trione (86%), mp 172–174 °C (lit.[9] mp 174–175 °C).

Registry No. 1, 79-37-8; **2a**, 91466-83-0; **2b**, 91466-84-1; **2c**, 91466-85-2; **2d**, 91466-86-3; **2e**, 91466-87-4; **2f**, 91466-88-5; **2g**, 91466-89-6; **3a**, 91466-90-9; **3b**, 91466-91-0; **3c**, 91466-92-1; **3d**, 91466-93-2; **3e**, 91466-94-3; **3f**, 91466-95-4; **6**, 6495-70-1; **7a**, 91466-96-5; **7b**, 91466-97-6; **7c**, 91466-98-7; **7e**, 91466-99-8; **7h**, 91467-00-4; **7i**, 91467-01-5; **7k**, 91467-02-6; **7l**, 91467-03-7; **7m**, 91467-04-8; **8a**, 91467-05-9; **8b**, 91467-06-0; **8c**, 91467-07-1; **8d**, 91467-08-2; **8e**, 91467-09-3; **8f**, 91467-10-6; **8g**, 91467-11-7; **8h**, 91467-12-8; **8i**, 91467-13-9; **8k**, 91467-14-0; **8l**, 91467-15-1; **8m**, 91467-16-2; **8n**, 91467-17-3; **10**, 91467-18-4; **11a**, 91467-19-5; **11b**, 30593-00-1; **13a**, 91467-20-8; **13b**, 91467-21-9; **13c**, 91467-22-0; **13d**, 91467-23-1; **14**, 91467-24-2; **15**, 91467-25-3; **20** (R = Ph, R′ = Me), 91467-26-4; **21a** (R = $CHMe_2$, R′ = Me), 91467-27-5; **21b** (R = $CHMe_2$, R′ = Me), 91467-28-6; **24** (R = Ph), 6488-59-1; **24** (R = $CHMe_2$), 3621-68-9; **24** (R = C_6H_{11}), 3621-71-4; CH_3-NCS, 556-61-6; C_2H_5-NCS, 542-85-8; C_4H_9-NCS, 592-82-5; C_6H_{11}-NCS, 1122-82-3; $C_6H_5CH_2$-NCS, 622-78-6; C_6H_5-NCS, 103-72-0; 4-$CH_3OC_6H_4$-NCS, 2284-20-0; CH_3-NCO, 624-83-9; C_2H_5-NCO, 109-90-0; C_3H_7-NCO, 110-78-1; *iso*-C_3H_7-NCO, 1795-48-8; C_4H_9-NCO, 111-36-4; *t*-C_4H_9-NCO, 1609-86-5; C_6H_{11}-NCO, 3173-53-3; $C_6H_5CH_2$-NCO, 3173-56-6; 4-$CH_3OC_6H_4CH_2$-NCO, 56651-60-6; 2-$ClC_6H_4CH_2$-NCO, 55204-93-8; C_6H_5-NCO, 103-71-9; 4-$CH_3C_6H_4$-NCO, 622-58-2; 4-$CH_3OC_6H_4$-NCO, 5416-93-3; dimethyl oxalate, 553-90-2; methyl phenylcarbamate, 2603-10-3; methyl cyclohexylcarbamate, 5817-68-5; aniline, 62-53-3; methoxalyl chloride, 5781-53-3; ethoxalyl chloride, 4755-77-5; methyl isopropylcarbamate, 5602-90-4; *N,N′*-diphenylcarbodiimide, 622-16-2; *N,N′*-diisopropylcarbodiimide, 693-13-0; *N,N′*-dicyclohexylcarbodiimide, 538-75-0.

Supplementary Material Available: Tables of crystallographic data, information about methodology, full experimental details, and bond distances and angles for 8 (12 pages). Ordering information is given on any current masthead page.

Synthesis of DL-Slaframine

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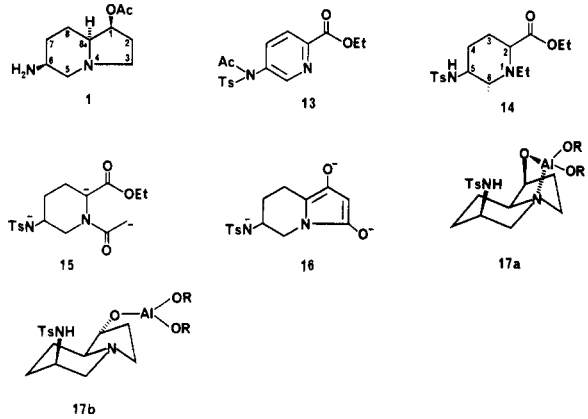
Received January 9, 1984

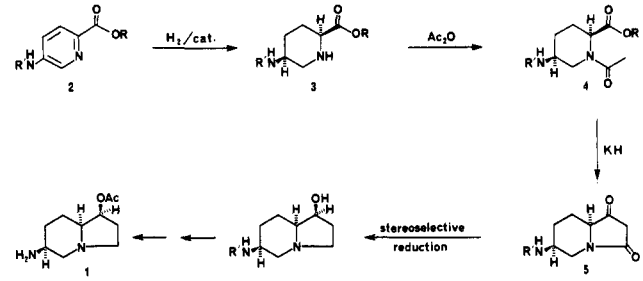
A stereoselective synthesis of DL-slaframine (1) is described, beginning with ethyl 5-nitropicolinate (6). The key step is formation of the octahydroindolizine nucleus via a potassium hydride cyclization of *N*-acetylpipecolate ester 8 to give β-keto lactam 9. Relative stereochemistry of C-6 and C-8a of 1 is set during catalytic reduction of picolinate ester 2, and this cis relationship of substituents is retained during the cyclization process. The relative configuration of C-1 is established via a stereoselective reduction of β-keto lactam 9 with L-Selectride (Aldrich). The yield of slaframine obtained from 6 is 12%.

The mycotoxin slaframine (1), produced by *Rhizoctonia leguminicola*, has been of interest since its isolation and identification as the agent responsible for excessive salivation in livestock consuming mold-infested legume feeds.[1]



The structure,[2] biosynthesis,[3] and metabolism[3a] of this alkaloid have been studied. Slaframine is of interest as a stimulator of the parasympathomimetic exocrine glands.

Scheme I. General Synthetic Approach



Studies have indicated that the stimulation is brought about by a metabolite of slaframine rather than by the alkaloid itself.

Three syntheses of DL-slaframine have been published. The initial one, reported in 1970 by Rinehart and coworkers, was based on the catalytic reduction of an appropriately substituted picolinic acid derivative followed by a potassium *tert*-butoxide catalyzed cyclization to close the five-membered ring.[4] This synthesis lacked stereoselectivity, giving a mixture of all possible diastereoisomers; the overall yield of slaframine was less than 0.1%. Subsequent work in Rinehart's laboratory by Christophel produced some improvements in the synthesis, most notably in the preparation of the key picolinate.[5] In 1973, Gensler and Hu published a stereoselective synthesis based on glutamic acid in which both rings were formed by Dieckmann cyclizations and the requisite cis,cis stereochem-

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(2) Gardiner, R. A.; Rinehart, Jr., K. L.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639.

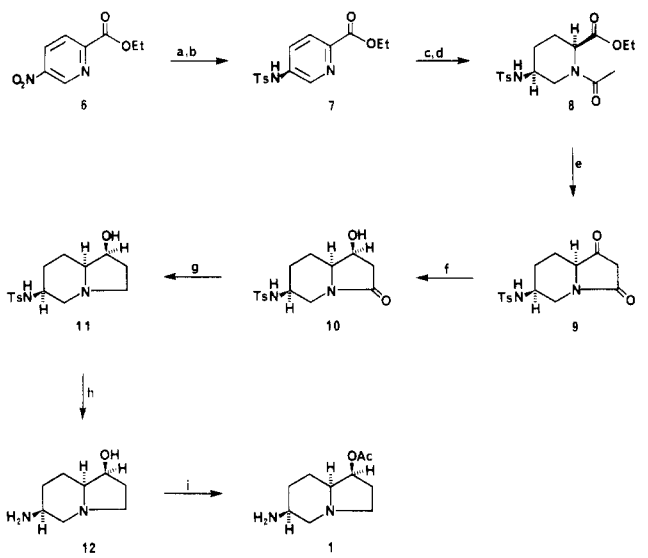
(3) (a) Guengerich, F. P.; Broquist, H. P. In "Bioorganic Chemistry;" van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. 2, Chapter 4. (b) Clevenstine, E. C.; Broquist, H. P.; Harris, T. M. *Biochemistry* **1979**, *18*, 3658. (c) Clevenstine, E. C.; Walter, P.; Harris, T. M.; Broquist, H. P. *Ibid.* **1979**, *18*, 3663. (d) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 6863.

(4) Cartwright, D.; Gardiner, R. A.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 7615.

(5) Christophel, W. PhD Thesis, University of Illinois at Urbana–Champaign, 1976.

0022-3263/84/1949-3681$01.50/0

Scheme II. Synthesis of DL-Slaframine from 6[a]



[a] (a) H_2, Pd/C, EtOH; (b) TsCl, pyridine; (c) H_2/PtO_2, HOAc, Ac_2O; (d) Ac_2O; (e) KH; (f) L-Selectride; (g) BH_3·THF; (h) Na, NH_3; (i) HOAc, HCl.

istry[6] was obtained by catalytic reductions of a ketone (C-1) and an oxime (C-6).[7] The overall yield for this synthesis was 0.3%. A recent synthesis by Weinreb and co-workers used an intramolecular imino Diels–Alder reaction to simultaneously create both rings of the octahydroindolizine nucleus.[8] The cyclization was not stereoselective at C-1 giving almost twice as much of the unwanted epimer. Development of a method for conversion of the epi cyclization product back to slaframine resulted in an overall yield of ~1.5% (based on commercially available starting materials).

It is doubtful whether any of these syntheses is efficient enough to be attractive for large scale preparation of slaframine. Furthermore, large quantities are not readily prepared by fermentation since alkaloid production is normally carried out in stationary cultures. Attempts to scale up via agitated cultures have led to reduced yields of the alkaloid. Below we present a new synthesis of slaframine which gives both high stereoselectivity and improved yields.

The general synthetic route chosen for this synthesis is outlined in Scheme I. The key step in this synthesis is the formation of the octahydroindolizine nucleus by the intramolecular acylation of *N*-acetylpipecolate **4** to give keto lactam **5**. Relative stereochemistry of C-6 and C-8a of **1** is set during catalytic reduction of picolinate ester **2** to give **3** and this cis relationship of substituents is retained during the cyclization process. The relative configuration of the third chiral center, C-1, is established by a stereoselective reduction using a bulky reducing agent.

The synthesis of slaframine is outlined in Scheme II. The picolinic acid derivative **6** was prepared from 2-chloro-5-nitropyridine by the method of Christophel.[5] Catalytic reduction (Pd/C, EtOH) of the nitro group and protection of the resultant amine as a tosylamide gave **7** (77% yield). Catalytic reduction of **7** with PtO_2 in acetic acid/acetic anhydride proceeded to give the pipecolate derivative, which was immediately treated with excess acetic anhydride to form the stable ethyl *N*-acetyl-5-(*p*-toluenesulfonamido)pipecolate **8** (64% yield from **7**, after chromatography). This catalytic reduction proceeded to give the cis stereochemistry at positions 2 and 5 of the pipecolate ring, as required for slaframine. Two additional minor products, **13** and one tentatively assigned as **14**, were obtained as well as a small amount of unreduced starting material **7**. Compound **13** represented unreduced starting material **7** which had been acetylated during acetic anhydride treatment. Compound **14** may result from reduction of a pipecolate–acetaldehyde adduct.

Cyclization of the five-membered ring posed a risk in that ionization of the C-2 position of pipecolate (C-8a of octahydroindolizine) could lead to loss of the desired stereochemistry which had been established by catalytic reduction. Two prior slaframine syntheses, utilizing alkoxide-catalyzed Dieckmann cyclizations, had encountered this problem and had yielded stereoisomeric mixtures of products.[4,7]

The potassium hydride cyclization (**8** → **9**) was expected to proceed without loss of stereochemistry at the C-2 position of pipecolate as ionization of the starting material at this position would render the ester group resistent to attack by the acetamide anion (**15**). Potential problems still existed as either exchange of the C-8a position of the product during workup or kinetic protonation of an intermediate such as **16** could give mixtures of products. The cyclization reaction of **8** with potassium hydride led to a single stereoisomer, as evidenced by ^{13}C NMR, indicating that the above complications had not occurred. Quenching and workup of the reaction in D_2O/DCl led to product containing significant deuterium incorporation at only the C-2 methylene and tosylamide NH, confirming that ionization at C-8a had not occurred. Thus, cyclization of the five-membered ring with potassium hydride eliminates the equilibration problems encountered with the previous Dieckmann cyclizations.

The next step required in the synthesis was introduction of the correct stereochemistry at C-1 during reduction of the keto lactam **9**. BH_3·THF (or $LiAlH_4$) could be used to reduce the keto lactam; however, the C-1 epimers of 1-hydroxy-6-(*p*-toluenesulfonamido)octahydroindolizine were produced in comparable amounts. It was thought that equilibration of the isomeric mixture, or of the undesirable trans isomer **17b** with aluminum isopropoxide/2-propanol/2-propanone would result in the desired cis isomer **17a** which, unlike **17b**, could be stabilized by aluminum complex formation. Treatment with aluminum isopropoxide or potassium *tert*-butoxide, however, resulted in no discernable equilibration.

A bulky reducing agent was next investigated. Use of the highly hindered monohexylborane (to reduce ketone) followed immediately by BH_3·THF (to reduce lactam) led to a low yield (~15% from **8**) of product **11**. Reduction with a hindered $LiAlH_4$ derivative, $LiAl(O\text{-}t\text{-}Bu)_3H$, gave only starting material. L-Selectride (lithium tri-*sec*-butylborohydride) (Aldrich) reduction of keto lactam **9**, however, proceeded to give the desired *cis*-1-hydroxy lactam **10** (42% from **8**). While some **10** was produced at 0 °C, higher yields were obtained at low temperature (−107 °C). The *cis,cis*-1-hydroxy-3-oxo-6-(*p*-toluenesulfonamido)octahydroindolizine (**10**) was then reduced with BH_3·THF in excellent yield (90%) to give the required *cis,cis*-1-hydroxy-6-(*p*-toluenesulfonamido)octahydroindolizine (**11**).[9]

(6) "Cis" and "trans" refer to the relative configurations at two sites, in particular, the C-8a and C-1 or C-8a and C-6 positions of the octahydroindolizine ring.

(7) Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, *38*, 3848.

(8) Gabao, R. A., Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065.

(9) Weinreb and co-workers[8] have addressed the problem of reduction of a related β-keto lactam. In their case, 9-BBN and a subsequent treatment with BH_3·THF were utilized.

Detosylation of 11 proceeded smoothly in sodium/liquid NH_3 to give the *cis,cis*-1-hydroxy-6-aminooctahydroindolizine (deacetylslaframine, **12**) in high yield (93%) and purity (>95%). The deacetylslaframine **12** was acetylated as the hydrochloride salt in acetic acid/HCl to give slaframine **1**. This selective acylation worked well (69% yield), although longer reaction times produced significant amounts of N-acetylated product. The one-step procedure is more direct than earlier routes from deacetylslaframine involving protection of the C-6 amino group, acetylation at C-1, and then deprotection. The synthetic DL-slaframine had chemical and physical properties identical with those of authentic material isolated from *R. leguminicola* and was obtained in an overall 12% yield from **6**, or 5% yield from the commercially available 2-chloro-5-nitropyridine. This route thus represents a substantial improvement over the previously described syntheses.

Experimental Section

Melting points were obtained with a Thomas Hoover capillary melting point apparatus, unless otherwise specified, and are uncorrected. ^1H NMR spectra were recorded on a JEOL MH-100 (100 MHz) or a JEOL FX-90Q (90 MHz) NMR spectrometer. The latter instrument, operating at 22.50 MHz, was used to obtain ^{13}C NMR spectra. Infrared spectra were recorded on a Perkin-Elmer 621 or 727 infrared spectrophotometer. Mass spectra were obtained with a LKB 9000 mass spectrometer, and high-resolution mass spectra were obtained with a VG Micromass 7070 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Silica gel for column chromatography, unless otherwise noted, was obtained from Davison (grade 62, 60–200 mesh). Short column chromatography[10] was carried out by using Merck silica gel 60G (TLC grade). Tetrahydrofuran (THF) was distilled from sodium/potassium alloy and benzophenone ketyl under nitrogen and used immmediately.

2-Methyl-5-nitropyridine. The method of Christophel was followed[5,11] by using 2-chloro-5-nitropyridine (0.315 mmol, 50 g, Aldrich) and sodium diethyl malonate (0.315 mmol). Yield: 23.8 g (55% yield); mp 106.5–108.5 °C (lit.[11a] mp 108–110 °C).

5-Nitropicolinic Acid.[12] Concentrated sulfuric acid (40.5 mL) was placed in a three-neck round-bottom flask fitted with a thermometer and mechanical stirrer. 2-Methyl-5-nitropyridine (39.9 mmol, 5.5 g) was added with stirring. Powdered chromium trioxide (119.4 mmol, 11.94 g, Fisher) was added in small portions with stirring; a water bath was employed to maintain the temperature below 70 °C. After the addition was complete, the mixture was allowed to cool to room temperature and poured onto ice/water (400 mL). The solid was collected and washed well with cold water. Recrystallization from water gave 5.59 g of 5-nitropicolinic acid (83% yield) as white plates, mp 209.5–210.5 °C (lit.[12] mp 210–212 °C).

Ethyl 5-Nitropicolinate (6). 5-Nitropicolinic acid (36.7 mmol, 6.17 g) was esterified by using absolute ethanol, benzene, and Dowex 50W × 8 (H^+ form) following the procedure of Christophel.[5] The yield of unrecrystallized white solid product was 6.96 g (97%), mp 102–104.5 °C (lit mp[4] 107–108 °C).

Ethyl 5-(*p*-Toluenesulfonamido)picolinate (7). Ester **6** (10.2 mmol, 2.0 g) in 95% ethanol (100 mL) was hydrogenated by using 10% palladium-on-carbon (0.4 g, Matheson Coleman & Bell) under 3 atm of hydrogen. After 7 h, the catalyst was removed by filtration (Celite) and the solvent was evaporated under reduced pressure to give crude ethyl 5-aminopicolinate. This intermediate, dissolved in dry pyridine (17 mL), was treated with *p*-toluenesulfonyl chloride (12.16 mmol, 2.32 g). After 10 min at room temperature, the mixture was heated on a steam bath for 15 min, cooled, then poured into water, and extracted with methylene chloride. The organic extracts were dried (Na_2SO_4), filtered, and then evaporated. The crude product was recrystallized from ethyl acetate, giving 2.5 g (77% yield from **6**) of **7**, mp 188–190 °C. Additional recrystallization from ethyl acetate gave mp 188.5–189.5 °C; ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 7 Hz), 2.38 (3 H, s), 4.40 (2 H, q, J = 7 Hz), 7.24 (2 H, d, J = 8 Hz), 7.70 (3 H, d, d, J = 9 Hz, 8 Hz), 8.04 (1 H, d, J = 9 Hz), 8.23 (1 H, s), 8.43 (1 H, d, J = 3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.27, 21.47, 61.88, 125.76, 126.68, 127.27 (2X), 129.98 (2X), 135.72, 136.92, 141.09, 143.69, 144.72, 164.55; IR (KBr) 1725, 1585, 1490, 1325, 1220, 1150, 1010, 900 cm^{-1}; MS, m/e (relative intensity) 320 (6, M^+), 276 (3), 275 (2), 248 (100), 155 (10), 91 (50). Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.13; H, 5.09; N, 8.67.

Ethyl *N*-Acetyl-5-(*p*-toluenesulfonamido)pipecolate (8). Ester **7** (3.12 mmol, 1.0 g), dissolved in acetic acid/acetic anhydride (60 mL/40 mL), was treated with platinum oxide (50 mg, Alfa) and hydrogen (4 atm) for 2 h. The catalyst was removed by filtration (Celite). Fresh platinum oxide (100 mg) was added and hydrogenation was continued for four days. After removal of the catalyst, the solvent was evaporated in vacuo. Acetic anhydride (50 mL) was immediately added to the residue, and the mixture was allowed to stir for several days at room temperature. After removal of the acetic anhydride in vacuo, the residue was purified by short column chromatography (40% ethyl acetate in hexane). The major product was **8** (0.73 g, 64% yield from **7**), a viscous oil which slowly crystallized to a white solid. Recrystallization from ethyl acetate/hexane gave colorless plates, mp 106.5–107.5 °C: ^1H NMR ($CDCl_3$) δ 1.21 (3 H, t), 1.30–2.37 (4 H, m), 2.02 (3 H, s), 2.41 (3 H, s), 2.80–3.17 (2 H, m), 3.77 (1 H, d, J = 9 Hz), 4.10 (2 H, q, J = 7 Hz), 5.20 (1 H, d, J = 4 Hz), 5.80 (1 H, d, J = 6 Hz), 7.24 (2 H, d, J = 8 Hz), 7.70 (2 H, d, J = 8 Hz): ^{13}C NMR ($CDCl_3$) δ 13.94 (q), 21.25 (2x, q), 25.10 (t), 27.92 (t), 49.05 (t), 49.80 (d), 50.40 (d), 61.13 (t), 126.73 (2X, d), 129.60 (2X, d), 137.84 (s), 143.42 (s), 170.34 (2X, s); IR (KBr) 3150, 1725, 1610, 1435, 1205, 1150 cm^{-1}; MS, m/e (relative intensity) 325 (1), 323 (2), 322 (1), 295 (36), 253 (100), 213 (2), 197 (38), 167 (18), 155 (15), 154 (16), 125 (44), 91 (26), 82 (50). Anal. Calcd for $C_{17}H_{24}N_2O_5S$: C, 55.42; H, 6.56; N, 7.60. Found: C, 55.59; H, 6.62; N, 7.51.

A second fraction (0.32 g) from the column was found to be unreduced material, most of which had been acetylated to form ethyl 5-(*N*-acetyl-*p*-toluenesulfonamido)picolinate (**13**). This acetylated material was recrystallized from ethyl acetate to give white plates, mp 169.5–170 °C: ^1H NMR ($CDCl_3$) δ 1.46 (3 H, t, J = 7 Hz), 2.05 (3 H, s), 2.47 (3 H, s), 4.52 (2 H, q, J = 7 Hz), 7.34 (2 H, d, J = 8 Hz), 7.82 (2 H, d, d, J = 8 Hz, 8 Hz), 8.27 (1 H, d, J = 8 Hz), 8.47 (1 H, d, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.27, 21.63, 25.10, 62.32, 125.70, 128.95 (2X), 129.82 (2X), 135.45, 136.43, 138.76, 145.75, 148.89, 150.19, 164.11, 168.93; IR (KBr) 1750, 1723, 1713, 1365, 1353, 1300, 1217, 1170 cm^{-1}; MS, m/e (relative intensity) 320 (77), 317 (2), 298 (3), 275 (5), 256 (14), 248 (100), 210 (19), 191 (17), 155 (18), 139 (13), 91 (89). Anal. Calcd for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73. Found: C, 56.64; H, 5.13; N, 7.61.

Also obtained from the column was a compound tentatively assigned as ethyl *N*-ethyl-5-(*p*-toluenesulfonamido)pipecolate (**14**, 60 mg), which was recrystallized from ethanol/water to give white needles, mp 83–85 °C (Kofler): ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 7 Hz), 1.26 (3 H, t, J = 7 Hz), 1.41–1.95 (4 H, m), 2.41 (3 H, s), 2.13–2.68 (4 H, m), 3.04 (1 H, dd, J 4.5 Hz, 7.5 Hz), 3.48 (1 H, m), 4.16 (2 H, q, J = 7 Hz), 5.26 (NH, d), 7.28 (2 H, d, J = 8.5 Hz), 7.77 (2 H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 11.45 (q), 13.94 (q), 21.15 (q), 25.43 (t), 28.14 (t), 48.83 (t, d, 2X), 53.22 (t), 60.10 (t), 61.94 (d), 126.68 (d, 2X), 129.39 (d, 2X), 138.22 (s), 142.88 (s), 172.56 (s); IR (KBr) 3120, 1720, 1465, 1445, 1325, 1180, 1150, 1080 cm^{-1}; MS, m/e (relative intensity) 281 (100), 199 (2), 155 (8), 153 (10), 110 (25), 91 (13); high-resolution MS (CI, NH_3) calcd for $[C_{17}H_{27}N_2O_4S]^+$ 355.1691, found 355.1722.

***cis*-1,3-Dioxo-6-(*p*-toluenesulfonamido)octahydroindolizine (9).** The procedure of Clevenstine et al. for the preparation of 1,3-dioxooctahydroindolizine was followed.[3c] Potassium hydride (2.7 mmol, oil dispersion, Alfa) was added to a two-neck round-bottom flask and washed with pentane under nitrogen. The potassium hydride was resuspended in THF (10 mL) and stirred while ester **8** (0.679 mmol, 0.25 g) was added in THF (4 mL) over 5 min. After 3 h, the THF was removed in vacuo and ice/water was added to the residual solid with ice bath cooling. The mixture was washed with methylene chloride. The aqueous phase was acidified to pH 6 (in ice bath) by dropwise addition of ice cold 1 N hydrochloric acid. The resulting milky white

(10) Hunt, B. J.; Rigby, W. *Chem. Ind. (London)* **1967**, 1868.
(11) (a) Dummel, R. J.; Mosher, H. S. *J. Org. Chem.* **1959**, *24*, 1007. (b) Cooper, G. H.; Richard, R. L. *J. Chem. Soc. C* **1971**, 772.
(12) Cooper, G. H.; Richard, R. L. *Synthesis* **1971**, 31.

solution was extracted repeatedly with methylene chloride and the combined extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give keto lactam **9** as a glass. To prevent dimer formation, **9** was either used immediately or stored at −10 °C as a dilute solution in methylene chloride: ^1H NMR ($CDCl_3$) δ 1.2–2.2 (4 H, m), 2.43 (3 H, s), 2.83 (1 H, d, J = 14 Hz), 3.06 (2 H, s), 3.64 (2 H, m), 4.17 (1 H, d, J = 14 Hz), 6.16 (1 H, d, J = 7.5 Hz), 7.31 (2 H, d, J = 8.5 Hz), 7.76 (2 H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 20.28 (t), 21.42 (q), 27.97 (t), 40.92 (t), 43.74 (t), 46.77 (d), 63.89 (d), 126.95 (2X, d), 129.71 (2X, d), 137.57 (s), 143.42 (s), 168.61 (s), 205.34 (s); IR (CH_2Cl_2, 0.5 mm) 2985–3310, 1775, 1700, 1328, 1148, 1183 cm^{-1}; MS, m/e (relative intensity) 322 (44, M^+), 294 (4), 223 (6), 210 (25), 172 (5), 167 (80), 155 (52), 151 (100), 150 (25), 138 (36), 123 (13), 112 (12), 97 (18), 95 (11), 91 (74); high-resolution MS calcd for $C_{15}H_{18}N_2O_4S$ 322.0987, found 322.0979.

***cis,cis*-1-Hydroxy-3-oxo-6-(*p*-toluenesulfonamido)octahydroindolizine (10).** L-Selectride (1 M in THF, 2.2 mL, Aldrich) was placed in a round-bottom flask which had been cooled to −107 °C (isooctane/liquid N_2) under nitrogen. Keto lactam **9** in THF (30 mL) was added dropwise over 30 min with stirring. After 2 h, the mixture was warmed to 0 °C. Water was added and then 1 N hydrochloric acid to pH 5–6. The solvents were removed in vacuo and the residue, after addition of water, was extracted with methylene chloride. The combined extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. This crude product purification by short column chromatography (4% methanol in chloroform) gave 93 mg of **10** (42% yield from **8**) as an oil. Crystallization from ethyl acetate gave white plates, mp 212–216 °C: ^1H NMR ($CDCl_3$) δ 1.5 (2 H, m), 2.0 (2 H, m), 2.42 (3 H, s), 2.58–2.89 (2 H, m), 3.5 (2 H, m), 4.07 (1 H, d, J = 13.5 Hz), 4.31 (1 H, t, J = 5 Hz), 6.93 (1 H, d, J = 9 Hz), 7.30 (2 H, d, J = 8.5 Hz), 7.79 (2 H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.06, 21.52, 27.43, 41.57, 45.47, 46.82, 61.34, 66.60, 126.95 (2X), 129.71 (2X), 138.38, 143.20, 175.06; IR (KBr) 3300, 3200, 1675, 1445, 1325, 1150, 1085 cm^{-1}; MS, m/e (relative intensity) 325 (2), 324 (2), 253 (1), 210 (3), 169 (25), 153 (100), 140 (15), 122 (16), 114 (25), 91 (27). Anal. Calcd for $C_{15}H_{20}N_2O_4S$: C, 55.54; H, 6.21; N, 8.64. Found: C, 55.64; H, 6.30; N, 8.60.

***cis,cis*-1-Hydroxy-6-(*p*-toluenesulfonamido)octahydroindolizine (11).** Compound **10** (0.287 mmol, 93 mg) and THF (11 mL) were placed in a two-neck round-bottom flask under nitrogen. The suspension was chilled in an ice bath and BH_3·THF (1 M, 1.3 mL, Aldrich) was added with stirring. The mixture was refluxed for 1 h in an oil bath, during which time most of the solid appeared to dissolve. The mixture was cooled in an ice bath, and 6 N hydrochloric acid (6 mL) was added dropwise. The THF was distilled off. Water was added to the residue and the acidic solution was extracted with methylene chloride. The extract was washed with 1 N hydrochloric acid; the washings were combined with the aqueous solution. The resulting solution was basified with potassium carbonate to pH 10 and extracted with methylene chloride. The final methylene chloride extract was dried (Na_2SO_4), filtered, and evaporated in vacuo to give crude **11** as an oil (80 mg, 90% yield). This material could be crystallized from methanol/water to give small white needles, mp 147–148.5 °C (Kofler): ^1H NMR ($CDCl_3$) δ 1.29–2.06 (10 H, m), 2.42 (3 H, s), 2.83 (2 H, m), 3.55 (1 H, s), 4.05 (1 H, br s) 6.4 (NH, broad), 7.28 (2 H, d, J = 8.5 Hz), 7.81 (2 H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 19.68, 21.39, 28.97, 33.01, 48.45, 52.11, 57.14, 67.76, 72.80, 126.81 (2X), 129.47 (2X), 138.73, 142.82; IR (KBr) 3370–3620 (br), 3050–3370 (br), 1440, 1315, 1145, 1110, 1085, 1000 cm^{-1}; MS, m/e (relative intensity) 310 (3, M^+), 292 (6), 173 (1), 160 (2), 155 (100), 139 (6), 138 (14), 137 (7), 126 (28), 112 (24), 94 (10), 91 (17). Anal. Calcd for $C_{15}H_{22}N_2O_3S$: C, 58.04; H, 7.14; N, 9.02. Found: C, 57.91; H, 7.21; N, 9.00.

***cis,cis*-1-Hydroxy-6-aminooctahydroindolizine (12).** Compound **11** (0.258 mmol, 80 mg) was placed in a two-neck round-bottom flask fitted with a dry ice condenser; gaseous ammonia was introduced until ~12 mL had condensed. Sodium (washed with pentane) was added in small portions until a dark blue color persisted for 1 h (310 mg sodium). Solid $NaOAc·3H_2O$ was then added until the color of the reaction mixture changed from blue to grey. The ammonia was allowed to evaporate, water was added, and the mixture was extracted with chloroform:ethanol (2:1). The extract was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography [chloroform:methanol:concentrated ammonium hydroxide (10:8:1)] to give **12** as an oil (93% yield). Chemical and spectroscopic characteristics were identical with those of authentic deacetylslaframine: ^1H NMR ($CDCl_3/D_2O$) δ 1.5–2.32 (9 H, m), 3.0 (3 H, m), 4.06 (1 H, br d, J = 4.5 Hz); ^{13}C NMR (D_2O/~5% NaOD) δ 19.52, 30.63, 32.26, 45.37, 53.33, 59.45, 69.20, 72.45; IR (CH_2Cl_2, 0.5 mm) 3000–3700, 2930, 2800, 1600, 1110 cm^{-1}; MS, m/e (relative intensity) 156 (2, M^+), 155 (2), 138 (54), 113 (51), 100 (67), 96 (20), 82 (14), 70 (100).

DL-Slaframine (*cis,cis*-1-Acetoxy-6-aminooctahydroindolizine, 1). Compound **12** (0.115 mmol, 18 mg) was dissolved in methanol and the solution was saturated with dry HCl. The solvent was removed in vacuo, dry acetic acid (14 mL) was added and the flask, fitted with a condenser and drying tube, was immersed in a 75 °C oil bath for 1 h (longer reaction times led to a significant amount of N-acetylation). The mixture was cooled to room temperature and the solvents were removed in vacuo. After addition of water, sodium bicarbonate and potassium carbonate to give pH 10, the solution was extracted with methylene chloride. The extract was dried (Na_2SO_4), filtered and evaporated; the residue was purified by column chromatography [silica gel 60 (Merck 9385, 230–400 mesh), chloroform:methanol:concentrated ammonium hydroxide (120:20:1)] to give 15.8 mg (69% yield) of **1**. Chemical and spectral characteristics were identical with those of authentic slaframine. ^1H NMR ($CDCl_3$) δ 1.4–2.3 (8 H, m), 2.07 (3 H, s), 2.13 (3 H, s), 3.04 (3 H, m), 5.2 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 19.74, 20.98, 30.52, 30.84, 45.85, 53.06, 59.45, 67.52, 74.94, 170.8 IR (CH_2Cl_2, 0.5 mm) 2915, 2780, 1725, 1595, 1365, 1095, 1015 cm^{-1}; MS, m/e (relative intensity) 198 (17, M^+), 181 (4), 168 (5), 155 (80), 142 (70), 139 (22), 138 (100), 137 (10), 128 (10), 122 (17), 121 (15), 120 (12), 112 (14), 111 (26), 100 (24), 96 (32), 95 (23), 94 (30), 82 (30), 70 (79).

Registry No. (±)-**1**, 30591-15-2; **6**, 30563-98-5; **7**, 90866-93-6; (±)-**8**, 90866-94-7; (±)-**9**, 90866-97-0; (±)-**10**, 90866-98-1; (±)-**11**, 90866-99-2; (±)-**12**, 90899-84-6; **13**, 90866-95-8; **14**, 90866-96-9; 2-methyl-5-nitropyridine, 21203-68-9; 2-chloro-5-nitropyridine, 4548-45-2; sodium diethyl malonate, 996-82-7; 5-nitropicolinic acid, 30651-24-2.