Chemistry of Cyclic Tautomers of Tryptophan: Formation of a Quaternary Center at C3a and Total Synthesis of the Marine Alkaloid (+)-*ent*-Debromoflustramine B

Milan Bruncko, David Crich,* and Raghu Samy

University of Illinois at Chicago, Department of Chemistry (M/C111), 845 West Taylor Street, Chicago, Illinois 60607-7061

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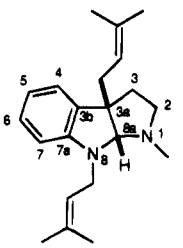
A diastereoselective synthesis of the unnatural (+)-enantiomer of the marine alkaloid (−)-debromoflustramine B (**1**) from a cyclic tautomer (**9**) of L-tryptophan is described. The optical rotation of the synthetic **1** is opposite to that of the natural material enabling the configuration of the natural product to be established as 3a*S*,8a*R*. As natural flustramine B has been converted to (−)-debromoflustramine B its absolute configuration may also be set as 3a*S*,8a*R*. The synthetic scheme involves radical bromination of **9** at C3a followed by allylation, at C3a, with allyltributyltin to give **21**. The allyl group is then converted to the C3a prenyl derivative **23** by oxidative cleavage and Wittig reaction. The remainder of the synthesis involves removal of the now extraneous carbomethoxy group from C2 and selective removal of the two nitrogen protecting groups and alkylation of the resulting amines. Oxidation of **9** with ceric ammonium nitrate to give mixtures of the C3a nitrato- and hydroxy-derivatives **18** and **19** is also described.

Debromoflustramine B (**1**) is an alkaloid recently isolated by Christophersen[1] from the marine bryozoan *Flustra foliacea* (L) which had earlier yielded the bromo analogue flustramine B (**2**) and its isomer flustramine A (**3**).[2]

These substances belong to the hexahydropyrrolo[2,3-*b*]indole class of alkaloids, the most appreciated of which is the calabar bean alkaloid and acetylcholinesterase inhibitor, physostigmine (**4**). A recent addition to the class is the dimeric pseudophrynamine A (**5**) isolated from the skin of the Australian frog *Pseudophryne coriacea*.[3] The absolute configuration of **1**, **2**, **3**, and **5** has not been assigned unambiguously but is presumed to be the same in each case because of the close similarities in the CD spectra. Other closely related substances include the urochordamins,[4] ardeemin,[5] roquefortine D,[6] the amauromines,[7] and 3a−3a-coupled dimeric species such as calycanthidine and chaetocin.[8] These alkaloids, from very diverse biological origins, have in common the hexahydropyrrolo[2,3-*b*]indole structure of a cyclic tryptophan tautomer bearing a carbon side chain at C3a.

The synthesis of physostigmine in particular has been intensively investigated since the time of Robinson,[9] Julian and Pikl,[10] and Hoshino.[11] Numerous, diverse



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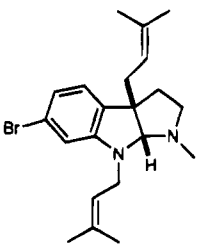

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routes for the racemic synthesis of **4** have been and continue to be developed but, until the recent work of Overman,[12] its efficient asymmetric synthesis has proven to be more problematic owing to difficulties in controling absolute stereochemistry at the quaternary carbon C3a.[13–15] Synthetic work on the flustramines has focused on the racemic debromo series and has mainly relied on sequences involving alkylation at C-3 of tryptamine derivatives followed by cyclization onto the resulting indolenium ions.[16,17] Racemic syntheses of pseudophrynamine and its constituent monomers which employ related strategies have also been reported.[18] Herein we

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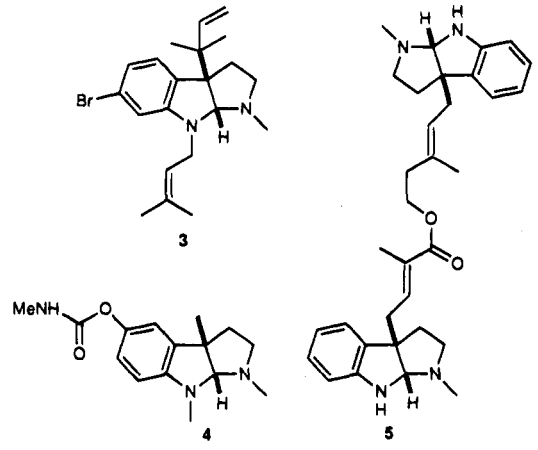
outline a conceptually different approach to the 3a-alkylhexahydropyrrolo[2,3-*b*]indole-type alkaloids in which the quaternary carbon center and alkyl side chain are introduced after formation of the diazabicyclo[3.3.0]-octane framework and illustrate the method with a diastereoselective synthesis of the (+)-enantiomer of the marine natural product (−)-debromoflustramine B (**1**).



The chemistry of cyclic tautomers of tryptophan has been studied extensively by Hino and his co-workers,[19] who published in 1981[20] the crucial observation that *N*-(methoxycarbonyl)-L-tryptophan methyl ester (**6**) in phosphoric acid underwent clean tautomerization to **7** and **8** and that under these equilibrating conditions the *endo*-carbomethoxy isomer **8** predominated to the extent of approximately 9:1 over the exo-isomer **7**. In this laboratory we have shown how sulfonylation of this mixture enables isolation of the stable crystalline sulfonamide derivative **9** in overall yields typically of around 80−85% as a diastereomerically and enantiomerically pure substance (Scheme 1).[21-23]

We considered that the ready availability of **9** in enantiomerically pure form made it an ideal starting material for the stereocontrolled synthesis of several of the hexahydropyrrolo[2,3-*b*]indole alkaloids. In any synthesis of any of these alkaloids, as typified by the target

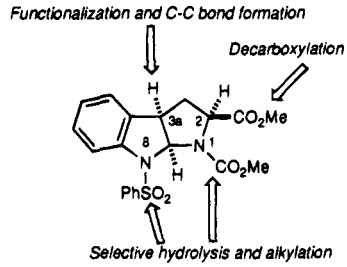
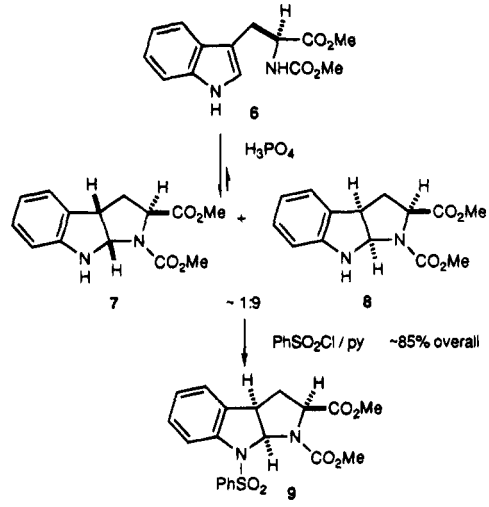
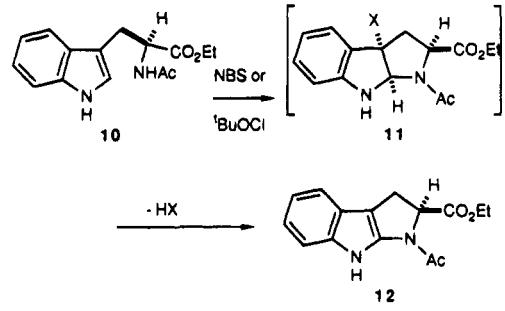


Figure 1.

Scheme 1



Scheme 2



molecule **1**, from **9** the key operations required, as summarized in Figure 1, are (i) functionalization and eventual C−C bond formation at C3a, (ii) reductive removal of the carbomethoxy group at C2, and (iii) sequential, selective deprotection and alkylation of the two nitrogen centers.

Of these operations, selective functionalization at C3a was the most daunting in view of the probable reactivity of H2 and H8a under radical or oxidizing conditions. Moreover, Witkop had reported in 1970 that treatment of *N*-acetyltryptophan ethyl ester (**10**) with NBS led to the isolation of a tetrahydropyrrolo[2,3-*b*]indole (**12**) suggesting that the presumed intermediate 3a-bromo derivative **11** underwent rapid dehydrobromination and could not be isolated (Scheme 2).[24] Similar results were observed on treatment of **10** with *tert*-butyl hypochlorite suggesting that the 3a-chloride suffered the same fate.[24]

In contrast, Hino had reported, in his studies on the functionalization of cyclic tryptamine tautomers, that chlorination of **13** with NCS in acetic acid gave, among

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(21) **9**, readily available on 50 g scale in a simple four-step sequence from L-tryptophan,[22b] is commercially available from Aldrich Chemical Co, Milwaukee, WI.

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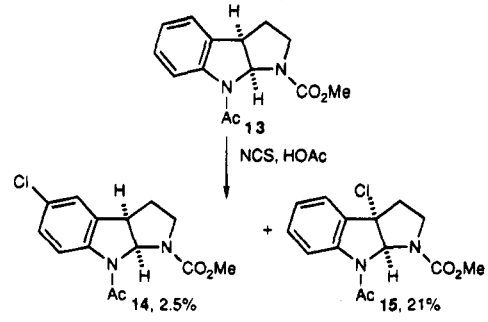
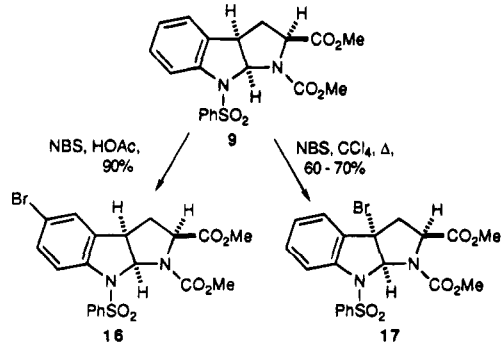
Scheme 3



Scheme 4

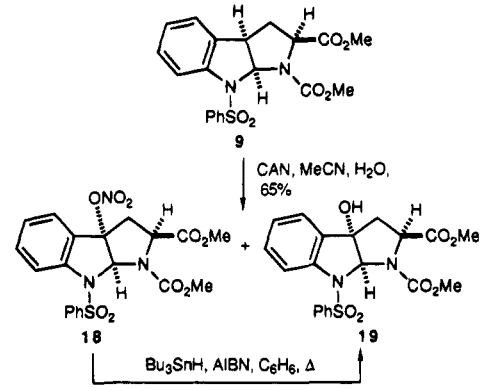


other products, a mixture of the 5- and 3a-chloro derivatives **14** and **15** in 2.5 and 21% yields, respectively (Scheme 3), indicating that at least the 3a-chloride could be isolated.[25] Hino was, however, of the opinion that C-3a chlorination was the result of opening of **13** to the indole tautomer followed by electrophilic chlorination at the indole C-3 and subsequent recyclization and not of direct chlorination on the hexahydropyrroloindole framework. Bromination of **13** with NBS in acetic acid cleanly gave the 5-bromo derivative.[25]

We began our investigation with a study of the bromination of **9**. In parallel with the observations of Hino, reaction of **9** with NBS in acetic acid resulted in clean bromination at C5 giving **16**, presumably by electrophilic aromatic substitution (Scheme 4). That substitution had occurred at C5 was confirmed by the observation of an NOE enhancement of the meta-doublet assigned as H4 on double irradiation of H3a. In contrast, treatment of **9** with NBS in CCl_4 at reflux resulted in benzylic bromination and isolation of the desired 3a-bromo derivative (**17**) typically in around 60–70% yield at approximately 90% conversion (Scheme 4). Attempts to drive the reaction to completion were detrimental and resulted in more complex reaction mixtures as competing processes came into play. The bromide **17**, which could not be isolated completely free of a minor impurity and which has so far resisted our attempts at crystallization, is stable to silica gel chromatography and shows no sign of elimination of HBr even after many months of standing in the laboratory under air. Evidently our fears as to the regioselectivity of radical bromination of **9** and the stability of **17** were largely unfounded.

We also briefly studied benzylic oxidation of **9** with ceric ammonium nitrate in aqueous acetonitrile at room temperature and were pleased to isolate mixtures of the

Scheme 5



3a-alcohol **19** and its nitrate ester **18** in approximately 65% combined yield with 35% recovered **9** (Scheme 5). As with the bromide **17**, both **18** and **19** were stable to chromatography and show no tendency toward elimination. The ratio of **18**:**19** in the reaction mixture varies with the amount of water in the reaction solvent; moreover, separation of **19** from unreacted starting material by chromatography was tedious. We therefore developed a protocol involving treatment of the nitrate **18** with tributyltin hydride and AIBN in benzene at reflux resulting in the reduction of the nitrate ester[26] and isolation of clean **19**. Evidently the ready formation and isolation of **19** opens up the possibility of the diastereoselective synthesis of the sporidesmins[27] from **9**, but we have not pursued this avenue.

The contrast between the evident stabilities of **15**, **17**, **18**, and **19**, as observed by Hino and ourselves, respectively, and the instability of **11** reported by Witkop is intriguing but can probably be rationalized by the additional electron-withdrawing groups on N8 in the former which destabilize the benzylic (C3a) cation inductively through the N8–C8a–C3a bonds. Further evidence for the destabilization of the putative C3a cation can be derived from the 70 eV EI mass spectra of **17** and **18** which show clear molecular ions (relative intensity 6 and 5%, respectively) and for which the principal mode of fragmentation does not involve loss of the 3a-substituent.

With the bromide **17** in hand we turned to C–C bond formation at C3a. Following several fruitless attempts at organometallic couplings with **17**, we focused our attention on radical reactions. Reaction of **17** in benzene at reflux with methyl vinyl ketone and tributyltin hydride resulted in isolation of **20** in 55% yield. An analogous reaction with methyl acrylate was also productive; however, it proved impossible to separate the addition product completely from minor amounts of telomeric addition products, which was not the case with **20**. Reaction of **9** with allyltributyltin[28] and AIBN in benzene at reflux provided **21** in 80% isolated yield (Scheme 6). The good yield for the formation of **21** and the versatility afforded by the double bond make it an ideal intermediate for the synthesis of a number of 3a-alkylhexahydropyrroloindole alkaloids.

Reaction of **21** with sodium metaperiodate and catalytic osmium tetraoxide under Lemieux–Johnson condi-

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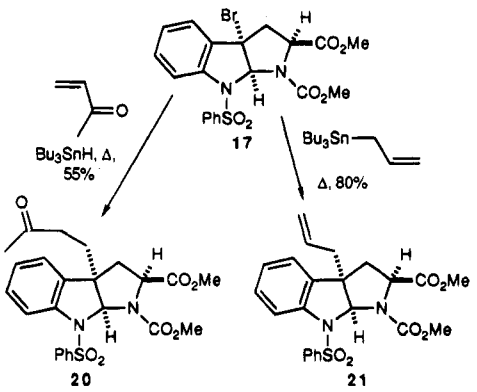
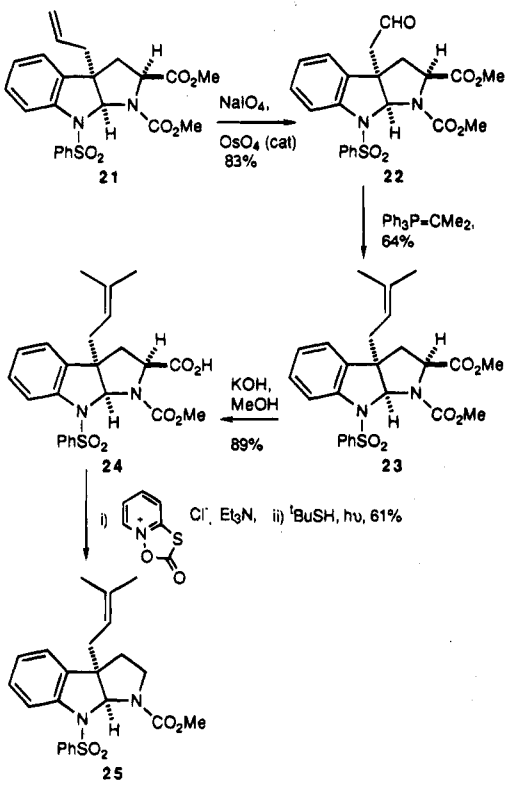
Scheme 6

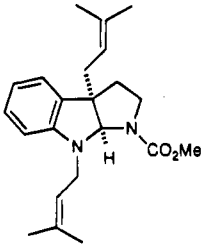


Scheme 7



tions provided the aldehyde **22** in 83% isolated yield. Subsequent Wittig reaction with isopropylidenetriphenylphosphorane gave **23**, with the complete prenyl side chain, in 64% yield (Scheme 7). No attempt at direct prenylation with 3-methyl-3-(tributylstannyl)-1-butene was made as Keck had already shown this type of reaction to be unproductive due to isomerization of the reagent to prenyltributylstannane.[29] Attempted direct radical prenylation of the bromide **17** by reaction with 3-methyl-3-(phenylthio)-1-butene and hexabutyldistannane[30] was not productive, the major isoalated product (47%) being the known[22] *N*1-(phenylsulfonyl) derivative of **6**. Removal of the now extraneous carbomethoxy group at C2 was achieved by treatment of **23** with aqueous methanolic KOH at room temperature to give the acid **24** in 89% yield followed by Barton reductive decarboxylation,[31] which afforded **25** in 61% yield.[32]

Finally, attention was turned to the selective deprotection and alkylation of the two secondary amines. In his synthesis of (±)-debromoflustramine B,[16a] Christophersen encountered problems in the hydrolysis of the carbamate group in **26** owing to the sensitivity of the prenylamine toward base.



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Consequently, we chose first to convert the N1 carbamate in **25** to the N1 methyl group leaving N8 protected as the sulfonamide and finally to remove the sulfonamide and introduce the potentially problematic prenyl group. Direct conversion of the carbamate group in **25** through to a methyl group by reduction with $LiAlH_4$ was attempted but we were unable to suppress reductive cleavage of the N1—C8a bond. Therefore, **25** was heated to reflux with aqueous methanolic KOH to give the amine **27** essentially quantitatively. Reductive amination of **27** with formaldehyde and sodium cyanoborohydride in acetic acid according to Borch[33] provided the requisite tertiary amine **28** and the corresponding amine–borane **29** in 27 and 59% yields, respectively. Brief treatment of **29** with methanolic KOH resulted in hydrolysis to **28** in 87% yield and so an overall yield of 79% for the transformation of **27** to **28**.[34] Interestingly, the amine–borane was isolated as a single diastereomer, but we have not so far been able to assign stereochemistry unambiguously. The last step of the synthesis involved reductive desulfonylation of **28** with sodium in liquid ammonia, and quenching of the amide anion with prenyl bromide enabling isolation of *ent*-**1** in 57% yield as a colorless oil (Scheme 8).

The optical rotation and CD spectrum of *ent*-**1** prepared in this manner were identical but opposite in sign to those of the natural material isolated by Christophersen.[1] The absolute configuration of the synthetic material [(+)-*ent*-**1**] is 3a*R*,8a*S*. Natural (−)-debromoflustramine B (**1**) therefore has absolute configuration 3a*S*,8a*R*. Moreover, as flustramine B (**2**) was converted to **1** by $LiAlH_4$ reduction by Christophersen[1] its absolute configuration is also 3a*S*,8a*R*.

The versatility provided by the 3a-allyl chain as well as the differentially protected ring nitrogens make **21** a very attractive intermediate for the synthesis of a number of other hexahydropyrrolo[2,3-*b*]indole alkaloids. Such studies are currently underway.

Experimental Section

General. Melting points were recorded on a Thomas hotstage microscope and are uncorrected. ^1H- and ^{13}C-NMR

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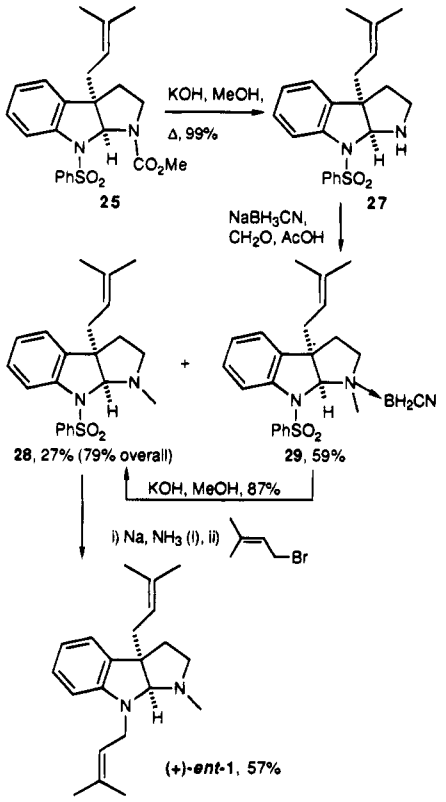
(31) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(32) The use of tryptophan as chiral starting material in diastereoselective synthesis of indole alkaloids followed by reductive removal of the stereodirecting ester group has previously been described, or at least alluded to, by other groups: (a) Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1983**, 1147. (b) Magnus, P.; Ludlow, M.; Kim, C. S.; Buniface, P. *Heterocycles* **1989**, *28*, 951. (c) Overman, L. E.; Robichaud, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 300. (d) Winkler, J. D.; Scott, R. D.; Willard, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 8971. (e) Huizenga, R.; Pandit, U. K. *Tetrahedron* **1991**, *47*, 4155.
(33) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.
(34) Synthesis and hydrolysis of amineboranes from BH_2CN: (a) Uppal, S. S.; Kelly, H. C. *J. Chem. Soc., Chem. Commun.* **1970**, 1619. (b) Weidig, C.; Uppal, S. S.; Kelly, H. C. *Inorg. Chem.* **1974**, *13*, 1763.

Scheme 8



spectra were run in $CDCl_3$ at 300 and 75 MHz, respectively, and chemical shifts are downfield from tetramethylsilane as internal standard. IR spectra were recored with a Perkin-Elmer 1605 FTIR spectrophotometer. Specific rotations were recorded with a Perkin-Elmer 241 polarimeter and the CD spectrum with a JASCO J-600 spectropolarimeter. All solvents were dried and distilled by standard procedures. All reactions were run under a dry nitrogen or argon atmosphere. THF was distilled, under N_2, immediately prior to use from sodium benzophenone ketyl. Ether refers to diethyl ether. Microanalyses were conducted by Midwest Microanalytical, Indianapolis, IN.

(+)-(2*S*,3a*R*,8a*S*)-5-Bromo-1,2-bis(methoxycarbonyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (16). The cyclic tautomer **9** (416.4 mg, 1 mmol) was added to a solution of NBS (213.6 mg, 1.2 mmol) in AcOH (10 mL) and the mixture stirred for 5 h at room temperature and then poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The extracts were washed with 5% NaOH (30 mL), water (30 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated to give a crude product which, after chromatography on silica gel (eluent: hexane/ethyl acetate 2/1), gave the 5-bromo derivative **16** as a white foam (446 mg, 90%): $[\alpha]_D$ = +102.9° (*c* = 1.47, $CHCl_3$); δ_H 2.39–2.56 (2H, m), 3.25 (3H, s), 3.56 (3H, s), 3.69 (1H, t, *J* = 6.5 Hz), 4.58 (1H, dd, *J* = 8.1 and 1.8 Hz), 6.27 (1H, d, *J* = 6.5 Hz), 7.13–7.17 (1H, m), 7.27–7.36 (2H, m), 7.37–7.45 (2H, m), 7.51 (1H, tt, *J* = 7.5 and 1.3 Hz), and 7.72–7.78 (2H, m); δ_C 33.45, 45.45, 51.93, 52.59, 58.94, 80.27, 117.63, 119.49, 126.57, 127.31, 128.96, 131.81, 132.85, 135.19, 139.86, 141.89, 154.41, and 170.89; *v* (CH_2Cl_2) 1720 cm^{-1}. Anal. Calcd for $C_{20}H_{19}BrN_2O_6S$: C, 48.50; H, 3.87; N, 5.66. Found: C, 48.59; H, 3.97; N, 5.76.

(+)-(2*S*,3a*S*,8a*S*)-3a-Bromo-1,2-bis(methoxycarbonyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (17). To a solution of **9** (1.00 g, 2.4 mmol) and AIBN (40 mg, 0.24 mmol) in CCl_4 (60 mL) was added NBS (430 mg, 2.4 mmol) at room temperature. The stirred reaction mixture was then brought to reflux for 30 min and cooled to room temperature and the succinimide removed by filtration. Removal of the solvent under vacuum and chromatrography on silica gel (eluent: hexane/ethyl acetate 1/1) gave the bromide **17** as a white foam (850 mg, 72%): $[\alpha]_D$ = +93.4° (*c* = 0.78, $CHCl_3$); δ_H (50 °C) 3.04 (1H, dd, *J* = 9.1 and 13.1 Hz), 3.17 (3H, s), 3.25 (1H, d, *J* = 13.1 Hz), 3.68 (3H, s), 4.61 (1H, d, *J* = 8.9 Hz), 6.36 (1H, s), 7.13 (1H, m), 7.25 (1H, d, *J* = 7.4 Hz), 7.31–7.40 (3H, m), 7.43 –7.57 (2H, m), and 7.63 (2H, d, *J* = 7.5 Hz); δ_C (50 °C) 44.72, 52.09, 52.93, 87.27, 113.92, 118.13, 119.37, 123.41, 124.57, 125.03, 125.58, 126.72, 127.46, 128.90, 129.22, 131.05, 133.12, 133.27, and 169.88; *v* (CH_2Cl_2) 1725, 1601, 1508, and 1373 cm^{-1}; HRMS calcd for $C_{20}H_{19}BrN_2O_6S$ 494.0155, found 494.0147 ($M^{\bullet+}$). The presence of a minor impurity in **17**, which could not be removed by either column chromatography or preparative TLC, is not detrimental to the further reactions described.

Reaction of 9 with CAN: (+)-(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-nitrato-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (18) and (+)-(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-hydroxy-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (19). To a solution of **9** (0.50 g, 1.2 mmol) in acetonitrile (25 mL) and water (5 mL) was added ceric ammonium nitrate (3.29 g, 6 mmol) and the mixture stirred overnight at room temperature. After dilution with ethyl acetate (30 mL) and washing with water (2 × 10 mL) the extracts were dried over $MgSO_4$ and concentrated to give a crude product mixture, chromatography of which on silica gel (eluent: hexane/ethyl acetate 1/1) gave first the nitrato derivative **18** (230 mg, 40%), the recovered substrate (175 mg, 35%), and finally the 3a-hydroxy derivative **19** (130 mg, 25%). **18** was a white foam: $[\alpha]_D$ = +132.4° (*c* = 1.19, $CHCl_3$); δ_H (50 °C) 2.85 (1H, dd, *J* = 9.5 and 12.9 Hz), 3.08 (1H, d, *J* = 12.9 Hz), 3.25 (3H, s), 3.67 (3H, s), 4.83 (1H, d, *J* = 9.3 Hz), 6.42 (1H, s), 7.14 (1H, t, *J* = 7.5 Hz), 7.35 (1H, d, *J* = 7.6 Hz), 7.41 (3H, m), 7.53 (1H, m), 7.59 (1H, m, *J* = 8.2 Hz), and 7.83 (2H, t, *J* = 7.4 Hz); δ_C (50 °C) 37.42, 52.41, 53.12, 58.55, 81.36, 95.84, 118.18, 125.38, 125.78, 126.31, 126.70, 128.77, 129.01, 130.86, 132.60, 133.30, 144.61, 154.13, and 169.66; *v* (CH_2Cl_2) 1713 cm^{-1}; HRMS calcd for $C_{20}H_{19}N_3O_9S$ 477.0842, found 477.0837 ($M^{\bullet+}$). **19** was a white crystalline solid: mp 188–189 °C (MeOH); $[\alpha]_D$ = +89.6° (*c* = 0.98, $CHCl_3$); δ_H (50 °C) 2.65 (1H, dd, *J* = 9.0 and 12.9 Hz), 2.77 (1H, d, *J* = 12.9 Hz), 3.17 (3H, s), 3.62 (3H, s), 4.66 (1H, d, *J* = 9.0 Hz), 5.91 (1H, s), 7.14 (1H, dt, *J* = 0.98 and 7.5 Hz), 7.25 (1H, m), 7.39 (3H, m), 7.53 (2H, m), and 7.82 (2H, m); δ_C (50 °C) 39.28, 51.98, 52.73, 59.10, 84.88, 85.85, 118.99, 123.16, 124.20, 125.82, 127.17, 127.80, 128.99, 130.77, 131.27, 133.20, 133.43, 139.82, 143.25, 154.72, and 170.52; *v* (CH_2Cl_2) 3578 and 1715 cm^{-1}.

Conversion of 18 to 19 with Tributyltin Hydride. To a solution of **18** (23.2 mg, 0.0486 mmol) in toluene (2 mL) was added tributyltin hydride (0.3 mL) and a crystal of AIBN. The reaction mixture was then heated to reflux for 4 h before cooling to room temperature and removal of volatiles. The oil so obtained was then partitioned between hexane and acetonitrile. The acetonitrile layer was concentrated under vacuum and then subjected to purification by preparative TLC on silica gel (eluent: ethyl acetate/hexane 1.5/1) to give **19** (9.8 mg, 47%), identical to the sample described above.

(+)-(2*S*,3a*R*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-(3-oxobutyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (20). To a solution of **17** (750 mg, 1.52 mmol) and methyl vinyl ketone (1.079 g, 15.2 mmol) in benzene (30 mL) at reflux was added tributyltin hydride (0.530 g, 1.82 mmol) dropwise over 2 h with the aid of a motor-driven syringe pump. The reaction mixture was then cooled to room temperature, and the volatiles were removed under vacuum. The residue was dissolved in acetonitrile (5 mL) and washed with hexane (3 × 25 mL). The acetonitrile was stripped off and the crude product purified by chromatography on silica gel (eluent: hexane/ethyl acetate 1/1) to give **20** as an oil (0.350 g, 55%): $[\alpha]_D$ = +31.3° (*c* = 0.4, $CHCl_3$); δ_H (50 °C) 1.90 (1H, m), 2.05 (1H, m), 2.02 (3H, s), 2.18 (1H, m), 2.35 (1H, dd, *J* = 9.0 and 12.9 Hz), 2.47 (1H, m), 2.70 (1H, d, *J* = 12.9 Hz), 3.20 (3H, s), 3.32 (3H, s), 4.66 (1H, d, *J* = 8.8 Hz), 6.09 (1H, s), 7.05 (2H, m), 7.23 (2H, m), 7.52 (3H, m), and 8.02 (2H, m); δ_C (50 °C) 29.89, 31.80, 38.09, 39.72, 51.96, 59.35, 82.74, 116.16, 123.75, 124.23, 125.31, 129.08, 129.28, 132.52, 133.07, 142.69, 170.83, and 207.08; *v* (CH_2Cl_2) 1748 and 1713 cm^{-1}; HRMS calcd for $C_{24}H_{26}N_2O_7S$ 486.1460, found 486.1458 ($M^{\bullet+}$).

(+)-(2*S*,3a*R*,8a*S*)-3a-Allyl-1,2-bis(methoxycarbonyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (21). To a solution of **17** (2.45 g, 4.95 mmol) in benzene (50 mL) was added allyltributyltin (3.28 g, 9.90 mmol) and AIBN (162 mg, 0.99 mmol) before the reaction mixture was heated to reflux for 18 h. After the mixture was cooled to room temperature, the solvent was removed under vacuum and the residue taken up in acetonitrile (10 mL) and washed with hexane (5 × 50 mL). Evaporation to dryness of the acetonitrile solution gave **21** as an oil (1.80 g, 80%), sufficiently pure for use in subsequent reactions: $[\alpha]_D = +25.5°$ ($c = 0.83$, $CHCl_3$); δ_H (50 °C) 2.17 (2H, m), 2.40 (1H, dd, $J = 9.0$ and 12.9 Hz), 2.61 (1H, d, $J = 12.9$ Hz), 3.18 (3H, s), 3.43 (3H, s), 4.63 (1H, d, $J = 8.8$ Hz), 5.04 (1H, dd, $J = 1.42$ and 17.0 Hz), 5.10 (1H, d, $J = 10.2$ Hz), 5.64 (1H, m), 6.03 (1H, s), 7.05 (2H, m), 7.22 (1H, m), 7.34 (1H, d, $J = 8.1$ Hz), 7.60 (3H, m), and 7.93 (2H, dd, $J = 4.9$ and 7.0 Hz); δ_C (50 °C) 38.42, 41.75, 51.82, 52.33, 59.61, 83.04, 116.83, 119.87, 123.94, 124.18, 126.36, 128.79, 128.92, 129.02, 131.78, 132.49, 134.64, 142.53, 154.46, and 170.91; ν (CH_2Cl_2) 1719 cm^{-1}; HRMS calcd for $C_{23}H_{24}N_2O_6S$ 456.1355, found 456.1354 ($M^{\bullet+}$). As with the bromide **17**, **21** contained a minor impurity which could not be removed chromatographically. It was found to be most expedient to carry this impurity forward as it is lost in the cleavage of the allyl group.

(+)-(2*S*,3a*R*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-(2-oxoethyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (22). Osmium tetraoxide (40 mg) and then, in two portions, sodium metaperiodate (1.925 g, 9 mmol) were added at room temperature to a stirred solution of **21** (1.41 g, 3.09 mmol) in THF (50 mL) and water (10 mL), and stirring was maintained for 3 h after which TLC analysis indicated complete consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and water (50 mL), the aqueous layer was further extracted with CH_2Cl_2 (2 × 30 mL), the combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under vacuum. Silica gel chromatography (eluent: hexane/ethyl acetate 2/1) of the crude product gave the aldehyde **22** as a white foam (1.17 g, 83%) which crystallized on trituration with ether to give a white solid: mp 157–158 °C; $[\alpha]_D = +43.2°$ ($c = 1.36$, $CHCl_3$); δ_H (50 °C) 2.28 (1H, d, $J = 17.8$ Hz), 2.53 (1H, dd, $J = 12.9$ and 9.0 Hz), 2.65 (1H, dd, $J = 17.8$ and 1.3 Hz), 2.80 (1H, d, $J = 12.9$ Hz), 3.17 (3H, s), 3.48 (3H, s), 4.64 (1H, d, $J = 9.0$ Hz), 6.16 (1H, s), 7.05 (1H, dt, $J = 1.1$ and 7.4 Hz), 7.11–7.15 (1H, m), 7.20–7.27 (1H, m), 7.39 (1H, d, $J = 8.1$ Hz), 7.42–7.50 (2H, m), 7.55 (1H, tt, $J = 7.4$ and 1.4 Hz), 7.87–7.92 (2H, m), and 9.54 (1H, t, $J = 1.3$ Hz); δ_C (50 °C) 38.20, 49.65, 51.88, 52.52, 59.55, 83.21, 56.20, 117.99, 124.29, 124.89, 126.55, 129.07, 129.55, 132.80, 134.36, 141.22, 142.26, 154.44, 170.79, and 197.90; ν (CH_2Cl_2) 1719 cm^{-1}; HRMS calcd for $C_{22}H_{22}N_2O_7S$ 458.1149, found 458.1148 ($M^{\bullet+}$). Anal. Calcd for $C_{22}H_{22}N_2O_7S$: C, 57.63; H, 4.84; N, 6.11. Found: C, 57.83; H, 4.96; N, 6.03.

(+)-(2*S*,3a*R*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-(3-methyl-2-buten-1-yl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (23). To a suspension of isopropyltriphenylphosphonium iodide (1.422 g, 3.29 mmol) in THF (10 mL) was added at 0 °C *n*-butyllithium (1.52 mL of 2 M in pentane). After the mixture was stirred for 2 h at that temperature the aldehyde **22** (1.102 g, 2.404 mmol) in THF (15 mL) was added by syringe. The stirred reaction mixture was allowed to warm to ambient temperature and then stirred for a further 24 h before it was diluted with ether (50 mL) and the precipitated phosphine oxide filtered off and washed with ether (3 × 30 mL). The combined ether phases were washed with brine (25 mL), dried ($MgSO_4$), concentrated, and purified by chromatography on silica gel eluting with hexane/ethyl acetate (2.5/1) to yield the 3a-prenylated derivative **23** as a white foam (0.740 g, 64%): $[\alpha]_D = +35.2°$ ($c = 2.0$, $CHCl_3$); δ_H (50 °C) 1.42 (3H, s), 1.68 (3H, s), 2.06–2.24 (2H, m), 2.38 (1H, dd, $J = 9.0$ and 12.8 Hz), 2.59 (1H, d, $J = 12.8$ Hz), 3.17 (3H, s), 3.41 (3H, s), 4.61 (1H, d, $J = 8.7$ Hz), 4.99–5.07 (1H, m), 6.01 (1H, s), 6.96–7.05 (2H, m), 7.14–7.21 (1H, m), 7.29 (1H, d, $J = 8.1$ Hz), 7.41–7.51 (3H, m), and 7.92–7.98 (2H, m); δ_C (50 °C) 17.85, 25.72, 36.02, 38.43, 51.77, 52.27, 57.32, 59.74, 83.21, 116.63, 117.56, 123.79, 124.02, 126.31, 128.84, 128.90, 132.39, 135.08, 136.54, 142.57, 154.55, and 171.05; ν (CH_2Cl_2) 1718 and 1603 cm^{-1}. Anal. Calcd for $C_{25}H_{28}N_2O_6S$: C, 61.97; H, 5.82; N, 5.78. Found: C, 61.98; H, 5.89; N, 5.79.

(+)-(2*S*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-3a-(3-methyl-2-buten-1-yl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic Acid (24). The ester **23** (1.012 g, 2.088 mmol) was stirred in MeOH (20 mL) with a solution of KOH (0.468 g, 8.352 mmol) in water (5 mL) until TLC control indicated complete consumption of the substrate. After removal of MeOH under vacuum water (20 mL) was added and the pH adjusted to 2–3 with dilute HCl, before extraction with ethyl acetate (3 × 15 mL), washing with brine (20 mL), drying ($MgSO_4$), and concentration under vacuum to give the acid **24** as a white foam (0.874 g, 89%): $[\alpha]_D = +44.5°$ ($c = 1.15$, $CHCl_3$); δ_H (50 °C) 1.42 (3H, s), 1.67 (3H, s), 2.11 (1H, dd, $J = 6.8$ and 14.4 Hz), 2.21 (1H, dd, $J = 8.3$ and 14.4 Hz), 2.40 (1H, dd, $J = 9.3$ and 13.1 Hz), 2.57 (1H, dd, $J = 1.5$ and 13.1 Hz), 3.48 (1H, s), 4.58 (1H, dd, $J = 1.6$ and 9.3 Hz), 4.96–5.04 (1H, m), 5.96 (1H, s), 6.96–7.06 (2H, m), 7.14–7.21 (1H, m), 7.32 (1H, d, $J = 8.1$ Hz), 7.39–7.46 (2H, m), 7.51 (1H, tt, $J = 1.4$ and 7.3 Hz), 7.89–7.93 (2H, m), and 8.73 (1H, broad s); δ_C (50 °C) 17.88, 25.74, 35.80, 38.43, 52.69, 57.22, 59.75, 83.59, 116.68, 117.58, 123.73, 124.36, 126.63, 128.97, 129.11, 132.63, 134.76, 136.64, 141.05, 142.03, 155.15, and 173.87; ν (CH_2Cl_2) 3478, 1767, and 1713 cm^{-1}. Anal. Calcd for $C_{24}H_{26}N_2O_6S$: C, 61.26; H, 5.57; N, 5.95. Found: C, 61.37; H, 5.60; N, 5.88.

(+)-(3a*R*,8a*S*)-1-(Methoxycarbonyl)-3a-(3-methyl-2-buten-1-yl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (25). The acid **24** (750 mg, 1.59 mmol) was dissolved in CH_2Cl_2 (15 mL) at room temperature under Ar in a flask covered with aluminum foil. Triethylamine (0.55 mL, 4 mmol) and then 1-oxa-2-oxo-3-thiaindolizinium chloride (393 mg, 2.07 mmol) were added and the reaction mixture stirred at room temperature for 1 h. *tert*-Butylmercaptan (1.79 mL, 15.9 mmol) was then added, the aluminum foil removed, and the yellow reaction mixture photolyzed, in a cold water bath, with a 250-W tungsten lamp for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (15 mL), washed with saturated NH_4Cl solution (10 mL), 5% KOH (2 × 15 mL), and brine (10 mL), and then dried ($MgSO_4$), evaporated, and purified by chromatography on silica gel (eluent: hexane/ethyl acetate 2/1) to yield **25** as a white crystalline solid (416 mg, 61%): mp 81–82 °C; $[\alpha]_D = +169.8°$ ($c = 1.53$, $CHCl_3$); δ_H (50 °C) 1.38 (3H, s), 1.62 (3H, s), 1.95–2.20 (4H, m), 2.83–2.95 (1H, m), 3.65 (3H, s), 3.77–3.85 (1H, m), 4.88–4.95 (1H, m), 5.99 (1H, s), 7.00–7.07 (2H, m), 7.17–7.24 (1H, m), 7.37–7.44 (2H, m), 7.47–7.53 (2H, m), and 7.84–7.89 (2H, m); δ_C (50 °C): 17.83, 25.67, 36.14, 36.36, 45.54, 52.33, 57.66, 83.12, 116.28, 118.15, 123.40, 124.44, 127.05, 128.46, 128.84, 132.73, 135.86, 135.89, 140.4, 142.01, and 154.82; ν (CH_2Cl_2) 1706 cm^{-1}. Anal. Calcd for $C_{23}H_{26}N_2O_4S$: C, 64.77; H, 6.14; N, 6.57. Found: C, 64.86; H, 6.22; N, 6.61.

(+)-(3a*R*,8a*S*)-3a-(3-Methyl-2-buten-1-yl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (27). The carbamate **25** (234 mg, 0.55 mmol) was heated to reflux with 5 M KOH in 9/1 MeOH/H_2O (10 mL) for 3 h. The reaction mixture was cooled to room temperature, diluted with water (50 mL), and extracted with ether (3 × 30 mL). The extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under vacuum giving the amine **27** which crystallized as a white solid from MeOH (200 mg, 99%): mp 65–66 °C; $[\alpha]_D = +216.2°$ ($c = 0.99$, $CHCl_3$); δ_H (50 °C) 1.41 (3H, s), 1.42 (3H, s), 1.83–2.02 (2H, m), 2.17–2.34 (2H, m), 2.61 (1H, s), 2.86 (1H, ddd, $J = 5.7$, 10.7, and 9.2 Hz), 2.99–3.07 (1H, m), 4.55 –4.63 (1H, m), 5.19 (1H, s), 6.94–7.05 (2H, m), 7.12–7.19 (1H, m), 7.37–7.43 (2H, m), 7.50 (1H, tt, $J = 1.4$ and 7.4 Hz), 7.53 (1H, d, $J = 8.1$ Hz), and 7.82–7.87 (2H, m); δ_C (50 °C) 17.85, 25.57, 37.64, 40.20, 44.20, 56.01, 86.80, 113.30, 119.41, 123.72, 123.88, 127.05, 127.97, 128.90, 132.83, 134.36, 136.27, 139.18, and 142.02; ν (CH_2Cl_2) 3371 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.57; N, 7.61. Found: C, 68.49; H, 6.65; N, 7.69.

(+)-(3a*R*,8a*S*)-1-Methyl-3a-(3-methyl-2-buten-1-yl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]-

indole (28) and the Amine–Borane 29. The amine **27** (88 mg, 0.239 mmol) was dissolved in acetonitrile (2 mL) with stirring and aqueous formaldehyde (0.5 mL of 37%) added followed, after 30 min, by sodium cyanoborohydride (75 mg, 1.194 mmol) and then acetic acid (0.045 mL). The reaction mixture was stirred for 1 h, and then further acetic acid (0.045 mL) was added. After being stirred for a further 1 h the reaction mixture was diluted with ether (6 mL), washed with 5% KOH (2 × 5 mL), dried ($MgSO_4$), and concentrated to give an oil (94.5 mg). Preparative TLC on silica gel (eluent: hexane/ethyl acetate 1/1) of this oil provided the amine **28** (24.7 mg, 27%, faster moving spot) and the amine–borane **29** (59.7 mg, 59%, slower moving spot). The amine–borane **29** was subsequently converted to **28** by heating to reflux with 1 M KOH in 9/1 MeOH/H_2O for 15 min in 87% yield, giving an overall yield of 79% for the amine **28**. The amine **28** was a white crystalline solid: mp 89–90 °C; $[\alpha]_D$ = +217.7° (c = 1.19, $CHCl_3$); δ_H 1.26 (3H, s), 1.65 (3H, s), 1.62–1.72 (1H, m), 1.76–1.87 (2H, m), 2.05 (1H, ddd, J = 6.7, 8.7, and 11.9 Hz), 2.50 (1H, dt, J = 5.6 and 9.0 Hz), 2.65–2.72 (1H, m), 2.68 (3H, s), 4.92 (1H, s), 4.96–5.04 (1H, m), 6.95–7.04 (2H, m), 7.15–7.22 (1H, m), 7.31–7.38 (2H, m), 7.45 (1H, tt, J = 1.3 and 7.5 Hz), 7.64 (1H, d, J = 8.1 Hz), and 7.69–7.74 (2H, m); δ_C 17.89, 25.76, 36.74, 36.87, 37.06, 52.70, 57.12, 91.22, 116.79, 118.91, 123.95, 124.67, 127.39, 128.79, 132.81, 134.93, 139.15, and 142.80; ν (CH_2Cl_2) 2937, 1600, 1352, and 1169 cm^{-1}. Anal. Calcd for $C_{22}H_{26}N_2O_2S$: C, 69.08; H, 6.89; N, 7.32. Found: C, 68.98; H, 6.75; N, 7.27. The amine–borane **29** was also a white crystalline solid: mp 132–133 °C; $[\alpha]_D$ = +203.5° (c = 0.78, $CHCl_3$); δ_H 1.04 (3H, s), 1.31 (1H, dd, J = 9.3 and 14.0 Hz), 1.63 (3H, s), 1.84 (1H, dd, J = 6.0 and 14.0 Hz), 1.97 (1H, dd, J = 5.0 and 12.9 Hz), 2.31–2.42 (1H, ddd, J = 10.6, 13.2, and 5.1 Hz), 2.54 (1H, dt, J = 6.0 and 12.8 Hz), 2.95 (3H, s), 3.49 (1H, dd, J = 6.2 and 10.6 Hz), 4.92 (1H, s), 4.93–5.00 (1H, m), 7.02 (1H, dd, J = 1.0 and 7.7 Hz), 7.12 (1H, dt, J = 1.0 and 7.5 Hz), 7.30–7.37 (1H, m), 7.40–7.47 (2H, m), 7.57 (1H, tt, J = 1.3 and 7.5 Hz), 7.70–7.75 (2H, m), and 7.78 (1H, d, J = 8.1 Hz); δ_C 17.69; 25.82, 34.70, 36.91, 46.16, 57.57, 59.92, 92.16, 116.60, 116.97, 124.16, 126.11, 127.33, 129.33, 129.42, 134.18, 135.95, 136.57, 136.59, and 140.56; ν (CH_2Cl_2) 2915, 2433, 1593, 1367, and 1174 cm^{-1}.

(+)-(3a*R*,8a*S*)-Debromoflustramine B (*ent* -1). The amine **28** (27.2 mg, 0.071 mmol) was dissolved in a mixture of THF (0.8 mL) and liquid ammonia (2 mL) and cooled, under N_2, to −50 to −60 °C with a dry ice–acetone bath. Sodium metal (4.9 mg, 0.21 mmol) was added, causing the reaction mixture to turn the characteristic deep blue of sodium in liquid ammonia before fading to a yellow color. After 5 min prenyl bromide (9.1 μL, 0.078 mmol) was added, resulting in complete decolorization of the reaction mixture. Ammonium chloride (50 mg) was added, and the cooling bath and N_2 atmosphere were removed. When evaporation of the ammonia was complete the residue was diluted with water (4 mL) and extracted with CH_2Cl_2 (3 × 4 mL). The extracts were dried ($MgSO_4$) and concentrated to give an oil which, after preparative TLC on silica gel (eluent: ethyl acetate/ethanol 3/1), yielded the unnatural enantiomer of debromoflustramine B (**1**) as a colorless oil (12.6 mg, 57%): $[\alpha]_D$ = +98.5° (c = 0.96, $CHCl_3$) (lit.[1] $[\alpha]_D$ for natural enantiomer = −98.2°) δ_H 1.58 (3H, s), 1.65 (3H, d, J = 1.1 Hz), 1.69 (3H, d, J = 1.1 Hz), 1.71 (3H, s), 1.90 (1H, ddd, J = 3.4, 5.8, and 11.9 Hz), 2.05 (1H, ddd, J = 11.9, 9.1, and 6.6 Hz), 2.42 (2H, d, J = 7.6 Hz), 2.49 (3H, s), 2.56 (1H, ddd, J = 5.8, 9.6, and 12.6 Hz), 2.67 (1H, ddd, J = 12.6, 6.6, and 3.4 Hz), 3.79 (1H, dd, J = 7.2 and 16.0 Hz), 3.92 (1H, dd, J = 5.7 and 16.0 Hz), 4.27 (1H, s), 4.92–5.00 (1H, m), 5.13–5.19 (1H, m), 6.41 (1H, d, J = 7.8 Hz), 6.65 (1H, ddd, J = 7.3, 1.0, and 7.8 Hz), 6.97 (1H, ddd, J = 7.3, 1.3, and 0.4 Hz), and 7.04 (1H, dt, J = 1.3 and 7.8 Hz); δ_C 18.05, 18.13, 25.72, 25.92, 37.95, 38.47, 39.05, 46.80, 52.77, 57.05, 91.35, 107.29, 117.40, 120.77, 121.41, 122.81, 127.50, 133.45, 134.08, 135.71, and 151.88; ν (CH_2Cl_2) 2931, 1603, and 1488 cm^{-1}; HRMS calcd for $C_{21}H_{30}N_2$ 310.240899, found 310.240866 ($M^{+\cdot}$); CD λ (c = 0.0101, EtOH) nm ($\Delta\epsilon$) 254 (+2.4), 306 (+3.6) (lit.[1] CD for natural enantiomer λ (c = 0.0089, EtOH) nm ($\Delta\epsilon$) 254 (−2.11), 306 (−2.11)).

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Supplementary Material Available: ^{1}H-NMR spectra of compounds **1**, **16–25**, and **27–29** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.