is parallel to the long axis. This is because $\psi_{5\to6}$ and $(C_1\psi_{4\to6} - C_2\psi_{5\to7})$ belong to the different irreducible representations of the symmetry group C_{2v} and do not mix with each other.

As a result, aza substitution at the β position is considered to cause the short-axis polarization, except for phthalazine, for which the polarization direction is determined by symmetry rule. On the other hand, α-azanaphthalene holds to the same polarization direction as that of naphthalene, which is long-axis polarized.

Conclusion

The ICD spectra of the β-CD_x complexes with some azanaphthalenes were measured in the wavelength region 200–400 nm. For quinoxaline and cinnoline, weak negative CD bands were induced by the lowest allowed $\pi^* \leftarrow$ n transition.

The polarizaion directions of the first $\pi^* \leftarrow \pi$ transitions in azanaphthalenes are closely associated with the location of aza nitrogen atoms and can be evaluated by the coefficents of the configurations in the corresponding lowest $\pi^* \leftarrow \pi$ states.

From the observation of the ICD band with mixed signs, the presence of the forbidden character is strongly suggested in the second absorption bands of isoquinoline, phthalazine, cinnoline, and quinazoline. Though the third absorption band in each case of azanaphthalenes was regarded as the mixture of $\pi^* \leftarrow \pi$ states composed of many configurations, the observation of positive ICD bands in this region indicated the predominance of the long-axis-polarized electronic transitions.

Finally, it can be mentioned that the ICD method using the inclusion phenomena of β-CD_x is a useful tool for the analysis of the polarization in the aromatic molecules.

Registry No. β-Cyclodextrin·quinoline, 83528-62-5; β-cyclodextrin·isoquinoline, 83528-63-6; β-cyclodextrin·quinoxaline, 83528-64-7; β-cyclodextrin·1,5-naphthyridine, 83542-59-0; β-cyclodextrin·phthalazine, 83528-65-8; β-cyclodextrin·cinnoline, 83528-66-9; β-cyclodextrin·quinazoline, 83542-53-4; β-cyclodextrin·pyrido[2,3-*b*]pyrazine, 83528-67-0.

A New Total Synthesis of the Fungal Toxin Slaframine

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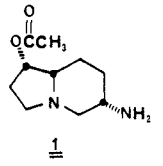
Abstract: Slaframine (**1**) has been synthesized from diene aldehyde **2**. An intramolecular imino Diels–Alder reaction has been used to produce the indolizidine skeleton and to establish the requisite stereochemistry of this fungal metabolite.

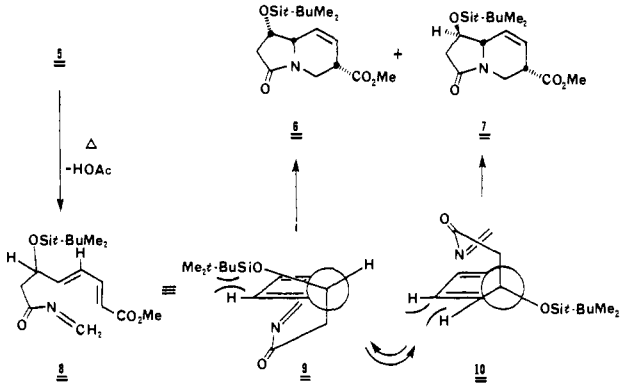
Slaframine (**1**), a neutrotoxic metabolite of *Rhizoctonia leguminicola*, is responsible for a disease characterized by excessive salivation in ruminants foraging on fungus-infected red clover hay.[1] The structure and absolute stereochemistry of this alkaloid were established by Rinehart et al.[2] in 1968. Aust has found that slaframine itself is not bioactive, but is oxidatively transformed in vivo to a compound that can then interact with muscarinic acetylcholine receptors, producing the observed symptoms.[3]



1

Work has also appeared recently on the biosynthesis of **1**.[4] To date, two total syntheses of slaframine have been reported.[5] Both relied heavily on classical Dieckmann chemistry to generate the indolizidine skeleton and upon catalytic hydrogenation to establish the three chiral centers of **1**. The first slaframine synthesis[5a] was nonstereoselective, but aided in confirmation of the proposed structure assignment. The second incorporated better stereocontrol,[5b] but it is not clear how selectively the stereochemistry contained in the six-membered ring of **1** was established. We now describe a completely new approach to slaframine that uses an intramolecular imino Diels–Alder cycloaddition[6] as the key step to efficiently construct the indolizidine ring system and to set the stereochemistry of **1**.

Scheme I



Our starting material for the synthesis was readily available[7] diene aldehyde **2** which was treated with the carbanion derived from bis(trimethylsilyl)acetamide (BSA)[8] in THF at −78 °C, followed by an acidic workup, affording β-hydroxy amide **3** (68%

(1) Rainey, D. P.; Smalley, E. B.; Crump, M. H.; Strong, F. M. *Nature (London)* **1965**, *205*, 203. Aust, S. D.; Broquist, H. P. *Ibid.* **1965**, *205*, 204.
(2) Gardiner, R. A.; Rinehart, K. L.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639 and references cited therein.
(3) Guengerich, F. P.; Aust, S. D. *Mol. Pharmacol.* **1977**, *13*, 185 and references cited therein.
(4) Clevenstine, E. C.; Broquist, H. P.; Harris, T. M. *Biochemistry* **1979**, *18*, 3659. Clevenstine, E. C.; Walter, P.; Harris, T. M.; Broquist, H. P. *Ibid.* **1979**, *18*, 3663.
(5) (a) Cartwright, D.; Gardiner, R. A.; Rinehart, K. L. *J. Am. Chem. Soc.* **1970**, *92*, 7615. (b) Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, *38*, 3848.
(6) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387 and references cited therein.
(7) Erhart-Subramanian, K. E. C.; Huisman, H. O.; de Koening, H. *Synth. Commun.* **1973**, *3*, 25.
(8) Morwick, T. *Tetrahedron Lett.* **1980**, *21*, 3227. We have found that the use of *sec*-butyllithium/TMEDA rather than *n*-butyllithium as originally reported significantly improved the yield of adduct **3**.

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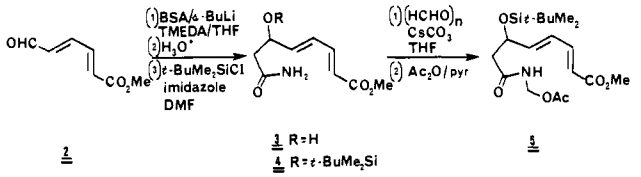
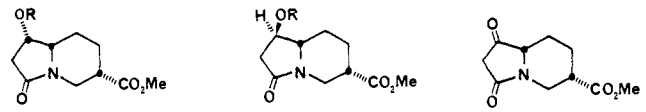


2 1 R=H 4 R=t-BuMe2Si 5

yield). This alcohol was transformed to the *tert*-butyldimethylsilyl ether **4**, using standard conditions[9] (76%).

In some of our previous imino Diels–Alder studies,[6] we converted various primary amides to "methylols" with aqueous formalin/NaOH. Application of this methodology to amide **4**, followed by acetylation of the crude adduct, gave irreproducible yields of the desired Diels–Alder precursor **5**. Thus, an improved alternative procedure has been developed which may be generally useful for synthesis of amide "methylol" derivatives.[10] Treatment of amide **4** with $CsCO_3$ and suspended paraformaldehyde in dry THF at room temperature,[6,11] followed by immediate acetylation of the crude product with acetic anhydride/pyridine, reproducibly afforded the acetate **5** (59%) and starting amide **4** (29%) which could be recycled.

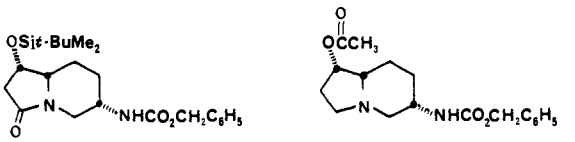
Thermolysis of **5** in refluxing *o*-dichlorobenzene for 4 h cleanly afforded an 82% yield of an easily separable 1:1.8 mixture of bicyclic lactams **6** and **7**, respectively.[12] The structure and stereochemistry of **6** and **7** were firmly established by their eventual conversion to slaframine and 1-epislaframine, respectively. We believe that this intramolecular imino Diels–Alder reaction occurs through the intermediate acylimine **8**, which cyclizes via conformation **9** or **10** (Scheme I).[6,13] The fact that **7** is formed in slightly larger amount than **6** is probably a result of a small vinyl hydrogen/silyl group nonbonded interaction present in conformer **9** and absent in **10**.[14] However, both isomers **6** and **7** could ultimately be converted into slaframine (vide infra). Catalytic hydrogenation of adducts **6** and **7** (10% Pd/C, MeOH, 1 atm) gave **11** and **13**, respectively, in nearly quantitative yields.



11 R=Sit-BuMe2 12 R=H 13 R=Sit-BuMe2 14 R=H 15

The incorrect epimer **13** was inverted by a short sequence involving cleavage of the silyl ether with concentrated HCl/THF, giving alcohol **14**, which upon oxidation with CrO_3/pyridine in CH_2Cl_2 afforded β-keto lactam **15**. Sodium borohydride reduction of **15** gave a 1:1 mixture of epimeric alcohols **12** and **14**. However, reduction of **15** with 9-BBN (THF, 0 °C; 45% from **13**) was completely stereoselective and produced *exclusively* the desired alcohol stereoisomer **12**.

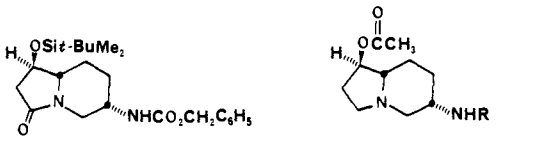
Completion of the synthesis of slaframine was readily accomplished from **11**. Hydrolysis of the ester group of **11** (5% KOH/MeOH, room temperature; 90%) gave the corresponding acid which was subjected to a standard Curtius rearrangement sequence without isolation of intermediates (EtOCOCl/pyridine, 0 °C; NaN_3, H_2O, 0 °C; THF, Δ; $C_6H_5CH_2OH$, room temperature) affording carbamate lactam **16** (48%). Without purification of any intermediates, lactam **16** was treated sequentially with (1) diborane in refluxing THF, (2) HCl/THF at reflux, and (3) acetic anhydride/pyridine at room temperature to yield the known[5a] carbamate ester **17** (50%). Catalytic hydrogenolysis of



16 17

17 (10% Pd/C, 10% HOAc/MeOH, 1 atm) gave racemic slaframine (90%) identical with natural material in its spectral characteristics and in TLC behavior.[15] Since slaframine itself is somewhat difficult to purify, it was further characterized by conversion to the known *N*-acetyl derivative which was identical with an authentic sample prepared from natural slaframine.[2,15]

A similar Curtius procedure was used to convert the epimeric ester **13** to the rearranged carbamate **18**. Reduction of the lactam



18 19 R=CO2CH2C6H5 20 R=H

carbonyl of **18** and acetylation as above led to indolizidine **19**, which upon catalytic hydrogenation yielded 1-epislaframine (**20**). This compound was clearly different in its TLC and spectral properties from slaframine. 1-Epislaframine was also characterized as its *N*-acetyl derivative.

Experimental Section

Melting points were taken on a Thomas-Hoover "Uni-Melt" capillary melting point apparatus equipped with a calibrated thermometer. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 197 spectrophotometer and were referenced to the 1601.4 absorbtion of polystyrene. Proton magnetic resonance spectra at 60 MHz were recorded on a Varian A-60A or EM-360 NMR spectrometer. Fourier transform ^1H NMR spectra and ^{13}C NMR spectra were obtained on a Brücker WM 360 (360 MHz) or on a Brücker WP 200 (200 MHz) spectrometer. All chemical shifts are reported in δ units, using tetramethylsilane as an internal standard. High- and low-resolution mass spectra were recorded by electron impact (EI) on an Associated Electrical Industries, Ltd., MS-902 double-focusing mass spectrometer. Chemical ionization mass spectra (CI) were recorded on a Finnegan 3200 quadrupole instrument. Analytical and preparative thin-layer chromatrography were done on Silica Gel 60 PF-254 (E.M. Merck). Liquid chromatography was carried out with 70–230 mesh Silica Gel 60 (E.M. Merck) as the stationary phase. Tetrahydrofuran (THF) was distilled first from lithium aluminum hydride and then from sodium benzophenone ketyl. Anhydrous magnesium sulfate was used as the drying agent in all workup procedures unless otherwise indicated.

Methyl (*E*,*E*)-5-Formyl-2,4-pentadienoate (2). This compound was prepared exactly as described for the corresponding ethyl ester.[7] The crude compound was purified by chromatography on silica gel eluting with hexane:ethyl acetate (8:2), giving **2** as a light yellow solid: mp 78–80 °C; IR ($CHCl_3$) 3010, 3000, 2870, 2720, 1720, 1690, 1600, 1440, 1320, 1290, 1270, 1220, 1170, 1140, 1100, 1040, 1000, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H), 6.3 (d, 1 H, J = 15 Hz), 6.4 (dd, 1 H, J = 15, 11 Hz), 7.4 (dd, 1 H, J = 15, 11 Hz), 9.7 (d, 1 H, J = 7 Hz); MS, m/z (relative intensity) 140 [M^+] (56.8), 125 (11.7), 111 (23.6), 109 (33.3), 97 (7.1), 81 (100), 69 (2.7).

Methyl (*E*,*E*)-6-Hydroxy-7-carbamoyl-2,4-heptadienoate (3). Distilled TMEDA (2.70 mL, 17.9 mmol) was carefully added to a stirred cyclohexane solution of *sec*-butyllithium (11.9 mL, 17.9 mmol) maintained at 0 °C under a nitrogen atmosphere. Stirring at 0 °C was continued for 30 min, and the reaction mixture was cooled to −78 °C with the concurrent addition of THF (5 mL). After 15 min, distilled bis(trimethylsilyl)acetamide (4.41 mL, 17.9 mmol) was slowly added, and the mixture was stirred at −78 °C for 3 h. Aldehyde ester **2** (0.5 g, 3.5 mmol) in THF (5 mL) was slowly added, and the mixture was stirred for an additional hour at −78 °C. The reaction mixture was treated with

(9) Ventkateswarlu, A.; Corey, E. J. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(10) Zaugg, H. E.; Martin, W. B. *Org. React. (N.Y.)* **1965**, *14*, 52.
(11) We are grateful to Dr. H. Zaugg (Abbott Laboratories) for suggesting this improved method of methylol formation.
(12) For reviews of the imino Diels–Alder reaction, see: Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. Weinreb, S. M.; Staib, R. R. *Tetrahedron*, in press.
(13) Nader, B.; Bailey, T. R.; Franck, R. W., Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 7573.
(14) Cf.: Nicolaou, K. C.; Magolda, R. L. *J. Org. Chem.* **1981**, *46*, 1508. Roush, W. R.; Myers, A. G. *Ibid.* **1981**, *46*, 1509.
(15) We are extremely grateful to Professor S. D. Aust for a generous sample of slaframine dipicrate and copies of spectra of **1** and its derivatives.

10% HCl and was allowed to warm to room temperature. The acidic aqueous THF solution was stirred at room temperature until TLC analysis indicated that β-hydroxy amide formation was complete, and the reaction mixture was continuously extracted with methylene chloride overnight. The organic layer was dried and concentrated in vacuo. Three runs using 0.27 g, 0.5 g, and 0.5 g of aldehyde ester **2** were combined and purified by silica gel column chromatography (80 g, ethyl acetate), affording 1.1 g (62%) of crystalline amide **3**: mp 116–120 °C; IR (Nujol) 3350, 3200, 1730, 1660, 1620, 1320, 1230, 1140, 1000 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.2 (d, 1 H, J = 6.1 Hz), 3.7 (s, 3 H), 4.5 (s, 1 H, br), 5.2 (d, 1 H, J = 4.6 Hz), 6.0 (d, 1 H, J = 15.3 Hz), 6.3 (dd, 1 H, J = 15.1, 4.6 Hz), 6.4 (dd, 1 H, J = 14.8, 11 Hz), 6.9 (s, 1 H, br), 7.3 (dd, 1 H, J = 15.4, 11 Hz); MS, m/z (relative intensity) 182 ([M^+] − 17) (2.9), 181 (12.7), 168 (1.5), 150 (75.9), 140 (13.4), 137 (16.3), 111 (94.4), 59 (100), 53 (47.2), 44 (40.3).

Anal. Calcd for $C_9H_{13}NO_4$: C, 54.27; H, 6.53; N, 7.04. Found: C, 54.20; H, 6.60; N, 6.96.

Methyl (*E*,*E*)-6-(*tert*-Butyldimethylsiloxy)-7-carbamoyl-2,4-heptadienoate (4). A solution of β-hydroxy amide **3** (0.5 g, 2.51 mmol), *tert*-butyldimethylsilyl chloride (0.93 g, 6.2 mmol), and imidazole (0.84 g, 12.3 mmol) in DMF (1.0 mL) was stirred at room temperature under nitrogen for 1 h. The crude reaction mixture was filtered through a silica gel column (20 g) eluting with ethyl acetate. Further purification by silica gel chromatography (50 g, 4:1 hexane:ethyl acetate) produced 0.589 g (75%) of the silylated amide **4** as a crystalline solid: mp 114–116 °C; IR ($CHCl_3$) 3500, 3420, 3375, 3000, 2960, 2940, 2900, 2860, 1740–1680 (br), 1620, 1580, 1460, 1440, 1380, 1320, 1260, 1140, 1080, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 3 H), 0.09 (s, 3 H), 0.9 (s, 9 H), 2.4 (dd, 1 H, J = 14.7, 6.6 Hz), 2.5 (dd, 1 H, J = 14.7, 4.9 Hz), 3.7 (s, 3 H), 4.7 (q, 1 H, J = 5.2 Hz), 5.6 (s, 1 H, br), 5.9 (d, 1 H, J = 15.6 Hz), 6.1 (dd, 1 H, J = 15.3, 5.2 Hz), 6.4 (dd, 1 H, J = 15.4, 11.4 Hz), 7.3 (dd, 1 H, J = 15.3, 11.3 Hz); MS, m/z (relative intensity) 313 [M^+] (0.1), 256 (81.1), 238 (20.2), 178 (24.9), 151 (7.6), 116 (100), 89 (3.9), 74 (88.0), 59 (14.0).

Anal. Calcd for $C_{15}H_{27}NO_4Si$: m/z 313.1709. Found: m/z 313.1718.

Methyl (*E*,*E*)-6-(*tert*-Butyldimethylsiloxy)-7-[(hydroxymethyl)carbamoyl]-2,4-heptadienoate Acetate (5). A mixture of powdered paraformaldehyde (0.062 g), anhydrous Cs_2CO_3 (0.422 g, 1.29 mmol), and amide **4** (0.689 g, 2.2 mmol) in 30 mL of dry THF was stirred under nitrogen at room temperature for 15 h. The reaction mixture was filtered and the solvent was evaporated in vacuo to a volume of about 10 mL. A solution of pyridine (1 mL) in acetic anhydride (6 mL) was added and the mixture was stirred for 5 h under nitrogen. The solvent was evaporated in vacuo and the residue was chromatographed on 40 g of silica gel (1:1, hexane:ethyl acetate) to give the methylol acetate **5** (0.503 g, 59%; mp 82–83 °C) and starting amide **4** (0.200 g, 29%).

5: IR ($CHCl_3$) 3460, 3380, 2960, 2940, 2860, 1760–1680 (br), 1650, 1620, 1500, 1440, 1365, 1320, 1240, 1140, 1080, 1000, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 3 H), 0.08 (s, 3 H), 0.9 (s, 9 H), 2.0 (s, 3 H), 2.4 (dd, 1 H, J = 14.6, 6.4 Hz), 2.5 (dd, 1 H, J = 14.6, 4.6 Hz), 3.7 (s, 1 H), 4.7 (m, 1 H), 5.18 (dd, 1 H, J = 10.4, 7.0 Hz), 5.24 (dd, 1 H, J = 10.4, 7.6 Hz), 5.9 (d, 1 H, J = 15.6 Hz), 6.1 (dd, 1 H, J = 15.3, 5.5 Hz), 6.4 (dd, 1 H, J = 15.1, 11.2 Hz), 7.3 (dd, 1 H, J = 15.4, 11.2 Hz); MS, m/z (relative intensity) 354 [M^+ − (OCH_3)] (0.7), 32, (34.9), 325 (1.6), 268 (71.7), 128 (100.0), 118 (23.4), 115 (3.6), 75 (94.0), 60 (17.7), 43 (65.3).

Anal. Calcd for $C_{18}H_{31}NO_6Si$: m/z 385.1921. Found: m/z 385.1929.

Cycloadducts 6 and 7. A solution of methylol acetate **5** (0.513 g, 1.33 mmol) in *o*-dichlorobenzene (100 mL) was refluxed for 4 h under nitrogen. The solution was cooled to room temperature and the solvent was removed in vacuo. The oily residue was chromatographed on silica gel (50 g) eluting with ethyl acetate, to give the epimeric cycloadducts **7** (0.249 g, 57%; oil) and **6** (0.145 g, 33%; mp 76–78 °C).

7: IR ($CHCl_3$) 3010, 2960, 2940, 2900, 2860, 1740, 1695, 1440, 1380, 1310, 1260, 1120, 820 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 2.46 (ddd, 1 H, J = 16.02, 8.85, 1.53 Hz), 2.66 (dd, 1 H, J = 16.02, 7.63 Hz), 2.95 (ddd, 1 H, J = 13.08, 5.0, 1.53 Hz), 3.17 (m, 1 H), 3.70 (s, 3 H), 3.91 (m, 1 H), 4.05 (dd, J = 16.17, 7.63 Hz), 4.57 (d, 1 H, J = 13.4 Hz), 5.93 (m, 1 H), 6.04 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.851 (q), −4.56 (q), 17.96 (s), 27.79 (q), 37.17 (t), 40.12 (d), 41.42 (t), 52.37 (q), 62.04 (d), 72.52 (d), 123.03 (d), 128.37 (d), 170.14 (s), 171.84 (s); MS, m/z (relative intensity) 325 [M^+] (0.7), 310 (3.2), 294 (1.6), 268 (100.0), 226 (88.1), 210 (3.1), 208 (21.4), 166 (28.1), 134 (22.8), 101 (53.0), 80 (31.0), 73 (48.0), 59 (37.3).

Anal. Calcd for $C_{16}H_{27}NO_4Si$: m/z 325.1710. Found: m/z 325.1730.

6: IR ($CHCl_3$) 3025, 2975, 2950, 2870, 1740, 1695, 1440, 1200, 1110, 960 cm^{-1}, ^1H NMR (360 MHz, $CDCl_3$) δ 0.0 (s, 6 H), 0.78 (s, 9 H), 2.26 (d, 1 H, J = 16.8 Hz), 2.61 (ddd, 1 H, J = 16.79, 4.88, 1.53 Hz), 2.91 (ddd, 1 H, J = 13.35, 4.88, 1.53 Hz), 3.13 (m, 1 H), 3.62 (s, 3 H), 4.14 (m, 1 H), 4.39 (m, 1 H), 4.61 (d, 1 H, J = 13.43 Hz), 5.70 (m, 1 H), 6.01 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.095 (q), −4.65 (q), 17.63 (s), 25.55 (q), 37.42 (t), 40.12 (d), 42.20 (t), 51.55 (q), 60.56 (d), 67.67 (d), 123.99 (d), 126.31 (d), 171.18 (s), 171.36 (s); MS, m/z (relative intensity) 325 [M^+] (0.1), 310 (4.9), 294 (2.6), 268 (100.0), 226 (18.6), 210 (1.7), 208 (12.2), 166 (11.9), 134 (20.1), 101 (30.0), 80 (29.5), 73 (40.9), 59 (32.5).

Anal. Calcd for $C_{16}H_{27}NO_4Si$: m/z 325.1727. Found: m/z 325.1707.

Preparation of Indolizidinones 11 and 13. A solution of cycloadduct **6** or **7** (0.100 g, 0.3 mmol) in methanol (35 mL) containing 10% Pd/C (40 mg) was stirred under 1 atm of hydrogen for 4 h. The mixture was filtered through Celite 545 and the solvent was removed in vacuo to give essentially pure saturated cycloadduct **11** or **13** (99 mg, 99%).

13 (oil): IR($CHCl_3$) 3000, 2960, 2940, 2860, 1730, 1690, 1440, 1255, 1110, 840 cm^{-1}; NMR (360 MHz, DCl_3) δ 4.57 (d, 1 H, J = 13.8 Hz), 3.99 (m, 1 H), 3.69 (s, 3 H), 3.21 (m, 1 H), 2.84 (m, 1 H), 2.69 (m, 1 H), 2.59–2.66 (m, 1 H), 2.26–2.34 (m, 2 H), 1.90 (m, 1 H), 1.60 (m, 1 H), 1.40 (m, 1 H); MS, m/z (relative intensity) 312 [M^+ − (CH_3)] (7.9), 296 (5.9), 270 (94.1), 242 (3.8), 238 (7.8), 228 (100), 194 (52.2), 164 (7.4), 136 (23.7), 101 (75.9), 89 (15.3), 75 (4.1), 73 (80.2), 55 (27.9).

Anal. Calcd for $C_{12}H_{20}NO_4Si$: m/z 270.1162 [M^+ − C_4H_9]. Found: m/z 270.1167.

11: mp 104–105 °C on recrystallization from ethyl acetate; IR ($CHCl_3$) 3000, 2960, 2940, 2850, 1740, 1690, 1440, 1380, 1320, 1100, 1000, 840 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.86 (s, 9 H), 1.41–1.45 (m, 4 H), 2.21–2.82 (m, 5H), 3.42 (m, 1 H), 3.68 (s, 3 H), 4.34 (m, 1 H), 4.57 (d, 1 H, J = 13.1 Hz); MS, m/z (relative intensity) 312 [M^+ − (CH_3)] (9.0), 296 (17.6), 270 (100.0), 242 (46.2), 238 (39.3), 228 (65.8), 194 (21.9), 164 (28.5), 136 (96.5), 101 (77.3), 89 (35.5), 75 (72.8), 73 (79.1), 55 (55.1).

Anal. Calcd for $C_{16}H_{29}NO_4Si$: C, 58.71, H, 8,86, N, 4.28. Found: C, 58.84; H, 8.84; N, 4.33.

Synthesis of β-Hydroxy Lactams 12 and 14. A solution of silyl ether isomer **11** or **13** (60 mg, 0.1, mmol) in THF (10 mL) containing 1 mL of 28% HCl was stirred at room temperature for 1 h. Acetic acid (0.25 mL) was added and the solution was carefully neutralized with 5% KOH. The mixture was extracted with ethyl acetate. The extract was dried over Na_2SO_4 and evaporated in vacuo to give the β-hydroxy lactam **12** or **14** (35 mg, 90%).

14: IR (film) 3600–3050, 2950, 2860, 1740, 1670, 1440 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.54 (d, 1 H, J = 12.2 Hz), 4.08 (m, 1 H), 3.67 (s, 3 H), 3.31 (1 H, m), 2.89 (1 H, m), 2.66–2.75 (2 H, m), 2.28–2.37 (2 H, m), 1.90–1.96 (1 H, m), 1.63–1.68 (1 H, m), 1.37–1.48 (1 H, m); MS, m/z (relative intensity) 213 [M^+] (47.8), 195 (35.5), 182 (20.1), 154 (100), 82 (97.4), 55 (23.4).

12: IR (film) 3600–3050, 2950, 2850, 1735, 1700–1660, 1440, 1260, 1210, 1180, 1100, 840, 800, 780 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.53 (1 H, d, J = 13.4 Hz), 4.37 (1 H, m), 3.70 (3 H, s), 3.45 (1 H, m), 2.25–2.84 (6 H), 1.59–1.93 (3 H); MS, m/z (relative intensity) 213 [M^+] (46.7), 195 (30), 182 (16.2), 154 (100), 82 (78.8), 55 (51.5).

Conversion of 14 to 12. To a solution of chromium trioxide (25 mg, 0.25 mmol) and pyridine (1 mL) in dry CH_2Cl_2 (2 mL) was added β-hydroxy lactam **14** (9 mg, 0.04 mmol) in CH_2Cl_2 (1 mL), and the resulting mixture was stirred under nitrogen for 2 h. Isopropyl alcohol (1 mL) was added and stirring was continued for 5 min. The mixture was diluted with ethyl acetate and was filtered. The filtered solid was washed with methanol and the filtrates were combined. Solvent evaporation in vacuo gave the β-keto lactam **15** (7 mg, 78%) as an unstable oil, which was used immediately without purification.

The crude β-keto lactam was dissolved in dry THF (2 mL) and was cooled to 0 °C. A solution (0.5 mL) of 9-borabicyclo[3.3.1]nonane (9-BBN) (0.5 M in THF) was added and the mixture was stirred under nitrogen for 2 h. Aqueous 5% HCl (0.5 mL) was added and the solvent was evaporated in vacuo. The residue was purified by preparative TLC on silica gel (methanol:ethyl acetate, 3:17) to yield 5 mg (57%) of β-hydroxy lactam **12**, identical with that produced above by hydrolysis of **11**.

Preparation of Carbamates 16 and 18. A solution of ester **11** (90 mg, 0.27 mmol) in methanol (5 mL) containing 5% aqueous KOH (5 mL) was stirred at room temperature for 1 h. The mixture was carefully neutralized with acetic acid and was extracted with ethyl acetate. The extract was dried over Na_2SO_4 and concentrated in vacuo to give the acid as a solid (77 mg, 90%): mp 134–137 °C; IR (film) 3700–2200, 2960, 2940, 2860, 1720–1640, 1460, 1440, 1260, 1100, 870, 840, 780 cm^{-1}; ^1H NMR (360 MHz), $CDCl_3$) δ 4.59 (1 H, d, J = 13.7 Hz), 4.45 (1 H, m), 3.45 (1 H, m), 2.72 (1 H, d, J = 13.4 Hz), 2.56 (2 H, m), 2.45 (1 H,

d, J = 12.8 Hz), 2.32 (1 H, dd, J = 5.5, 11.6 Hz), 1.70–1.30 (3 H, m), 0.87 (9 H, s), 0.07 (3 H, s), 0.06 (3 H, s); MS (CI) $M^+ + H$ (314).

The crude acid (77 mg, 0.25 mmol) was dissolved in dry THF (10 mL) and cooled to 0 °C under nitrogen. Pyridine (0.25 mL) was added followed by ethyl chloroformate (0.75 mL). The reaction mixture was stirred for 1 h and NaN_3 (0.600 g) in water (3 mL) was added. The resulting mixture was stirred for an additional 1 h at 0 °C. The mixture was diluted with water and extracted with ethyl acetate. The extract was dried over Na_2SO_4 and concentrated in vacuo to give the acyl azide as a colorless oil (76 mg) which was used without purification [IR (film) 2140, 1700 cm^{-1}].

The acyl azide was dissolved in dry THF (10 mL) and the solution was heated at reflux for 4 h. The solvent was removed in vacuo to give the crude isocyanate as an oil (69 mg) [IR (film) 2260, 1700 cm^{-1}] which was stirred in 3 mL of benzyl alcohol at room temperature for 12 h. Excess alcohol was removed in vacuo and the residue was purified by preparative TLC on silica gel eluting with ethyl acetate to give the benzyl carbamate **16** (55 mg, 52%) as a viscous oil: IR (film) 3500–3150, 2960, 2940, 2860, 1725–1680, 1530, 1500, 1470–1400, 1305, 1260–1200, 1090, 840, 780 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35 (s, 5 H), 5.0 (s, 2 H), 4.38 (m, 1 H), 4.08, (d, 1 H, J = 13.7 Hz), 4.01 (m, 1 H), 2.84 (d, 1 H, J = 13.1 Hz), 2.55 (ddd, 1 H, J = 9.1, 4.8, 1.6 Hz), 2.31 (dd, 1 H, J = 15.0, 2.1 Hz), 2.15 (d, 1 H, J = 13.4 Hz), 1.94–1.82 (m, 1 H), 1.68–1.59 (m, 1 H), 1.49–1.42 (m, 1 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H). MS, m/z (relative intensity) 418 [M^+] (0.4), 361 (14.5), 317 (17.2), 267 (18.7), 210 (46.2), 91 (100). ^{13}C NMR δ 173.4, 155.5, 136.4, 128.5, 128.1, 128.0, 77.2, 66.7, 61.2, 44.5, 41.2, 27.3, 25.7, 19.0, 18.1, −4.74, −5.06.

Anal. Calcd. for $C_{22}H_{34}N_2O_4Si$: m/z 418.2287. Found: m/z 418.2264.

With the methodology described above, ester **13** (99 mg, 0.30 mmol) was converted to the epimeric carbamate **18** (59 mg, 57%); IR (film) 3500–3150, 3060, 3030, 2960, 2940, 2860, 1720–1660, 1535, 1300, 1255, 1230, 1090, 1040, 940, 835, 780, 700 cm^{-1}; MS, m/z (relative intensity) 418 [M^+] (0.5), 403 (0.9), 361 (25.1), 317 (40.0), 267 (20.7), 253 (18.1), 210 (81.0), 91 (100); ^1H NMR (360 MHz, $CDCl_3$) δ 7.35 (5 H, s), 5.07 (2 H, s), 4.09 (1 H, d, J = 14.0 Hz), 4.03 (1 H, m), 3.97 (1 H, m), 3.21 (1 H, m), 2.87 (1 H, d, J = 13.7 Hz), 2.65 (1 H, dd, J = 8.0, 9.0 Hz), 2.29–2.36 (1 H, ddd, J = 9.1, 4.9, 1.6 Hz), 1.3 (1 H, m), 0.88 (9 H, s), 0.07 (3 H, s), 0.06 (3 H, s); ^{13}C NMR δ 172.5, 156.2, 77.2, 76.7, 71.8, 67.9, 64.7, 64.1, 52.1, 44.6, 44.1, 40.6, 30.7, 29.2, 27.5, 25.6, 24.8, 17.9, 0.99, −4.7, −4.8.

Anal. Calcd for $C_{22}H_{34}N_2O_4Si$: m/z 418.2289. Found: m/z 418.2289.

Preparation of Acetate Carbamates 17 and 19. To a stirred solution of carbamate **16** (55 mg, 0.13 mmol) in dry THF (15 mL) at 0 °C under nitrogen was added 1 M BH_3–THF (0.25 mL). The resulting solution was refluxed for 0.75 h. The solution was cooled to room temperature and 5% HCl (1 mL) was added. The solvent was removed in vacuo and the residue was hydrolyzed in refluxing THF:concentrated HCl (1:1) for 2 h. The solution was cooled to 0 °C and carefully basified with concentrated NaOH to pH 10, and the mixture was extracted with ethyl acetate. The extract was dried over Na_2SO_4 and the solvent was evaporated in vacuo. The resulting oil was dissolved in acetic anhydride (3 mL) and pyridine (0.25 mL) and the solution was stirred at room temperature for 0.5 h. The solvent was removed in vacuo and the residue was purified by preparative TLC on silica gel eluting with ethyl acetate to give 19 mg (45%) of acetate carbamate **17** as an oil: IR (film) 3425–3200, 3060, 3030, 2950, 2800, 1740–1700, 1495, 1450, 1370, 1310, 1240, 1110, 1090, 1070, 1025, 965, 910, 780, 770–740, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_2$) δ 7.37 (s, 5 H), 5.65 (m, 1 H), 5.25–5.17 (m, 1 H), 5.15 (d, 2 H, J = 1.53 Hz), 3.94 (m, 1 H), 3.09–2.99 (m, 2 H), 2.28–1.26 (m, 9 H), 2.07 (s, 3 H); MS, m/z (relative intensity) 332 [M^+] (1.4), 272 (8.7), 181 (100), 121 (43.6), 91 (58.3).

Anal. Calcd for $C_{18}H_{24}N_2O_4$: m/z 332.1736. Found: m/z 332.1733.

The above methodology was used to convert carbamate **18** (50 mg, 0.12 mmol) to the oily acetate carbamate **19** (20 mg, 50%): IR (film) 3450–3200, 3060, 3030, 2940, 2800, 1730, 1715, 1500, 1450, 1370, 1330, 1310, 1240, 1090 cm^{-1}; MS, m/z (relative intensity) 332 [M^+] (0.6), 272 (31.1), 181 (41.8), 164 (20.7), 121 (100), 108 (21.2), 91 (83.9); ^1H NMR (200 MHz), $CDCl_3$) δ 7.37 (s, 5 H), 5.60 (d, 1 H, J = 7.3 Hz), 5.09 (d, 2 H, J = 2.8 Hz), 4.74 (m, 1 H), 3.90 (m, 1 H), 2.83–2.95 (m, 2 H), 2.31–2.20 (m, 3 H), 2.05 (s, 3 H), 1.94–1.25 (6 H).

Anal. Calcd for $C_{18}H_{24}N_2O_4$: m/z 332.1736. Found: m/z 332.1712.

Racemic Slaframine (1). A solution of acetate carbamate **17** (10 mg, 0.05 mmol) in methanol:acetic acid (9:1, 8 mL) containing 10% Pd/C catalyst (1 mg) was stirred under hydrogen for 1 h at atmospheric pressure. The mixture was filtered through Celite 545 and the solvent was removed in vacuo to give essentially pure slaframine (**1**) as an oil identical with natural material[15] in TLC, IR, NMR, and MS properties (5.3 mg, 90%): IR (film) 3700–2200, 2950, 2800, 1735, 1570, 1400, 1240, 1110, 1030 cm^{-1}; MS, m/z (relative intensity) 198 [M^+] (12.0), 155 (77.9), 142 (76.6), 138 (75.7), 122 (17.2), 96 (29.1), 83 (36.3), 70.1 (72.7), 60 (32.7); ^1H NMR (360 MHz, $CDCl_3$) δ 5.22 (m, 1 H), 4.10 (m, 1 H), 3.08 (m, 5 H), 2.26–0.95 (6 H), 2.05 (s, 3 H).

Synthetic slaframine (8.0 mg, 0.04 mmol) was stirred at room temperature in acetic anhydride (1.0 mL) containing pyridine (3 drops) for 0.5 h. The solvent was removed in vacuo and the residue was purified by preparative TLC on silica gel eluting with ethyl acetate:methanol (8:2) to give *N*-acetylslaframine as an oil (5 mg, 52%) identical with a sample prepared by the same procedure from natural slaframine:[15] IR (film) 3700–3150, 3060, 2950, 2800, 1740, 1660, 1530, 1440, 1380, 1240, 1115, 1040, 1020 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.34 (m, 1 H), 5.25 (m, 1 H), 4.19 (m, 1 H), 3.13–2.99 (m, 2 H), 2.09 (s, 3 H), 2.01 (s, 3 H), 2.37–1.25 (9 H); MS, m/z (relative intensity) 181 (51.9), 121 (30.2), 94 (10.1), 43 (19.9).

Anal. Calcd for $C_{10}H_{15}NO_2$ [$M^+ - CH_3CONH_2$]: m/z 181.1031. Found: m/z 181.1111.

1-Epislaframine (20). Hydrogenolysis of acetate carbamate **19** (14 mg, 0.04 mmol), as described above, yielded 1-epislaframine (**20**) (8.0 mg, 95%) as a yellowish oil: IR (film) 3650–2400, 2940, 2860, 2800, 1735, 1560, 1450–1380, 1240, 1040 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.78 (m, 1 H), 3.95 (m, 1 H), 2.92 (m, 5 H), 2.42–1.20 (6 H), 2.05 (s, 3 H); MS, m/z (relative intensity) 198 [M^+] (0.2), 155 (2.3), 142 (2.8), 138 (5.4), 85 (0.2), 83 (0.9), 70 (3.3), 43 (4.2), 28 (100).

A solution of 1-epislaframine (8.0 mg, 0.04 mmol) in acetic anhydride (1.0 mL) and pyridine (3 drops) was stirred at room temperature for 0.5 h. The solvent was removed in vacuo and the residue was purified by preparative TLC on silica gel eluting with ethyl acetate:methanol (8:2) to give *N*-acetyl-1-epislaframine (6.0 mg, 63%) as an oil: IR (film) 3650–3100, 2925, 2850, 2800, 1735, 1650, 1525, 1440, 1370, 1240, 1175, 1090, 1040, 800 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.33 (m, 1 H), 4.77 (m, 1 H), 4.14 (m, 1 H), 2.89 (m, 2 H), 2.39–2.17 (m, 3 H), 2.05 (s, 3 H), 2.00 (s, 3 H), 1.96–0.82 (6 H); MS, m/z (relative intensity) 181 (57.4), 121 (100), 94 (22.7), 43 (37.6).

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Registry No. (±)-**1**, 30591-15-2; **2**, 40188-21-4; (±)-**3**, 83572-81-0; (±)-**4**, 83562-17-8; (±)-**5**, 83572-97-8; (±)-**6**, 83562-18-9; (±)-**7**, 83602-21-5; (±)-**11**, 83562-19-0; (±)-**11** acid, 83562-20-3; (±)-**11** acyl azide, 83562-21-4; (±)-**11** isocyanate, 83562-22-5; (±)-**12**, 83562-23-6; (±)-**13**, 83602-22-6; (±)-**14**, 83602-23-7; (±)-**15**, 83572-82-1; (±)-**16**, 83562-24-7; (±)-**17**, 30591-14-1; (±)-**18**, 83602-24-8; (±)-**19**, 83602-25-9; (±)-**20**, 83602-26-0; (±)-**20** (R = Ac), 83602-27-1; benzyl alcohol, 100-51-6.