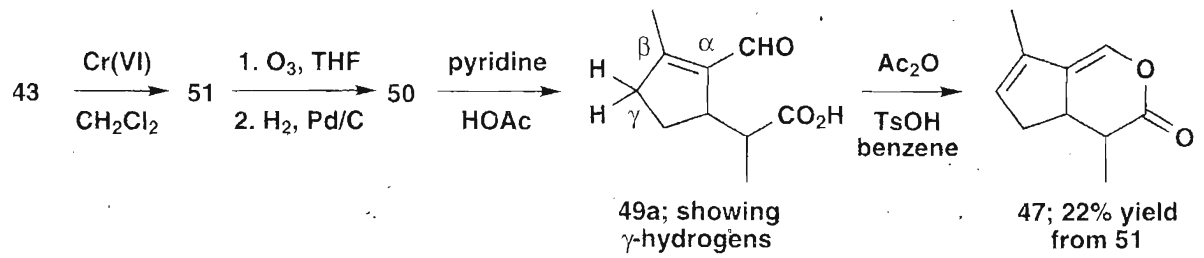
Answer 34.5: Disconnecting the structural C–O bond first **47a** is wise as it reveals that the unsaturated aldehyde is not conjugated so we must move the alkene into conjugation so that we can do an aldol disconnection **49**. We shall see later that this double bond ends up in the right place by a γ-deprotonation. Now we need to compare **50** with **43**.



Comparing structures **43a** and **50a** shows that reconnection of the 1,6-diCO relationship (chapter 27) is needed so revealing **51** that is an oxidation away from **43**.

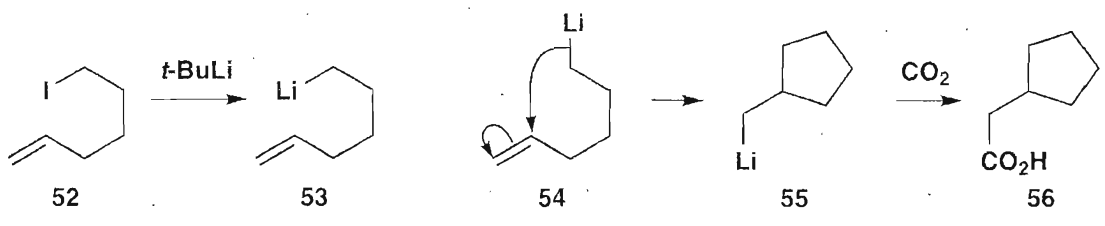


The synthesis[9] was very short: the alcohol **43** was oxidised to the acid **51** and the remaining steps carried out without isolation of intermediates. When **49** cyclises to **47**, probably via a mixed anhydride, enolisation takes place with removal of a proton from the γ-position **49a** to give the right structure.

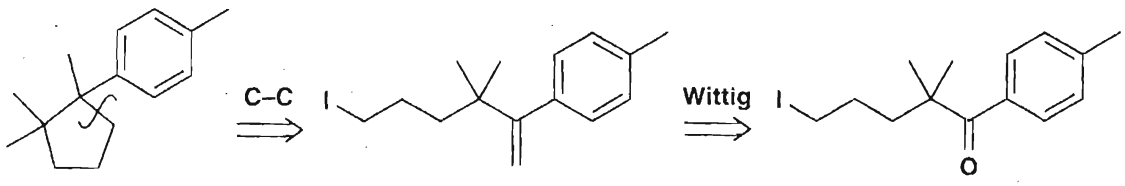


Cyclisation of Alkyl Lithiums onto Alkenes

In our comfortable world of nucleophiles and electrophiles we are content that organo-lithium reagents do not add to unactivated alkenes. But the very favourable cyclisation to give five-membered rings can overturn that. The lithium derivative **53** cyclises[10] onto the simple alkene **54** to give the new organo-lithium **55** that reacts with CO_2 to give the carboxylic acid **56**.

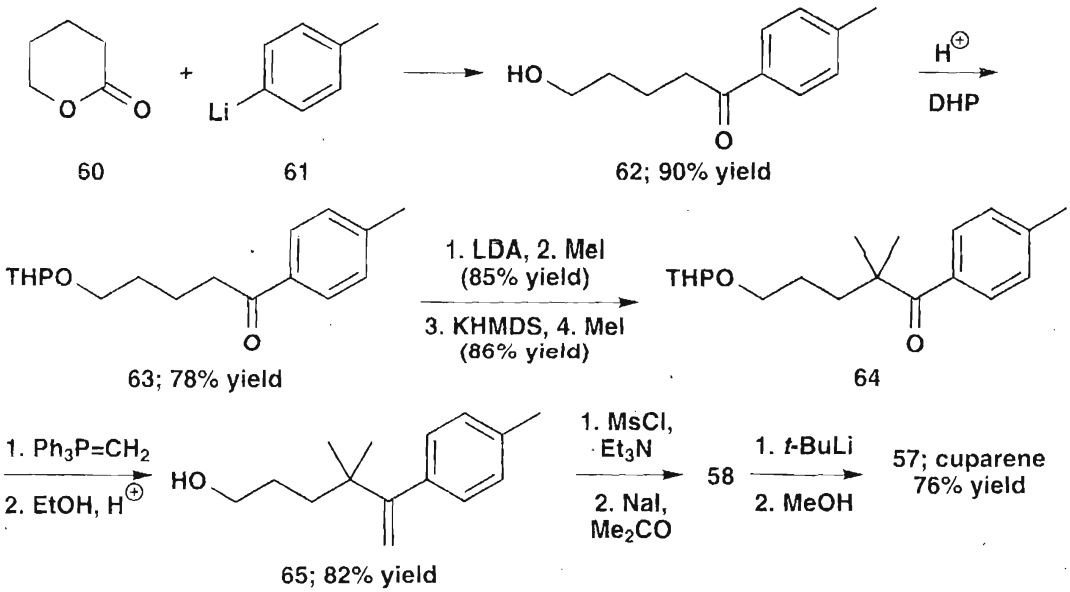


This was put to good use in a synthesis of the natural product cuparene **57**. The only 'normal' disconnection would be a Friedel-Crafts but the chemistry just revealed suggests that a cyclisation of **58** is possible and hence we can go back to the ketone **59**.



57; cuparene 58 59

The synthesis[11] starts with a more conventional organo-lithium reaction: acylation of **61** with the lactone **60**. It was necessary to protect the OH group as a THP derivative **63** during the double methylation and Wittig reactions before exchanging it for iodide and cyclisation of the organo-lithium. Methanol was used to protonate the product.



60 61 62; 90% yield

63; 78% yield 64

65; 82% yield

References

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2. H. O. House and B. M. Trost, *J. Org. Chem.*, 1965, **30**, 2502.
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10. W. F. Bailey, T. T. Nurni, J. J. Patricia and W. Wang, *J. Am. Chem. Soc.*, 1987, **109**, 2442.
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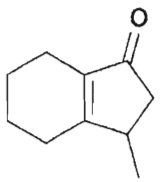
35 Strategy XVI: Pericyclic Reactions in Synthesis: Special Methods for Five-Membered Rings

Electrocyclic Reactions

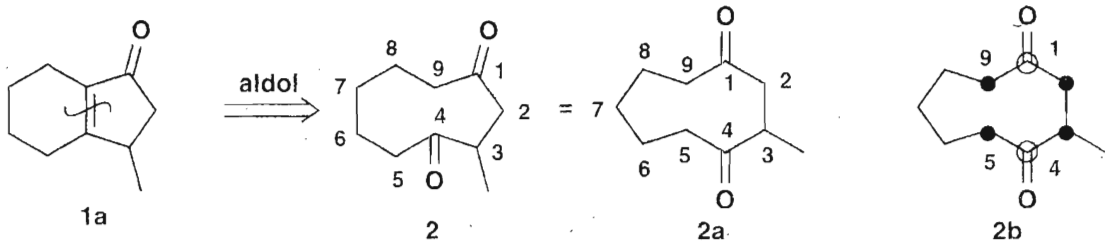
The Nazarov Reaction

Problem 35.1: Why do you reject the 'obvious' aldol disconnection in designing a synthesis for the bicyclic enone **1**? Suggest a better synthesis of **1**.



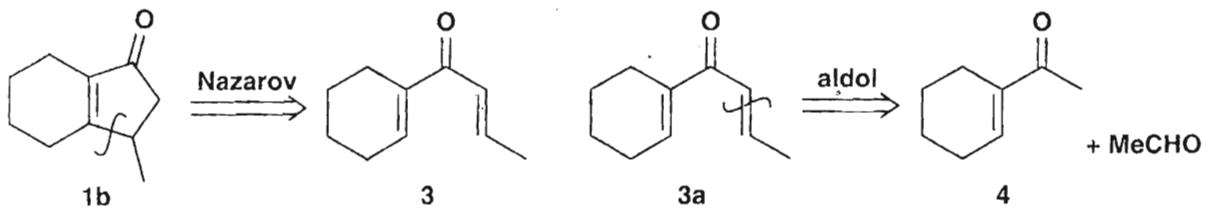
bicyclic enone **1**

Answer 35.1: The aldol disconnection **1a** gives a nine-membered cyclic diketone **2**, better drawn as **2a**, using numbers to make sure we get it right. There are two electrophilic centres (ringed in **2b**) and four enolisation sites (blobs in **2b**). We want the enolate at C-9 to react with the carbonyl group at C-4. But the cyclisation of C-5 onto C-1 is as likely as it would give a very similar cyclopentenone. There is no obvious way to make a specific enol equivalent at C-9 and, in any case, how are we to make **2**?

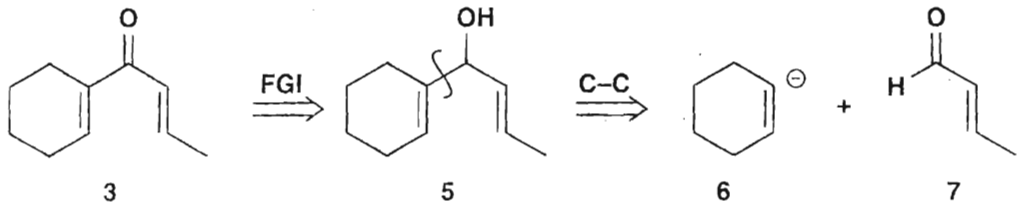


1a **2** **2a** **2b**

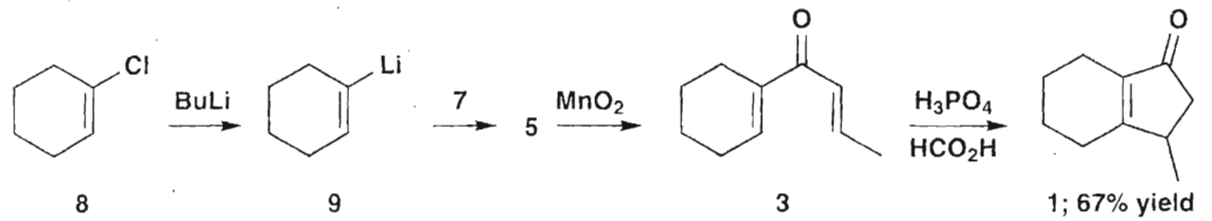
The Nazarov reaction offers a much simpler route. The Nazarov disconnection **1b** reveals a simpler dienone **3** that might be made by an aldol reaction of **4** and acetaldehyde. Providing you could make **4** and control the aldol reaction with a specific enolate to avoid self-condensation of the aldehyde, this would be a good synthesis.



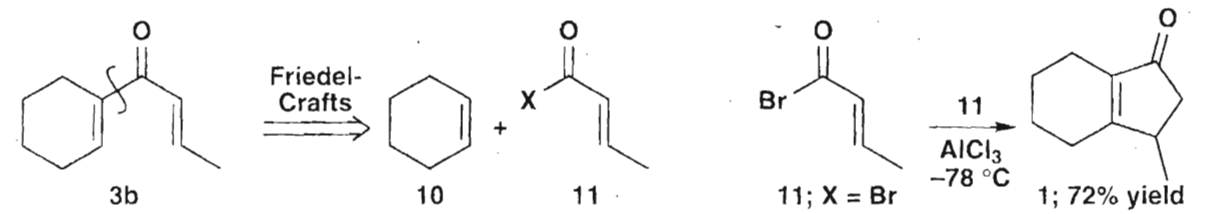
But **3** was actually made by a route mentioned in the textbook chapter. Changing the ketone into the alcohol **5** allows a C–C disconnection to a carbanion equivalent **6** and available crotonaldehyde **7**.



Direct attack by **6** on the carbonyl group of **7** is needed so the lithium derivative **9** is ideal. Oxidation with the best reagent for allylic alcohols, MnO_2, gives the ketone **3** and treatment with acid gives the bicyclic enone **1** in reasonable yield.[1]

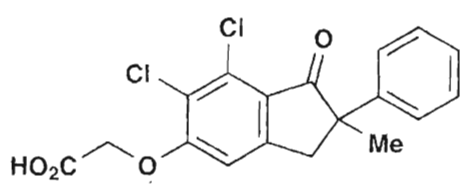


But the same disconnection as **5** can be used **3b** to plan an even shorter synthesis.[2] An aliphatic Friedel-Crafts reaction might give **3** or even **1** under the influence of a Lewis acid. In the event the acid bromide **11** with $AlCl_3$ at low temperature gave a reasonable yield of **1** from **10** with just 8% of **3**.



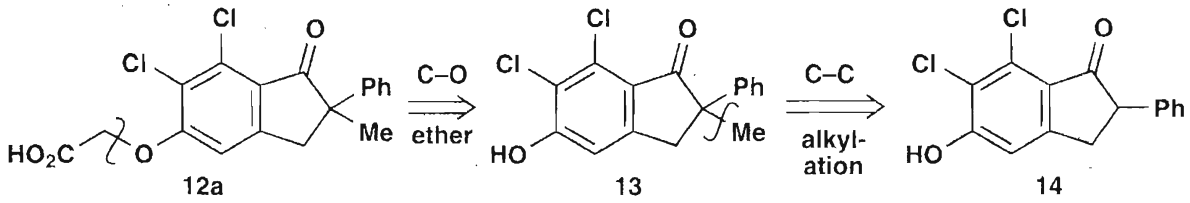
A Pharmaceutical Example

The indanone **12** is the Merck diuretic indacrinone. **Problem 35.2:** Suggest a synthesis of **12**.

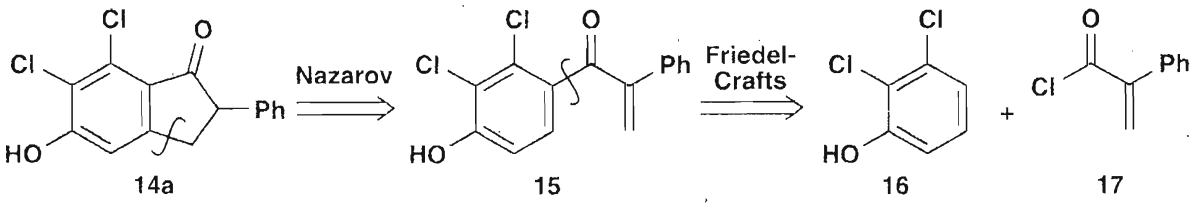


12
Merck's diuretic indacrinone

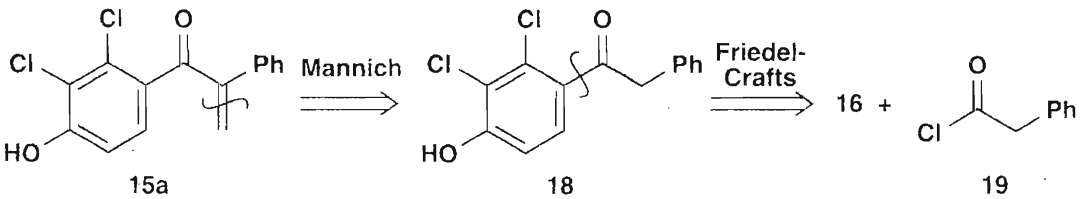
Answer 35.2: Removing the side chain **12a** reveals a simple indanone **13** that might be made by a Nazarov reaction providing that we also remove the methyl group **14** so that the alkene necessary for the Nazarov can be inserted. Alkylation of the enolate from **14** looks straightforward.



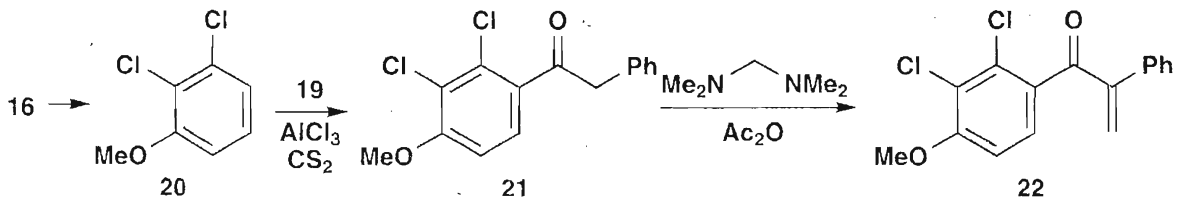
The Nazarov disconnection **14a** reveals an enone **15** and it is tempting to try the same strategy as in the last example and do the Friedel-Crafts disconnection immediately. We might have some doubts about the stability of the acid chloride **17** and Merck did not pursue this idea.



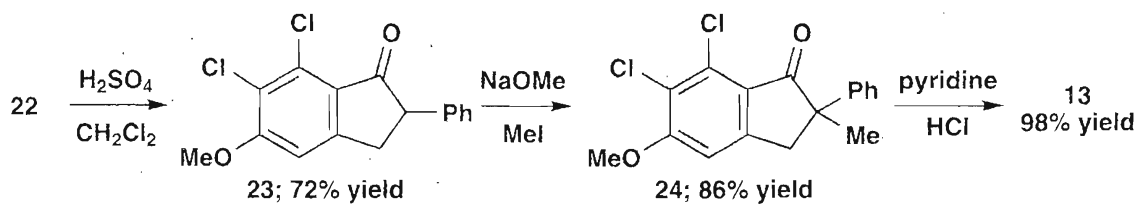
Since carbonyl compounds like **17** are usually made by Mannich reactions, it makes more sense to disconnect the enone first **15a** and then do the Friedel-Crafts disconnection **18**.



The starting material 2,3-dichlorophenol **16** is available and it turns out that the best way to get the right regioselectivity in **18** is not to use the Fries rearrangement, as you might reasonably have suggested, but to methylate the phenol first **20**. A conventional Friedel-Crafts reaction was followed by a Mannich reaction with an unusual reagent (an aminal of formaldehyde) that completed the 'aldol' and the elimination in one step to give **22**.

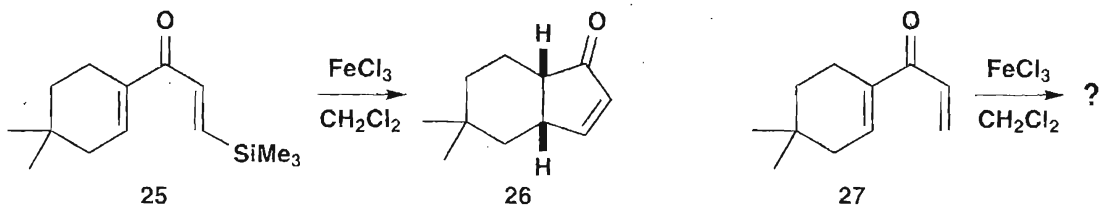


The Nazarov used sulfuric acid and the methylation needed only NaOMe as base. Now at last the protecting methyl group can be removed to expose the free phenol **13**. The final alkylation used ethyl bromo-acetate with K_2CO_3 as base and hydrolysis of the ester then gave **12**.



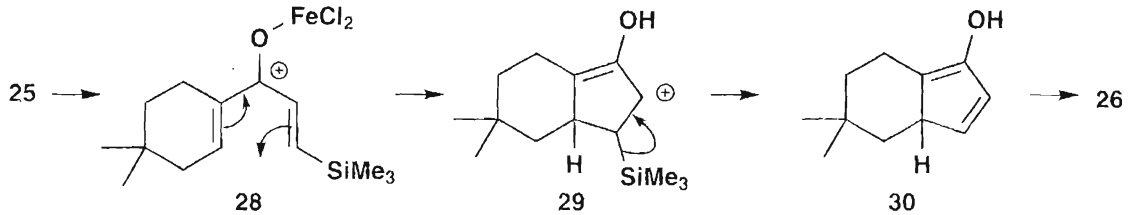
Silicon-Directed Nazarov Reactions

Problem 35.3: Explain the role of the Me_3Si group in the reaction of **25** with the Lewis acid $FeCl_3$. What product do you predict would be formed from **27** under the same conditions?



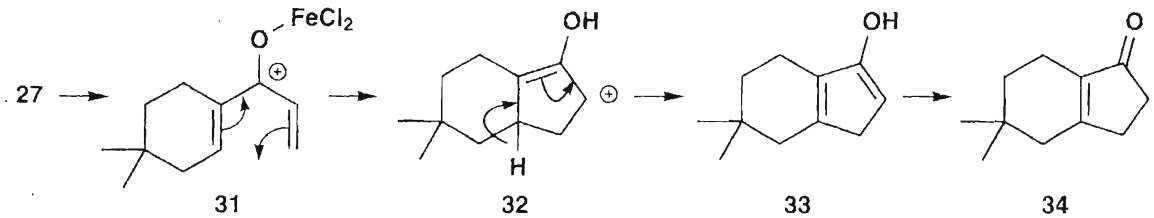
25 26 27

Answer 35.3: The electrocyclic reaction **28** gives the silicon-stabilised cation **29** from which the silyl group drops out to fix the alkene in **30**, the enol of **26**. The marked hydrogen in **29** is not lost.[3]



28 29 30

In the absence of the silyl group, the same cyclisation would occur but less favourably and now there is no reason to make the less stable alkene **26** so the marked hydrogen would be lost and the more substituted alkene **34** preferred as in the formation of **1**.

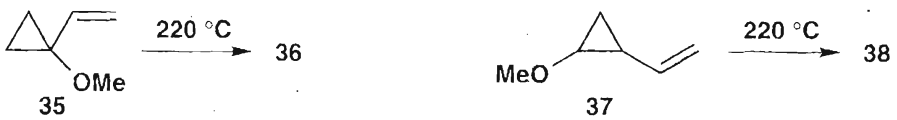


31 32 33 34

Sigmatropic Rearrangements

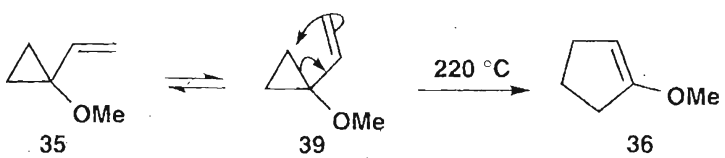
The Vinyl Cyclopropane to Cyclopentene Rearrangement

Problem 35.4: Predict the structure of the products from the rearrangement of **35** and **37**.



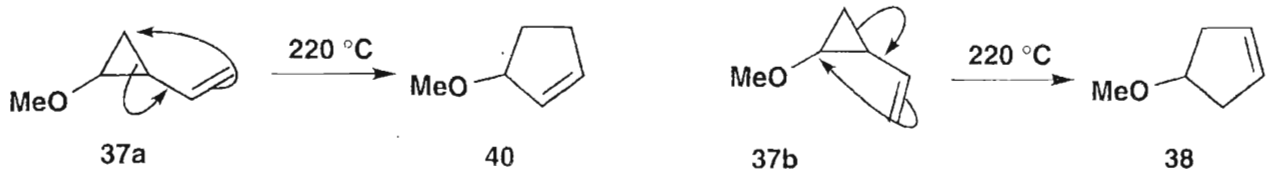
35 37

Answer 35.4: Drawing the concerted mechanism **39** (which may not be right) we find only one possible product,[4] the vinyl ether **36**.



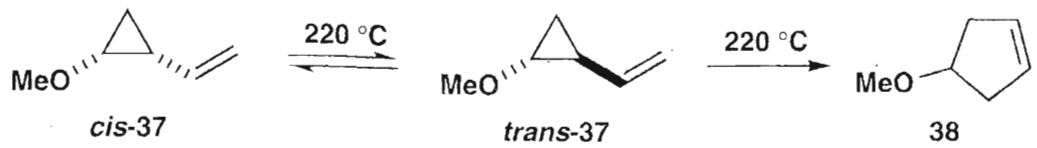
35 39 36

But there are two possibilities for the rearrangement of **37: 37a** or **37b**. In fact only **37b** occurs as **38** is the only product.



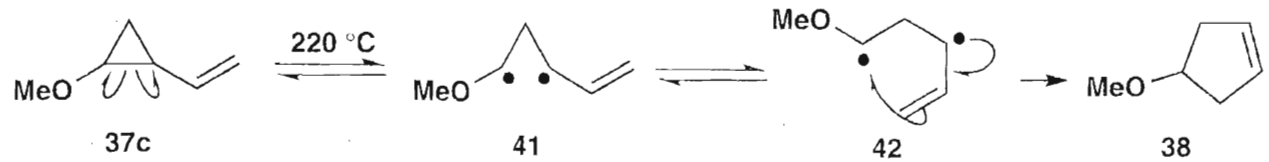
37a **40** **37b** **38**

Does adding the information that *cis*-**37** and *trans*-**37** equilibrate under the reaction conditions so that either gives the same product **38**, give you any evidence about the mechanism?



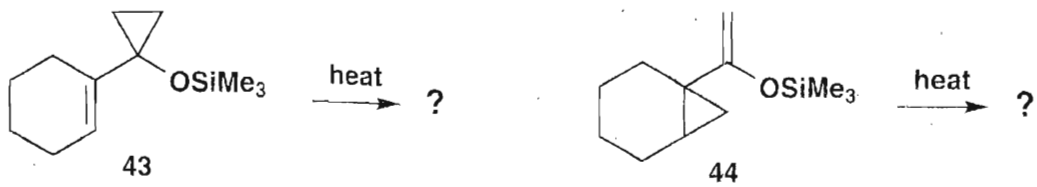
cis-**37** *trans*-**37** **38**

It might suggest that the reaction is a stepwise radical process with the diradical **41** as the more stable of the two possible intermediates. One radical is stabilised by the OMe group and the other is allylic. But there is still no agreement on the mechanism.



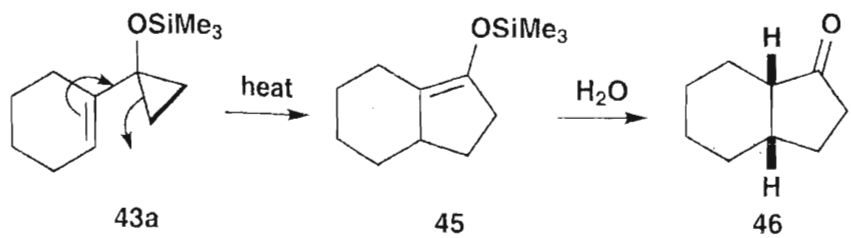
37c **41** **42** **38**

The alkene in such rearrangements can be a silyl enol ether. **Problem 35.5:** Predict the product of the rearrangement of these two compounds.



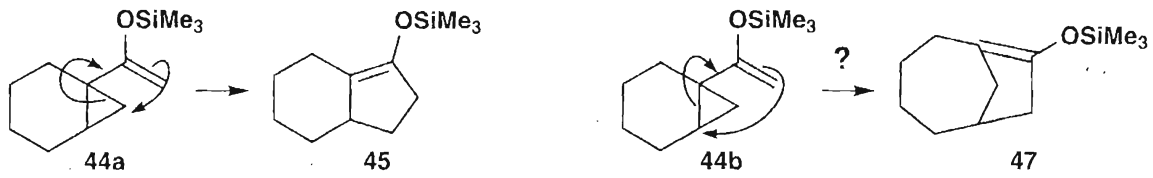
43 **44**

Answer 35.5: There is only one product from **43**, which is the silyl enol ether **45** again found by drawing the concerted mechanism **43a**. This is not usually isolated but gives the ketone **46** on work-up in 95% yield.[5] Either **45** or **46** is a good answer and the preferred stereochemistry of **46** is *cis*.



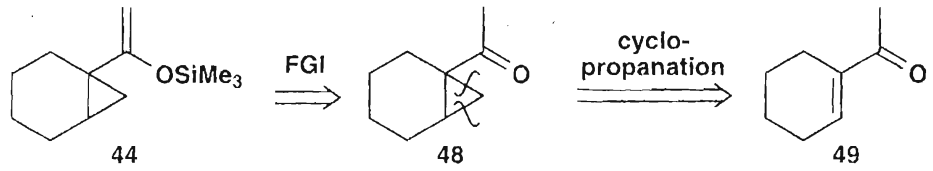
43a **45** **46**

Though there are in theory two possible products from **44**, one **47** has a bridgehead alkene and is almost certainly impossible. So the product of the rearrangement is again **45** and the ketone **46** is isolated in 99% yield.[6]

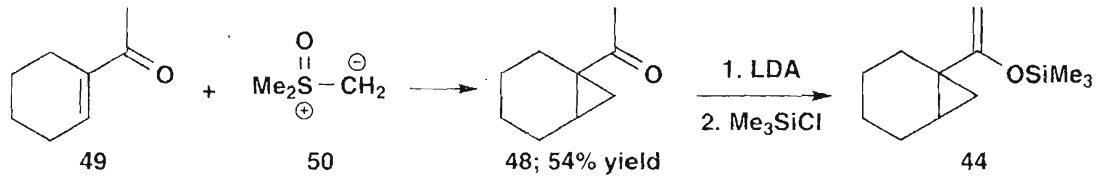


Problem 35.6: Suggest a synthesis of the starting material **44**. *Hint:* Chapter 30 in the textbook may help you.

Answer 35.6: The silyl enol ether obviously comes from the ketone **48** and removal of the three-membered ring with some carbene strategy in mind gives the available enone **49**.

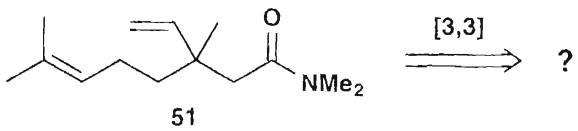


The synthesis needs Corey's sulfoxonium ylid **50** for this electrophilic alkene and the silylation is unambiguous as an enol can form only in the methyl group.[6,7]

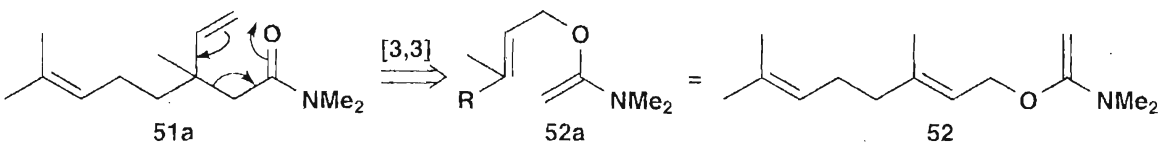


The Claisen Rearrangement

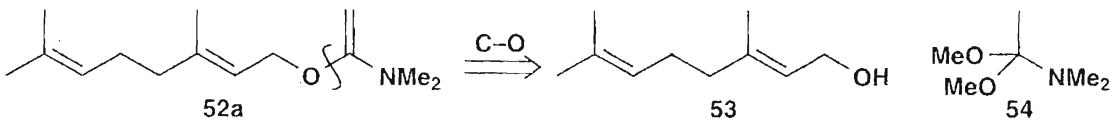
Problem 35.7: How would you make the amide **51** by a Claisen-style [3,3]-sigmatropic rearrangement?



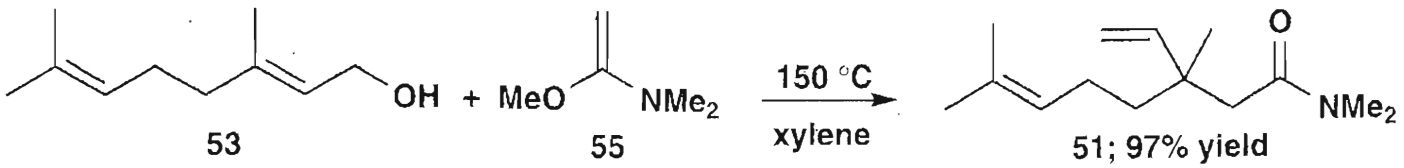
Answer 35.7: The essential preliminary is redrawing **51** so that we can draw the mechanism of the imaginary reverse reaction **51a**. Drawing the starting material in the same shape first **52a** and then straightening it out shows what we need **52**.



We find we have an allyl vinyl ether so, according to the textbook chapter, we need the allylic alcohol **53**, that is available geraniol, and an acetal **54** of the vinyl part.

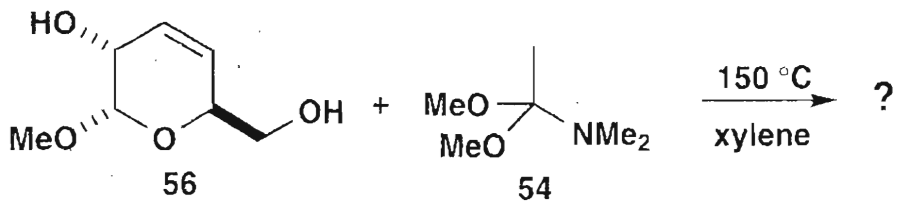


In fact Eschenmoser[8] used geraniol and the enol ether **55** as an alternative to **54**. Simply heating these together in xylene gave a 97% yield of **51**.



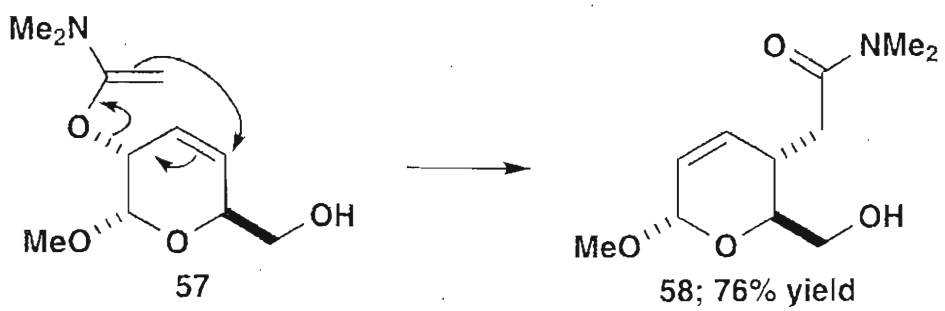
53 55 51; 97% yield

Problem 35.8: What product would be formed under the same conditions with **54** and the sugar-derived compound **56**?



56 54

Answer 35.8: Though **56** contains two alcohols, only one is allylic and that alone concerns us. The easiest way to find the product is to draw the intermediate in a conformation suitable for the reaction and draw the mechanism **57**. The key point is that the side chain is on the bottom face of the ring so it must be transferred to the bottom face of the ring[9] to give **58**.



57 58; 76% yield

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2. S. Hacini, R. Pardo and M. Santelli, *Tetrahedron Lett.*, 1979, 4553.
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8. D. Felix, K. Gschwend-Steen, A. E. Wick and A. Eschenmoser, *Helv. Chim. Acta*, 1969, **52**, 1030.
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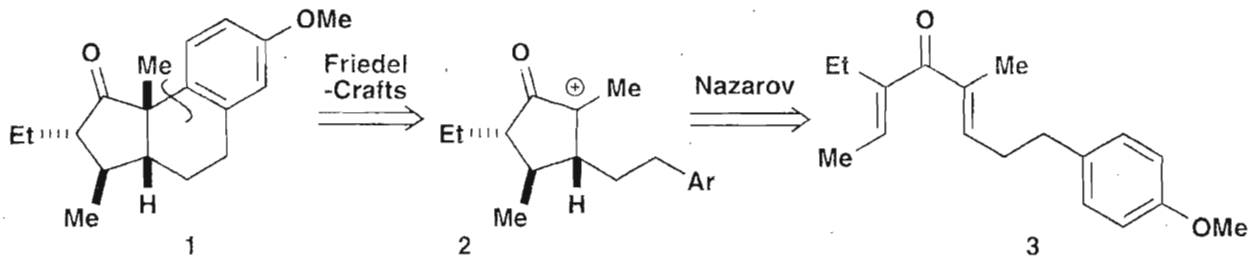
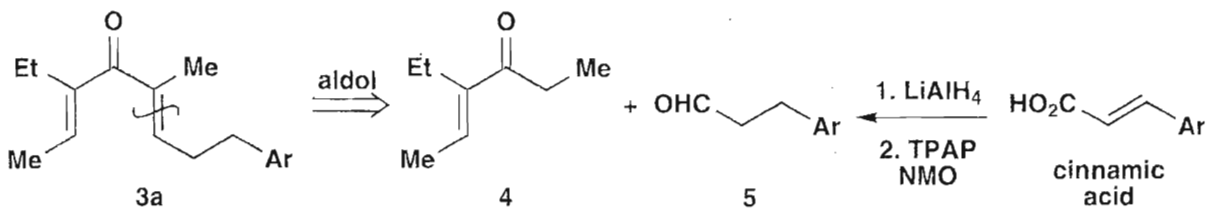
36 Six-Membered Rings

A Synthesis from the Textbook Chapter

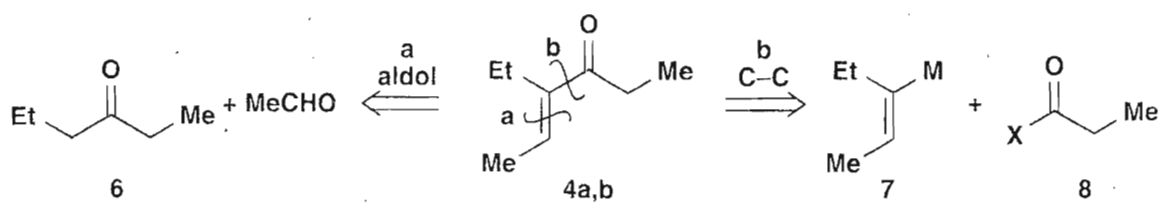
In the textbook we said: 'The Friedel-Crafts-like disconnection **1** suggests a most unlikely cation **2** until we realise that it would be formed in the Nazarov cyclisation of the dienone **3**'. We now discuss the synthesis of the dienone **3** in a reprise of the last chapter.



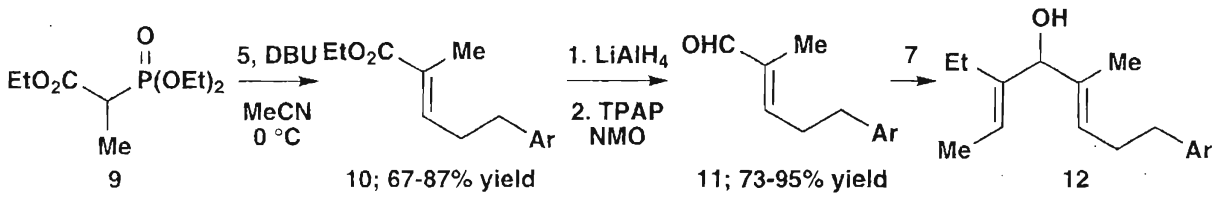
We need to start with one of the possible aldol disconnections and **3a** is nearer the middle of the molecule. The aldehyde **5** was easily made[1] from the available cinnamic acid by reduction to the saturated alcohol followed by oxidation with catalytic TPAP (Pr_4NRuO_4) and stoichiometric NMO.



Now what about the remaining enone **4**? A second aldol disconnection **4a** is hopeless as we should need to make a specific enolate from the nearly symmetrical hexan-3-one **6** for reaction with acetaldehyde. A better idea is to disconnect between the alkene and the carbonyl group **4b** with the idea of reacting some vinyl metal derivative **7** with some acylating agent **8**.

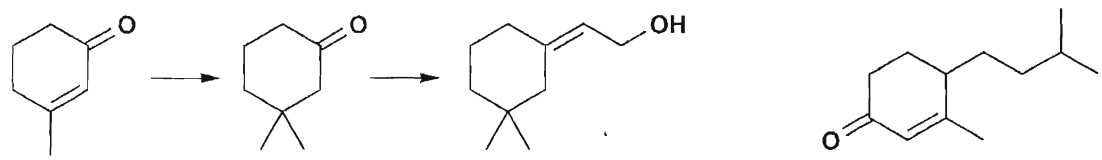


In fact, these reactions were used in a slightly different order. A Horner-Wadsworth-Emmons reaction (chapter 15) on **5** gave the unsaturated ester **10** which was then converted into the aldehyde **11** as in the synthesis of **5**. Either Grignard or organo-lithium versions of **7** gave the alcohol **12** in moderate yield and oxidation with $BaMnO_4$ gave the required dienone **3**.



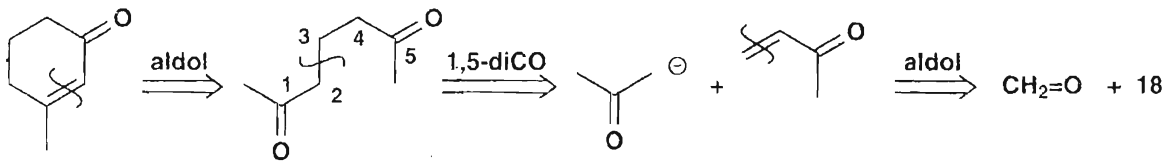
9 **10; 67-87% yield** **11; 73-95% yield** **12**

Enone **13** was needed to make the boll weevil pheromone **15** and enone **16** was needed for perfume synthesis. **Problem 36.1:** Consider both the Robinson annelation and Birch reduction approaches to these enones **13** and **16** and say which you prefer in each case.



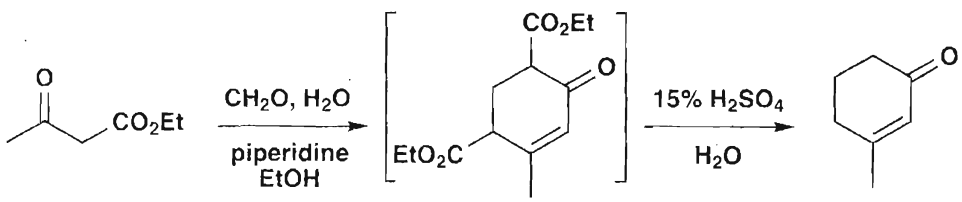
13 **14** **15** **16**

Answer 36.1: The Robinson annelation looks good for **13**. The sequence of aldol **13a**, Michael **17** and aldol disconnection **19** again gives formaldehyde and two molecules of an enolate equivalent of acetone **18** as starting materials. In addition, the diketone **17** is symmetrical so the cyclisation to **13** must be clear cut.



13a **17** **18** **19**

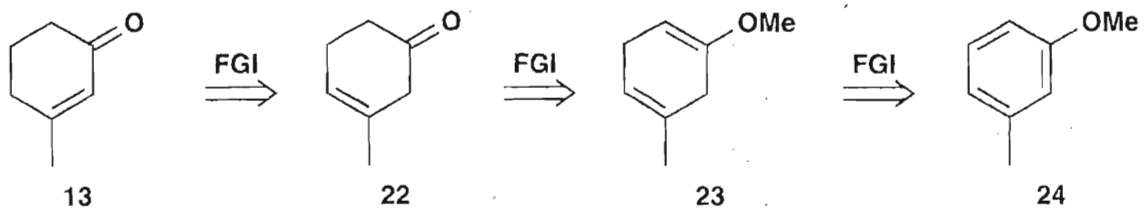
In practice there is a short cut discovered some time ago. If ethyl acetoacetate is used for **18**, condensation with aqueous formaldehyde and treatment with aqueous acid gives **13** in good enough yield for a one-step route.[2]



20 **21** **13; 61% yield**

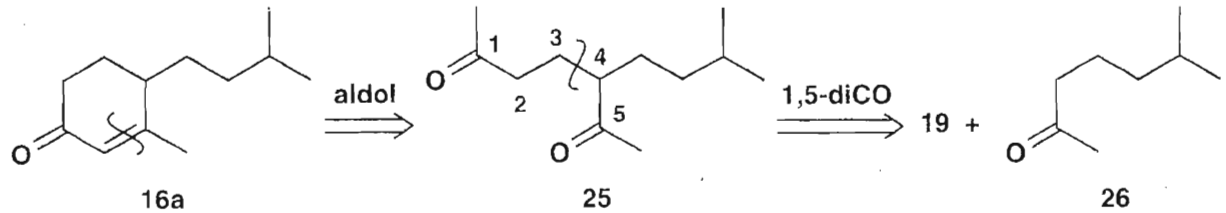
The Birch route, though not so easy to find, is also satisfactory. Changing the position of the alkene and the nature of the oxygen functionality gives us the kind of Birch reduction product **23** we have seen in the textbook. This is the only possible product from the reduction of **24** that has both functional groups on an alkene. In practice, sodium in liquid ammonia was used for

the reduction and hydrolysis in acid gave the more stable conjugated ketone[3] **13**, probably via enolisation of **22**.



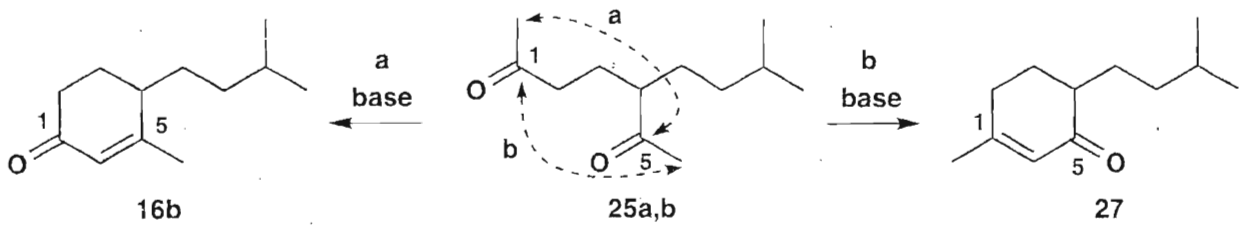
13 **22** **23** **24**

The Robinson annelation route to **16** looks all right to start with: the usual disconnections **16a** and **25** give **19** and a ketone **26** whose enolisation should be easily controlled.



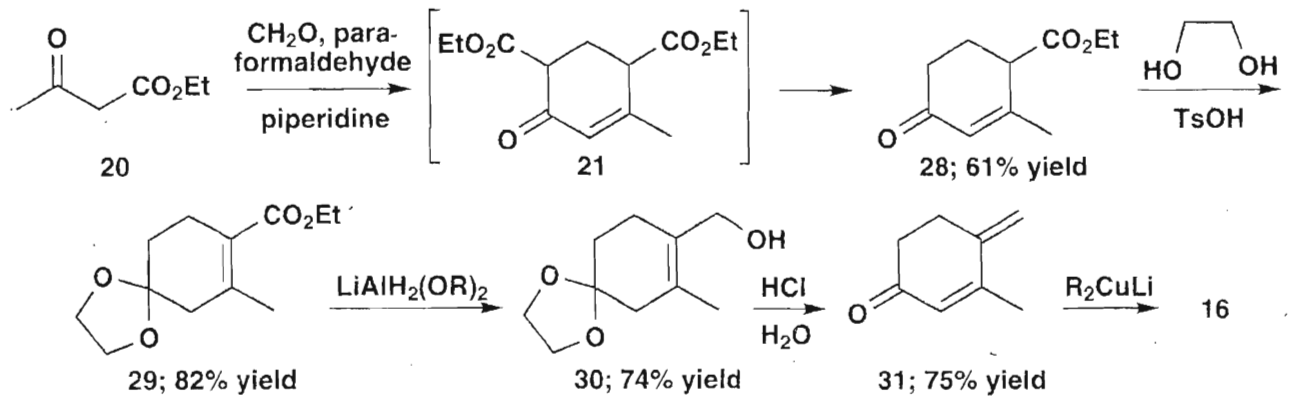
16a **25** **26**

But there is a hidden problem. The diketone **25** has two different methyl ketones and either methyl group could enolise and then attack the other carbonyl group to give **16** and a different cyclohexenone **27**. With such similar compounds, the ratio of **16:27** was 3:2.



16b **25a,b** **27**

A successful, if rather long-winded synthesis[4] comes from Hagemann's ester **28**, made by a variation of the synthesis of **13**. Then protection of the ketone and reduction of the ester give the alcohol **30** which was dehydrated and deprotected in one operation to the dienone **31**. Organo-copper reagents add to provide a general synthesis of compounds like **16**.

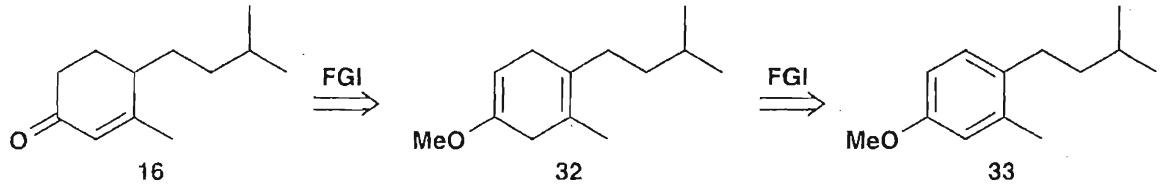


20 **21** **28; 61% yield**

29; 82% yield **30; 74% yield** **31; 75% yield**

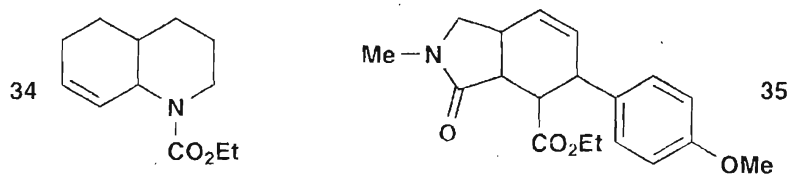
Birch reduction looks more promising as there is only one non-conjugated cyclohexadiene that has all three substituents on alkenes **32** and that would come from the aromatic ether **33**.

The preferred synthesis[4] uses lithium in ammonia to make **32** and hydrolysis with acidic ethanol gives **16** in 63% yield from **33**.

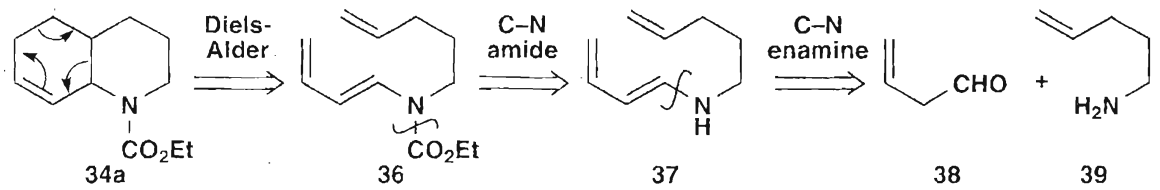


The Diels-Alder Route

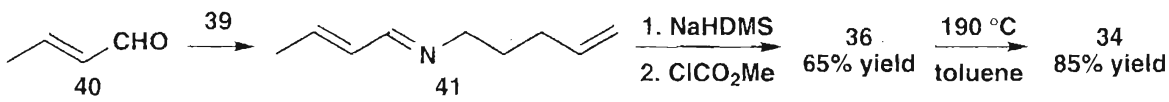
Problem 36.2: Suggest syntheses for these two heterocyclic compounds **34** and **35**.



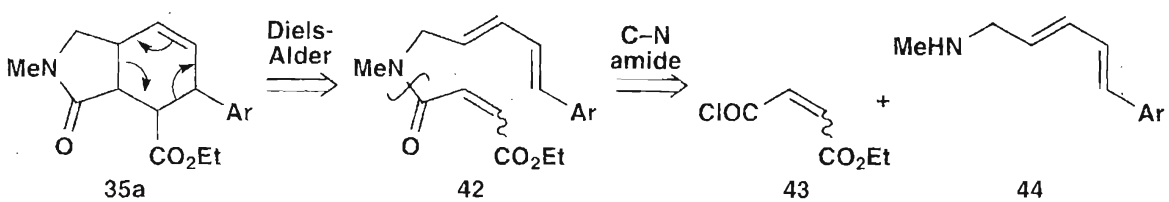
Answer 36.2: The Diels-Alder disconnection **34a** gives a linear unsaturated amide **36** that disconnects to the unstable-looking enamine **37**, made from the aldehyde **38** and the amine **39**.



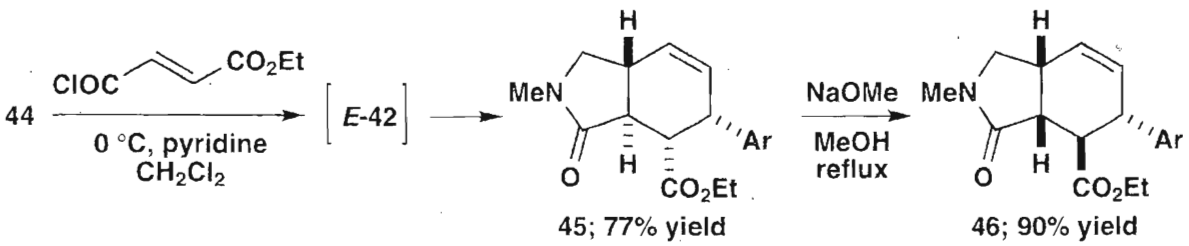
The aldehyde **38** exists as conjugated crotonaldehyde **40** and the enamine **37** exists as the imine **41**. Acylation in base gives **36** that cyclises in good yield[5] to the heterocycle **34**. Though there is no activating group on the dienophile, this does not matter in an intramolecular Diels-Alder reaction.



The second analysis follows a similar path, first reversing the Diels-Alder reaction **35a** and then separating the amide components of **42**. We have not specified any stereochemistry so either *E*-**43** or *Z*-**43** could be used and it will be interesting to see what the stereochemistry of **35** turns out to be.



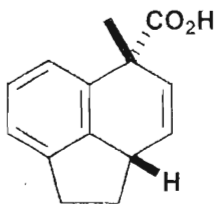
Using the fumarate derivative *E*-**43**, Gschwend and Meier[6] found that acylating **44** at low temperature gave a Diels-Alder adduct **45** but that treatment of this adduct with base gave a different adduct **46**. The intermediate *E*-**42** was never isolated. **Problem 36.3:** Explain these results, suggesting why this Diels-Alder reaction occurs at 0 °C while that of **36** required 190 °C.



Answer 36.3: The dienophile in **36** is a simple alkene with no conjugation to electron-withdrawing groups, but that in **42** has two carbonyl groups conjugated to the dienophile. The reaction therefore occurs much faster as the LUMO energy of the dienophile is closer to the HOMO energy of the diene. At 0 °C the kinetic product **45** is formed with standard *endo* selectivity but on heating in base the centres next to the carbonyl groups can equilibrate by enolate formation and the more stable thermodynamic adduct **46** with a *cis* ring junction and pseudo-equatorial CO_2Et and Ar groups is preferred.

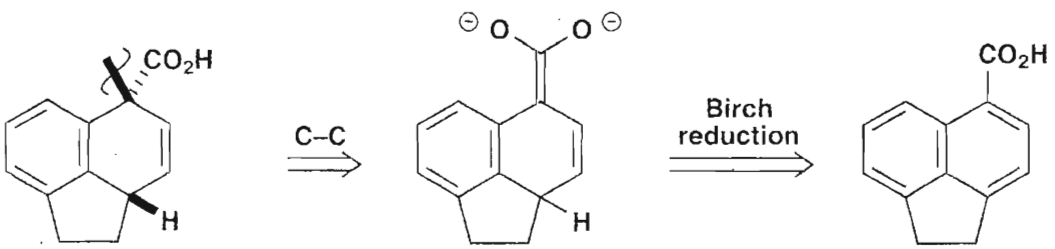
The Birch Reduction Route

Problem 36.4: How would you make the tricyclic compound **47**?



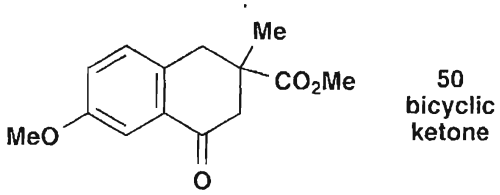
47
tricyclic compound

Answer 36.4: Birch reduction and methylation looks the best way to this compound and we shall need the available naphthalene derivative **49** as our starting material. You do not need to draw the acid enolate **48** if you prefer not to.



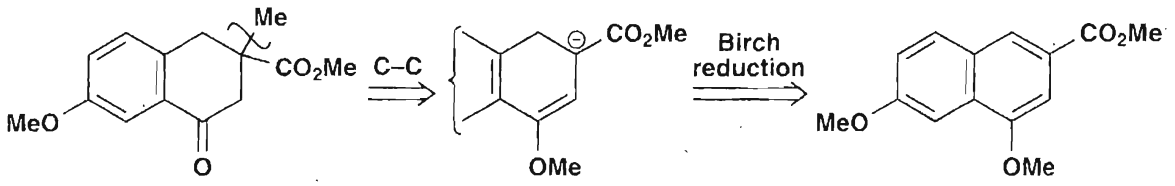
The reaction is carried out in a single step with potassium in liquid ammonia and *t*-BuOH to do the Birch reduction and form the enolate **48**. Quenching this with methyl iodide gives 83% yield of **47** as the *cis*-isomer alone.[7] Methylation occurs on the same face as the marked H atom in the planar intermediate **48**.

Now a slightly more difficult case. **Problem 36.5:** How would you make the bicyclic ketone **50**?



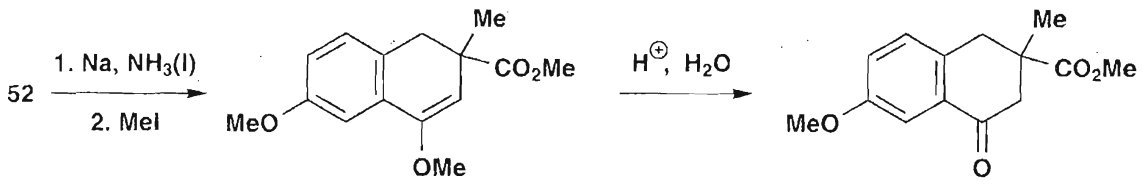
50
bicyclic
ketone

Answer 36.5: If we are to use Birch reduction, the methyl group must be inserted after the reduction and the ketone must come from a vinyl ether **52**.



50a **51** **52**

The Birch reduction could be carried out on the ester (the acid would have been all right too) and required sodium in liquid ammonia. It was quenched with methyl iodide to give **53**. Hydrolysis in aqueous acid gave[8] **50**. In both these cases, **47** and **50**, notice the preferred reduction of the ring with the electron-withdrawing group.



53; 72% yield **50; 70% yield**

References

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2. P. L. Robinson and S. A. Evans, *J. Org. Chem.*, 1985, **50**, 3860.
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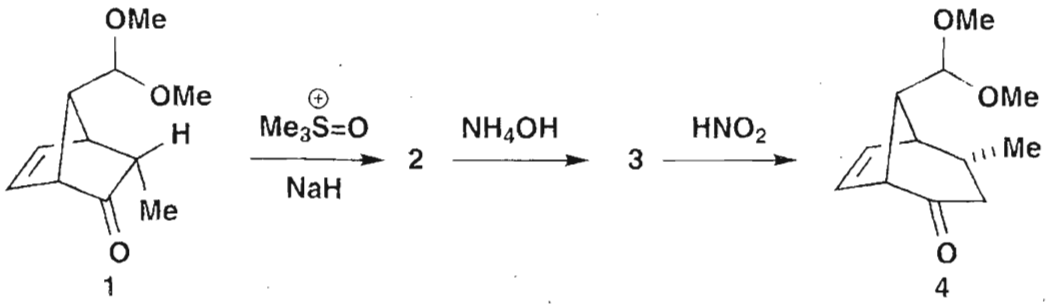
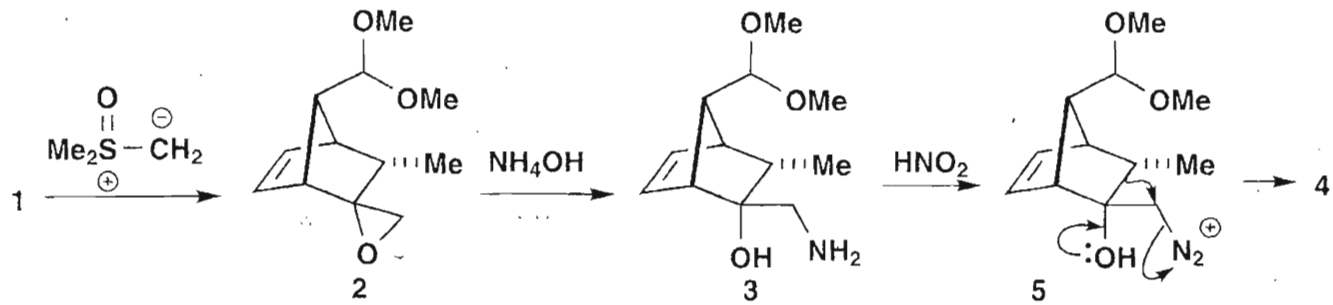
37 General Strategy C: Strategy of Ring Synthesis

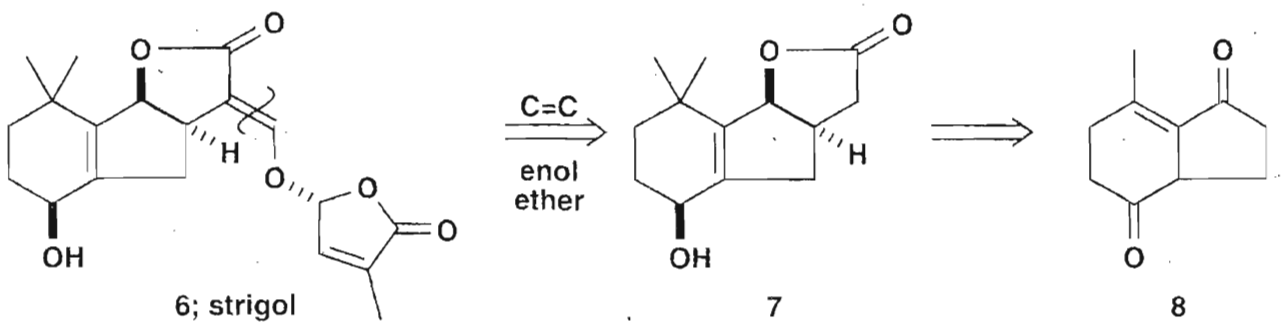
We start with a few developments from the textbook. We stated, but did not discuss, the conversion of ketone **1** into the ring expanded ketone **4**. The reagents are shown. **Problem 37.1:** What are the structures of **2** and **3**? All the reactions are in the textbook.



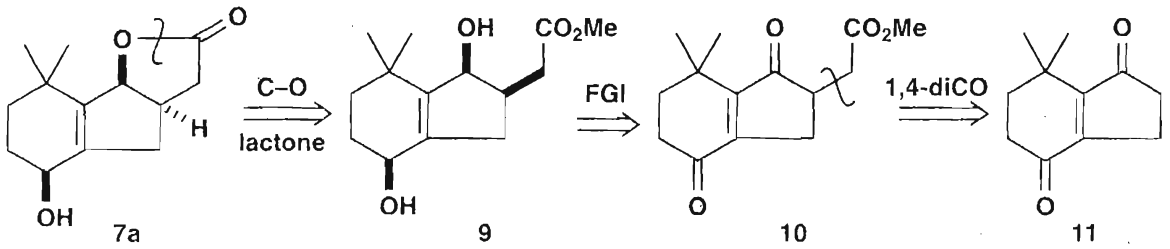
Answer 37.1: Sodium hydride gives the sulfoxonium ylid that reacts with the ketone **1** to give an epoxide **2** with attack from the top face. Ammonium hydroxide opens the epoxide at the less substituted centre to give the amine **3** that was not isolated but treated immediately with nitrous acid to initiate a rearrangement of the diazonium salt **5** with retention at the migrating group to give[1] **4**.



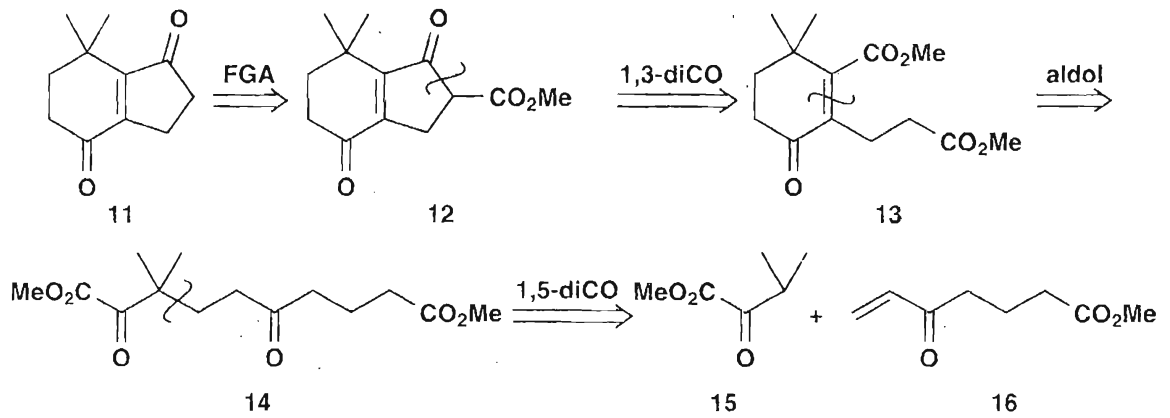
In the textbook we discussed Raphael's synthesis of strigol, the germination factor for the parasitic plant witchweed. There have been several syntheses mostly based on disconnection to the bicyclic lactone **7**. Raphael[2] made **7** from **8** as we explained in the textbook.



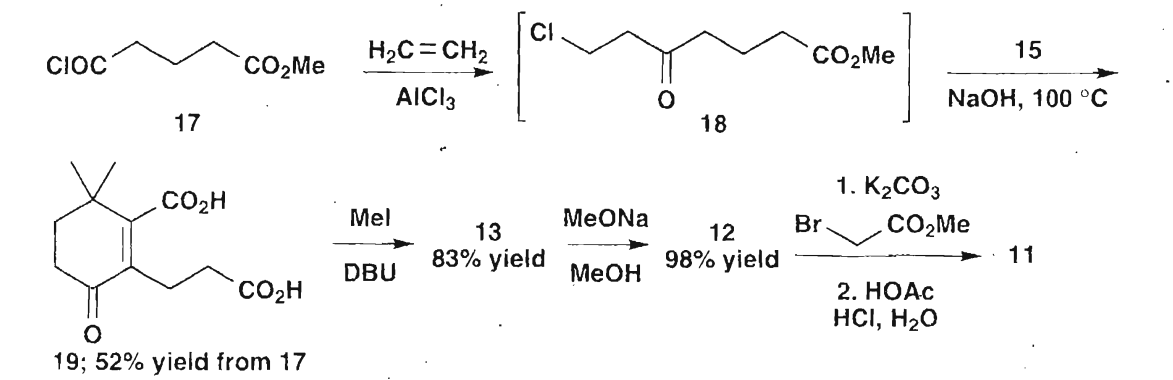
Other syntheses consider the lactone first **7a** and convert either one or both of the alcohols into carbonyl compounds. Then the side chain can be disconnected **10** to reveal a diketone **11** that is often an intermediate in strigol synthesis.



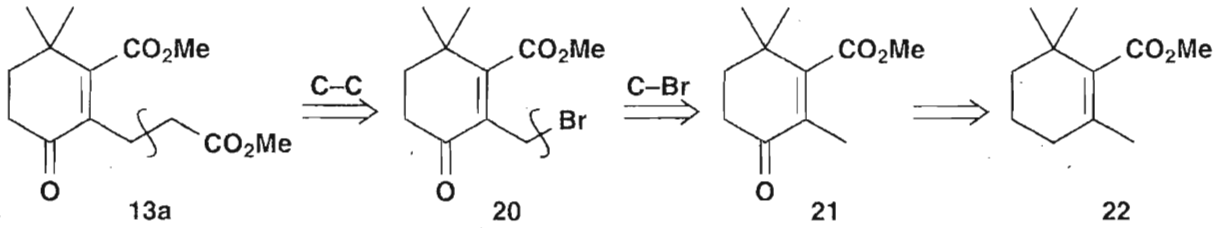
The strategy of adding an ester control group **12** has two purposes: it will make the alkylation easier and it allows a 1,3-diCO disconnection to give **13** and hence an aldol disconnection to the open chain compound **14**. This has a 1,5-diCO relationship so might be made from an enolate of **15** and the enone **16**.



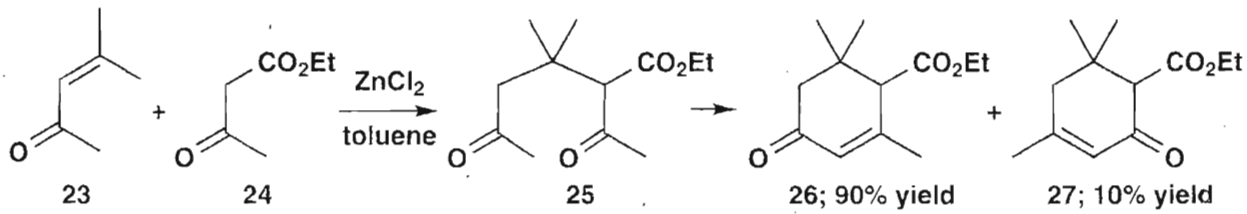
In fact[3] an aliphatic Friedel-Crafts reaction was used to make the β-chloroketone **18** that was added to the enolate from **15** to give **19** after hydrolysis and decarboxylation. Note than only one enolate can be formed from **15** and that only one six-membered ring can be formed by cyclisation of **14** even though **14** has four carbonyl groups. The alkylation of **12** needed only K_2CO_3 as base because of the ester control group.[4]



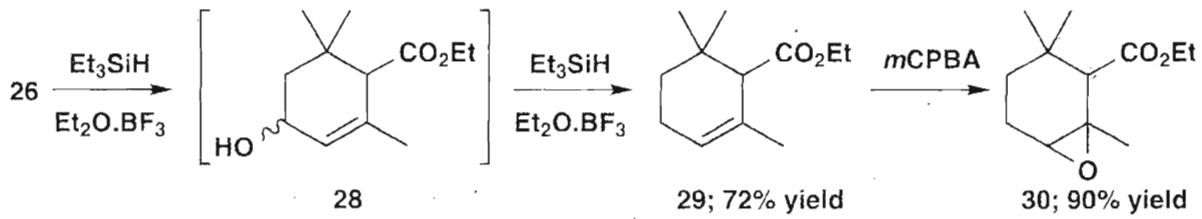
A related synthesis[5] assembles the six-membered ring in a different way. Disconnection **13a**, with alkylation of an enolate with an allylic bromide in mind, leads to a bromoketone **20**. Removal of the bromine from an allylic position (chapter 24) and, most drastically, removal of the ketone from **21**, again with allylic bromination in mind, simplifies the molecule considerably **22**.



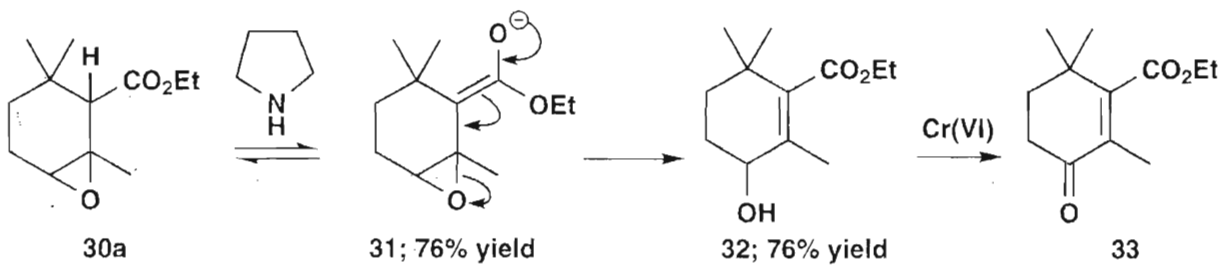
A short route to such compounds is the Lewis acid catalysed reaction of enone **23** with ethyl acetoacetate **24** which gives mostly enone **26**. This is a Robinson annelation of sorts and presumably starts with the conjugate addition of **24** to **23** to give **25** that cyclises mainly to **26**.



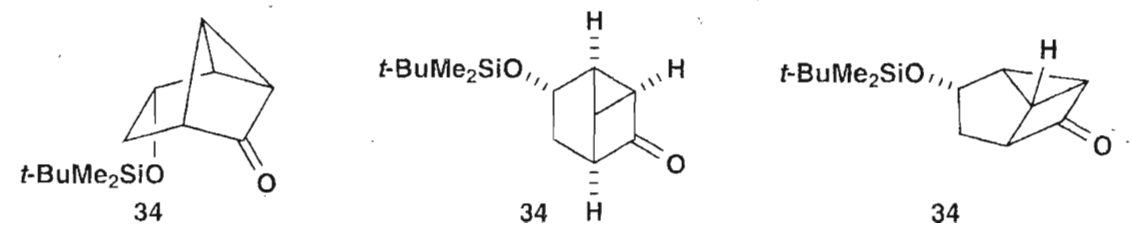
Reduction with triethyl silane removes the ketone to give **29**, no doubt by reduction to the alcohol **28** and then removal of the OH group via an allylic cation. Now epoxidation gives **30**. The stereochemistry of neither the alcohol **28** nor the epoxide **30** is important as both disappear in the next steps.



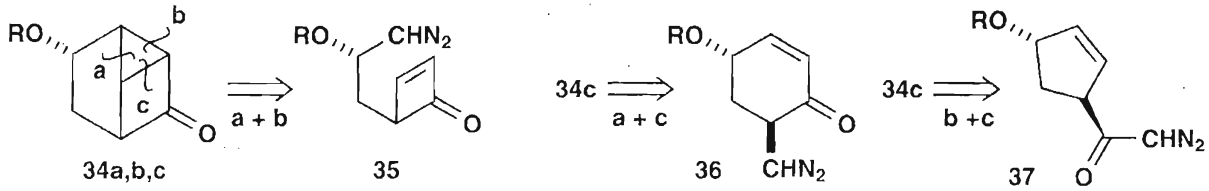
Treatment with an amine opens the epoxide by elimination **31** from the enolate (or enol) of **30** and finally oxidation with CrO_3 and H_2SO_4 gives **33**. Notice that the enone in **26** has been moved round the ring to **33** by this sequence.



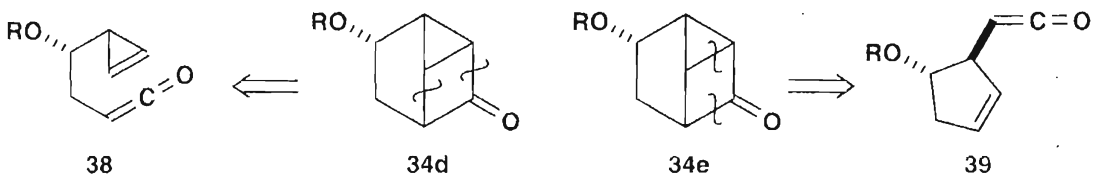
The tricyclic ketone **34** was a key intermediate in a Glaxo prostaglandin synthesis.[6] It contains 3-, 4-, 5- and 6-membered rings and can be represented in various ways such as the three below.
Problem 37.2: Suggest a strategy for the synthesis of **34**.



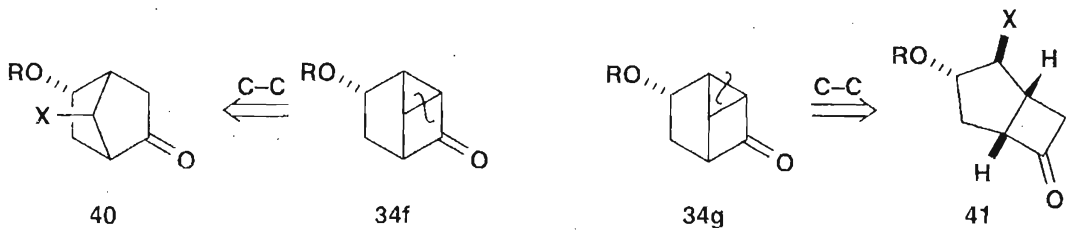
Answer 37.2: Starting with the three-membered ring, there are three different carbene disconnections giving **35, 36** and **37** as starting materials. It looks like a long stretch for the diazo group to reach the alkene in **35** or **36** but **37** looks just possible. Even so, **34** is very compressed and strained and none of these has been tried as far as we are aware.



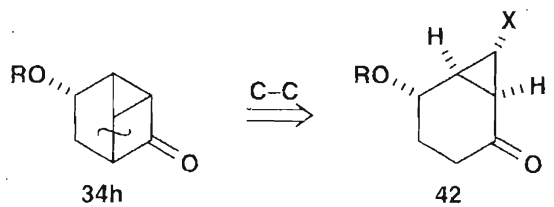
Alternatively, taking the four-membered ring, there are two ketene cycloaddition disconnections **34d** and **34e**. The first produces a very unstable cyclopropene as starting material but the second one **34e** gives a cyclopentene **39** that looks not too bad.



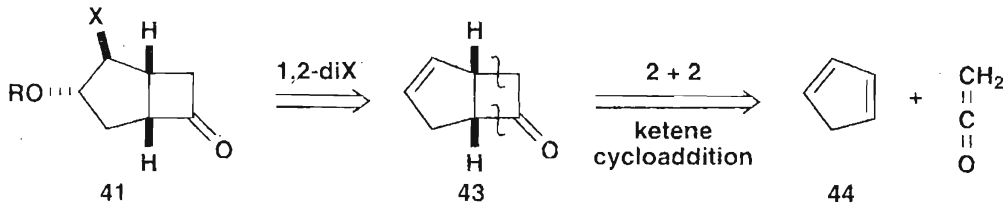
We should also investigate an ionic closure of two bonds with alkylation of an enolate in mind. One **34f** gives a reasonable compound **40** (X is a leaving group) but the other **34g** is more promising as **41** may remind you of a compound from chapter 33.



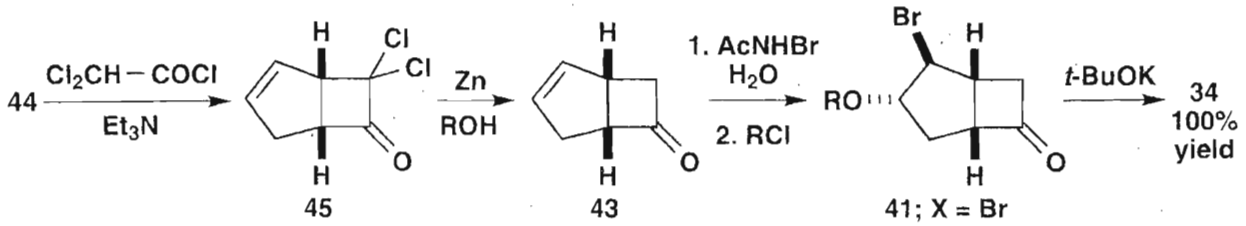
The third such disconnection **34h** is much worse than either **34f** or **34g**. Nucleophilic substitution would be required on a three-membered ring **42** and such reactions are known not to occur. Further, the reaction would close a four-membered ring, the most difficult to make by ionic cyclisations. In contrast, cyclisation of **40** or **41** would close a three-membered ring, one of the easiest.



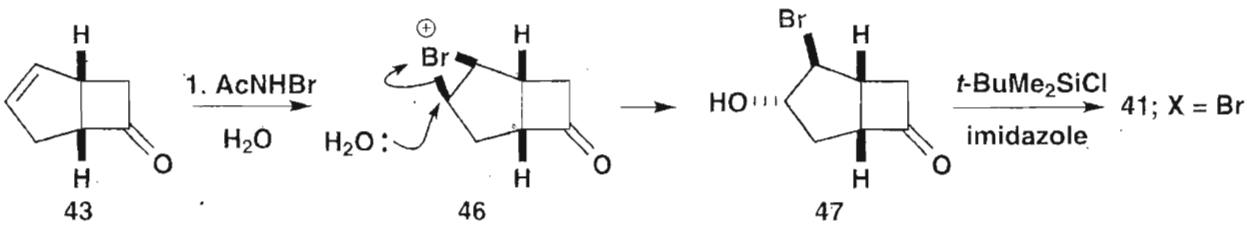
We continue with **41**. The neighbouring OR and X groups have a 1,2-diX relationship (chapter 6) and can be made by *trans* addition of, say bromine water, to an alkene **43**. Now we can disconnect the four-membered ring to cyclopentadiene **44** and ketene.



We already know from chapter 33 that these cycloadditions go best with dichloroketene and that the end of the diene attacks the carbonyl group of the ketene. The product **45** was dechlorinated with zinc to give **43** and bromination with *N*-bromo acetamide and water followed by silylation gave **41**; X = Br. The cyclisation to **34** needed *t*-butoxide and went in 100% yield.

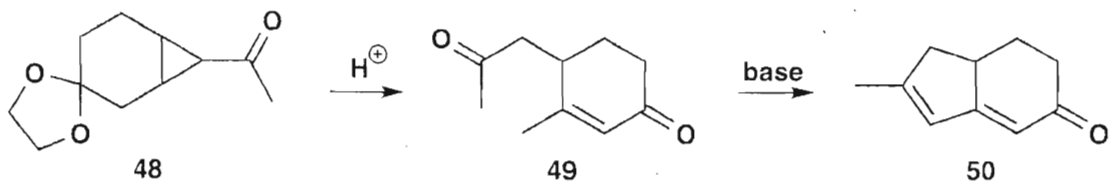


The stereochemistry of the bromination needs some thought. The alkene **43** is a folded molecule (chapter 38) of two fused small rings and reaction occurs on the outside (*exo* or convex) face, the top face in our diagram. Water then opens the bromonium ion **46** at the less hindered end and it must attack from the inside (*endo* or concave) face as inversion is required in an S_N2 reaction.

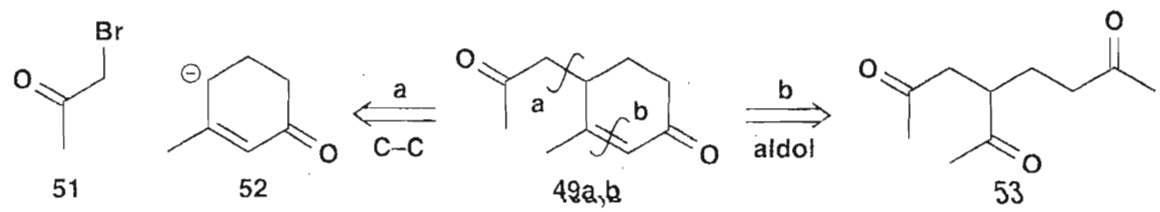


Development of Some Chemistry from the Textbook

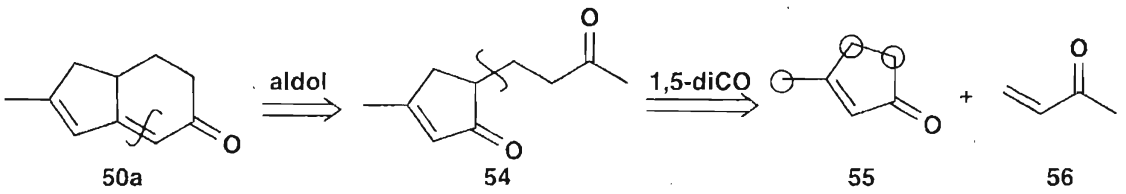
In chapter 37 of the textbook, cyclopropane **48** was target molecule **11**. We shall not discuss **48** further except to note that Stork actually needed it for the synthesis[7] of **50** via **49**. **Problem 37.3:** Consider more conventional approaches to ketones **49** and **50** and suggest reasons why they might be unsatisfactory.



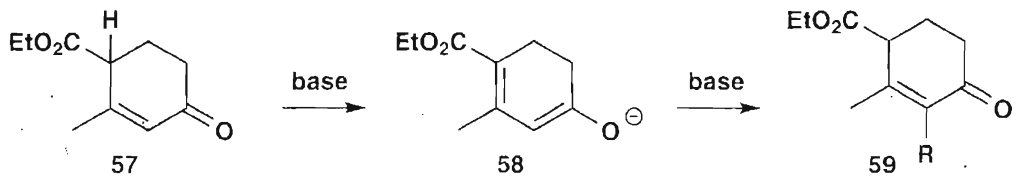
Answer 37.3: Two conventional approaches to **49** are **49a** and **49b**. The first leads to proposed alkylation of the extended enolate **52** by bromoacetone **51**. As this anion is conjugated over a five-atom system, there is a doubt as to where alkylation will occur. The second is the Robinson annelation **49b** leading back to the triketone **53**. The prospects of cyclising **53** to **49** are poor as we have three different methyl ketones with six different places to form an enolate and three different electrophilic carbonyl groups. We shall not pursue this.



Robinson annelation on **50** looks better **50a** as the intermediate **54** is only a diketone and cyclisation to **50** looks likely. The 1,5-diCO disconnection leads to a simple enone **56** and the cyclopentenone **55** is easily made by cyclisation of hexan-2,5-dione. But **55** has three positions (circled) where enolate formation is possible and control might be a problem. This is an extended enolate problem[8] related to the problem with **52**.

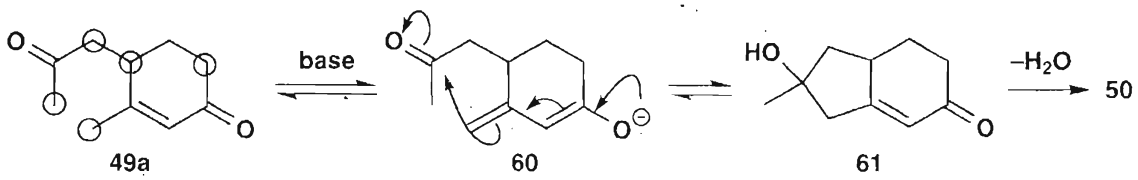


You might think that adding an ester group to **52** at the right position would solve that regioselectivity problem at least, especially when you realise that the starting material is Hagemann's ester **57** (Workbook, chapter 36). But the enolate **58** formed by removal of the marked proton in **57**, is conjugated over two carbonyl groups and is actually alkylated to give **59**.

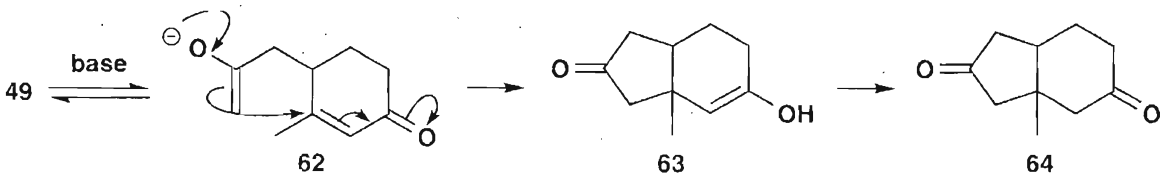


Problem 37.4: Why, in spite of all the problems we have just discussed in making **49**, is a route via **49** a good way to make **50**?

Answer 37.4: Though **49** has five possible sites for enolisation, a weak base will equilibrate all the enolates and only one cyclisation **60** leads to a stable enone product via the alcohol **61**.

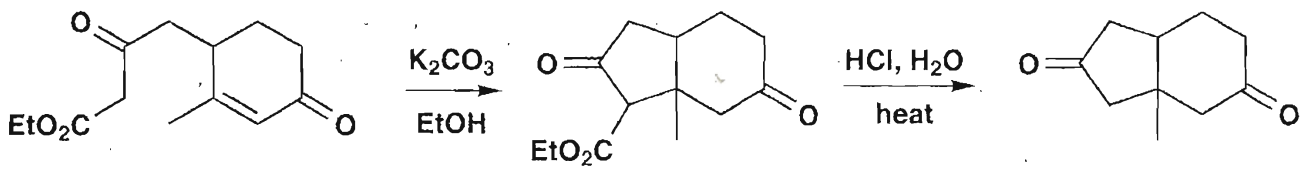


There is one other reasonable reaction: a similar 6/5 fused system **64** could be formed by conjugate addition of a methyl enolate onto the six-membered ring. This looks perfectly all right but **64** may be less stable than **50** as it has no conjugation.



In fact the regioselectivity can be altered by the addition of an ester group.[7] Much weaker base (K_2CO_3) is all that is needed to make the enolate from the keto-ester side chain in **65** and

is too weak to make an enolate like **60**. Conjugate addition follows and the product **66** can be hydrolysed and decarboxylated to give **64**.



65 66 64; 45% yield

Using only the chemistry we have explored in earlier chapters, particularly 18 to 36, it is possible, by careful choice of substituents and conditions, to control regioselectivity in many cyclisations. It is not so easy for open chain target molecules.

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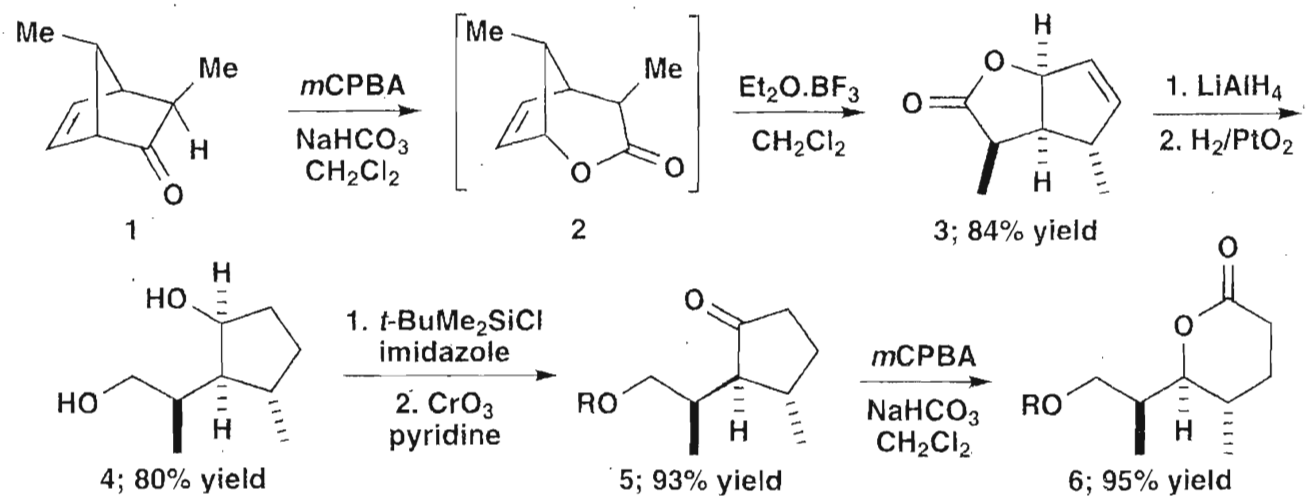
7. G. Stork, D. F. Taber and M. Marx, *Tetrahedron Lett.*, 1978, 2445; see note 3.
8. *Strategy and Control*, chapter 11.

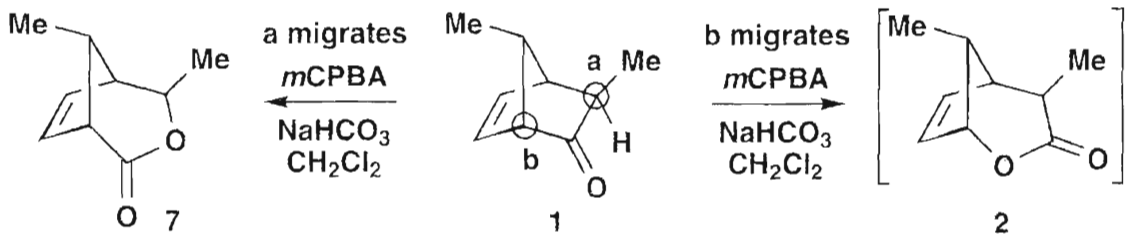
38 Strategy XVII: Stereoselectivity B

The Prelog-Djerassi Lactone

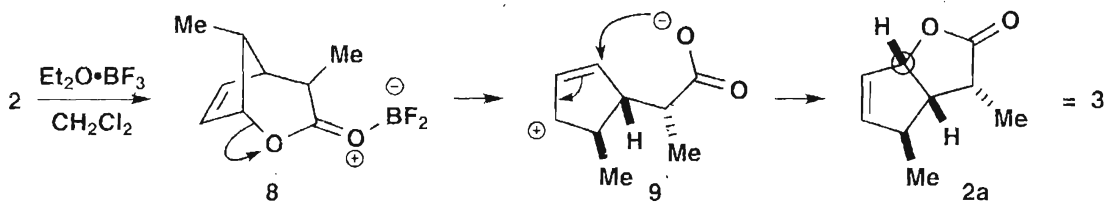
One of the more instructive syntheses by Baeyer-Villiger rearrangement[1] starts with a Diels-Alder adduct **1** and uses two such rearrangements. One gives the lactone **2** that rearranges into the isomeric lactone **3** while the other converts the cyclopentanone **5** into the lactone **6** in the style of the strategy mentioned in the main text. **Problem 38.1:** Comment on the regioselectivity of the two Baeyer-Villiger rearrangements. There is also a migration that is not a Baeyer-Villiger rearrangement that converts **2** into **3**. **Problem 38.2:** Explain what is happening here.



Answer 38.1: The first rearrangement, **1** to **2**, has two potential migrating groups circled and marked **a** and **b**. Both are secondary. The bridgehead **b** migrates, which is unusual, but this is probably because it is allylic. The most important aspect is that it migrates with retention of configuration. The other case, **5** to **6**, is more straightforward: the secondary centre migrates rather than the primary and again does so with retention of configuration.

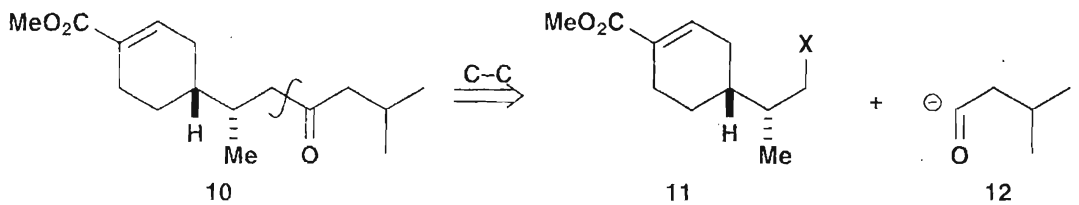


Answer 38.2: The Lewis acid attaches itself to the carbonyl oxygen and the bond to the allylic group breaks **8** to leave an allylic cation that joins to the carboxylate group at its other end. The drawing **2a** shows what we get with our mechanism: turning **2a** over reveals that it is **3**. The only new centre is ringed: the three-atom chain must cyclise onto the planar cation on the same side to which it is already joined. In other words, the 5/5 ring junction must be *cis*.

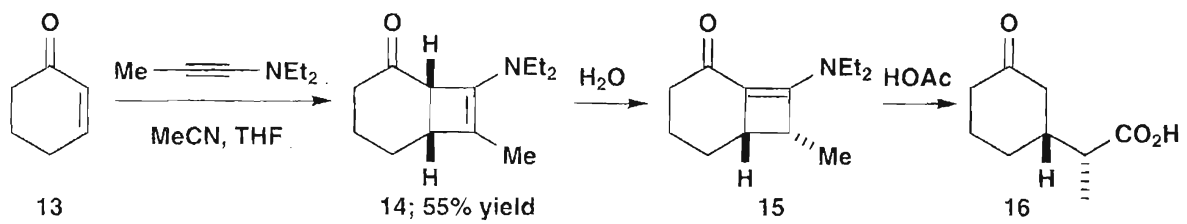


The Ficini Synthesis of Juvabione

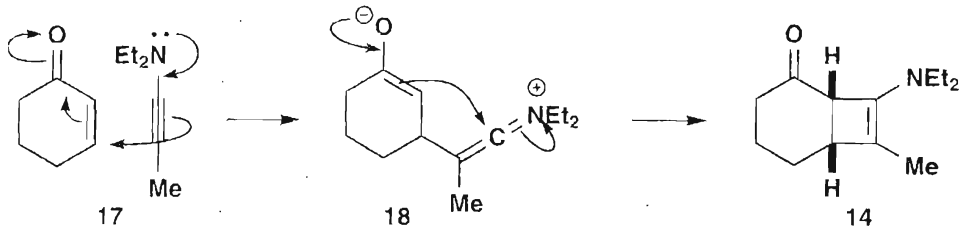
Juvabione **10** is a natural product that shows juvenile hormone activity and prevents insects from reaching maturity. Ficini[2] chose to disconnect the acyl side chain leaving an intermediate **11** (with both chiral centres) and an acyl anion equivalent **12**.



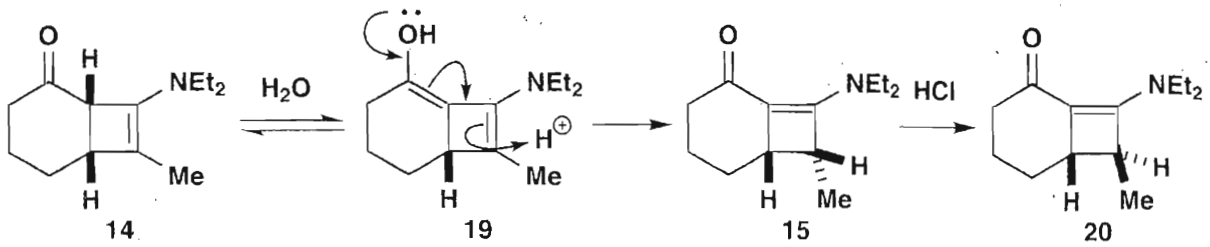
Part of the reason for this choice of disconnection was chemistry already known to the Ficini group.[3] Reaction of cyclohexenone **13** with an ynamine gives the cyclobutene **14**. Reaction with water isomerises this to the conjugated enone **15** and treatment with 60% aqueous acetic acid gives the ketoacid **16** with the right stereochemistry for juvabione. **Problem 38.3:** Explain all these reactions, not forgetting the stereochemistry.



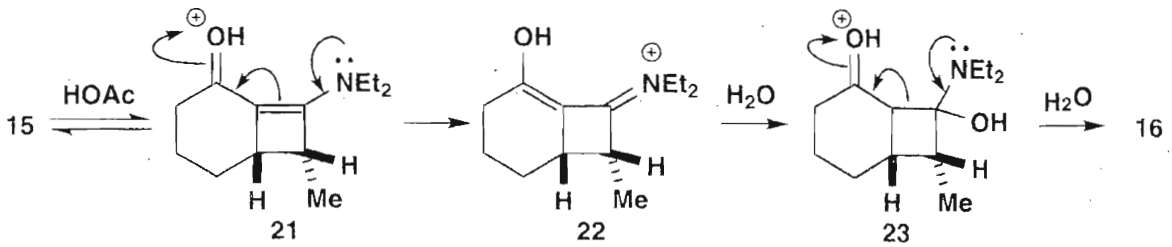
Answer 38.3: You might reasonably have drawn the first reaction as a [2 + 2] cycloaddition, arguing that the ynamine has a central carbon very like that of a ketene. Or you might have drawn an ionic mechanism with the ynamine acting as an enamine **17** and the intermediate cyclising in the only way it can **18** to give the *cis* ring junction in **14**.



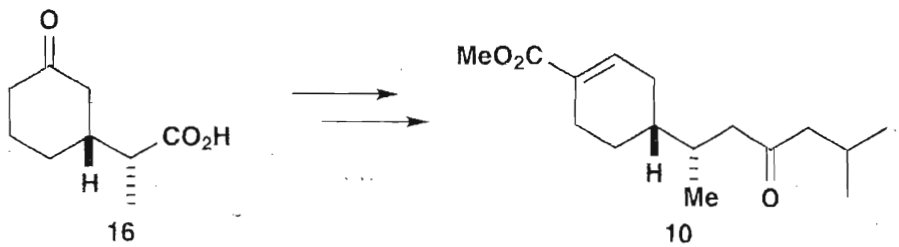
Isomerisation of **14** into **15** in water must involve formation of the extended enol and protonation at the far end **19** to give the conjugated product. The proton adds on the less hindered *exo* face. This reaction must be carried out with care as more vigorous conditions isomerise **15** to the more stable isomer **20** with the methyl group *exo*.



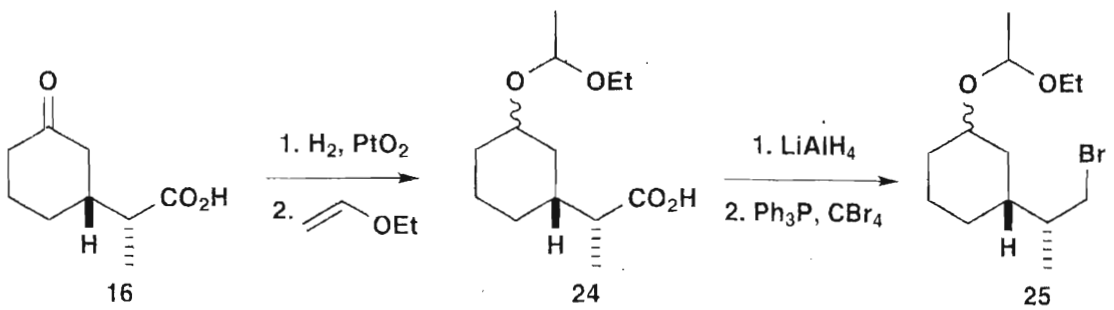
The last step opens the strained four-membered ring in aqueous acid. Presumably the alkene must move first **21**. Then, after addition of water to the iminium ion **22**, fragmentation of the single bond **23** opens the four-membered ring and gives **16** after further hydrolysis. An alternative would be conjugate addition of water to the enone **20**. Whatever the details, this is a reverse aldol reaction where a four-membered ring product is in equilibrium with an open chain product of a kind that we have mentioned in previous chapters. This reaction must also be carried out with care to avoid epimerisation of the side-chain methyl group.



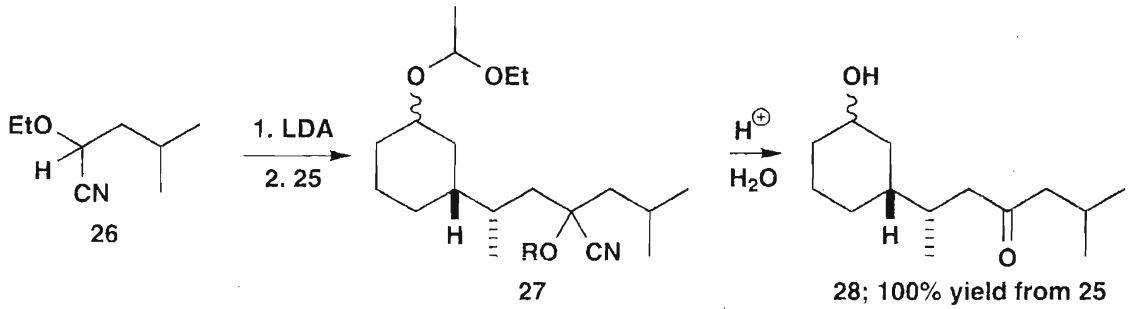
So Ficini had her starting material. **Problem 38.3:** How do you suggest she should proceed from **16** towards **10**?



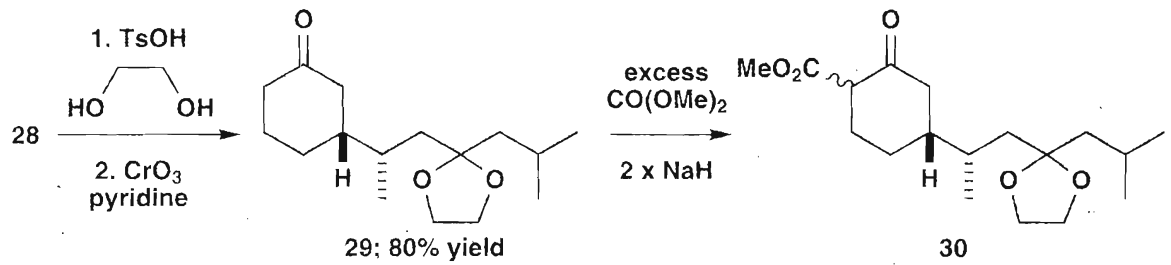
Answer 38.3: Two jobs have to be done. The side chain must be extended and the ketone in **16** must be transformed into the unsaturated ester with the regioselective addition of an extra carbon atom. The first task is more urgent because enolisation of **16** could cause epimerisation. But we don't want to make another ketone without masking the existing one. So the ketone in **16** was reduced and protected as a mixed acetal **24** and the acid reduced and converted to the bromide **25**.



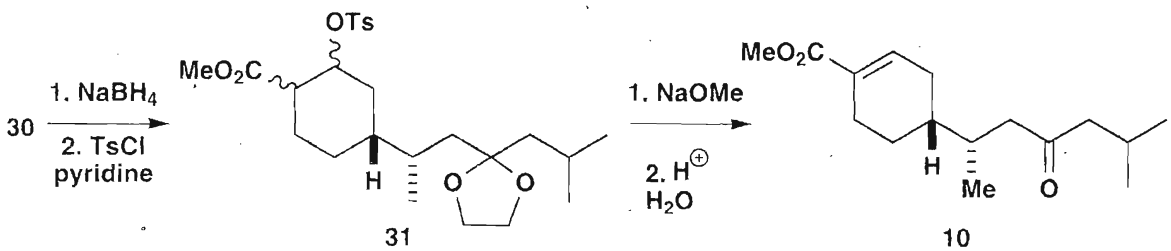
Now the side chain can be added and they chose the anion of the protected cyanohydrin **26** as the equivalent of **12**. Hydrolysis of both the acetal and the cyanohydrin gave **28** in 50% overall yield from the starting material **16**.



Now we approach the key regioselectivity issue but the ketone in the side chain must first be protected before the ketone in the ring is revealed. There is a subtle point here that you may not have noticed. It would not have done to propose putting the carbonyl group in the ring where the CO_2Me group ends up as then the chiral centre on the ring would not be chiral. This carbonyl group must not be removed until the ester is in place to preserve the lack of symmetry. Experiments showed that carboxylation with dimethyl carbonate led to reaction on the less hindered side of the ketone **30**.

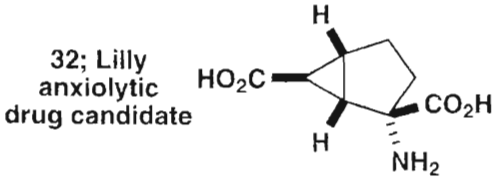


Now the ketone was reduced and tosylated before elimination and hydrolysis of the acetal gave juvabione **10** with both chiral centres intact. It is irrelevant that the tosylate is a mixture of diastereoisomers as the elimination is by the E1cB mechanism so all give the same unsaturated ester. In any case, the alkene has to be *cis* inside a six-membered ring. The overall yield of juvabione from **16** was 13% for the 11 steps. The main point is to control the stereochemistry in the side-chain from a rigid four-membered ring.

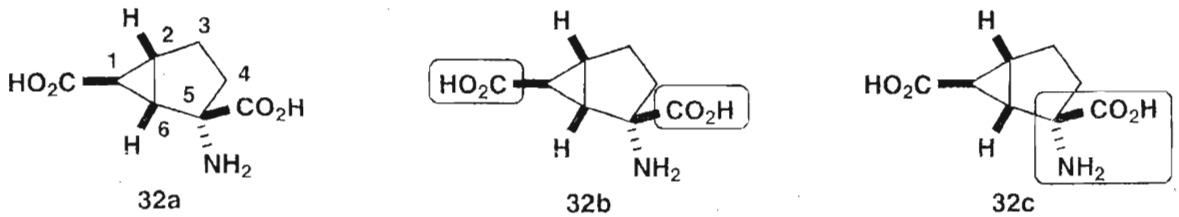


A Pharmaceutical Example

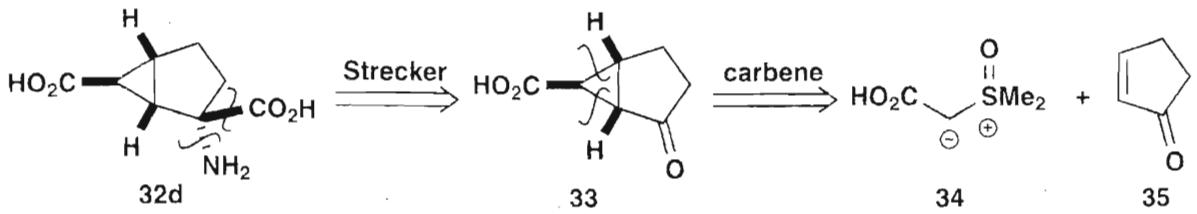
The bicyclic compound **32** is a drug candidate from the Lilly research centre.[4] **Problem 38.4:** Don't try to synthesise **32** yet, but just assess the stereochemical problems associated with designing a synthesis. You might find it helpful to re-read the first paragraph in the textbook under the heading 'synthesis of molecules with many chiral centres' at the bottom of page 289.



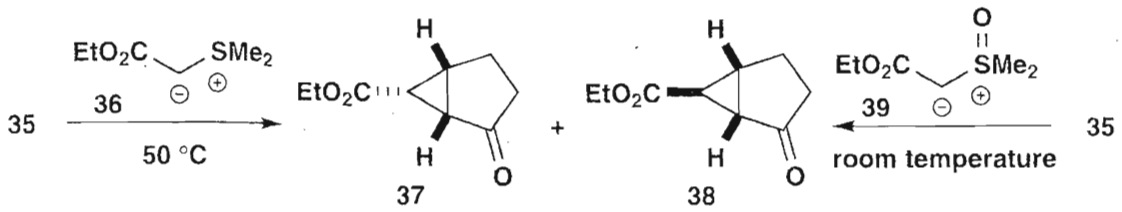
Answer 38.4: We see a small molecule with fused three and five-membered rings and only eight carbon atoms, four of which are chiral centres **32a**. A good sign is that all the chiral centres are around the rings and another is that two of them (C-2 and C-6 in **32a**) are always going to be *cis* as the 3/5 ring junction must be *cis*. It might be awkward that there are two different carboxylic acids but they are both *exo* (on the concave or outside face) and are ringed in **32b**. One acid has a 1,1-relationship with the amine **32c** and that might make synthesis easier but we shall need to add the amine first and the acid second to get the stereochemistry right. **Problem 38.5:** Suggest a synthesis for **32**.



The α-amino acid might be made by the Strecker synthesis[5] that does indeed add the amine to the ketone **33** first and the acid second. The ketone **33** looks an ideal candidate for sulfur ylid chemistry on cyclopentenone.

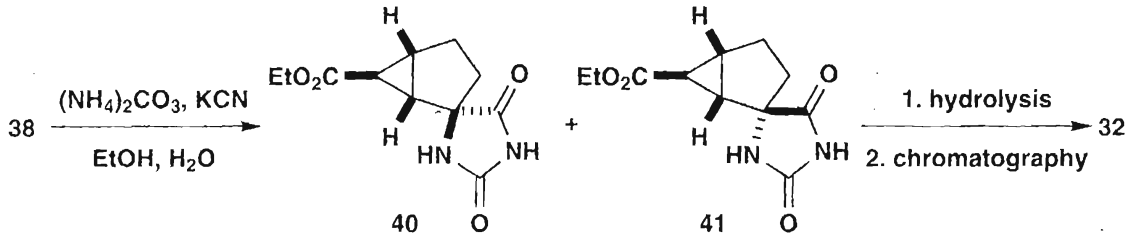


So far so good. Experiments showed that much depended on the reagents and conditions in both the 'carbene' addition to **35** and the Strecker reaction. We might expect sulfur ylid chemistry to give **38** with the ester group on the *exo* face of the folded molecule. But if the sulfonium ylid **36** was used, **38** and **37** were formed in a ratio of 69:31 and only 41% of **38** could be isolated. Fortunately, if the more stable ylid **39** was used, the ratio dramatically increased to 98:2 in favour of the thermodynamically more stable **38**.



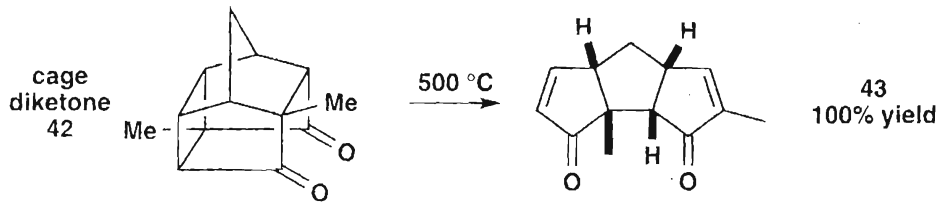
The stereoselectivity of the Strecker reaction was also affected by conditions. Reaction with ammonium carbonate and KCN in aqueous ethanol gave the spirocyclic heterocycles **40** and **41** in reasonable yield but the ratio depended on temperature. At 50 °C, the ratio of **41:40** was 78:22 but at 35 °C it improved to 87:13 and 73% of **41** was isolated. Hydrolysis gave **32**. It is all very

well to predict which stereoisomer might be favoured but conditions often have to be found in the laboratory to get the best ratio.



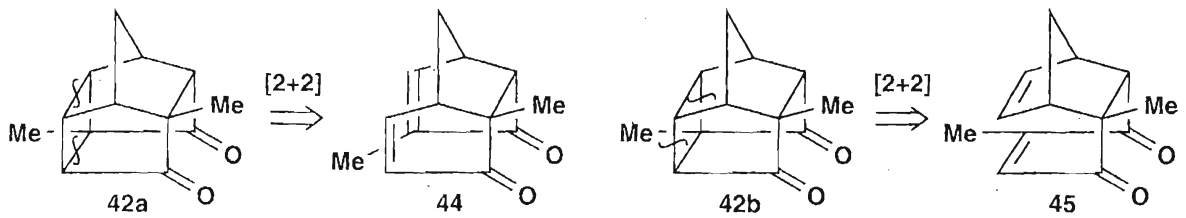
The Synthesis of a Cage Molecule

The cage diketone **42** was needed[6] to make the tricyclic dione **43** with full control over stereochemistry. **Problem 38.6:** Assess the stereochemical problems in making **42**.

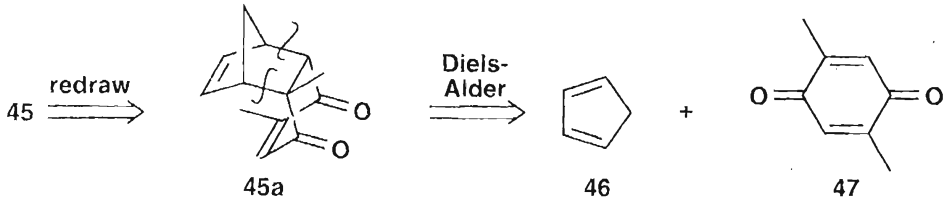


Answer 38.6: This cage molecule can exist only with the stereochemistry shown. Although there are *eight* chiral centres, none can be changed without breaking a bond. The problem lies not in **42** itself but in any precursor we might make as that would have to have the right stereochemistry to link up into **42**. **Problem 38.7:** Which ring would you like to disconnect first?

Answer 38.7: The compound has five five-membered rings, one six-membered and one four-membered ring. It seems more promising to get rid of the four-membered ring immediately. There are two [2 + 2] disconnections **42a** and **42b**. Which do you prefer?

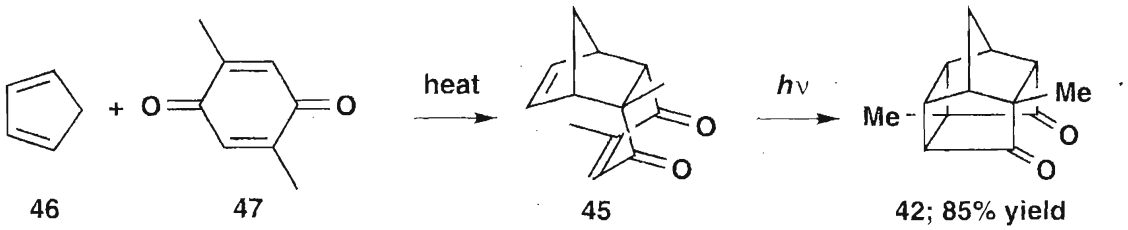


There is nothing wrong with **44** except the problem of making it with that stereochemistry. On the other hand, **45** has preserved the six-membered ring that, when redrawn, looks like an ideal Diels-Alder candidate **45a**. Disconnection reveals cyclopentadiene and the symmetrical quinone **47**.



The synthesis was very simple: cyclopentadiene and the quinone were dissolved in methanol at 20–30 °C to give 80–90% of the crystalline adduct[7] **45**. All the stereochemistry in **45**, and

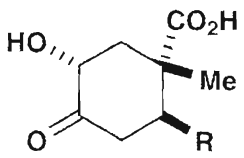
hence all that in **42**, comes from the *endo* selectivity of this Diels-Alder reaction. This reaction makes four chiral centres and the photochemical cycloaddition, that goes in superb yield[6] thanks to the proximity of the two alkenes, adds the other four. **Problem 38.8:** So, is **42**, with its eight chiral centres, a single enantiomer or not? The answer is at the end of the chapter.



46 47 45 42; 85% yield

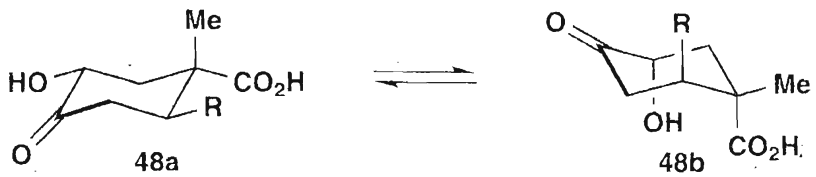
Conformational Control

We finish with an example of control of stereochemistry around a six-membered ring by means of conformation. **Problem 38.9:** How could you synthesise **48** with full control over stereochemistry so that a variety of substituents R could be added?

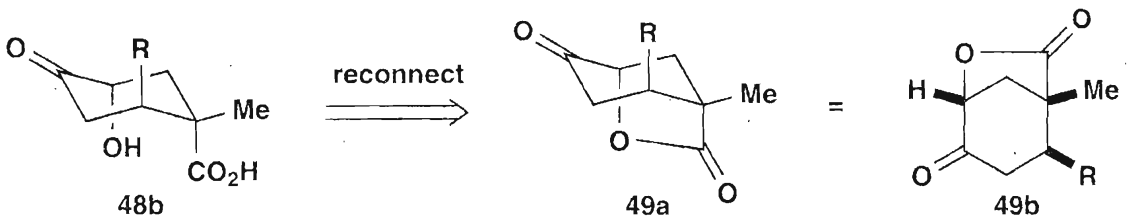


48

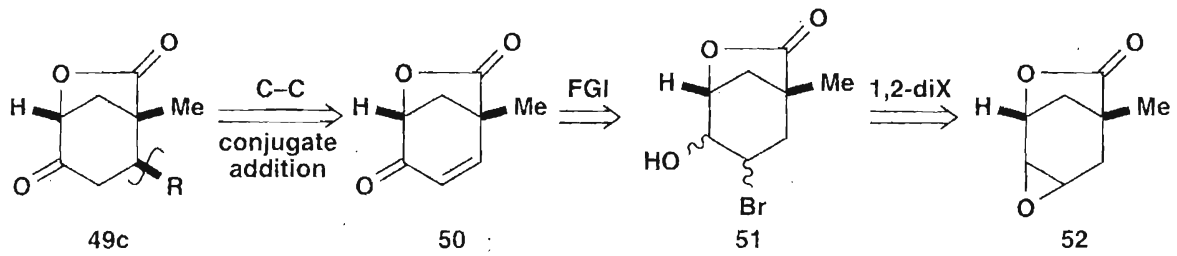
Answer 38.9: There are two chair conformations of **48**. One **48a** looks the more stable as it has three equatorial and only one axial substituent. But it will be **48b** that will lead us to a solution. What possibility emerges from the shape of the molecule in **48b**?



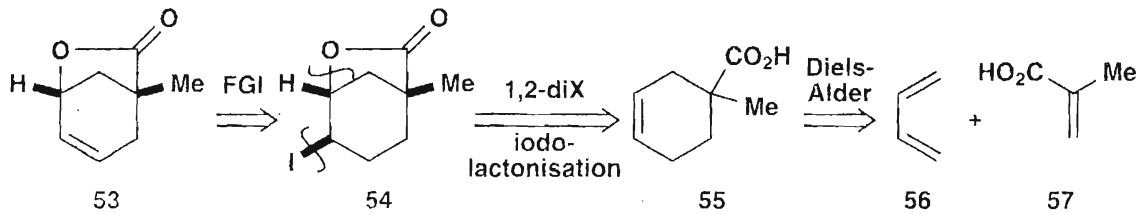
The OH and CO_2H groups could be reconnected in a bridging lactone **49** that fixes the conformation and provides a block across the bottom face of the molecule. Now we can be certain which groups are axial and which equatorial. It would make sense to leave the lactone bridge in place as long as possible.



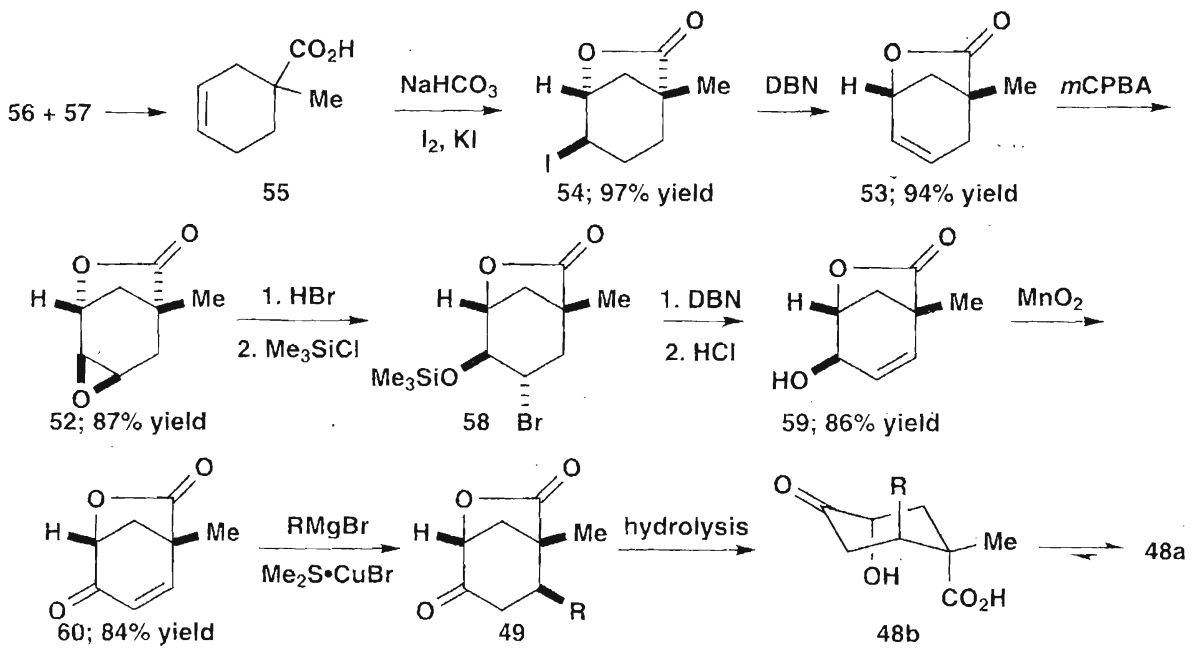
It also makes sense to disconnect R as soon as possible so that it can be added at the end of the synthesis. The relationship ('1,3') with the ketone suggests conjugate addition to the enone **50**. Now you might begin to see a way of introducing the bridging lactone: iodolactonisation. This will mean changing functional groups to get back to the much simpler epoxide **52**.



The epoxide **52** obviously comes from the alkene **53** and that in turn from the iodolactone **54**. Now we can disconnect **54** back to the simple cyclohexene **55** – an obvious Diels-Alder product from butadiene **56** and available methacrylic acid **57**.



The synthesis[8] roughly follows the analysis so we shall concentrate on the stereochemistry. The acid **55** is treated with iodine in $NaHCO_3$ so that it is the anion that reacts. The iodine and the lactone bridge are formed by *anti*-addition. Elimination of iodide can occur only to give **53** as the marked (equatorial) hydrogen in **54** is not *anti*-peri-planar to the axial iodine. The epoxide **52** must form on the top face as the bottom face is blocked by the lactone bridge. To see this clearly, we suggest you draw conformational diagrams like **48b** or **49b**. Now HBr gives *trans* addition and the diaxial product **58**. Elimination and oxidation give the enone **60** to which a copper-catalysed Grignard addition occurs axially. Hydrolysis of **49** initially gives the less stable **48b** but this flips to **48a**. The question of diaxial products from cyclohexenes and cyclohexene oxides is discussed[9] in Clayden and in *Strategy and Control*.



Answer 38.8: No, of course not! Both starting materials **46** and **47** are flat achiral molecules and no asymmetry is introduced in solvent or catalyst. Even if you stir the solution clockwise, you still can't make one enantiomer unless you introduce asymmetry at the molecular level.

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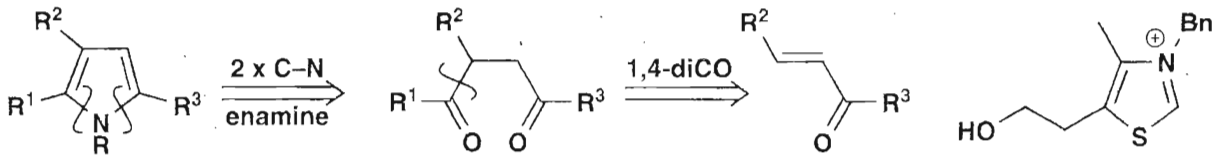
9. Clayden, *Organic Chemistry*, chapter 33; *Strategy and Control* p. 414.

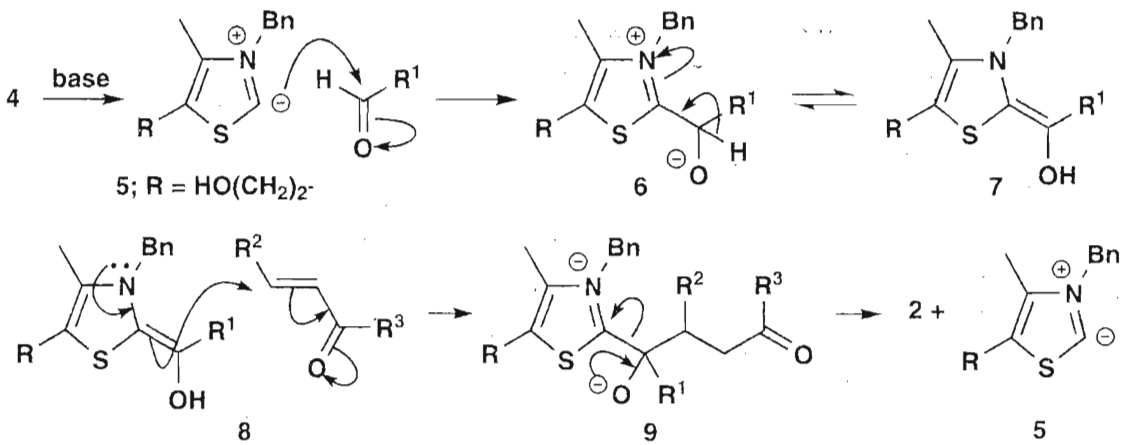
39 Aromatic Heterocycles

The Mechanism of the Stetter Synthesis of 1,4-diCarbonyl Compounds

In the textbook we discussed the synthesis of pyrroles **1** from 1,4-diketones **2** which we made by conjugate addition of a d^1 reagent to an enone **3**. We chose a catalytic method, devised by Stetter,[1] that uses the thiazolium salt **4** to convert an aldehyde R^1CHO into the d^1 reagent. We now reveal the mechanism of this reaction.

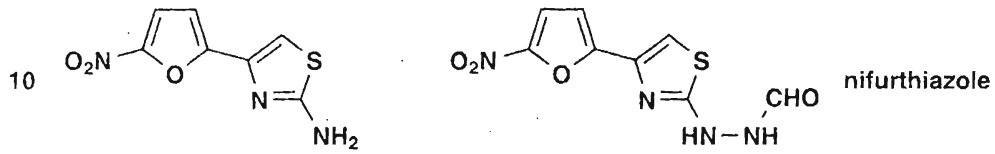


Base converts the cation **4** into the ylid **5** with a negative charge stabilised both by the positive nitrogen and by the sulfur atom. This adds to the aldehyde to give a zwitterion with an acidic hydrogen on what was the aldehyde **6**. The neutral intermediate **7** has a strange alkene bonded to O and N atoms: it is both an enol and an enamine and is the d^1 reagent. So either end of the double bond could act as the nucleophile but the enamine wins and its conjugate addition to the enone **8** makes the vital C–C bond. Fragmentation of the intermediate **9** gives the 1,4-diketone **2** and regenerates the ylid **5** for the next cycle.

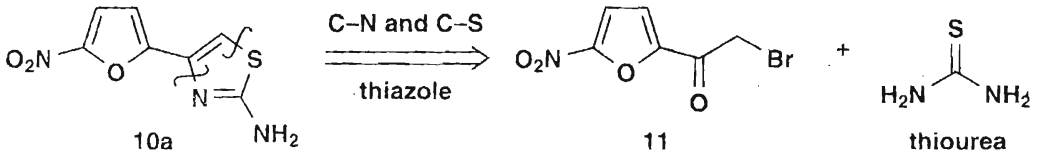


The Synthesis of Five-Membered Heterocycles

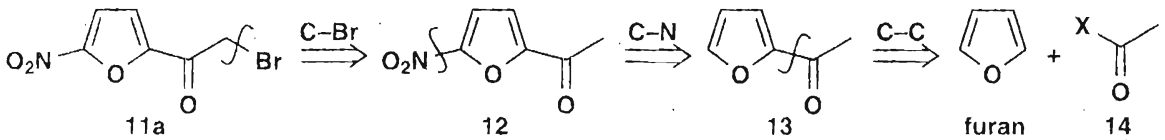
Problem 39.1: Suggest a synthesis for **10** which was needed as an intermediate in the synthesis of the antimicrobial nifurthiazole – an unusually helpful name.



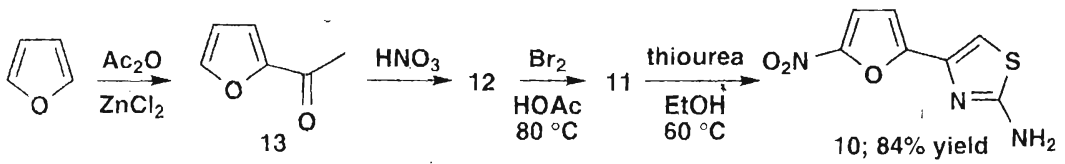
Answer 39.1: We have a furan and a thiazole here. It looks as though we may be able to nitrate a furan to make the left hand half of the molecule but we shall have to make the thiazole by ring synthesis, so let's disconnect that first **10a**. Remembering to let the sulfur attack the alkyl halide and the nitrogen the carbonyl group leads us to an α-halo ketone **11** for reaction with thiourea.



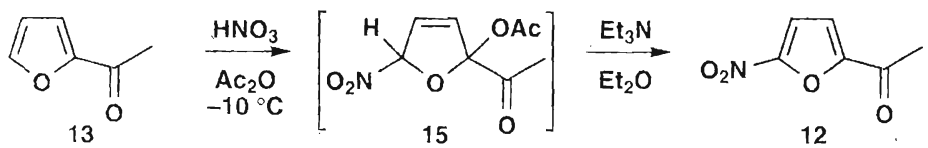
The bromo-ketone **11** comes from the parent ketone **12**. Now you might reasonably have disconnected either the nitro or the acetyl group but in fact it is known that furyl ketones such as **13** are nitrated in the right position for our purpose. Finally, some sort of Friedel-Crafts reaction on furan with an acylating agent **14** completes the analysis.



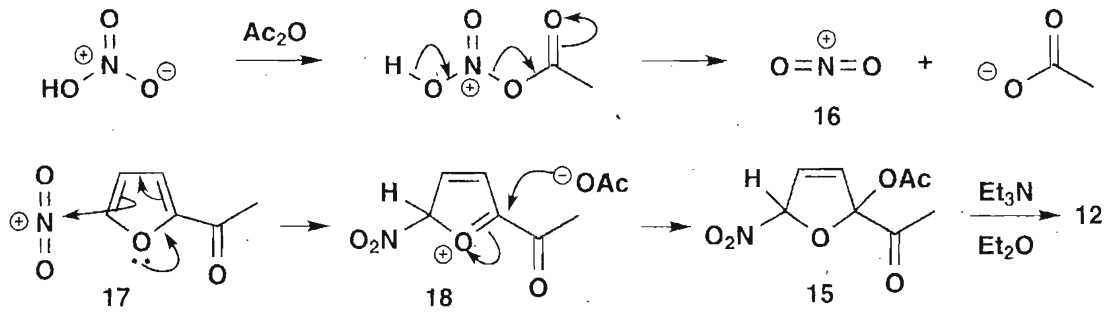
The published synthesis[2] uses acetic anhydride and the mild Lewis acid[3] $ZnCl_2$. Bromination in acetic acid gives **11** without any bromination of the furan ring as it is deactivated by both nitro group and ketone.[4]



In fact the nitration is rather more complicated. Nitration at low temperature with the nitric acid/acetic anhydride mix gives the non-aromatic intermediate **15**. Treatment with Et_3N gives the product[5] **12**. **Problem 39.2:** Explain these two reactions.

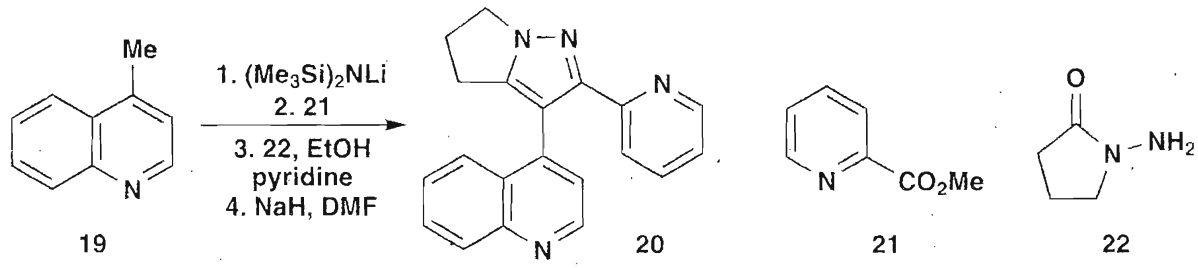


Answer 39.2: Reaction between HNO_3 and Ac_2O gives the nitronium ion NO_2^+ **16** that attacks **17** the free α-position on **13**. Acetate captures the intermediate cation **18** to give **15**. Elimination of acetate with a weak base, either by a concerted or E1cB mechanism, restores the aromaticity.

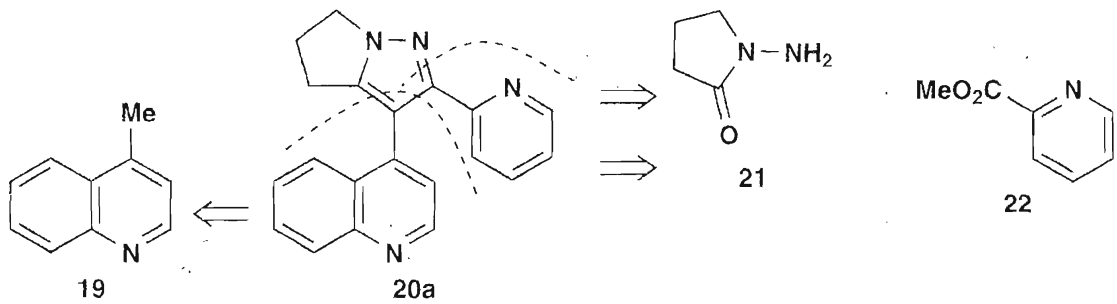


Mechanisms in Heterocyclic Chemistry

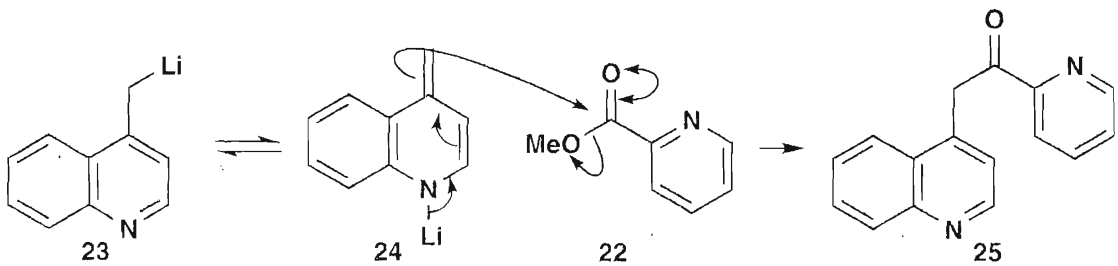
Some of you may feel unfamiliar with the world of heterocyclic chemistry and some practice at mechanisms may be helpful. **Problem 39.3:** What is going on in this synthesis? Work out the structures of the intermediates and the mechanisms of the reactions. *Hint*: If you are stuck, numbering the atoms arbitrarily in reagents and product may help to decide which parts of **20** come from **21** and **22**.



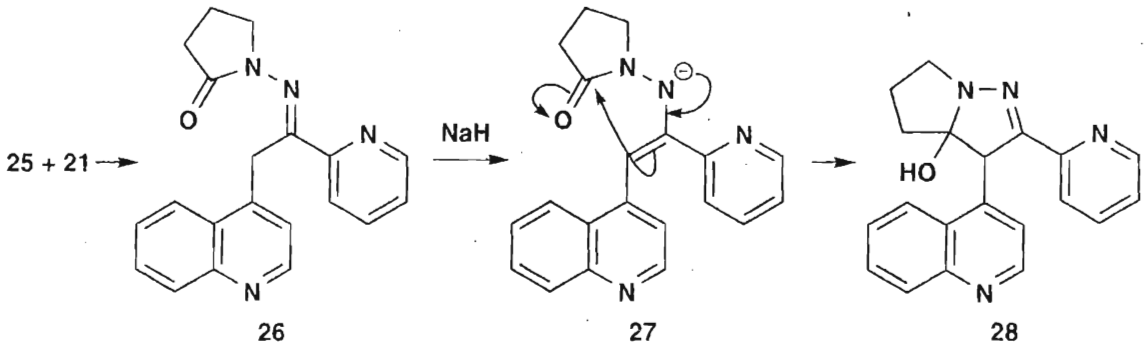
Answer 39.3: It is obvious which part of **20** comes from **19** and pretty obvious which part comes from **22** which leaves us only with the part from **21**. This is work from Lilly.[6]



The base removes a proton from the methyl group of **19** to give **23** or **24** which attacks the acyl group of **22** to give the new ketone **25**. This is the first intermediate that can be isolated.



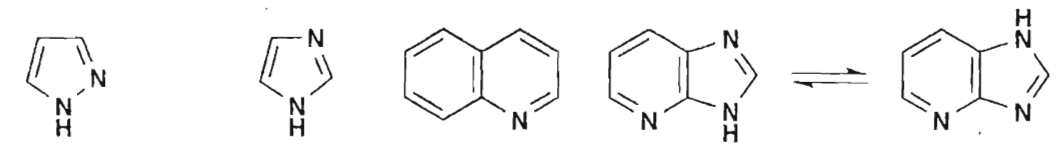
Now the more nucleophilic terminal nitrogen of the acyl hydrazine **22** attacks the ketone in **25** to give the hydrazone **26**. Base removes a proton to give an aza-enolate that cyclises **27** to give the intermediate **28** that immediately dehydrates to form the aromatic pyrazole **20**.



26 27 28

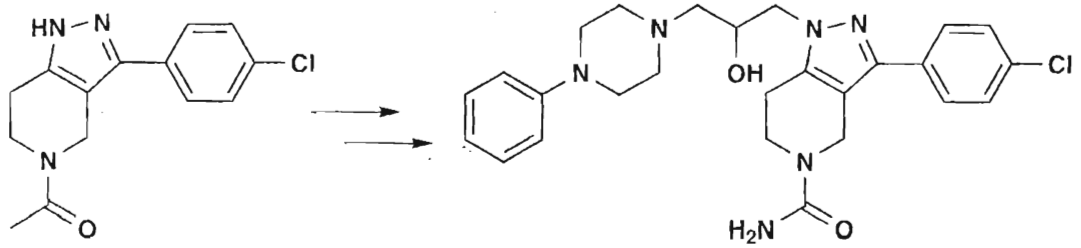
Pyrazole, Imidazole and Quinoline

We shall now concentrate on ring systems that were barely mentioned in the textbook: pyrazole **29**, imidazole **30**, quinoline **31** and a fused imidazo-pyridine **32**. You will be glad that we are not going to use the official names for systems like **32**. But you should notice that imidazole and pyrazole both have tautomers: the NH can be either nitrogen, not that it makes any difference, and **32** exists as two rapidly interconverting tautomers **32a** and **32b**.



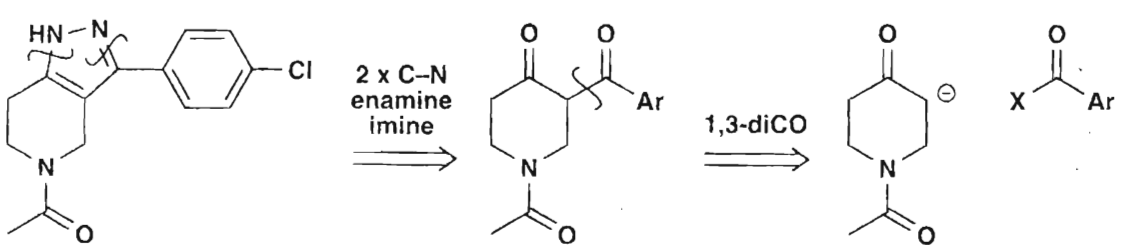
29 pyrazole **30** imidazole **31** quinoline **32a** ⇌ **32b** imidazo-[4,5-*b*]pyridine

Pyrazole **33** is Johnson and Johnson's core structure for a series of inhibitors **34** of the cysteine protease cathepsin.[7] **Problem 39.3:** Suggest a synthesis of **33**. *Hint:* Only normal C–X and C–C disconnections are needed.



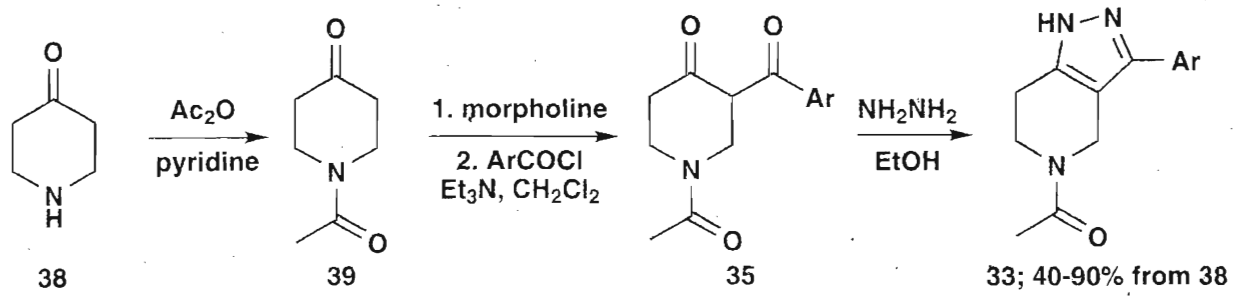
33 **34; inhibitor of cysteine proteases**

Answer 39.3: Disconnecting both C–N bonds **33a** reveals a 1,3-diketone **35** that can be made by acylation of an enolate equivalent **36**. The two nitrogens remain bonded to each other in a molecule of hydrazine NH_2 NH_2.



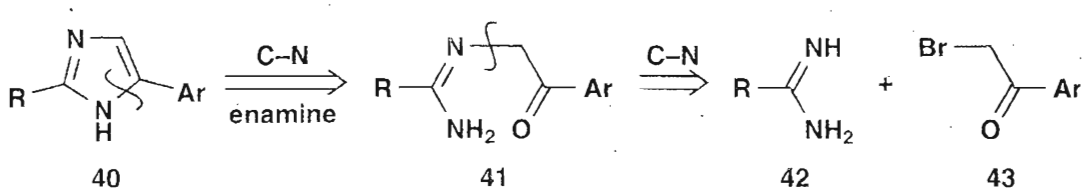
33a **35** **36** **37**

The synthesis started from the amino ketone **38**, made in chapter 19 of the textbook. *N*-Acylation and enamine formation with morpholine allows *C*-acylation with a variety of acid chlorides to give the 1,3-diketone **35** that reacts with hydrazine to give the pyrazole.

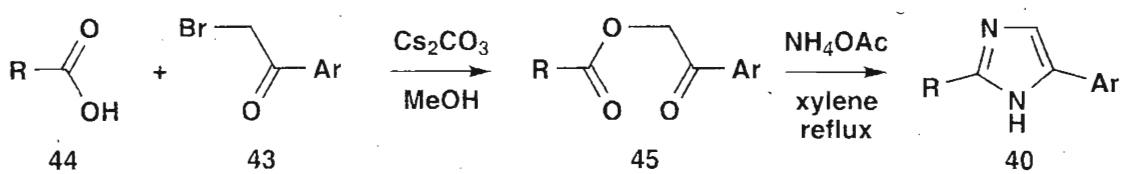


A Synthesis of Imidazoles

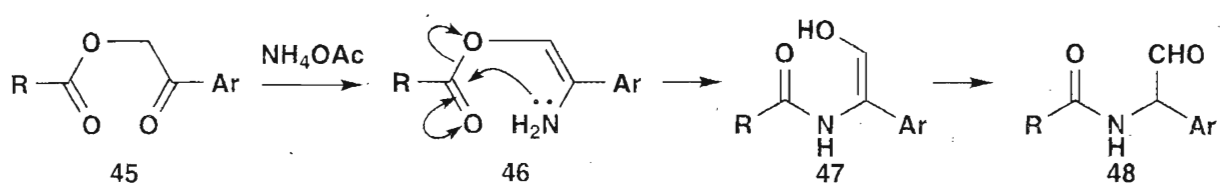
Imidazoles **40** (where R is an alkyl group) were needed for drugs to treat epilepsy.[8] There are four C–N bonds that could be disconnected but the result will be much the same wherever you start. Disconnecting the enamine reveals a ketone **41** and another C–N disconnection gives possible starting materials as the amidine **42** and the α-haloketone **43**. If you continue with the other two C–N bonds you discover that **42** is a derivative of a carboxylic acid and two molecules of ammonia.



Amidines can easily be made from nitriles and ammonia and there is no doubt that this synthesis will work as, unlike the synthesis of thiazoles, there is no regioselectivity issue. However, Libertore and her co-workers chose a short cut. They decided to join the carboxylic acid **44** directly to the α-haloketone **43** and treat the product **45** with an excess of ammonia. Amazingly this gave the imidazole **40**.

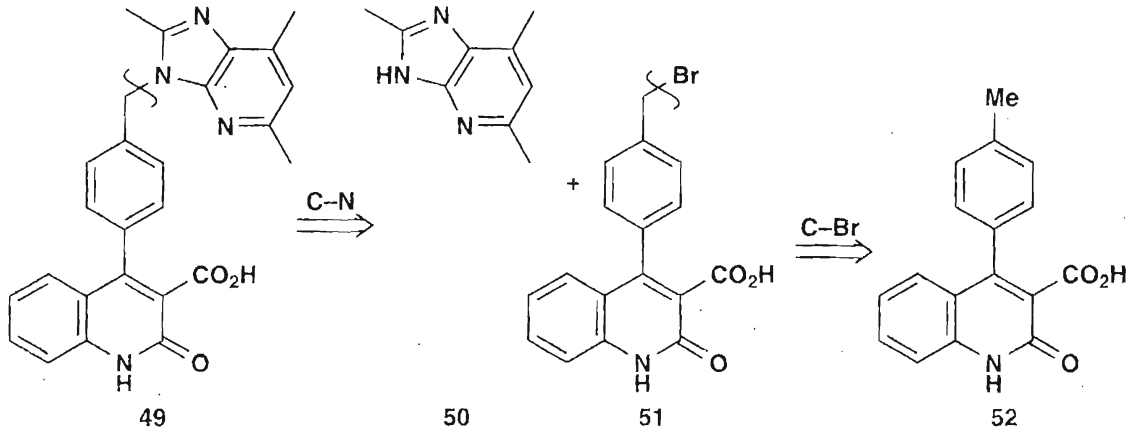


The mechanism is perhaps not immediately obvious. Ammonia must attack the ketone and then cyclisation **46** established the right C–N–C connectivity. The product **47** is the enol of an aldehyde **48** and addition of the second molecule of ammonia to the aldehyde followed by cyclisation would give **40**. They do not suggest a mechanism but this is reasonable.



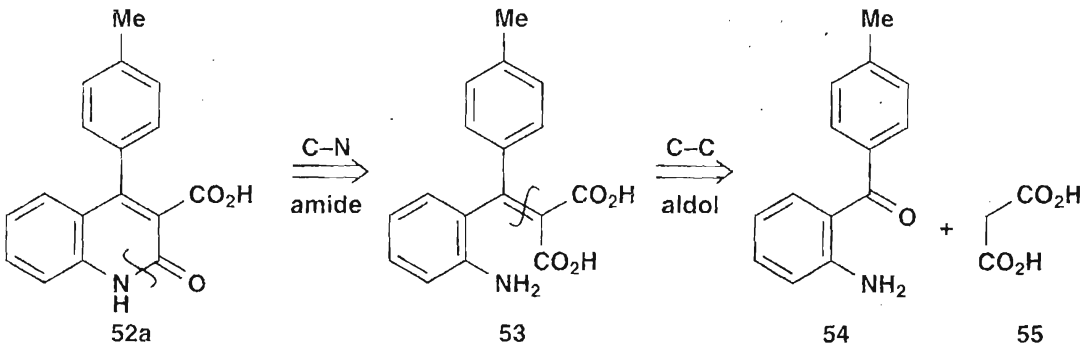
A Synthesis of Quinolines and of Fused Imidazo-Pyridines

The angiotensin II inhibitor **49** for the treatment of hypertension combines these two ring systems.[9] Disconnection somewhere in the middle **49** gives much simpler starting materials **50** and **52** and we'll look at each of these. The quinoline **52** is the easier. **Problem 39.4:** Using only standard C–N and C–C disconnections, suggest a synthesis of **52**.



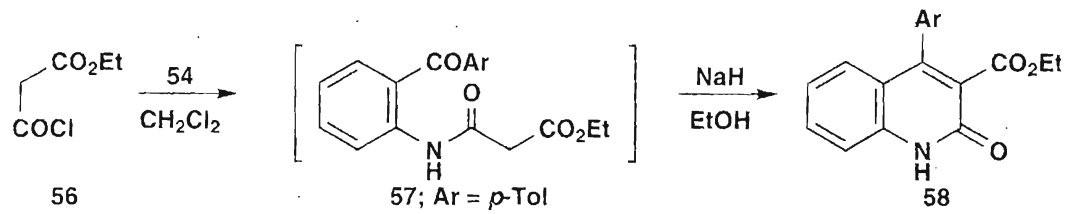
49 50 51 52

Answer 39.4: Straightforward! Lactam disconnection **52a** reveals an obvious aldol condensation product **53** between some derivative of malonic acid **55** and the ketone **54**.



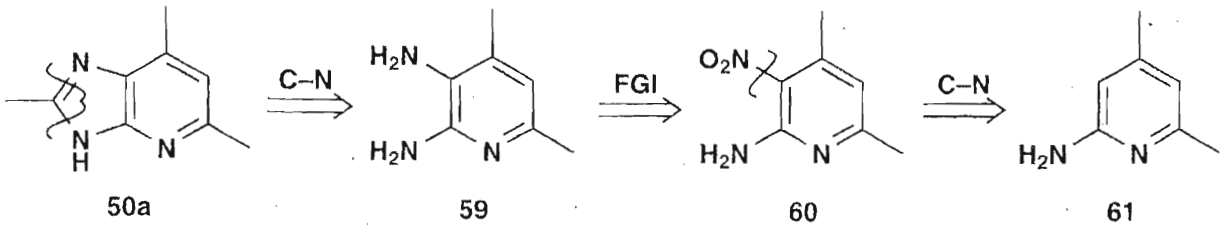
52a 53 54 55

In fact the half ester, half acid chloride of malonic acid **56** was used in condensation with **54** to give the ester **57** and this was cyclised to **58**, the ester of **52**, which was used in the rest of the synthesis. We shall return shortly to the synthesis of **54** after the next section.

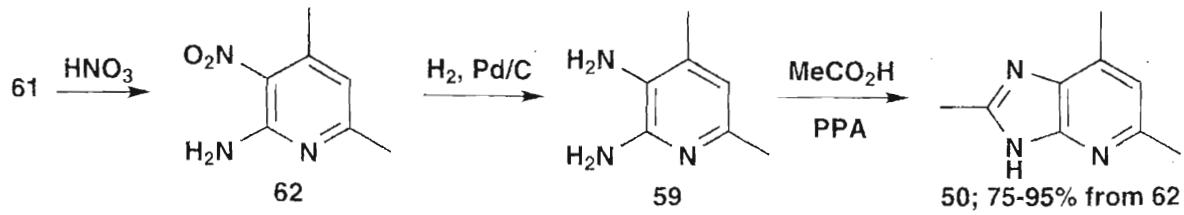


56 57; Ar = *p*-Tol 58

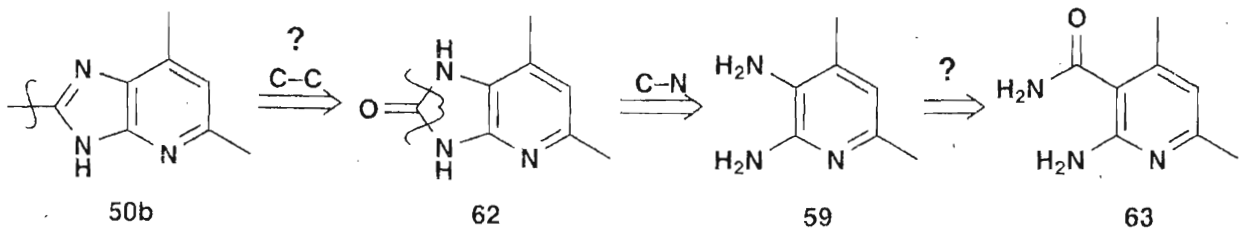
The other starting material for **49**, the fused imidazo-pyridine **50**, is more interesting and more challenging. One synthesis[10] disconnects the five-membered ring first **50a** and puts in one amino group by nitration and reduction of **61**. Why this one? Because the starting material **61** is commercially available.



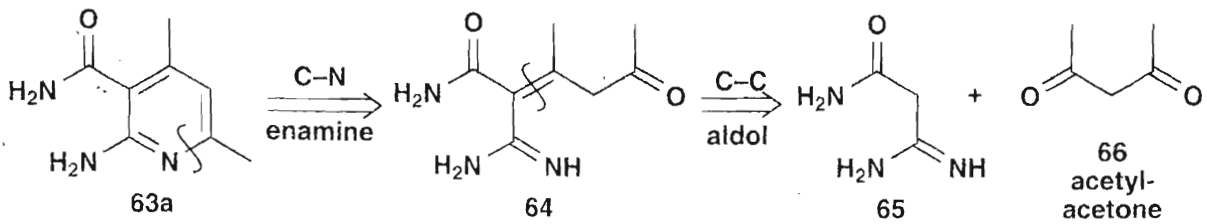
Pyridines normally react badly with electrophiles but here the amino group of **61** activates the *ortho* position to substitution to give **62**. Reduction by catalytic hydrogenation gives the diamine **59** without touching the pyridine ring and reaction with acetic acid and polyphosphoric acid gives **50**.



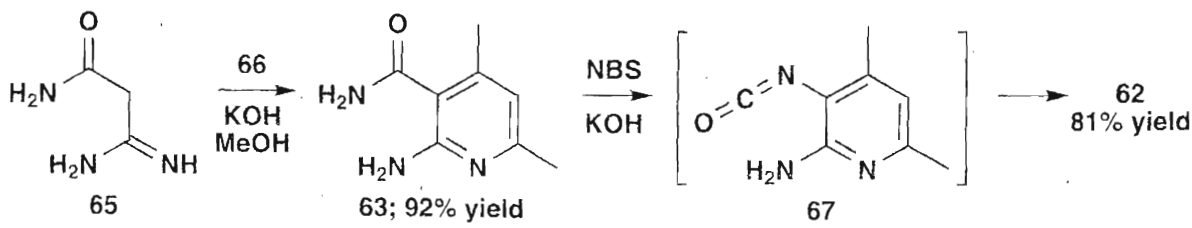
A later synthesis[11] is more inventive. A C–C disconnection **50b** back to the imide **62**, obviously derived from **59**, and an equivalent of CO_2. Now the chemists at Merck decided to make **59** by a different route, perhaps to avoid the potentially poor nitration step. They propose a rearrangement route from the amide **63**.



They prefer to make the pyridine by ring synthesis and so disconnect one C–N bond **63a** and then do an aldol disconnection of **64** to reveal two available starting materials: malonamidine **65** and acetyl acetone **66**.

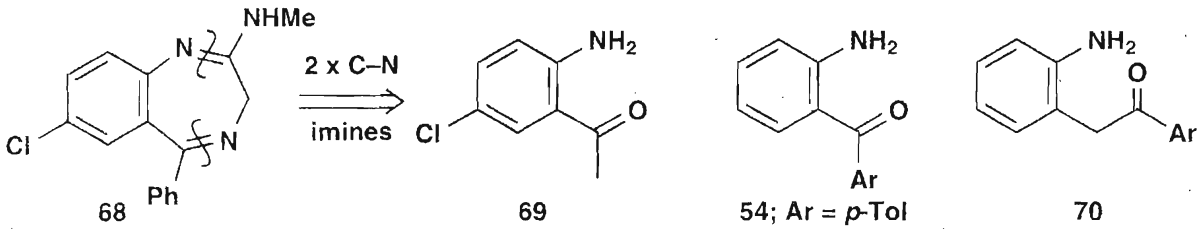


Condensation of **65** and **66** in base gives **63** directly and the Curtius rearrangement followed treatment of **63** with NBS in base to give **62**, via the isocyanate **67**, in excellent yield. This imide was converted into **50** with diethyl carbonate $(EtO)_2CO$, $EtCO_2H$ and $MgCl_2$ in a remarkable 81% yield. The mechanism is discussed in the paper.



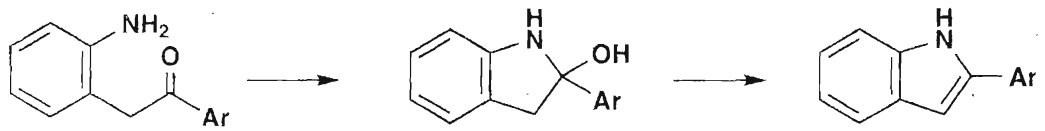
The Synthesis of o-Amino Diaryl Ketones

Benzodiazepines such as **68** are important in the treatment of many diseases of the nervous system. Two C–N imine disconnections take us back to **69**, an *o*-amino benzophenone in the same class as one starting material **54** for the quinoline **52**. More generally, amino-ketones are often unstable. **Problem 39.5:** Why would we not expect **70** to exist?



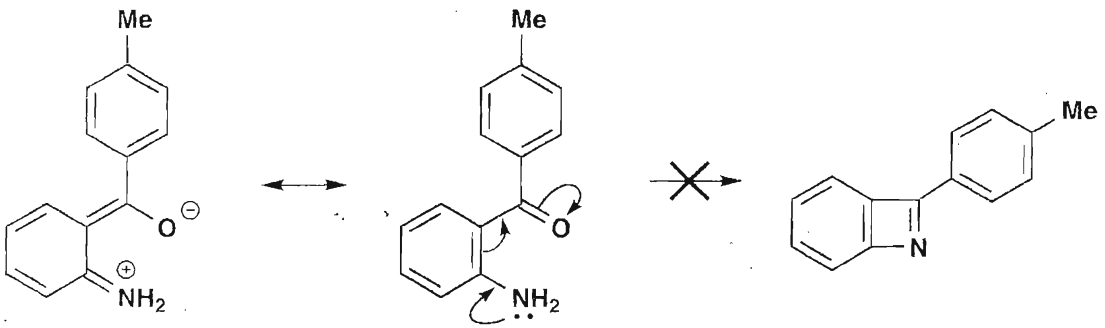
68 69 54; Ar = *p*-Tol 70

Answer 39.5: Cyclisation to the indole **72** would be very rapid. Amines are nucleophilic and ketones are electrophilic and five-membered rings are quick to form so the intermediate **71** would form and then dehydrate rapidly as the product **72** is aromatic. **Problem 39.5:** So why are aminoketones like **69** and **54** stable?



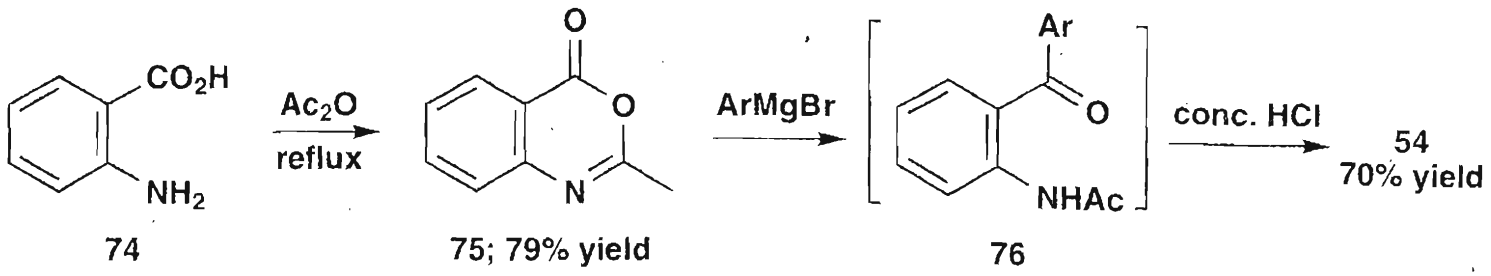
70 71 72

Answer 39.5: Two main reasons: cyclisation to give a four-membered ring **73** is slow and there is something very wrong with this particular four-membered ring. It is anti-aromatic having four π-electrons, or eight if you count all the benzene electrons. The amino ketone itself **54** is stabilised by strong conjugation **54b** between the amino and carbonyl groups.



54a 54b 73

Making ketones such as **54** is difficult but there are many methods.[12] Probably the best starts with acylation of available anthranilic acid **74** with acetic anhydride under reflux to give the new heterocycle **75** that, unlike **73**, is aromatic and has no acidic hydrogens. The aromaticity comes from two electrons from the alkene, two from the imine, two from a lone pair on oxygen but *none* from the carbonyl group as that is outside the ring. Addition of Grignard reagents to **75** gives amides **76** which can easily be hydrolysed to **54**. So here is a new heterocycle **75** in a new role: allowing a reaction to occur that would not occur on any non-heterocyclic equivalent with an acidic hydrogen such as **74**. Aromatic heterocycles can be useful intermediates in synthesis as well as target molecules in their own right.



74 75; 79% yield 76

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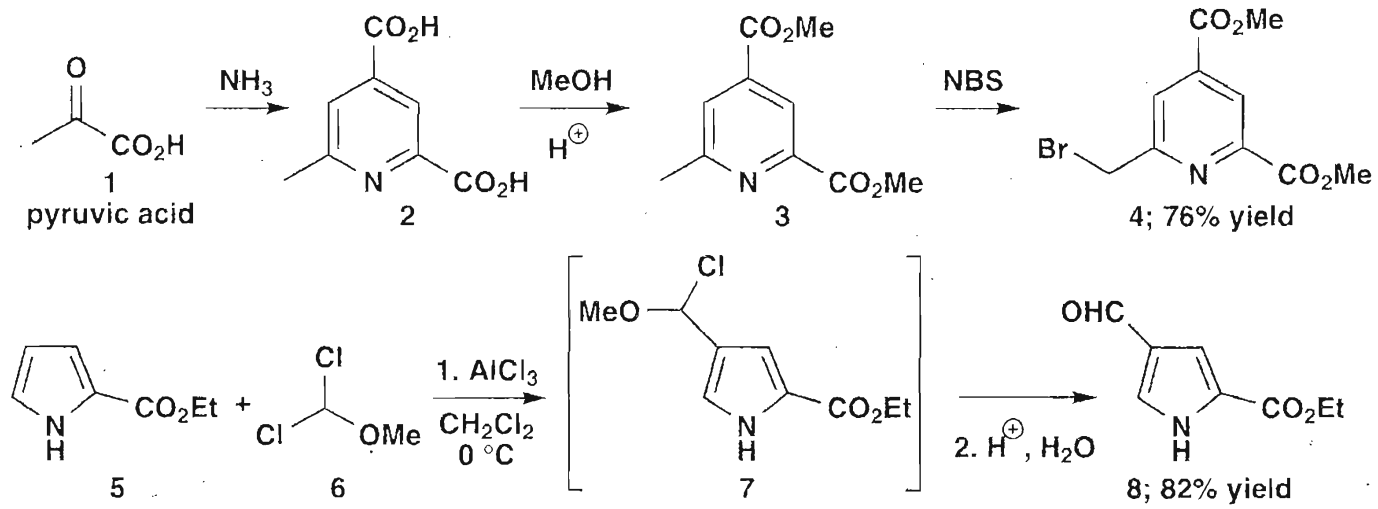
40 General Strategy D: Advanced Strategy

The Synthesis of Methoxatin

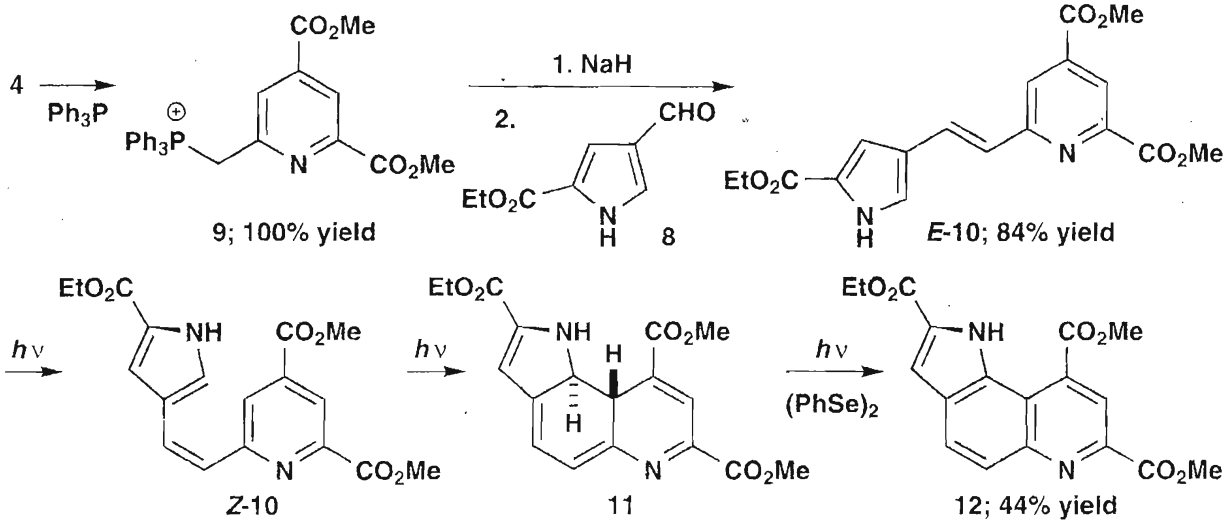
The textbook chapter featured the chemistry of methoxatin (pp. 315–319) and we start with a couple of problems on these syntheses.

Problem 40.1: The first synthesis was by Hendrickson[1] and was described as 'convergent'. Work out how many steps there are in the longest linear sequence of this synthesis. You may prefer to work from the textbook or else to set out the synthesis in full for yourself.

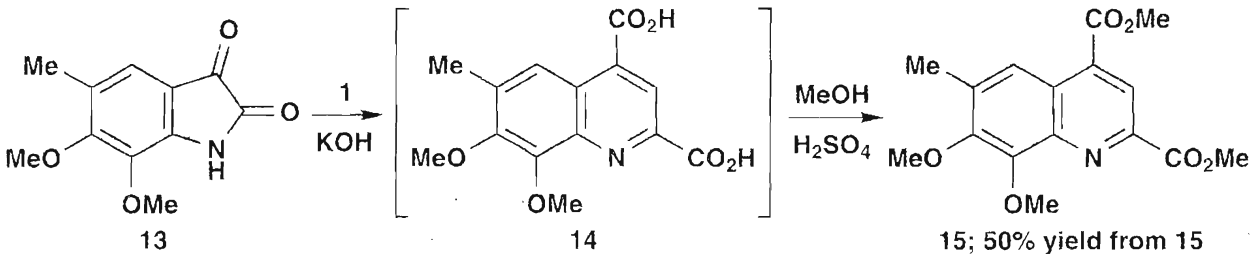
Answer 40.1: One branch involves making the pyridine **4** by a three-step sequence from pyruvic acid **1**. The second makes the pyrrole aldehyde **8** from the pyrrole carboxylic ester **5** in a two-step sequence.



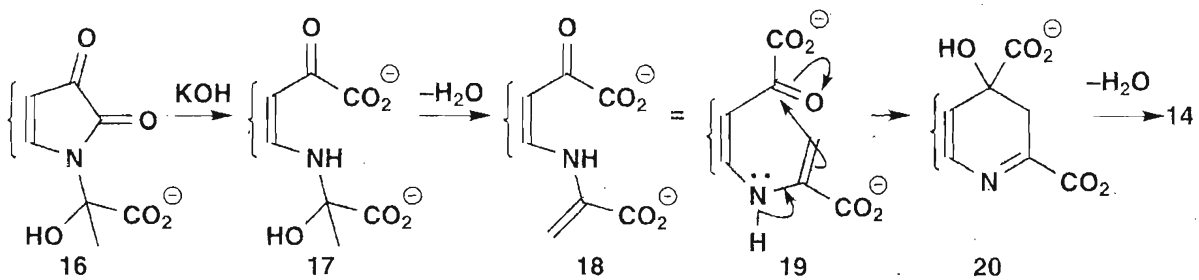
The two come together in a Wittig reaction followed by three photochemical steps. You might have decided to include making the phosphonium salt **9** in the first branch and you might decide to count the last three steps as one or two or three. In any case the longest linear sequence is the sum of the longer branch (**1** to **4**) and the combined steps (2, 3, or 4, depending how you count them). This gives a total of between five and eight steps in all – a small number for such a big synthesis.



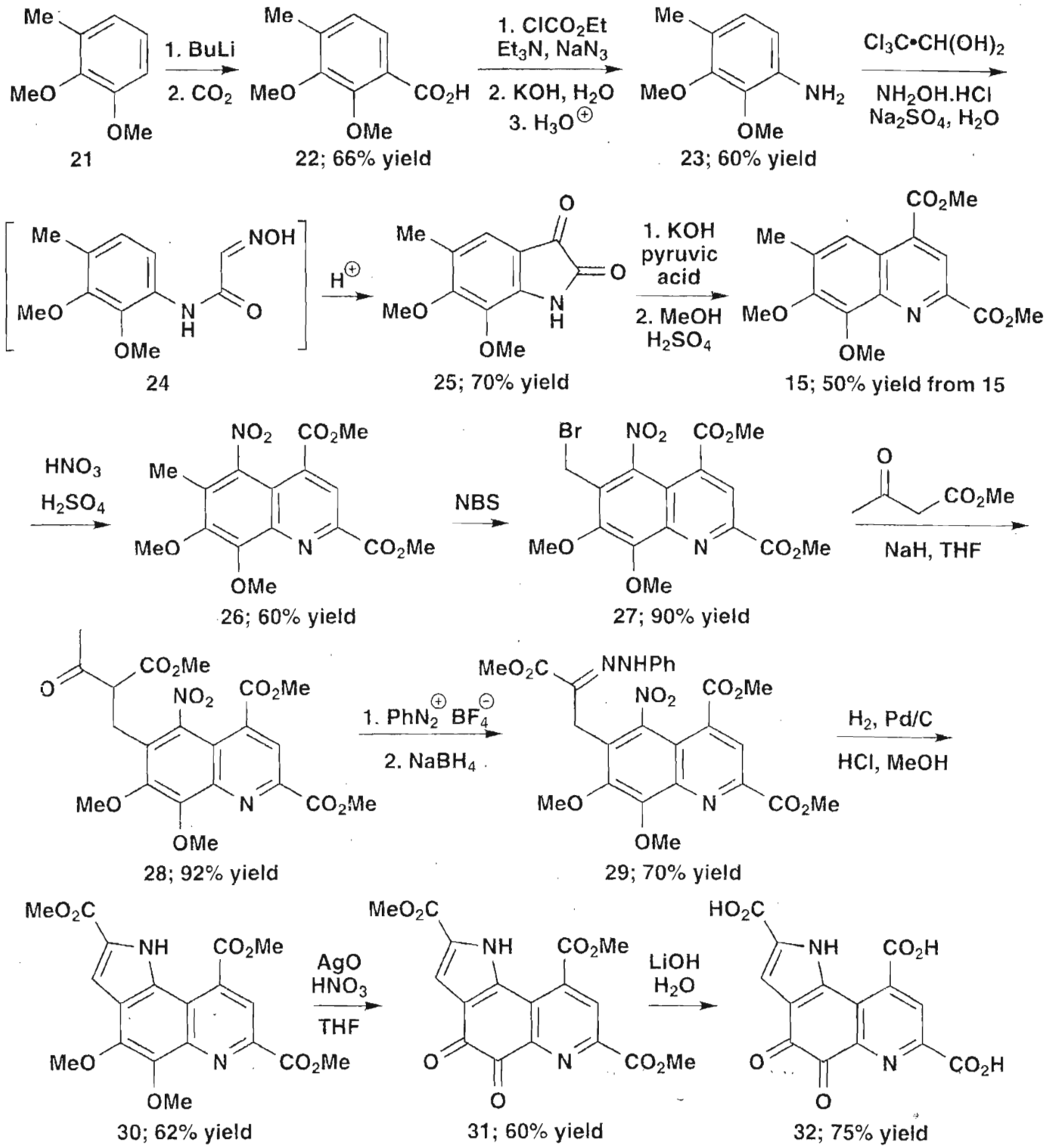
Weinreb's synthesis[2] contains a particularly interesting reaction: the conversion of the five-membered heterocycle **13** into the quinoline **15** with pyruvic acid **1** (again). **Problem 40.2:** Suggest a mechanism for this reaction.



Answer 40.2: There is no suggestion in the rather old original work[3] as to mechanism. Our suggestion is that the amide nitrogen of **13** attacks the ketone of pyruvic acid **1** to give **16**, that the imide is hydrolysed to give the enamine **18** and that this cyclises **19** to give **20** and loss of water gives **14**. You may have as good or better ideas.

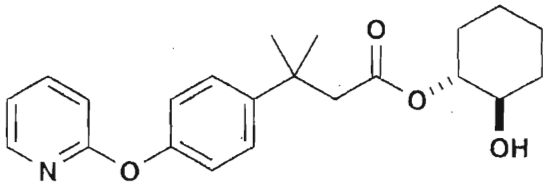


The whole of Weinreb's synthesis is laid out here from **21** to methoxatin **32**. It is of course linear. **Problem 40.3:** What is the overall yield? Before you calculate it, what do you guess it might be: 20%, 5%, 1%?



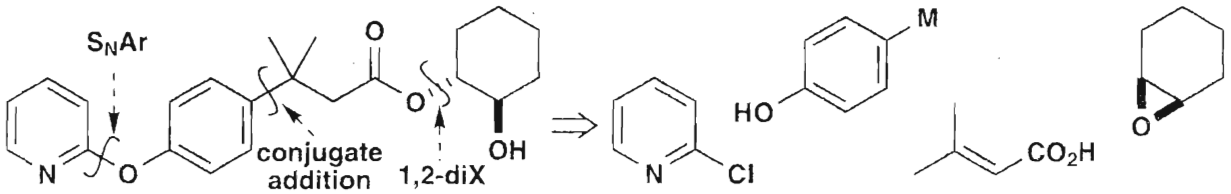
Answer 40.3: We make it 1.3%. There are 11 steps and only one has a yield as low as 50% while several have yields of 90% or over. Yet the overall yield is 1.3%. This was the first synthesis and it proved the structure of methoxatin but it also ought to convince you of the need for convergent syntheses.

Now for something a bit different. **Problem 40.4:** Which bonds would you like to disconnect in the synthesis of this molecule **33**? We confess that this is a made-up problem. Once you have chosen your starting materials decide in which order you would like to assemble them.

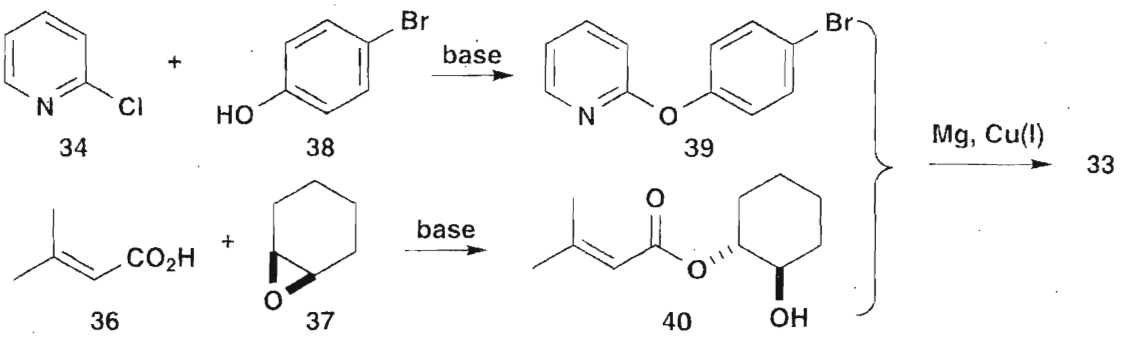


target molecule 33

Answer 40.4: The disconnections all correspond to simple reactions (if yours don't agree, that doesn't necessarily mean they're wrong). We suggest these with the metal being copper or a copper-catalysed Grignard or organo-lithium reagent.

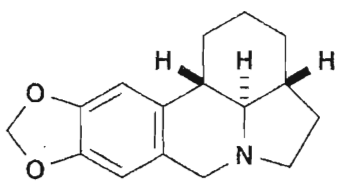


You could combine these in a linear fashion or in a convergent fashion. We hoped you'd choose the convergent, perhaps like this, via **39** and **40**. Nucleophilic substitution is possible on the pyridine **36** but not on a bromobenzene. Protection of the OH in **40** might be needed.



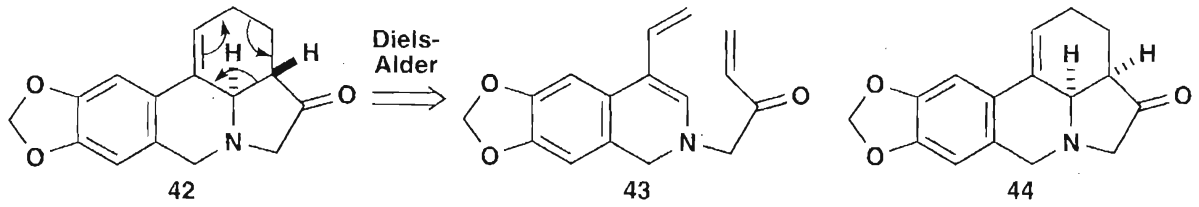
The Key Reaction Strategy: Diels-Alder Reactions

We saw a synthesis of a lycorane **41** in the textbook that had the Diels-Alder reaction as the key step. Stork's synthesis[4] also uses the Diels-Alder reaction but in a completely different way. Stork did no preliminary disconnections but simply inserted one alkene and one carbonyl group into the structure to make a Diels-Alder disconnection ideal. **Problem 40.5:** Can you suggest where to put the alkene and the carbonyl group?

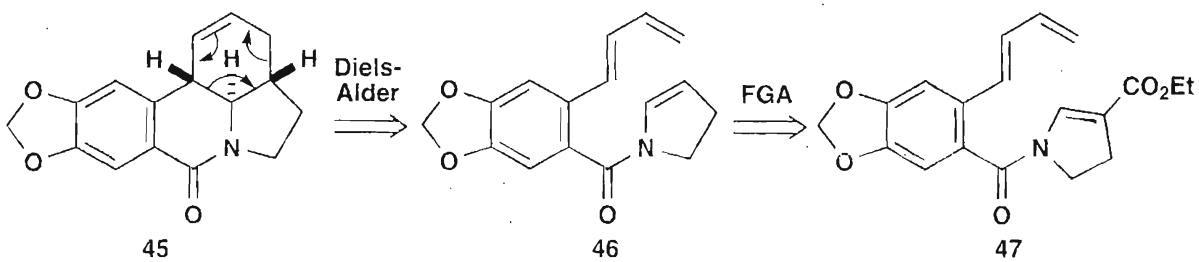


β-lycorane 41

Answer 40.5: There are several possibilities such as **42** that puts the carbonyl group where it is conjugated with the dienophile **43**. Stork rejected these as they would lead, most likely, to the *endo*-adduct **44** that would have a *cis* ring junction. Adduct **42** is the *exo*-adduct.

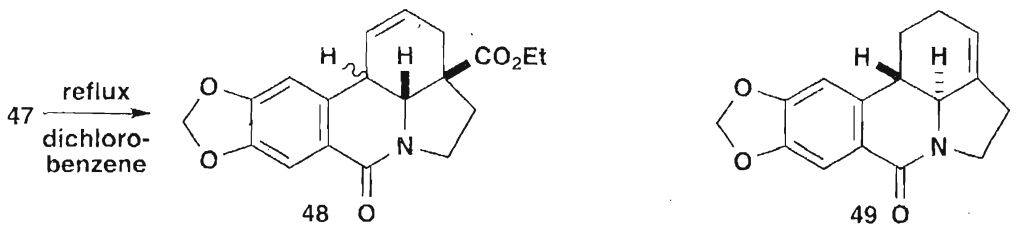


As it happened, Stork had already tried[5] the Diels-Alder reaction following from disconnection **45**. The Diels-Alder was enhanced by a second carbonyl group **47**. There is a problem with **46**: the stereochemistry of the dienophile is inevitably *cis* in a five-membered ring but those hydrogen atoms in **45** must be *trans*. Adding a CO_2Et group also gave an opportunity to avoid that problem.

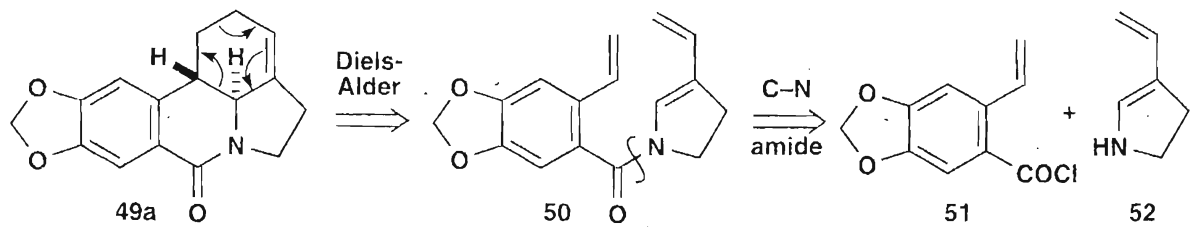


Though the Diels-Alder went in good yield (84%), it gave a roughly 1:1 mixture of epimers of **48**, neither having the stereochemistry required for lycorane. Stork's ultimate choice was **49**.

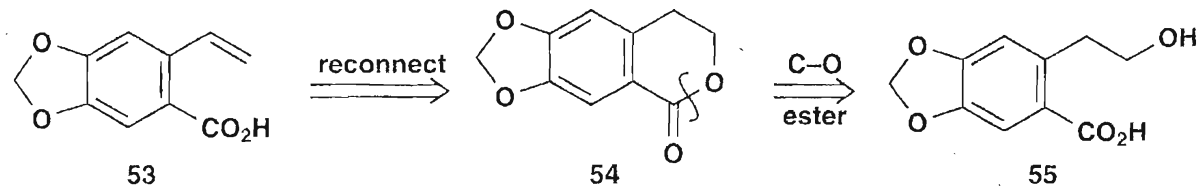
Problem 40.6: Continue the analysis.



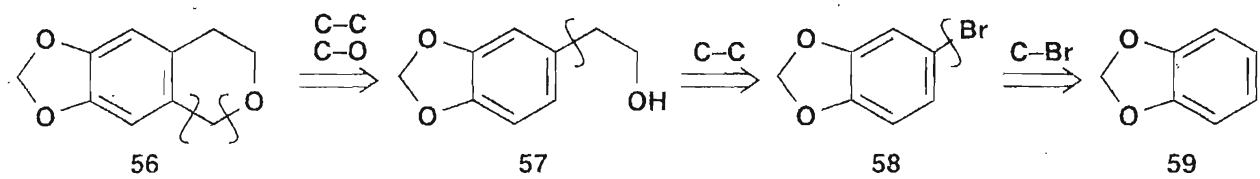
Answer 40.6: Reversing the Diels-Alder **49a** gives us the amide **50** which is simply disconnected to some acid derivative **51** and the enamine **52**. Now they have to be made: any suggestions?



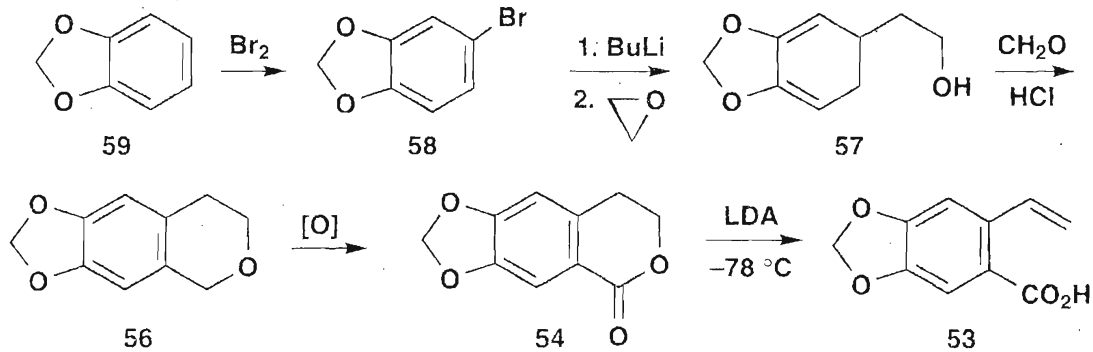
These days we should probably make the acid **53** by a palladium-catalysed coupling of an aromatic acid derivative with a vinyl halide.[6] But Stork reconnected the two side chains as the lactone **54** obviously derived from **55**. This now becomes an exercise in regioselectivity such as those in chapter 2.



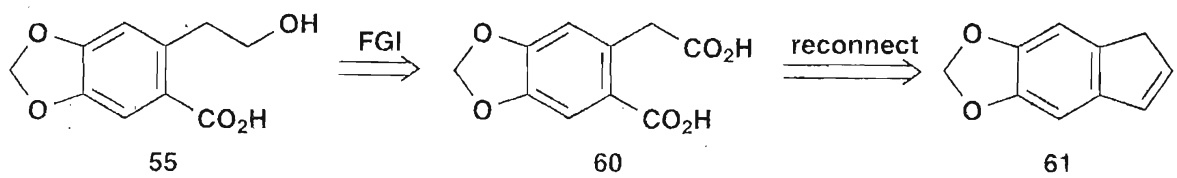
Either **54** or **55** could be derived from **56** that could come from a Prins-style capture of the alcohol **57** with formaldehyde. And **57** could be made by addition of ethylene oxide to a Mg or Li derivative of **58**, derived in turn from bromination of available **59**.



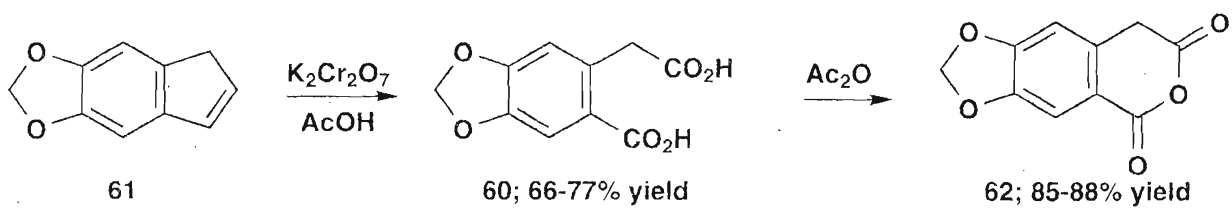
The synthesis would then follow this pattern with regioselective bromination of reactive **59** in the *para* position, lithiation by Li/Br exchange and reaction with ethylene oxide, Prins-style ring closure to the cyclic ether **56**, oxidation to the lactone **54** and elimination to **53**.



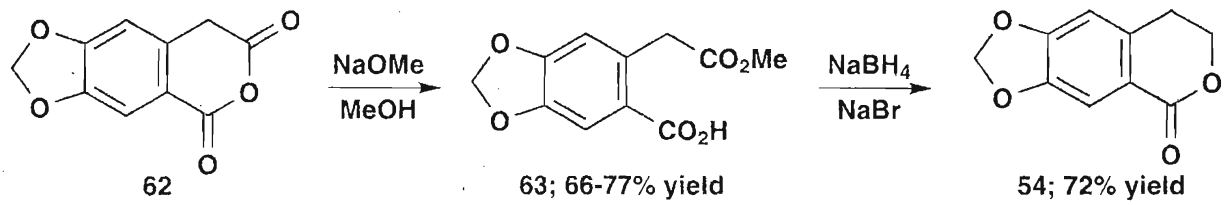
No doubt this would all work but Stork preferred a shorter route that depended on the ready availability of the indene **61**. A more conventional reconnection (chapters 26 and 27) of the diacid **60** takes us back to **61**.



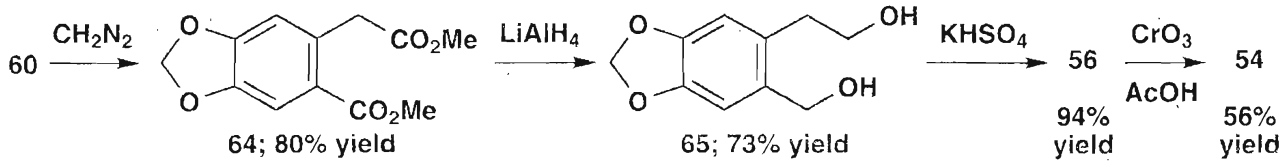
The synthesis was based on previous work[7] in which the anhydride **62** was the key intermediate that allowed regioselectivity between the two carbonyl groups.



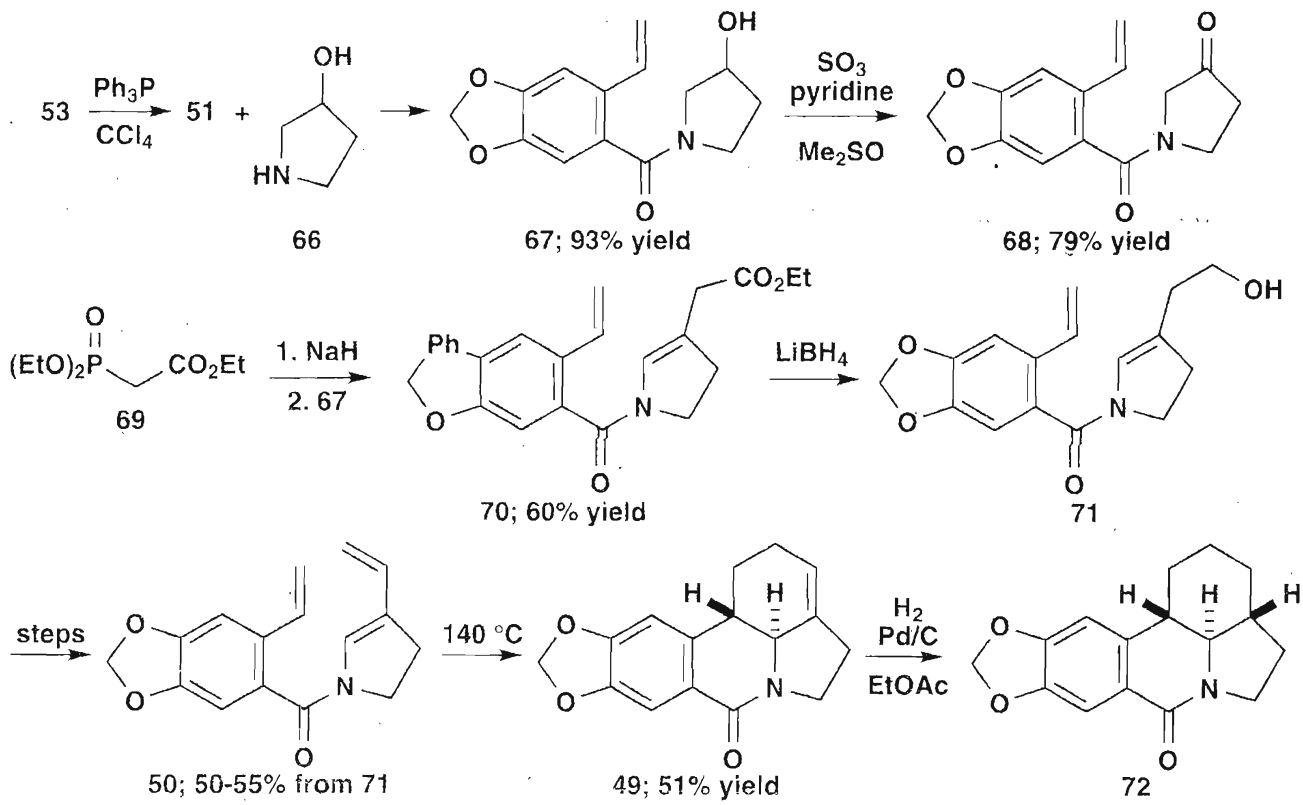
The shortest way to the lactone **54** is to open the anhydride with acidic methanol.[8] Reaction occurs selectively at the carbonyl group not conjugated to the aromatic ring. Reduction with $NaBH_4$ activated with NaBr gives the lactone **54** on acidic work-up.[9]



An alternative[10] is to reduce the diester **64** to the diol **65**, cyclise it in acid to the benzopyran **56** and oxidise that with Cr(VI) to the lactone **54**. Elimination with LDA, as suggested above, gave the acid **53** in over 90% yield. You will notice that some steps are the same as those we suggested in the first synthesis.



We have one starting material. Now what about the other, the vinyl pyrroline **52**? In fact this part of **50** was developed after a simple coupling of the acid chloride **51** with available 3-pyrollidinol **66**. Oxidation, Horner-Wadsworth-Emmons olefination and reduction gave the alcohol **71** as the alkene in **70** has migrated to the thermodynamically more stable enamine. Then some selenium chemistry[11] gives **50** which does indeed do the Diels-Alder reaction to give the right diastereoisomer of **49**. Catalytic hydrogenation gives **72**. This amide had been made from lycorane and had already been converted into lycorane giving a formal synthesis of lycorane.



This last example gives you an idea of the variations in strategy both found and needed in the planning of a synthesis of a reasonably complex molecule. We remind you that another synthesis was given in the textbook to emphasise that there is no 'right' answer to a synthesis problem.

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Index