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On the Synthesis of Protopine Alkaloids

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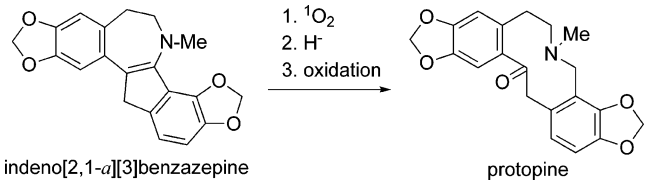
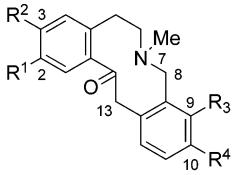


For the synthesis of protopine alkaloids, we studied a reaction sequence based on a ring enlargement of indeno[2,1-*a*][3]benzazepines by a singlet oxygen oxygenation, followed by conversion of an amide carbonyl group of the resultant 10-membered keto-lactam to a methylene group, which is the last step for completion of the synthesis. The key substances, indeno[2,1-*a*][3]benzazepines, were prepared by Bischler−Napieralski cyclization of alkoxy-substituted 1-(2-bromobenzyl)-3-benzazepin-2-ones. Steric effects of the substituents in this synthesis were examined.

Introduction

Protopine and related alkaloids, which have the unique structural feature of a nitrogen-containing 10-membered cyclic ketone (dibenzazocine ring), are widely distributed in the families Berberidaceae, Fumariaceae, Papaveraceae, Ranunculaceae, and Rutaceae[1] and have been reviewed as a group of isoquinoline alkaloids.[2] The major protopine alkaloids (**1**) have four alkoxyl groups at the 2, 3, 9, and 10 positions. The 1-, 11-, or 12-alkoxyl group has been found in the minor components.[1d] It was shown in 1978−1981 that allocryptopine and protopine exhibited an antiarrhythmic effect[3] and that protopine has antibacterial[4] and antianalgesic[5] activities. More recently, other notable pharmacological properties of the alkaloids, including activities for inhibition of rabbit blood platelet aggregation[6] and calcium influx through both voltage- and receptor-operated calcium channels,[7] anti-cholinergic,[8] antihistaminic,[8] anti-thrombotic,[6b,9] anti-inflammatory,[9] and anti-hemeostatic activities,[6b] as well as activities against hepatotoxicity induced by actoaminophen and CCl_4,[10] have been found.



1a, muramine $R^1=R^2=R^3=R^4=OMe$
1b, cryptopine $R^1=R^2=OMe$, $R^3+R^4=OCH_2O$
1c, allocryptopine $R^1+R^2=OCH_2O$, $R^3=R^4=OMe$
1d, protopine $R^1+R^2=R^3+R^4=OCH_2O$

Synthesis of protopine alkaloids has been achieved by the transformation of protoberberine alkaloids based on a ring-

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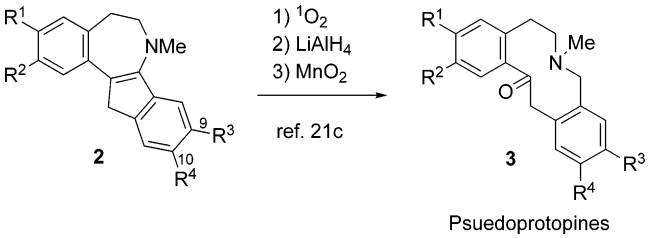
opening reaction by Hofmann degradation of their *N*-methochlorides (Perkin's method)[11] leading to the formation of muramine (**1a**), allocryptopine (**1c**), and protopine (**1d**), K_2CrO_4 oxidation of the *N*-oxide (Bentley's method)[12] to **1a**,**b**,**c**, photooxidation of tetrahydroberberine methiodide (Hanaoka's method)[13] to **1c**, or von Brown reaction to **1a** (Rönsch's method).[14] Brossi reported another transformation of phthalideisoquinoline alkaloids, *β*-hydrastine and α-narcotine, via Perkin-type Hofmann degradation of the derived isoindolo[1,2-*b*][3]benzazepine methiodides to **1c**.[15] 13-Oxoprotopine or 13-oxoallocryptopine has been prepared by oxidative methods with air or $Hg(OAc)_2$.[16−18] Pseudoallocryptopine and pseudoprotopine have also been prepared from the corresponding tetrahydroprotoberberine *N*-metho salts.[11d,g] Biotransformation of *N*-metho salts of tetrahydroprotoberberine alkaloids to protopine, 13-oxoallocryptopine, or 13-methylallocryptopine by Corydarlis species callus cultures has been achieved by Tani[19] and Takao.[20] We developed a ring-enlargement reaction based on $^1O_2$ oxygenation of indeno[2,1-*a*][3]benzazepines **2** followed by further elaboration of the resultant 10-membered keto-lactams, which successfully produced pseudo-type protopines **3** (Scheme 1).[21] We herein describe an application of the method to the synthesis of the above-mentioned representative protopine alkaloids muramine (**1a**) and protopine (**1d**).

SCHEME 1. Ring Enlargement Based on $^1O_2$ Oxygenation



Results and Discussion

The method requires an indeno[2,1-*a*][3]benzazepine with alkoxyl groups at its 2-, 3-, 8-, and 9-positions, such as **4**. First, radical cyclization of 1-(2-bromobenzyl)-4,5-dihydrobenzazepine **8** to **4d** was tested under the reaction conditions used for a 5-endo cyclization of 1-(2-bromobenzyl)-3,4-dihydroisoquinolines to dibenz[*b*,*d*]indolizidines.[22]

As shown in Scheme 2, 3-benzazepin-2-one **5b**[23] was treated with benzyl chloride **6**[24] (1.1 equiv) in the presence of NaH (2 equiv) in a boiling 10:1 THF−DMF mixture for 5 h to give 2-benzyl-3-benzazepine **7** in 64% yield. This was converted by DIBALH reduction to **8** (53%), which was subjected to radical cyclization with AIBN and Bu_3SnH in boiling benzene, toluene, or *o*-xylene. However, none of the desired **4d** was obtained, but **9** was formed at 160 °C in 50% isolated yield. The structure of **9** was determined by the fact that a radical coupling of **7** followed by DIBALH reduction of the product **10** also gave **9** and the fact that irradiation of the *N*-Me group of **9** resulted in significant NOE on C-7 hydrogen, as depicted in Scheme 2. Attempts to obtain **4d** through Heck cyclization of **8** were unsuccessful.

It has been reported that 3-(2-bromophenyl)propanoic acid **11** was cyclized in PPA to an indanone **12** in 72−75% yield (Scheme 3).[25] The corresponding propanoic acid derivative **15** was prepared by a modification of the method reported by us[21c,26] that involves condensation of the corresponding benzonitrile with benzaldehyde followed by reduction of a double bond of **13** with $NaBH_4$-pyridine[27] and hydrolysis of the CN group of **14**, and it was subjected to cyclization using PPA at 80 °C for 1 h to afford 1-indanone **16** in 12% yield. Its transformation to 11-bromoindeno[2,1-*a*][3]benzazepine **17a**, which is equivalent to **4a**, by hydrolysis under basic conditions[24] as well as acidic conditions,[28] failed. In addition, treatment of propionitrile **14** with BuLi did not produce any indanones. Thus, the attempt to establish a route via 1-indanone[21c] was abandoned.

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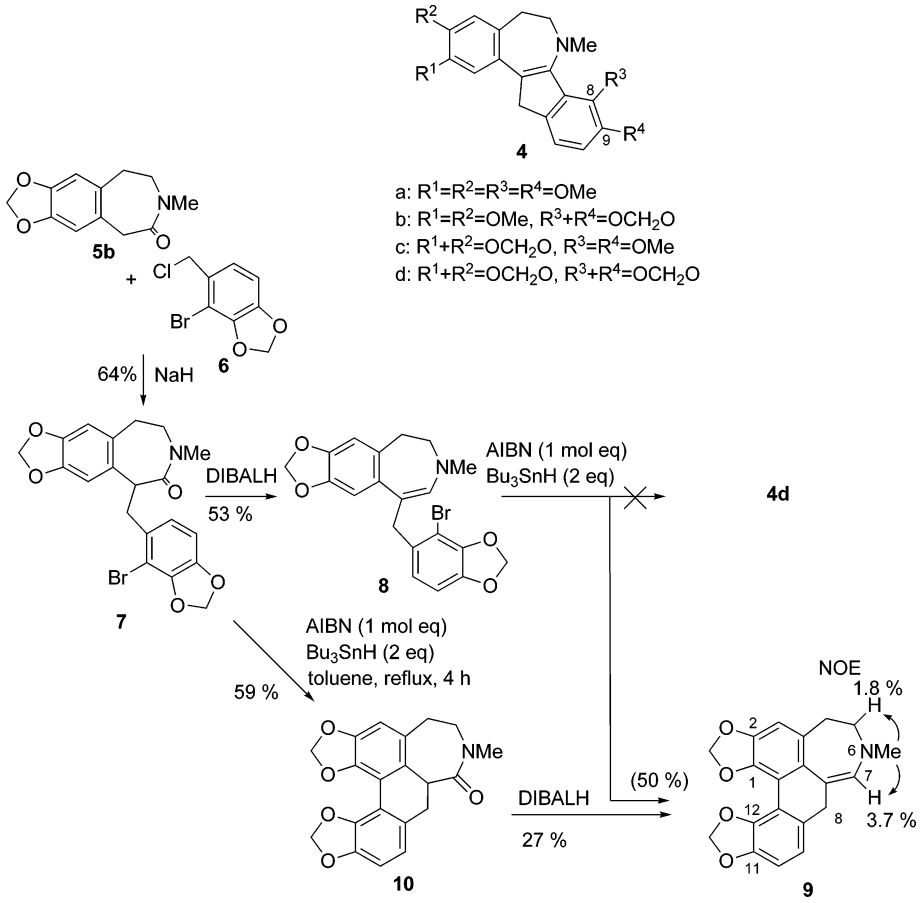
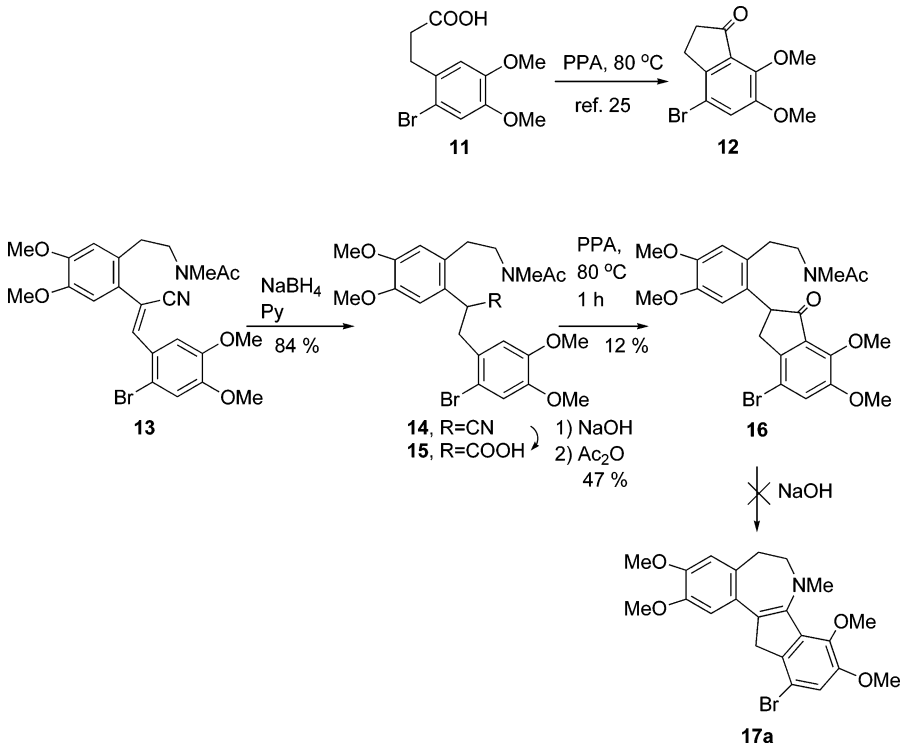
SCHEME 2. Attempt To Prepare 4d

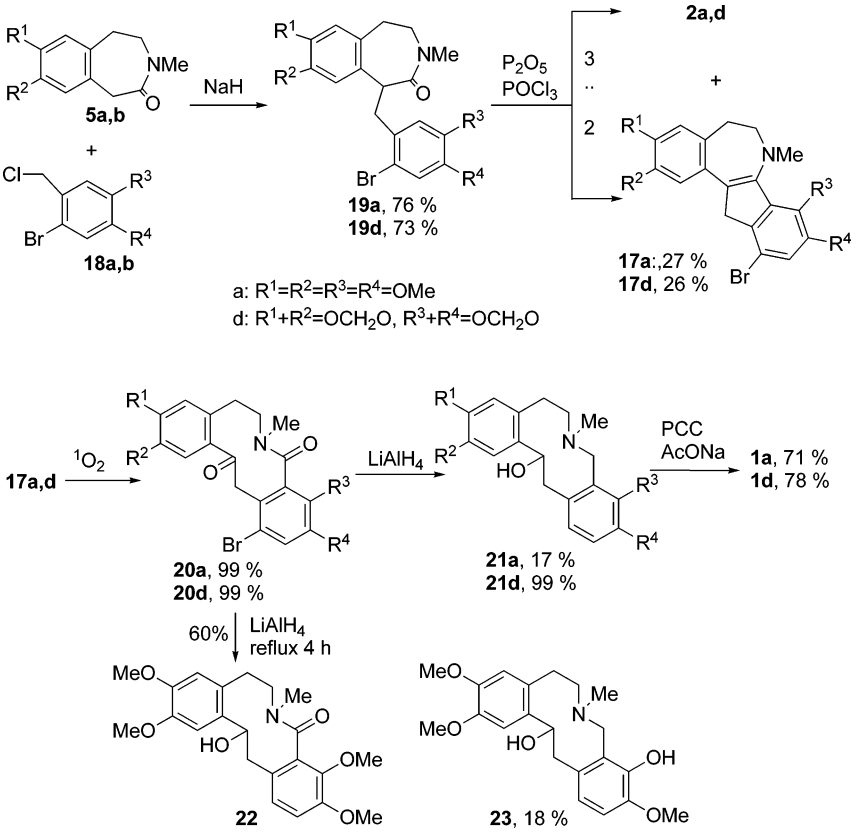


SCHEME 3. Attempt To Prepare 17a



We have reported that a standard Bischler−Napieralski cyclization proceeded well to give indeno[2,1-*a*][3]benzazepines **2** in good yields.[24] Similar treatment of **19a**,**d**, which were prepared from 3-benzazepin-2-ones and benzyl chlorides (**5a** and **18a**, or **5b** and **18b**), with $POCl_3$ or P_2O_5 in boiling toluene, did not induce their cyclization. Banwell's modification using

SCHEME 4. Synthesis of Protopine (1d) and Muramine (1a)



Tf_2O together with 4-DMAP[28] did not work. Wang's modification (P_2O_5 in boiling $POCl_3$)[29] consumed **19a**,**d** after 2 h to give the desired **17a**,**d** together with the respective debromo isomers **2a**,**d**[21b] in a 2:3 ratio. Separation by column chromatography on alumina gave pure **17a**,**d**, but only in 27% and 26% yields (Scheme 4).

Nevertheless, the photo-oxygenation ($^1O_2$ with Rose Bengal in MeOH−CH_2Cl_2) of the formed indenoazepines **17a**,**d** was tested and found to proceed smoothly to give 12-bromo-8-oxomuramine, **20a**, and 12-bromo-8-oxoprotopine, **20d**, both quantitatively. The latter, methylenedioxy-substituted lactam, was quantitatively converted by treatment with $LiAlH_4$ (10 mol equiv) in boiling THF for 15 h to dihydroprotopine[30] (**21d**), PCC oxidation of which afforded protopine[31] (**1d**) in 78% yield. In contrast, treatment of the former, 9,10-dimethoxy-substituted lactam (**20a**), with $LiAlH_4$ (10 mol equiv) in boiling THF for 4 h gave no muraminol (**21a**), but gave 8-oxomuraminol (**22**) in 60% yield. Longer treatment in boiling DME (20 h) afforded muraminol[14] (**21a**) together with 9-hydroxymuraminol (**23**). These results may be accounted for by the steric hindrance caused with *N*-Me and vicinal dimethoxy groups rather than electronic reasons.[32] PCC oxidation of **21a** produced muramine[14] (**1a**) in a good yield similar to that of protopine (**1d**), although a larger amount of muraminol was not obtained by either reduction of 8-oxomuraminol (**22**) with BH_3•THF or methylation of a phenolic OH of **23** with Me_2SO_4−KOH or Na_2CO_3.

Thus, it was found that protopine (**1d**) was readily synthesized in a reaction sequence involving a ring-enlargement of bromide **17d** (an equivalent for indeno[2,1-*a*][3]benzazepine **4d**) by a singlet oxygen oxygenation, but a more efficient method is necessary for reduction of a sterically hindered amide group with a 7,8-dimethoxy group to a methylene group. A 7,8-methylenedioxyindeno[2,1-*a*][3]benzazepine, bulgaramine (**4b**), was recently found in nature,[33] and its short-step synthesis via cyclopentannulation of Fisher aminocarbene complexes was reported by Moser's group.[34] This will be a solution to a practical method for preparation of indeno[2,1-*a*][3]benzazepines.

Experimental Section

1-[2-Bromo-4,5-(methylenedioxy)benzyl]-7,8-(methylenedioxy)-3-methyl-1,2,4,5-tetrahydro-3*H*-3-benzazepin-2-one (19d). To a stirred suspension of **5b**, mp 170−171 °C (EtOH) (lit.[23] mp 167−168 °C) (3.29 g, 15.0 mmol), and NaH (0.72 g, 30.0 mmol) in dry DMF and THF (1:10 volume %, 80 mL) under N_2 was added 2-bromo-4,5-methylenedioxybenzyl chloride [**18b**, 4.12 g, 16.5 mmol, freshly prepared from the corresponding 2-bromobenzyl alcohol with $SOCl_2$, mp 62−63 °C (petroleum ether) (lit.[35] mp 64−65 °C)]. The mixture was heated at 80 °C in an oil bath for 5 h, poured into water (300 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with water (5 × 100

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mL), dried (Na_2SO_4), and concentrated. The residue was crystallized from CH_2Cl_2−EtOH to give **19d**, mp 218−219 °C (CH_2Cl_2−EtOH), as colorless crystals (4.94 g, 76%): IR (Nujol) 1627 cm^{-1}; ^1H NMR δ 2.90 (s, 3H), 2.93−3.04 (m, 1H), 3.16 (dd, J = 4.3, 13.5 Hz, 1H), 3.21−3.41 (m, 2H), 3.53 (dd, J = 9.6, 13.5 Hz, 1H), 3.84−3.94 (m, 1H), 4.43 (dd, J = 4.3, 9.6 Hz, 1H) 5.91, 5.92 (each s, each 1H), 5.93 (s, 2H), 6.62, 6.74, 6.97, 6.99 (each s, each 1H); EI-MS *m*/*z* (relative intensity) 433 (M^+, 0.40), 431 (M^+, 0.34), 352 [$(M - Br)^+$, 100], 215 (17), 213 (18), 190 (71). Anal. Calcd for $C_{20}H_{18}BrO_5N$: C, 55.57; H, 4.20; Br, 18.48; N, 3.24. Found: C, 55.37; H, 4.31; Br, 18.72; N, 3.28.

11-Bromo-2,3,8,9-bis(methylenedioxy)-5,6,7,12-tetrahydroindeno[2,1-*a*][3]benzazepine (17d). To a stirred solution of 3-benzazepin-2-one **19d** (2.17 g, 5.0 mmol) in $POCl_3$ (7.5 mL) was added P_2O_5 (1.70 g, 12 mmol). The mixture was refluxed for 2 h, cooled, basified with a 2 N NaOH solution (100 mL) containing ice (15 g), and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with a 2 N NaOH solution (50 mL) and water (50 mL) and dried (Na_2SO_4). The solvent was evaporated to give a 3:2 mixture of **17d** and **2d** (1.83 g), which was subjected to column chromatography with Al_2O_3 using 20% hexane−CH_2Cl_2 as eluent to give **17d**, mp 255−257 °C (CH_2Cl_2−EtOH), as pale yellow crystals [560 mg, 27%, R_f 0.85 (5% MeOH−CH_2Cl_2)]: IR (Nujol) 1623, 1558 cm^{-1}; ^1H NMR δ 2.89 (s, 3H), 2.95 (distorted t, J = 4.3 Hz, 2H), 3.20 (distorted t, J = 4.3 Hz, 2H), 3.69 (s, 2H), 5.96, 6.05 (each s, each 2H), 6.69, 6.87, 7.08 (each s, each 1H); EI-MS *m*/*z* (relative intensity) 415 (M^+, 99), 413 (M^+, 100), 400 (41), 398 (42), 372 (17), 370 (18), 334 (20), 261 (25). Anal. Calcd for $C_{20}H_{16}BrNO_4$: C, 57.99; H, 3.89; Br, 19.29; N, 3.38. Found: C, 58.03; H, 3.96; Br, 19.12; N, 3.36. A less mobile fraction with R_f 0.7 gave **2d**, mp 150−151 °C (95% EtOH) (lit.[21b] 150−151 °C), as colorless crystals (200 mg, 12%).

12-Bromo-5,6,7,8,13,14-hexahydro-7-methyl-2,3,9,10-bis(methylenedioxy)dibenz[*c*,*g*]azecine-8,14-dione (20d). A solution of **17d** (560 mg, 1.35 mmol) and Rose Bengal (11 mg) in MeOH (150 mL) and CH_2Cl_2 (90 mL), contained in a Pyrex test tube (diameter; 40 mm × length; 360 mm) equipped with a sintered glass bubbler, was cooled with a stream of cold water from the side of the test tube. O_2 gas was introduced through the bubbler, and the mixture was irradiated with a 500 W tungsten lamp at 18 °C for 20 min. The solvents were evaporated, and the residue was dissolved in CH_2Cl_2 (30 mL), washed with water (5 × 30 mL), and dried over Na_2SO_4. The solvent was evaporated to give a residue (796 mg), which was purified by preparative TLC with silica gel developed with 3% MeOH−CH_2Cl_2. A main band with R_f 0.5 gave **20d**, mp >200 °C dec (EtOAc), as colorless crystals (596 mg, 99%): IR (Nujol) 1683, 1644, 1627, 1616 cm^{-1}; ^1H NMR two rotamers (1:2.4) δ 2.63−2.79 (m, 1H), 2.71, 2.97 (two s, 3H, 1:2.4), 3.37−3.44 (m, 3H), 4.00, 4.32 (two d, J = 15.8 Hz, 1H, 2.4:1), 4.46, 4.55 (two d, J = 15.8 Hz, 1H, 1:2.4), 5.92−6.05 (m, 4H), 6.50, 6.70 (two s, 1H, 2.4:1), 6.96 (s, 1H), 7.05, 7.07 (two s, 1H, 2.4:1); EI-MS *m*/*z* (relative intensity) 447 (M^+, 11), 445 (M^+, 12), 404 [$(M - Ac)^+$, 10], 402 [$(M - Ac)^+$, 13], 242 (98), 240 (100), 214 (44), 212 (45). Anal. Calcd for $C_{20}H_{16}BrNO_6$: C, 53.83; H, 3.61; Br, 17.91; N, 3.14. Found: C, 53.87; H, 3.60; Br, 17.83; N, 3.13.

Dihydroprotopine (21d). To a stirred mixture of $LiAlH_4$ (200 mg, 5.27 mmol) in dry THF (10 mL) at rt was added dropwise a solution of **22d** (224 m0, 0.5 mmol) in dry THF (15 mL). After the mixture was refluxed for 15 h, water (1 mL), a 2 N NaOH solution (2 mL), and water (3 mL) were added dropwise to quench $LiAlH_4$. The resulting mixture was filtered, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (30 mL), washed with water (30 mL) containing Rochelle salt (3 g), water (30 mL), and brine (30 mL) and dried (Na_2SO_4). The CH_2Cl_2 layer was concentrated to give a residue (223 mg) which was purified by preparative TLC with silica gel developed with 5% MeOH−CH_2Cl_2. A main band with R_f 0.4−0.8) gave **21d**, mp 149−151 °C (Et_2O−hexane) (lit.[30] mp 147−148 °C), as colorless crystals (177 mg, 99%), whose spectral data were identical with those previously reported.[30]

Protopine 1d. A mixture of dihydroprotopine (**21d**) (71 mg, 0.2 mmol), PCC (89 mg, 0.4 mmol), and NaOAc (8 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 2 h. A 1 N HCl solution (3 mL) and EtOH (1 mL) were added dropwise, and the mixture was stirred at rt for 15 min, basified by addition of a diluted NH_4OH solution, and extracted with CH_2Cl_2 (3 × 10 mL) after addition of Rochelle salt (2 g). The organic layers were washed with water (3 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC with alumina developed with 1% MeOH−CH_2Cl_2. A main band with R_f 0.4−0.8 gave protopine (**1d**), mp 205−206 °C (MeOH) [lit.[31] mp 207−208 °C], as colorless crystals (55 mg, 78%), whose spectral data were identical with those previously reported.[31]

1-(2-Bromo-4,5-dimethoxybenzyl)-7,8-dimethoxy-3-methyl-1,2,4,5-tetrahydro-3*H*-3-benzazepin-2-one (19a). Similarly, **5a**, mp 138−140 °C (EtOH) (lit.[23] 137−138 °C) (2.36 g, 10.0 mmol), NaH (0.48 g, 20.0 mmol), and 2-bromo-4,5-dimethoxybenzyl chloride [**18a**, 2.79 g, 10.5 mmol], mp 63−65 °C (Et_2O−hexane) (lit.[36] mp 60−61 °C), gave a residue (5.02 g), which was crystallized from CH_2Cl_2−EtOH to give **19a**, mp 183−185 °C (CH_2Cl_2−EtOH), as colorless crystals (3.40 g, 73%): IR (Nujol) 1639 cm^{-1}; ^1H NMR δ 2.95 (s, 3H), 3.01−3.58 (m, 5H), 3.79, 3.84, 3.84, 3.85 (each s, each 3H), 3.79−3.95 (m, 1H), 4.44 (dd, J = 3.6, 5.6 Hz, 1H), 6.59, 6.61, 6.97, 7.00 (each s, each 1H); EI-MS *m*/*z* (relative intensity) 465 (M^+, 0.9), 463 (M^+, 1.0), 384 [$(MH - Br)^+$, 94], 229 (32), 206 (100). Anal. Calcd for $C_{22}H_{26}BrNO_5$: C, 56.90; H, 5.64; Br, 17.21; N, 3.02. Found: C, 57.03; H, 5.63; Br, 17.06; N, 3.05.

11-Bromo-2,3,8,9-tetramethoxy-5,6,7,12-tetrahydroindeno-[2,1-*a*][3]benzazepine (17a). 3-Benzazepin-2-one **(19a**, 0.93 g, 2.0 mmol) was treated with P_2O_5 (0.60 g, 4.2 mmol) in boiling $POCl_3$ (3 mL) for 2 h. The crude product (0.82 g, a 3:2 mixture of **17a** and **2a**) was subjected to column chromatography with alumina using 30% hexane−CH_2Cl_2 as eluent to give **17a**, mp 169.5−171.5 °C (EtOH), as pale yellow crystals [230 mg, 26%, R_f 0.85 (5% MeOH−CH_2Cl_2)]: IR (Nujol) 1601, 1583, 1572, 1552 cm^{-1}; ^1H NMR δ 3.04 (s, 3H), 3.02 (distorted t, J = 4.3 Hz, 2 H), 3.18 (distorted t, J = 4.3 Hz, 2 H), 3.69 (s, 2H), 3.86, 3.89, 3.91, 3.97 (each s, each 3H), 6.73, 6.92, 7.09 (each s, each 1H); EI-MS *m*/*z* (relative intensity) 447 (M^+, 99.9), 445 (M^+, 100), 432 [$(M - CH_3)^+$, 47.0], 430 [$(M - CH_3)^+$, 47.2], 389 (10.0), 387 (11.0). Anal. Calcd for $C_{22}H_{24}BrNO_4$: C, 59.20; H, 5.42; Br, 17.90; N, 3.14. Found: C, 59.14; H, 5.27; Br, 17.86; N, 3.16. A less mobile fraction with R_f 0.65 gave **2a**, mp 182−183 °C (EtOH) (lit.[21b] mp 182−183 °C), as colorless crystals (110 mg, 15%).

12-Bromo-7-methyl-2,3,9,10-tetramethoxy-5,6,7,8,13,14-hexahydrodibenz[*c*,*g*]azecine-8,14-dione (20a). A mixture of **17a** (280 mg, 0.63 mmol) and Rose Bengal (6 mg) in MeOH (70 mL) and CH_2Cl_2 (10 mL) was oxygenated at 18 °C for 15 min. The residue (327 mg) was subjected to column chromatography on silica gel (3% MeOH−CH_2Cl_3) to afford **20a** [297 mg, 99%, R_f 0.2−0.4 (3% MeOH−CH_2Cl_2)], as a mixture of two rotamers (5:1): IR (Nujol) 1687, 1630 cm^{-1}; ^1H NMR δ 2.43−2.46, 2.79−2.93 (two m, 1H, 5:1), 2.63, 3.02 (two s, 3H, 1:5), 3.31−3.47 (m, 3H), 3.76, 3.80, 3.81, 3.88, 3.91, 3.93, 3.97 (seven s, 12H, 5:5:6:1:1:1:5), 3.97, 4.34 (two d, J = 15.8 Hz, 1H, 5:1), 4.48, 4.58 (two d, J = 15.8 Hz, 1H, 5:1), 6.43, 6.70 (two s, 1H, 5:1), 6.96 (s, 1H), 7.06, 7.13 (two s, 1H, 5:1); EI-MS *m*/*z* (relative intensity) 479 (M^+, 6.1), 477 (M^+, 6.1), 436 [$(M - Ac)^+$, 9.3], 434 [$(M - Ac)^+$, 9.5], 258 (98.5), 256 (100). Anal. Calcd for $C_{22}H_{24}BrNO_6$: C, 55.24; H, 5.06; Br, 16.70; N, 2.93. Found: C, 55.11; H, 5.07; Br, 16.51; N, 2.76. Recrystallization from EtOAc−hexane gave a main rotamer, mp 175−176 °C (EtOAc−hexane), as colorless crystals (234 mg, 78%).

7-Methyl-2,3,9,10-tetramethoxy-5,6,7,8,13,14-hexahydrodibenz[*c*,*g*]azecin-8-on-14-ol (22). To a stirred mixture of $LiAlH_4$

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(36 mg, 0.92 mmol) in dry THF (2.7 mL) at rt was added dropwise a solution of **20a** (44 mg, 0.09 mmol) in dry THF (2 mL). After the mixture was refluxed for 4 h, water (4 mL) was added to quench $LiAlH_4$. The resulting mixture was filtered, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), washed with water (20 mL) containing Rochelle salt (2 g), water (20 mL), and brine (20 mL), and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue (42 mg) by preparative TLC with silica gel developed with 7% MeOH−CH_2Cl_2 afforded **22**, mp 203−205 °C (EtOAc−hexane), as colorless crystals (21.8 mg, 60%, R_f 0.4−0.5): IR (Nujol) 3448, 1624 cm^{-1}; ^1H NMR δ 2.01 (d, J = 2.6 Hz, 1H), 2.51 (dd, J = 7.9 Hz), 2.75 (dd, J = 10.6 Hz), 3.00 (dd, J = 7.9 Hz, 1H), 3.17−3.26 (m, 1H), 3.23 (s, 3H), 3.41 (dd, J = 7.9 Hz, 1H), 3.68−3.76 (m, 1H), 3.73, 3.75, 3.76, 3.92 (each s, each 3H), 5.13−5.19 (m, 1H), 6.26 (s, 1H), 6.45, 6.51 (AB type, J = 8.3 Hz, each 1H), 6.99 (s, 1H); EI-MS m/z (relative intensity) 401 (M^+, 17), 209 (30), 192 (30), 179 (100). Anal. Calcd for C, 65.82; H, 6.78; N, 3.49. Found: C, 65.68; H, 6.81; N, 3.36.

Muraminol (21a) and 7-Methyl-9,14-dihydroxy-2,3,10-trimethoxy-5,6,7,8,13,14-hexahydrodibenz[*c*,*g*]azecine (23). To a stirred mixture of $LiAlH_4$ (188 mg, 4.95 mmol) in dry THF (14 mL) at rt was added dropwise a solution of dibenz[*c*,*g*]azecine-8,-14-dione **20a** (215 mg, 0.45 mmol) in dry THF (9 mL). After the mixture was refluxed for 20 h, water (20 mL) was added dropwise to quench $LiAlH_4$. The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), washed with water (20 mL) containing Rochelle salt (2 g) and water (2 × 20 mL), and dried (Na_2SO_4). The CH_2Cl_2 layer was concentrated to give a residue (129 mg) which was purified by preparative TLC with alumina developed with 0.5% MeOH−CH_2Cl_2. A band with R_f 0.5−0.7 afforded muraminol (**21a**), mp 178−179 °C (THF−Et_2O) (lit.[14] mp 175−176 °C), as colorless crystals (29 mg, 17%), whose spectral data were identical with those previously reported by Rönsch.[14] A band with R_f 0.3−0.5 gave **23**, mp 145−148 °C ($CHCl_3$), as colorless crystals (30 mg, 18%): IR ($CHCl_3$) 3514 cm^{-1}; ^1H NMR δ 2.33 (s, 3H), 2.56−2.59 (m, 2H), 2.93−3.01 (m, 2H), 3.14 (m, 2H), 3.73, 4.00 (AB type, J = 14.2 Hz, each 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.91 (s, 3H), 5.60 (br, 1H), 6.45 (s, 1H), 6.56 (d, J = 8.2 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 7.03 (s, 1H); EI-MS m/z (relative intensity) 373 (M^+, 35), 224 (23), 206 (44), 194 (100), 179 (37), 151 (66). Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.46; H, 7.08; N, 3.58.

Muramine (1a). According to Rönsch's method,[14] muraminol (**21a**, 25 mg, 0.064 mmol) was treated with PCC (28 mg, 0.13 mmol) and AcONa (2.8 mg, 0.03 mmol) in CH_2Cl_2 (3.2 mL) at rt for 2 h and purified by preparative TLC with alumina developed with 1% MeOH−CH_2Cl_2 to afford muramine (**1a**), mp 177−178 °C (acetone) (lit.[14] mp 176−177 °C), as colorless crystals (17.4 mg, 71%, R_f 0.4), whose spectral data were identical with those previously reported by Rönsch.[14]

Supporting Information Available: Experimental procedures and characterization data for compounds **7**−**10** and **13**−**16**, as well as ^1H NMR spectra for compounds **1a**,**d**, **7**−**10**, **13**−**17a**,**d**, and **19a**,**d**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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