CH_2CH_3); IR (KBr) ν_{max} 3364, 3082, 2985, 1735, 1707, 1635, 1347, 1242, 1100 cm^{-1}; FABHRMS (NBA/NaI) m/e 338.1011 ($M + Na^+$, $C_{17}H_{17}NO_5$ requires 338.1004).

Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.53; H, 5.59; N, 4.47.

9-(Benzyloxy)-3-(ethoxycarbonyl)-1-methoxy-7,8-dihydro-6*H*-cyclopent[*g*]isoquinolin-8-one (9a). A solution of **2a** (72 mg, 0.24 mmol) in DMF (2.0 mL) was treated sequentially with K_2CO_3 (100 mg, 0.7 mmol, 3.0 equiv), Bu_4NI (10 mg, 0.25 mmol, 0.1 equiv), and $PhCH_2Br$ (100 μL, 0.75 mmol, 3.0 equiv). The reaction mixture was stirred at 70 °C (6 h) before it was cooled to 25 °C, diluted with H_2O (30 mL), extracted with CH_2Cl_2 (20 mL × 3), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 20 cm, 20% EtOAc–hexane) afforded **9a** (88 mg, 94 mg theoretical, 94%) as an off-white solid: mp 157–158 °C (CH_2Cl_2–EtOAc, off white solid); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (1 H, s, C4-H), 7.66 (2 H, d, J = 7.2 Hz, Ph), 7.57 (1 H, s, C5-H), 7.41 (2 H, t, J = 7.2 Hz, Ph), 7.34 (1 H, t, J = 7.2 Hz, Ph), 5.19 (2 H, s, $PhCH_2$), 4.44 (2 H, q, J = 7.2 Hz, CH_2CH_3), 4.12 (3 H, s, OCH_3), 3.24 (2 H, m, CH_2CH_2), 2.77 (2 H, m, CH_2CH_2), 1.44 (3 H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.2 (e, C8), 165.3 (e), 162.4 (e), 156.6 (e), 155.3 (e), 144.1 (e), 140.9 (e), 136.9 (e), 130.2 (e), 128.7 (o, two aromatic CH), 128.4 (o, two aromatic CH), 128.1 (o), 120.5 (o), 117.7 (o), 115.5 (e), 77.7 (e, $PhCH_2$), 61.6 (e, CH_2CH_3), 54.1 (o, OCH_3), 37.2 (e, CH_2CH_2), 25.1 (e, CH_2CH_2), 14.2 (o, CH_2CH_3); IR (KBr) ν_{max} 2946, 1735, 1712, 1616, 1567, 1348, 1257, 1115 cm^{-1}; FABHRMS (NBA) m/e 392.1498 ($M + H^+$, $C_{23}H_{21}NO_5$ requires 392.1498).

Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.19; H, 5.12; N, 3.58.

9-(Benzyloxy)-1-ethoxy-3-(ethoxycarbonyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinolin-8-one (9b). A solution of **2b** (270 mg, 0.86 mmol) in DMF (15.0 mL) was treated sequentially with K_2CO_3 (1.0 g, 7.2 mmol, 8.4 equiv), Bu_4NI (50 mg, 0.14 mmol, 0.16 equiv), and $PhCH_2Br$ (300 μL, 2.5 mmol, 2.9 equiv). The reaction mixture was stirred at 25 °C (38 h) before it was diluted with H_2O (100 mL), extracted with CH_2Cl_2 (60 mL × 3), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 12 cm, 20% EtOAc–hexane) afforded **9b** (318 mg, 347 mg theoretical, 92%) as an off-white solid: mp 159–160 °C (CH_2Cl_2–EtOAc, pale yellow plates); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (1 H, s, C4-H), 7.64 (2 H, d, J = 7.0 Hz, Ph), 7.59 (1 H, s, C5-H), 7.39 (2 H, t, J = 7.0 Hz, Ph), 7.33 (1 H, t, J = 7.0 Hz, Ph), 5.26 (2 H, s, $PhCH_2$), 4.63 (2 H, q, J = 7.0 Hz, CH_2CH_3), 4.45 (2 H, q, J = 7.0 Hz, CH_2CH_3), 3.26 (2 H, m, CH_2CH_2), 2.78 (2 H, m, CH_2CH_2), 1.45 (3 H, t, J = 7.0 Hz, CH_2CH_3), 1.31 (3 H, t, J = 7.0 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.2 (e, C8), 165.4 (e, CO_2Et), 162.2 (e), 157.0 (e), 155.2 (e), 144.3 (e), 141.1 (e), 137.0 (e), 128.4 (o, two aromatic CH), 128.2 (o, two aromatic CH), 128.0 (o), 120.4 (o), 117.5 (o), 115.6 (e), 96.1 (e), 77.8 (e, CH_2Ph), 63.0 (e, CH_2CH_3), 61.6 (e, CH_2CH_3), 37.2 (e, CH_2CH_3), 25.2 (e, CH_2CH_2), 14.3 (o, CH_2CH_3), 14.26 (o, CH_2CH_3); IR (KBr) ν_{max} 2929, 1734, 1706, 1616, 1559, 1333, 1228, 1105, 1043 cm^{-1}; FABHRMS (NBA/CsI) m/e 538.0615 ($M + Cs^+$, $C_{24}H_{23}NO_5$ requires 538.0631).

Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.15; H, 5.71; N, 3.44.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA42056) and the preliminary studies of I. C. Jacobson.

Supplementary Material Available: ^1H NMR of **5a–b**, **6b**, **7b**, and **9b** (5 pages). This material is contained in many 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.

Synthesis of (–)-Slaframine and Related Indolizidines

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An enantioselective synthesis of the indolizidine alkaloid (–)-slaframine **1** is reported. Reductive double cyclization of the azido epoxy tosylate **48** afforded the indolizidine **52**, which was converted to (–)-slaframine in two steps. The cyclization substrate **48** was prepared in optically pure form from L-glutamic acid. A similar sequence starting with the epoxide **49** allowed the synthesis of (–)-1,8a-diepislaframine **56**. Other routes to slaframine were investigated, often using an intramolecular cycloaddition of an azide with an alkene as a key step. Although these routes did not produce slaframine, they illustrated novel and efficient methods for the assembly of the indolizidine skeleton. Cyclization of the azidodiene **20** afforded the indolizidine **21** in one step as a single diastereomer, presumably a result of a chairlike transition state in the initial dipolar cycloaddition. Desulfurization and deprotection produced (–)-8a-epidesacetoxyslaframine **27**. Cyclopropylimine rearrangement of **30** gave the indolizidine **31**, which was also converted into (–)-8a-epidesacetoxyslaframine **27**. Dipolar cycloaddition of **38** gave the 1-pyrroline **39**, which was converted to the indolizidine **40** in one operation using Evans' double alkylation of the 1-metalloenamine derivative of **40**. Attempted oxidation of **40** to the ketone **41** was unsuccessful, precluding a reductive amination approach to slaframine.

Forages contaminated with the fungus *Rhizoctonia leguminicola* are responsible for a disease in ruminants known as "black patch".[1] The most obvious symptom associated with ingestion of contaminated feed is excessive salivation, which is thought to be caused by the alkaloid slaframine **1**.[1-5] It has been proposed that slaframine is oxidized in the liver to an active metabolite which is a muscarinic agonist.[1] Beyond its potential in the treatment of diseases involving cholinergic dysfunction, slaframine has been under active investigation for its potentially

(1) Broquist, H. P. *Ann. Rev. Nutr.* **1985**, *5*, 391–409.

(2) General reviews: (a) Reference 1. (b) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, pp 183–308. (c) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, pp 1–54.

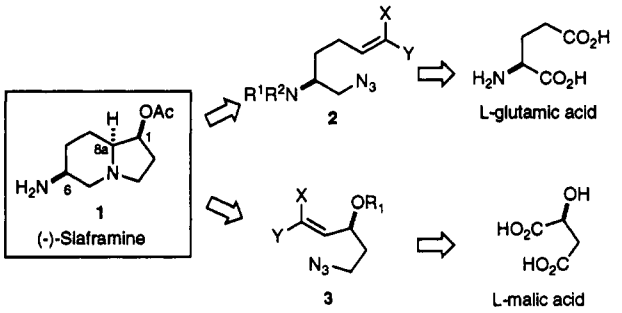
(3) Isolation: (a) Rainey, D. P.; Smalley, E. B.; Crump, M. H.; Strong, F. M. *Nature (London)* **1965**, *205*, 203–204. (b) Aust, S. D.; Broquist, H. P. *Nature (London)* **1965**, *205*, 204.

(4) Structure determination: Gardiner, R. A.; Rinehart, K. L., Jr.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639–5640.

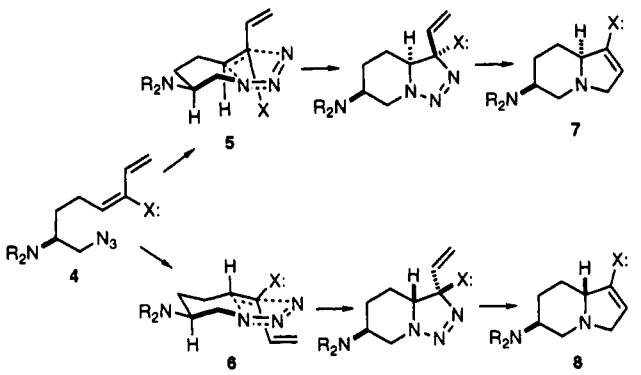
(5) Biosynthesis: Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940–949 and earlier references therein.

0022-3263/92/1957-3977$03.00/0

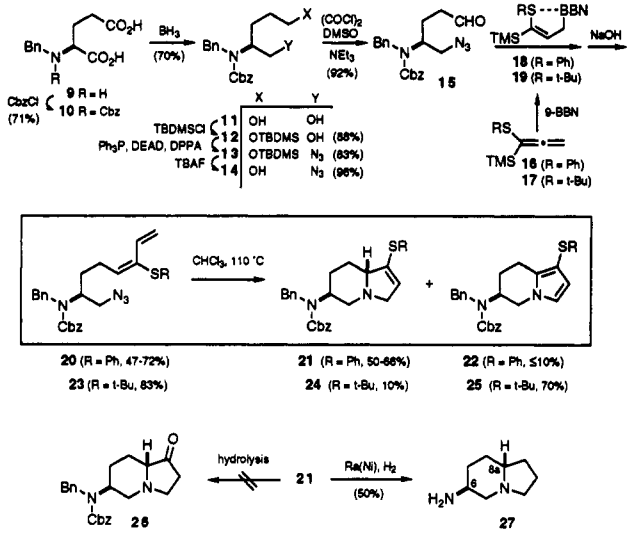
Scheme I



Scheme II



Scheme III



beneficial effects on ruminant digestive function.[6] Unfortunately, slaframine is an air-sensitive compound which is not easily obtained in significant quantities by fermentation. A useful synthetic route would be desirable, given the growing interest in this alkaloid. We have evaluated several potential synthetic routes to slaframine which rely upon the chemistry of azides, and we now wish to report a full account of the first synthesis of the natural enantiomer of slaframine as well as the synthesis of some related indolizidines.[7] Verification of the previously proposed absolute stereochemistry of slaframine is obtained, and the last step in its synthesis involves a simple conversion of a stable precursor of slaframine into the free alkaloid.

Total syntheses of racemic slaframine have been reported by Rinehart,[8] Gensler,[9] Weinreb,[10] Harris,[11] and Flitsch.[12] A formal total synthesis has been reported by Shono.[13] It is interesting to note that the racemate is produced in each synthesis, even when optically active materials such as L-glutamic acid[9,12] or L-lysine[13] are used as starting materials. Given that the determination of the absolute stereochemistry of slaframine rests largely on indirect methods,[14] an unambiguous stereochemical confirmation is desirable. Our synthesis of slaframine confirms that the absolute stereochemistry of this alkaloid is 1*S*,6*S*,8a*S*, as had been previously proposed. Since the publication of our preliminary account of this work,[7] Cha has reported a synthesis of (−)-slaframine, also using azide chemistry.[15]

We[16-18] and others[15,19,20] have been interested in developing general synthetic methods for the preparation of indolizidine and pyrrolizidine alkaloids based upon the intramolecular 1,3-dipolar cycloaddition of azides with functionalized alkenes, such that both rings are formed in a single synthetic operation. Two basic approaches to slaframine were envisioned, as shown in Scheme I. Cyclization of **2**, derived from L-glutamic acid, or **3**, derived from L-malic acid, would provide access to the basic skeleton of slaframine in optically active form. The groups X and Y would incorporate the remaining carbon atoms required, as well as other functional groups as necessary,

(6) (a) Froetschel, M. A.; Amos, H. E.; Evans, J. J.; Croom, W. J., Jr.; Hagler, W. M., Jr. *J. Anim. Sci.* **1989**, *76*, 827–834 and earlier references therein. (b) Jacques, K.; Harmon, D. L.; Croom, W. J., Jr.; Hagler, W. M., Jr. *J. Dairy Sci.* **1989**, *72*, 443–452 and earlier references therein.

(7) Preliminary accounts of a portion of this work have appeared: (a) Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1991**, *56*, 1976–1978. (b) Heidt, P. C.; Bergmeier, S. C.; Pearson, W. H. *Tetrahedron Lett.* **1990**, *31*, 5441–5444.

(8) Cartwright, D.; Gardiner, R. A.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 7615–7617.

(9) Gensler, W. J.; Hsu, M. W. *J. Org. Chem.* **1973**, *38*, 3848–3853.

(10) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065–7068.

(11) Schneider, M. J.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3681–3684.

(12) Dartmann, M.; Flitsch, W.; Krebs, B.; Pandl, K.; Westfechtel, A. *Liebigs Ann. Chem.* **1988**, 695–704.

(13) Shono, T.; Matsumura, Y.; Katoh, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. *J. Am. Chem. Soc.* **1990**, *112*, 2368–2372.

(14) In Rinehart and Broquist's elucidation of the structure of slafr-amine,[4] the (*S*)-configuration of *N*-acetyl-*O*-deacetylslaframine at C-1 was based on Horeau's indirect method for the determination of the configuration of secondary alcohols. For a description of Horeau's method, see: Horeau, A. In *Stereochemistry, Fundamentals and Methods*; Kagan, H. B., Ed.; Georg Theime: Stuttgart, 1977; Vol. 3, pp 51–94. The relative configuration of C-1 versus C-8a was based on the similarity of the ^{1}H-NMR spectrum of N-acetylslaframine to one of the known diastereomers of 1-acetoxyindolizidine, again an indirect method. We have confirmed this assignment using difference NOE ^{1}H NMR spectroscopy on our synthetic (−)-*N*-acetylslaframine hydrochloride, which showed a 13% enhancement of the methine proton signal at C-8a when the methine proton at C-1 was irradiated, consistent with the cis disposition of these two protons. The relative configuration of C-6 versus C-1 and C-8a was established by Rinehart and Broquist, who determined that the proton at C-6 was equatorial by analysis of ^{1}H NMR coupling constants. Assuming a trans ring juncture, this allowed the assignment of the stereochemistry at C-6 relative to C-8a. The relative stereochemistry has also been confirmed by synthesis.[8-12]

(15) Choi, J.-R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469–6472.

(16) Cyclization of azides with 1,3-dienes: (a) Pearson, W. H. *Tetrahedron Lett.* **1985**, *26*, 3527–3530. (b) Pearson, W. H.; Celebuski, J. E.; Poon, Y.-F.; Dixon, B. R.; Glans, J. H. *Tetrahedron Lett.* **1986**, *27*, 6301–6304. (c) Pearson, W. H.; Poon, Y.-F. *Tetrahedron Lett.* **1989**, *30*, 6661–6664. (d) Pearson, W. H.; Bergmeier, S. C.; Degan, S.; Lin, K.-C.; Poon, Y.-F.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, *55*, 5717–5738. See also ref 19.

(17) Cyclization of azides with alkylidenecyclopropanes: See ref 7b.

(18) Cyclization of azides with ω-haloalkenes: Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett.* **1990**, *31*, 7571–7574. See also ref 20.

(19) (a) Hudlicky, T.; Frazier, J. O.; Kwart, L. D. *Tetrahedron Lett.* **1985**, *26*, 3523–3526. (b) Hudlicky, T.; Seoane, G.; Price, J. D.; Gadamasetti, K. G. *Synlett* **1990**, 433–440 and earlier references cited therein.

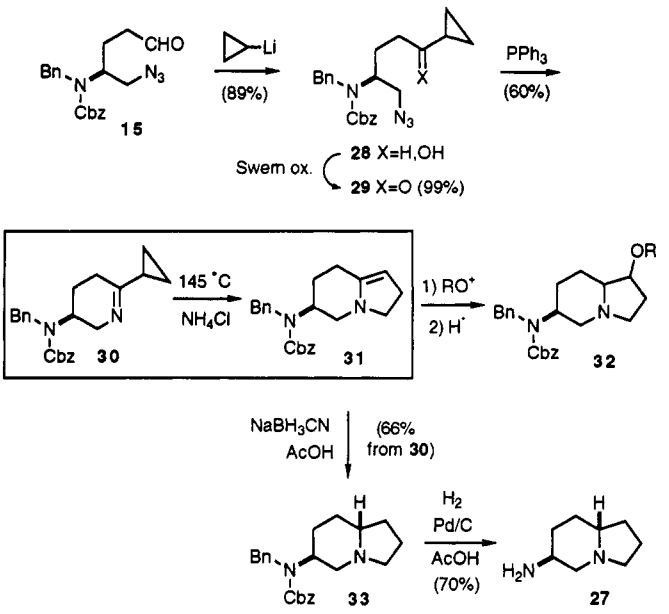
(20) (a) Bennett, R. B., III; Choi, J.-R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580–2582. (b) Bennett, R. B., III; Cha, J. K. *Tetrahedron Lett.* **1990**, *31*, 5437–5440.

to control the chemistry of the intermediate 1,2,3-triazoline and facilitate the formation of the second ring.

Our first approach was based on the cyclization of azides with 1,3-dienes, a process developed for alkaloid synthesis by us[16] and by Hudlicky's group.[19] We have shown that the indolizidine ring system may be assembled in one operation, as long as an electron-donating group is strategically placed on the diene.[16b-d] Application to the synthesis of slaframine would involve the conversion of **4** to **7**, as shown in Scheme II. Important concerns were the diastereoselectivity of the cycloaddition of **4** and the transformation of the 3-pyrroline **7** to the desired acetoxy group of slaframine. At the time this work was initiated, very little was known about the diastereoselectivity of the dipolar cycloaddition of azides with alkenes,[21] and there was no model to follow in the literature. Examination of molecular models showed that better overlap of the azide and the alkene was possible in a boatlike transition state **5**, which would produce the correct relative stereochemistry for slaframine. However, the preference for staggered groups in the tether connecting the azide and diene may outweigh the slightly skewed orientation of the dipole and dipolarophile in the chair-like transition state **6**, which would lead to the undesired 8a-epi isomer **8**. The geometry of the diene has been shown to be relatively unimportant.[16c,d]

The synthesis of azido diene **20** and its cyclization is shown in Scheme III. L-Glutamic acid was N-benzylated according to Rapoport[22] to provide **9**, which was further protected as its *N*-carbobenzyloxy derivative **10**. Diborane reduction of both carboxylic acids afforded the diol **11**. Selective silylation of **11** produced **12**, presumably because of the differing steric and electronic environments of the two hydroxyl groups. Conversion of **12** to the azide **13** was accomplished with a Mitsunobu reaction.[23] Deprotection of **13** to the alcohol **14** followed by Swern oxidation[24] gave the key azido aldehyde **15**. Conversion of **15** to the sulfur-substituted diene **20** was accomplished in a stereoselective manner using the allyl borane reagent **18**, obtained from the allene **16** by hydroboration.[25] This method was inspired by a similar synthesis of 2-[(trimethylsilyl)-methyl]-1,3-butadienes developed by Wang.[26] Attempted synthesis of oxygen-substituted dienes using related borane chemistry[27] was unsuccessful and restricted our cyclization studies to sulfur-substituted dienes. Previous studies[16b,d] had also shown that sulfur-substituted dienes underwent more efficient cyclizations than oxygen-substituted dienes. Heating azido diene **20** produced the indolizidine **21** which was accompanied by small amounts of the pyrrole **22**. At this point, we were unable to assign the stereochemistry at C-8a, although **21** appeared to be a single stereoisomer by ^1H and ^{13}C NMR. We hoped to hydrolyze **21** to ketone **26**, which would be reduced, acetylated, and deprotected to give slaframine. Unfortunately, extensive efforts to hydrolyze the vinyl sulfide to the ketone **26** were unsuccessful,[28] presumably due to complexation of the electrophilic reagent at the basic nitrogen atom.

Scheme IV



Model studies showed that *tert*-butylthioenol ethers were more easily hydrolyzed to ketones.[29] Therefore, we prepared the *tert*-butylthiodiene **23** from **15** and the allyl borane **19**, derived from hydroboration of **17**. Cyclization of **23** was efficient, but provided the pyrrole **25** as the major product, accompanied by small amounts of the desired pyrroline **24**. Strict exclusion of oxygen did not lower the amount of pyrrole formed, and the use of various additives and different solvents was also unsuccessful.[16c,d]

While the cyclization reaction had been shown to successfully generate the slaframine skeleton, the difficulties associated with the functionalization of vinyl sulfides in the presence of a basic nitrogen atom led us to abandon this route. The only successful transformation of **21** was its reduction to (-)-8a-epidesacetoxyslaframine **27**, where it was possible to assign the relative stereochemistry of C-8a and C-6. The stereochemistry of C-8a proved to be opposite that required for slaframine. If no stereochemical scrambling had occurred during the reduction, it follows that the cyclization product **21** had the stereochemistry shown, which supports a chairlike transition state in the initial intramolecular cycloaddition (see **6** in Scheme II). Since this work was completed, we have found other examples supporting a chairlike transition state.[16d]

Another approach to slaframine is shown in Scheme IV. We recently reported that azides may undergo 1,3-dipolar cycloaddition with alkylidenecyclopropanes to give cyclopropylimines, which rearrange to bicyclic Δ^2-pyrrolines

(21) See ref 16d and the references cited therein.

(22) Petersen, J. S.; Gregor, F.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539-4547.

(23) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977-1980.

(24) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(25) Pearson, W. H.; Lin, K.-C.; Poon, Y.-F. *J. Org. Chem.* **1989**, *54*, 5814-5819.

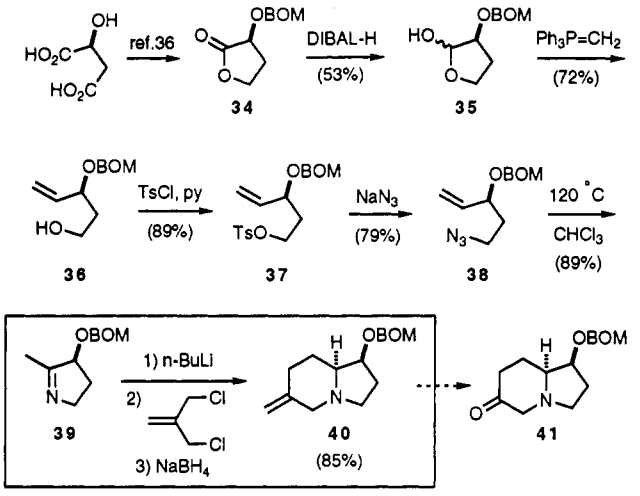
(26) Wang, K. K.; Gu, Y. G.; Liu, C. *J. Am. Chem. Soc.* **1990**, *112*, 4424-4431 and references cited therein.

(27) Pearson, W. H.; Schkeryantz, J. M. *Synthesis* **1991**, 342-346.

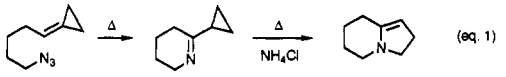
(28) Mercuric ion promoted hydrolysis generally caused oxidation to the pyrrole. Acids (HCl, TFA, HBr) and Lewis acids (e.g., $TiCl_4$), either anhydrous or aqueous, resulted in either no reaction or substantial destruction of the molecule. *N*-Alkylation with a potentially removable group (e.g., methylation, allylation, or reaction with 3-iodopropanol) led to quaternization. We had hoped that this would prevent oxidation to the pyrrole, and in the case of the 3-hydroxypropylammonium ion, the pendant hydroxyl group would speed hydrolysis by intramolecular assistance. Indeed, hydrolytic conditions (with or without Hg^{2+}) gave no pyrrole, but hydrolysis of the vinyl sulfide was still not possible. Reduction of the vinyl sulfide to the sulfide was not possible, nor was selective oxidation to a sulfoxide or sulfone.

(29) For example, 2,3,5,7a-tetrahydro-7-(*tert*-butylthio)-1*H*-pyrrolizine was prepared in 91% yield by the cyclization of (*Z*)-7-azido-3-(*tert*-butylthio)hepta-1,3-diene in $CDCl_3$ at 100 °C for 48 h. Hydrolysis of this vinyl sulfide to the ketone was accomplished quantitatively with HCl. (Degan, S. Ph.D. thesis, University of Michigan, 1991. Bergmeier, S. Ph.D. thesis, University of Michigan, 1991).

Scheme V

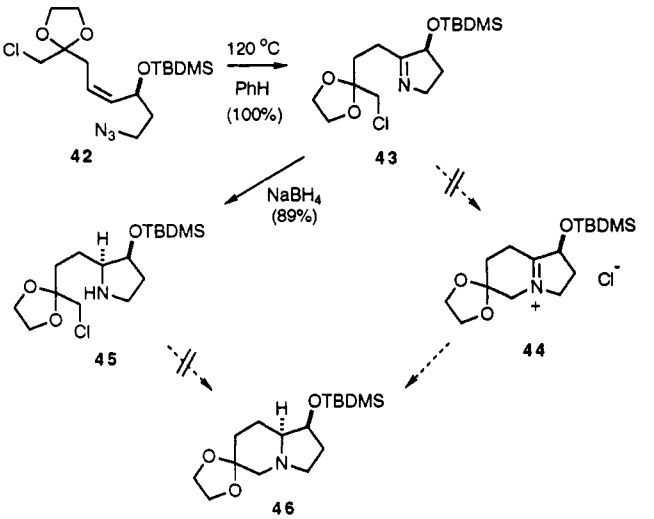


upon thermolysis in the presence of ammonium chloride (eq 1).[7b] The cyclopropylimine rearrangement was popularized by Stevens[30] and extended by other groups,[31] although it has not been carried out on these types of cyclopropylimines. We felt that the resultant enamine functionality could be used to introduce the desired acetoxy group for the synthesis of slaframine. This would formally require the addition of water across the double bond in an anti fashion. While hydroboration has been used to hydrate enamines in a syn fashion,[18,32] anti hydration is rare.[33,34] For example, Yamanaka has reported the reaction of an enamine with benzoyl peroxide followed by reduction of the intermediate iminium ion with sodium borohydride to produce a β-(benzoyloxy)amine.[33]



Conversion of **15** directly to an alkylidene cyclopropane[7b] was not possible due to the unreactivity of cyclopropylidenetriphenylphosphorane with this particular aldehyde. Hence, the cyclopropylimine **30** was prepared by a more conventional approach (Scheme IV). Addition of cyclopropyllithium to the aldehyde **15** followed by Swern oxidation[24] and an intramolecular aza-Wittig reaction[35] produced **30**. Heating **30** in the presence of ammonium chloride provided a clean solution of the enamine **31**, which was not purified. Addition of oxygen electrophiles (benzoyl peroxide, *m*-CPBA, 2-(phenylsulfonyl)-3-phenyloxaziridine) followed by $NaBH_4$ or $NaBH_3CN$ produced a complex mixture of products which contained **32**. Unfortunately, the yield and stereoselectivity of these reactions were too low to pursue. However, reduction of the enamine **31** provided the indolizidine **33** in 66% overall yield from **30** as a single stereoisomer, showing that this route is a viable one for the synthesis of simple indolizidines. The stereochemistry of **33** at C-8a is consistent with axial delivery of hydride to an intermediate iminium ion. Deprotection of **33** produced (−)-8a-epidesacetoxyslaframine **27**, identical to the material prepared in Scheme III.

Scheme VI



Malic acid was also considered as a starting material for the synthesis of slaframine. Two routes are shown in Schemes V and VI, both aimed at synthesizing a C-6 ketone, e.g., **41**. Gensler[9] had shown that a ketone could be converted to the C-6 amino group of slaframine by reduction of its oxime derivative. We envisioned an intramolecular 1,3-dipolar cycloaddition reaction for the formation of the five-membered ring. Scheme V relies on incorporation of the remaining carbons by alkylation chemistry, while Scheme VI attempts to produce the indolizidine skeleton in a single reaction.

Reduction of the known lactone **34**,[36] derived from malic acid, produced the lactol **35**. Wittig reaction, tosylation, and azide displacement produced the azidoalkene **38**. Heating **38** at 120 °C smoothly produced the 1-pyrroline **39**.[37] We then turned to methodology developed by Evans[38] for the bisalkylation of imines to introduce the remaining ring. Deprotonation of **39** with *n*-BuLi followed by bisalkylation with 3-chloro-2-(chloromethyl)-1-propene and reduction of the resultant iminium ion with sodium borohydride gave the indolizidine **40** in good yield as a single stereoisomer having the correct configurations at C-8 and C-8a for slaframine. Unfortunately, ozonolysis of **40** or its perchlorate salt[39] followed by reductive workup and oximation produced none of the oxime derivative of **41**. Attempts at isolation of the intermediate ketone **41**, if present, also proved fruitless, as did osmium-based oxidation of **40**. Apparently, oxidation of the alkene in the presence of the tertiary nitrogen atom was responsible for these poor results. Nonetheless, an efficient and conven-

(30) (a) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193. (b) Stevens, R. V. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, p 439.

(31) (a) Pinnick, H. W.; Chang, Y.-H. *Tetrahedron Lett.* **1979**, 837. (b) Wasserman, H. H.; Dion, R. P. *Ibid* **1982**, *23*, 1413. (c) Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1983**, *24*, 3409. (d) Wasserman, H. H.; Dion, R. P.; Fukuyama, J. M. *Tetrahedron* **1989**, *45*, 3203. (e) Wasserman, H. H.; Dion, R. P.; Fukuyama, J. M. *Heterocycles* **1989**, *28*, 629. (f) Vaultier, M.; Lambert, P. H.; Carrie, R. *Bull. Soc. Chim. Belg.* **1985**, *94*, 449. (g) Boeckman, R. K., Jr.; Jackson, P. F.; Sabatucci, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 2192. (h) Boeckman, R. K., Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250. (i) Boeckman, R. K., Jr.; Goldstein, S. W.; Walters, M. A. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI: Greenwich, 1990; Vol. 1, pp 1–41.

(32) Goralski, C. T.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1987**, *52*, 4014–4019.

(33) Yamanaka, E.; Maruta, E.; Kasamatsu, S.; Aimi, N.; Sakai, S. *Tetrahedron Lett.* **1983**, *24*, 3861–3864.

(34) Formation of α-amino ketones from enamines by oxidation: (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron Lett.* **1988**, *29*, 4365. (b) Lawesson, S. L.; Jakobsen, H. J.; Larsen, E. H. *Acta Chem. Scand.* **1963**, *17*, 1188. (c) Augustine, R. L. *J. Org. Chem.* **1963**, *28*, 581.

(35) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.

(36) Collum, D. B.; McDonald, J. M., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.

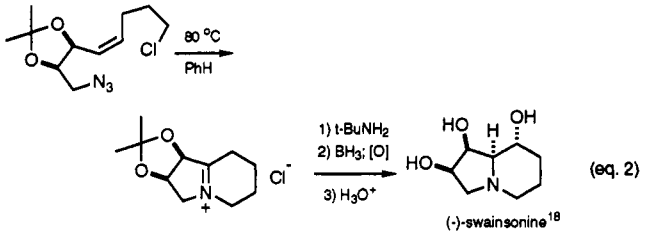
(37) Such intramolecular cycloadditions are now commonly used. For recent examples, see ref 16d and references cited therein.

(38) Evans, D. A. *J. Am. Chem. Soc.* **1970**, *92*, 7593.

(39) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548.

ient entry into the indolizidine ring system (39 → 40) was demonstrated.

In Scheme VI, an indolizidine bearing a C-6 ketone was again targeted, but was protected as a ketal rather than as an alkene. It was reasoned that hydrolysis of a ketal would be much less problematic than ozonolysis of an alkene. In addition, a tandem ring formation approach was sought, modelled on our successful synthesis of (−)-swainsonine.[18] The key step in the swainsonine synthesis is shown in eq 2. Cha and co-workers had independently



(eq. 2)

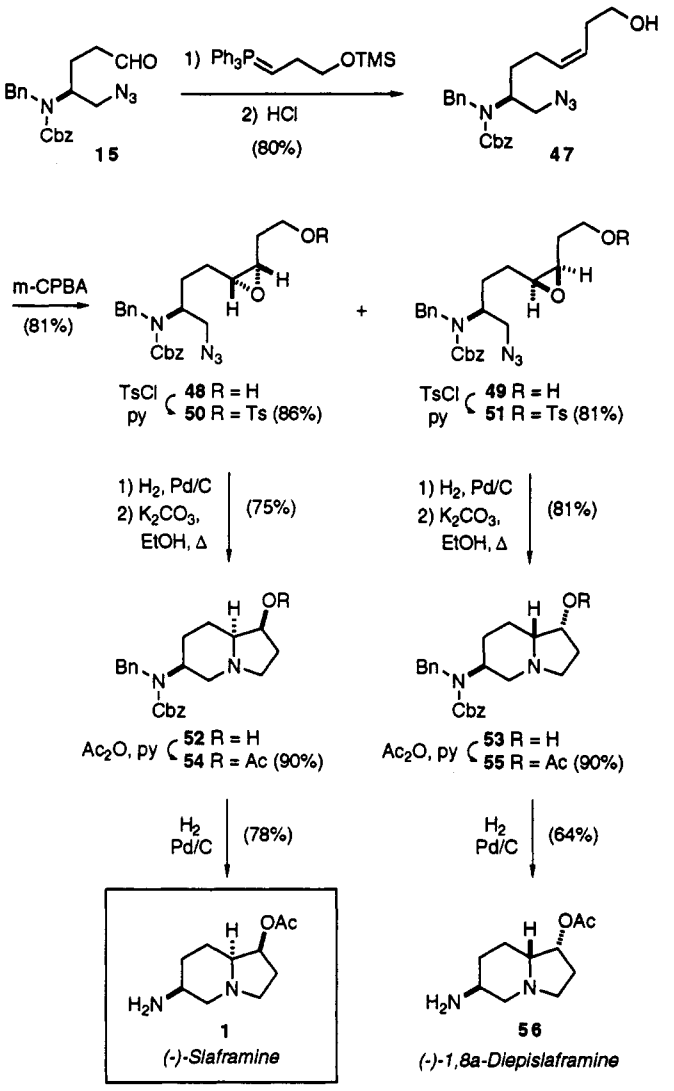
reported similar double cyclizations centered around an azide cycloaddition in their work on swainsonine[20] and in a closely related synthesis of slaframine.[15]

Heating azidoalkene 42[40] produced 43 quantitatively, but the desired N-alkylation to produce 44 had not occurred as desired. Further attempts to cyclize 43 (e.g., Bu_4NI, 140 °C) or the derived amine 45 were unsuccessful, perhaps due to the steric and electronic deactivating influence of the ketal. Hydrolysis of 43 to the chloro ketone was also very difficult without destruction of the molecule. Cha recently reported a successful approach to slaframine using a similar strategy, except that the desired C-6 amino group of slaframine was installed before the cycloaddition reaction.[15]

Although we had developed some interesting routes to the indolizine skeleton of slaframine, none were amenable to the functional group manipulations required to finish the syntheses. Therefore, a more conventional approach based on the ring opening of epoxides with amines was examined and found to be successful (Scheme VII). This general approach has been used by several groups for the synthesis of hydroxylated indolizidine alkaloids[41] and has been used by our group for the total synthesis of (+)-7-epiaustraline and (−)-7-epialexine.[42]

The *Z*-alkene 47 was produced by a very stereoselective Wittig reaction on the aldehyde 15 with a silyloxy-substituted ylide.[43] Epoxidation of 47 with *m*-chloroperbenzoic acid was nonselective, producing diastereomeric epoxides 48 and 49 in equal amounts, but in excellent yield.

Scheme VII



Attempts at carrying out hydroxyl-directed epoxidations with various transition-metal oxidants were not fruitful. Modest diastereoselectivity could be achieved, but the yields were prohibitively low.[44] Separation of 48 and 49 was straightforward using preparative HPLC, but a stereochemical assignment was not possible at this stage. Tosylation of 48 afforded 50. Selective reduction of the azide 50 to an amine in the presence of the two benzyl-protecting groups was accomplished by hydrogenolysis with hydrogen and palladium catalyst. The resultant amine was not isolated but was directly heated in refluxing ethanol containing potassium carbonate. An intramolecular epoxide opening and subsequent alkylation of the nitrogen by the tosylate ensued, affording the indolizidine 52. Acetylation of the secondary alcohol of 52 gave 54 which was deprotected to (−)-slaframine 1 by hydrogenolysis using a greater amount of palladium catalyst. Synthetic (−)-slaframine showed $[\alpha]^{25}_D = -33°$ (c = 1.6, $CHCl_3$). No optical rotation had been reported for natural slaframine. Since the preliminary account of this work appeared, Cha has completed an enantioselective synthesis of (−)-slaframine and reports $[\alpha]^{25}_D = -38°$ (c = 0.16, $CHCl_3$).[15] The ^1H and ^{13}C NMR spectra of our synthetic

(40) Prepared in 70–80% yield from the *tert*-butyldimethylsilyl analogue of lactol 35 by a Wittig reaction with 2 equiv of KHMDS and 2 equiv of $ClCH_2C(OCH_2CH_2O)CH_2CH_2PPh_3^+I^-$ in THF at −78 °C. The phosphonium salt was prepared from chloromethyl vinyl ketone (Howard, A. S.; Katz, R. B.; Michael, J. P. *Tetrahedron Lett.* **1983**, *24*, 829–830) by the following sequence: (1) HBr (1.5 equiv) and ethylene glycol (3 equiv) at 80 °C for 16 h gave 4-bromo-2-(ethylenedioxy)-1-chlorobutane (70%). (2) NaI (2 equiv), acetone, 23 °C, 16 h; then PPh_3 (1 equiv), toluene, reflux, 40 h followed by recrystallization from hexane gave the desired phosphonium iodide (64% yield).

(41) For representative examples of related heterocyclic syntheses using intramolecular epoxide openings, see: (a) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165–168. (b) Pilard, S.; Vaultier, M. *Tetrahedron Lett.* **1984**, *25*, 1555–1556. (c) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420–422. (d) Setoi, H.; Takeno, H.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 3948–3950. (e) Kim, Y. G.; Cha, J. K. *Tetrahedron Lett.* **1989**, *30*, 5721–5724. (f) Carpenter, N. M.; Fleet, G. W. J.; de Bello, I. C.; Winchester, B.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1989**, *30*, 7261–7264.

(42) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513–5516.

(43) (a) Takahashi, T.; Miyazawa, M.; Ueno, H.; Tsuji, J. *Tetrahedron Lett.* **1986**, *27*, 3881–3884. (b) Salomond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 790–792. For the preparation of $Ph_3P^+(CH_2)_3OH\ Br^-$, see: (c) Kunz, H. *Leibigs Ann. Chem.* **1973**, 2001–2009.

(44) For example, the following oxidation conditions gave ratios of 48:49 and combined yields as shown: (a) Ti(O-*i*-Pr)$_4$, *t*-BuOOH: 60:40 (50%); (b) VO(acac)$_2$, *t*-BuOOH: 55:45 (50%); (c) Ti(O-*i*-Pr)$_4$, *t*-BuOOH, (+)-diisopropyl tartrate: 37:63 (10%); (d) Ti(O-*i*-Pr)$_4$, *t*-BuOOH, (−)-diisopropyl tartrate: 60:40 (10%).

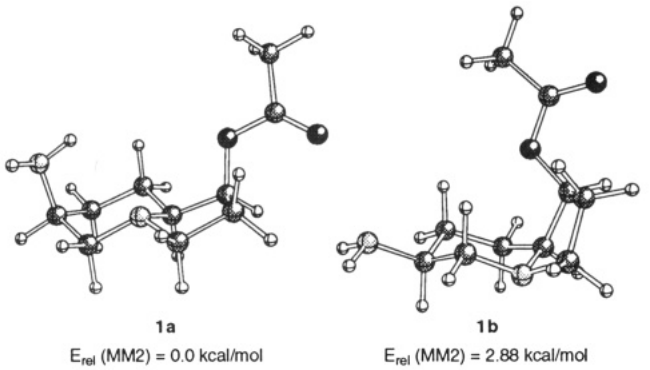
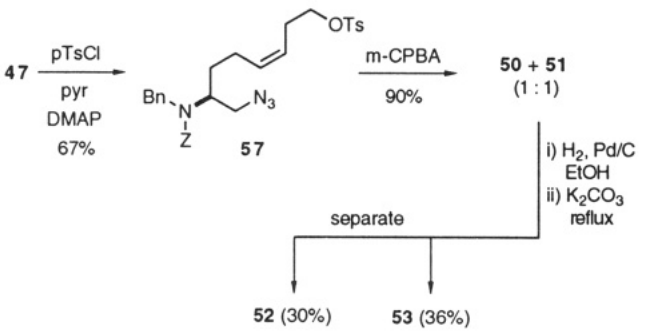


Figure 1.

Scheme VIII



material matched spectra of synthetic racemic slaframine kindly provided by Professor Harris.[11] Based on the absolute stereochemistry of L-glutamic acid, natural slaframine has the 6*S* configuration. The relative stereochemistry of the three stereocenters in slaframine rests on NMR[4,14] and synthetic studies.[8-12] For example, Rinehart and Broquist assigned the relative configuration of C-6 versus C-1 and C-8a by noting that the coupling constants of H-6 supported an equatorial disposition of this proton and by assuming a trans ring juncture.[4] This assignment is supported here by NOE studies[14] and by molecular mechanics calculations. The global minimum energy conformation (modified MM2 force field)[45] of slaframine was found to be **1a**, with an axial amino group and a trans ring juncture, supporting the NMR studies of Rinehart and Broquist.[4] The lowest energy conformation which had an equatorial disposition of the amino group was found to be **1b**, 2.88 kcal/mol higher in energy than **1a**. The absolute configuration of (−)-slaframine is confirmed to be 1*S*,6*S*,8a*S*.

Acetylation of synthetic **1** gave *N*-acetylslaframine, mp 139–141 °C, $[\alpha]^{25}_D = -11.2°$ (c = 1.45, EtOH) (lit.[4,46] mp 140–142 °C, $[\alpha]^{25}_D = -15.9°$, c = 5, EtOH) which showed spectral characteristics identical with those of racemic *N*-acetylslaframine provided to us by Harris.

A similar sequence afforded (−)-1,8a-diepislaframine **56** in good yield from the epoxy tosylate **51**. This material was clearly different in all respects from (−)-**1**.

An alternate route to slaframine was explored which avoided the HPLC separation of epoxides **48** and **49** (Scheme VIII). Epoxidation of **57**, derived from **47** by tosylation, gave a 1:1 mixture of **50** and **51**, which were directly reduced and cyclized, affording a mixture of **52** and **53**. Separation was easily accomplished by column chromatography, producing these two indolizidines in 30% and 36% isolated yields overall from the mixture of **50** and **51**. The isolated yield of **52** was slightly lower than the sequence shown in Scheme VII, but this route may, in principle, be more readily carried out on a large scale, since the separation of **49** from **53** is easier than **48** from **49**.

In conclusion, the first synthesis of natural (−)-slaframine **1** was accomplished in 5% overall yield in 12 steps from *N*-benzyl-L-glutamic acid. An equal amount of (−)-1,8a-diepislaframine **56** was also produced in approximately the same yield (9% overall yield of **1** + **56**) and should provide valuable information regarding structure–activity relationships in these biologically interesting alkaloids. The synthesis of (−)-slaframine also served to verify the absolute stereochemistry of the natural alkaloid. Finally, the immediate precursor of (−)-slaframine is a stable compound and may be easily stored. Hydrogenolysis of **54** in ethanol followed by filtration of the catalyst and concentration affords pure (−)-slaframine. This may allow convenient on-site access to samples of slaframine for biological studies.[49]

Experimental Section

General. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane, chloroform, pyridine, hexane, benzene, toluene, acetonitrile, ethyl acetate, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and triethylamine were distilled from calcium hydride immediately before use. All reactions were conducted under an atmosphere of dry nitrogen. Chromatography refers to liquid chromatography on silica gel (230–400 mesh) according to the method of Still[48] unless otherwise noted.

(*S*)-*N*-Benzyl-*N*-(benzyloxycarbonyl)glutamic Acid (10). (*S*)-*N*-Benzylglutamic acid **9**[22] (58.4 g, 246 mmol) was dissolved in water (1 L) containing $NaHCO_3$ (70 g, 833 mmol). Benzyl chloroformate (59 g, 345 mmol) was quickly added, and the reaction was stirred at room temperature for 3 h. The mixture was extracted with ether (3 × 250 mL), acidified to pH 3 with concentrated HCl, and extracted with EtOAc (3 × 250 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give 59.7 g (71%) of **10** as a clear, viscous oil, R_f 0.4 (50:48:2 hexane–EtOAc–acetic acid): $[\alpha]^{25}_D = -41.2°$ (c 2.94, $CHCl_3$); IR (neat) 3090 (br), 1710 (s), 1453 (s), 1422 (w), 1244 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 10.6 (bs, 2 H), 7.25 (m, 10 H), 5.18 (s, 2 H), 4.72–4.55 (m, 1 H), 4.53–4.40 (m, 1 H), 4.35–4.18 (m, 1 H), 2.45–1.95 (m, 4 H); MS (CI, NH_3) m/z (rel int) 372 (M^+, 100), 328 (45), 310 (20), 248 (27), 238 (24), 220 (22), 136 (13), 119 (52), 102 (51); HRMS calcd for $C_{20}H_{21}NO_6H$ (MH^+) 372.1447, found 372.1442. Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.60. Found: C, 64.49; H, 5.54; N, 3.21.

(*S*)-2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-1,5-pentanediol (11). A solution of BH_3·THF (430 mL of a 1.0 M solution in THF, 430 mmol) was slowly added to a solution of the diacid **10** (53.2 g, 143 mmol) in THF (400 mL) at 0 °C. After ca. one-third of the BH_3·THF solution had been added, the reaction became very thick and the flask was shaken manually while the addition continued. After ca. two-thirds of the BH_3·THF had been added, the reaction could be stirred normally. After all of the BH_3·THF

(45) Minimizations were carried out with BAKMDL on an IBM RS/6000 computer. BAKMDL is the batch mode minimizer sister program of MODEL, by Professor Kosta Steliou, Department of Chemistry, University of Montreal, Montreal, Quebec, Canada, H3C 3J7. We thank Professor Mark Midland, University of California—Riverside, for the UNIX version of BAKMDL. Calculations were carried out with the statistical search on coordinates option.

(46) Cha has now reported an even higher rotation for this compound, $[\alpha]^{25}_D = -18.8°$, c = 0.4, EtOH).[15] The rotation of our synthetic *N*-acetylslaframine is lower than both literature values. Since we were concerned that some racemization had occurred during manipulations on compounds **9** and **10**, the enantiomeric purity of the alcohol **12** was determined by a Mosher's ester analysis,[47] and it was found to be enantiomerically pure.

(47) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(48) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(49) **Note Added in Proof.** Two additional syntheses of (−)-slaframine have recently been completed by Professors Mukund Sibi and Spencer Knapp. We thank them for sharing their results with us prior to publication.

had been added, the reaction was warmed to room temperature and stirred for 18 h. The excess borane was quenched by the addition of water (25 mL) and brine (250 mL). The mixture was extracted with EtOAc, and the organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed (EtOAc) to give 34.6 g (70%) of **11** as a thick viscous oil, R_f 0.35 (EtOAc): $[\alpha]^{25}_D$ = +1.30° (*c* 9.9, $CHCl_3$); IR (neat) 3407 (s, br) 2949 (s), 1677 (s), 1453 (s), 1418 (s), 1242 (s), 1058 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.25 (m, 10 H), 5.14 (s, 2 H), 4.70–4.25 (m, 2 H), 4.2–3.75 (m, 1 H), 3.70–3.40 (m, 4 H), 1.80–1.20 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 157.5, 136.4, 128.6, 128.5, 128.1, 128.0, 127.4, 67.5, 63.9, 62.2, 60.1, 49.4, 29.2, 25.0; MS (CI, NH_3) *m/z* (rel int) 344 (MH^+, 100), 326 (4), 300 (2), 248 (4), 210 (2), 192 (66), 119 (9); HRMS calcd for $C_{20}H_{25}NO_4H$ (MH^+) 344.1862, found 344.1862. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.64; H, 6.95; N, 4.28.

(*S*)-2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]pentan-1-ol (12). Pyridine (2.7 mL, 33 mmol) and DMAP (0.22 g, 1.8 mmol) were added to a solution of **11** (10.5 g, 30.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C. A solution of *tert*-butyldimethylsilyl chloride (2.8 g, 18.4 mmol) in CH_2Cl_2 (30 mL) was added over 30 min, and then the reaction was allowed to stir at room temperature for 18 h. Concentration and chromatography (25% EtOAc/hexane) gave 6.5 g (88% based on recovered starting diol **11**) of **12** as a clear thick oil. Further elution with EtOAc gave 5.1 g of the diol **11**. Data for **12**: R_f 0.25 (25% EtOAc/hexane); $[\alpha]^{25}_D$ = +5.13° (*c* 2.3, $CHCl_3$); IR (neat) 3440 (br), 1695 (s), 1453 (s), 1250 (s), 1097 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (m, 10 H), 5.17 (bs, 2 H), 4.70*, 4.30*, (AB quartet, J_{AB} = 16 Hz, 0.6 H), 4.51, 4.43, (AB quartet, J_{AB} = 15.8 Hz, 1.4 H), 4.07* (bs, 0.3 H), 3.83 (bs, 0.7 H), 3.63–3.53 (m, 4 H) 2.76 (bs, 1 H), 1.68–1.23 (m, 4 H), 0.87 (s, 9 H), 0.01 (s, 6 H), (* indicates a resonance which corresponds to ca. 30% of the minor carbamate rotamer); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 157.3, 136.3, 128.4, 128.3, 127.8, 127.7, 127.1, 67.3, 63.9, 62.5, 60.1, 49.4, 29.4, 25.8, 24.9, 18.1, 0.5; MS (CI, CH_4) *m/z* (rel int) 458 (MH^+, 12), 442 (10), 440 (11), 426 (14), 414 (25), 378 (14), 350 (35), 292 (25), 181 (12), 91 (100); HRMS calcd for $C_{26}H_{39}NO_4SiH$ (MH^+) 458.2727, found 458.2701. Anal. Calcd for $C_{26}H_{39}NO_4Si$: C, 68.23; H, 8.59; N, 3.06. Found: C, 67.90; H, 8.69; N, 2.96.

(*S*)-2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-1-azido-5-[(*tert*-butyldimethylsilyl)oxy]pentane (13). Triphenylphosphine (4.6 g, 17.6 mmol), diethyl azodicarboxylate (3.1 g, 17.6 mmol), and diphenylphosphoryl azide (4.8 g, 17.6 mmol) were added sequentially to a solution of the alcohol **12** (7.3 g, 16.0 mmol) in THF (20 mL), and the solution was stirred at room temperature for 48 h. Concentration and chromatography of the resultant residue (5% EtOAc/hexane) gave 6.4 g (83%) of **13** as a slightly pink oil, R_f 0.40 (10% EtOAc/hexane): $[\alpha]^{25}_D$ = +10.9° (*c* 5.4, $CHCl_3$); IR (neat) 2099 (s), 1700 (s), 1454 (s), 1247 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz, carbamate rotamers present) δ 7.30 (m, 10 H), 5.25, 5.21 (2 s, 2 H), 4.70–4.40 (m, 2 H), 3.99 (m, 1 H), 3.6–3.4 (m, 3 H), 3.35–3.25 (m, 1 H), 1.8–1.5 (m, 2 H), 1.5–1.3 (m, 2 H), 0.91 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.0, 149.8, 138.3, 136.4, 130.0, 128.7, 128.4, 128.0, 127.9, 127.4, 126.0, 120.1, 67.2, 62.3, 57.4, 53.1, 49.2, 29.4, 26.4, 25.8, 18.2, 0.1; MS (CI, NH_3) *m/z* (rel int) 483 (MH^+, 26), 455 (16), 426 (16), 382 (14), 350 (10), 292 (12) 234 (10), 181 (6), 91 (100); HRMS calcd for $C_{26}H_{38}N_4O_3SiH$ (MH^+) 483.2791, found 483.2775. Anal. Calcd for $C_{26}H_{38}N_4O_3Si$: C, 64.70; H, 7.94; N, 11.61. Found: C, 64.30; H, 7.65; N, 11.39.

(*S*)-4-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-5-azidopentan-1-ol (14). Tetrabutylammonium fluoride (40 mL of a 1 M solution in THF, 40 mmol) was added to a solution of **13** (6.36 g, 13.2 mmol) in THF (13 mL), and the solution was stirred at room temperature for 4 h. Saturated aqueous NH_4Cl (20 mL) was added, most of the THF was evaporated in vacuo, and the residue was extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and then concentrated. The residue was chromatographed (40% EtOAc/hexane) to give 4.67 g (96%) of **14** as a clear oil, R_f 0.40 (50% EtOAc/hexane): $[\alpha]^{25}_D$ = +13.8° (*c* 3.56, $CHCl_3$); IR (neat) 3441 (br), 2100 (s), 1695 (s), 1453 (s), 1416 (s), 1233 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.30 (m, 10 H), 5.22, 5.18 (two s, 2 H total), 4.65–4.32 (m, 2 H), 3.96 (m, 1 H), 3.46–3.23 (m, 4 H), 2.25, 2.0 (two bs, 1 H total), 1.64–1.34 (m, 4 H); MS (CI, CH_4) *m/z* (rel int) 369 (MH^+, 11), 341 (14), 325 (16), 324 (15), 312 (13), 268 (18), 233 (12), 178 (17), 91 (100); HRMS calcd for $C_{20}H_{24}N_4O_3H$ (MH^+) 369.1939, found 369.1927. Anal. Calcd for $C_{20}H_{24}N_4O_3$: C, 65.2; H, 6.56; N, 15.21. Found: C, 65.19; H, 6.61; N, 15.12.

(*S*)-4-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-5-azidopentanal (15). A solution of dimethyl sulfoxide (1.95 mL, 27.5 mmol) in CH_2Cl_2 (13 mL) was added to a cold (−78 °C) solution of freshly distilled oxalyl chloride (1.20 mL, 13.8 mmol) in CH_2Cl_2 (25 mL) over 20 min. After 30 min, a solution of **14** (4.60 g, 12.5 mmol) in CH_2Cl_2 (13 mL) was added and the mixture stirred for 1 h. A solution of Et_3N (8.7 mL, 62.5 mmol) in CH_2Cl_2 (13 mL) was then added, and the mixture was allowed to warm to room temperature over 2 h, then diluted with CH_2Cl_2 and washed sequentially with water, 1 M HCl, 10% aqueous Na_2CO_3, and brine. The organic phase was dried ($MgSO_4$) and concentrated, and the resultant residue was passed through a plug of silica gel, eluting with 20% EtOAc/hexane to give 4.19 g of **15** (92%) as a pale yellow oil, R_f 0.30 (25% EtOAc/hexane): $[\alpha]^{25}_D$ = +12.7° (*c* 2.45, $CHCl_3$), IR (neat) 2101 (s), 1722 (s), 1698 (s), 1454 (s), 1415 (s), 1231 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz, carbamate rotamers present) δ 9.44, 9.35 (two s, 1 H total), 7.32 (m, 10 H), 5.19 (s, 2 H), 4.60 (apparent doublet, J = 15.7 Hz, 1 H), 4.31 (m, 1 H), 3.79 (m, 1 H), 3.67–3.15 (m, 2 H), 2.21–1.76 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 200.5, 156.0, 137.9, 136.1, 128.6, 128.5, 128.2, 128.0, 127.9, 127.6, 67.4, 57.2, 52.8, 50.2, 40.2, 21.9; MS (CI, NH_3) *m/z* (rel int) 367 (MH^+, 31), 339 (98), 337 (22), 323 (91), 319 (78), 310 (24), 266 (24), 233 (23), 231 (53), 203 (23), 187 (23); HRMS calcd for $C_{20}H_{22}N_4O_3H$ (MH^+) 367.1770, found 367.1765. Anal. Calcd for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05; N, 15.29. Found: C, 65.63; H, 6.36; N, 15.14.

(*S*)-(*E*)-7-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-8-azido-3-(phenylthio)octa-1,3-diene (20). 9-BBN (9.4 mL of a 0.5 M solution in THF, 4.7 mmol) was added to 1-(phenylthio)-1-(trimethylsilyl)propadiene (**16**)[25] (1.04 g, 4.7 mmol), and the solution was stirred at 35–40 °C for 2 h. After the solution was cooled to room temperature, the aldehyde **15** (1.47 g, 4.2 mmol) was added. After 12 h, 20% NaOH (20 drops) was added, and the mixture was stirred for 3 h and then diluted with Et_2O/petroleum ether (1:1, 100 mL). The organic phase was dried ($MgSO_4$) and concentrated, and the resultant residue was chromatographed (5% EtOAc/hexane) to give 1.10 g (47%) of **20**, R_f 0.36 (10%, EtOAc/hexane): $[\alpha]^{25}_D$ = −1.3° (*c* 2.4, $CHCl_3$); IR (neat) 2101 (s), 1698 (s), 1452 (s), 1414 (s), 1228 (s), 1025 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz, carbamate rotamers present) δ 7.23 (m, 15 H), 6.50–6.35 (m, 1 H), 5.95–5.80 (m, 1 H), 5.62 (d, J = 16.1 Hz, 1 H), 5.18 (m, 3 H), 4.62–4.50 (m, 1 H), 4.49–4.35 (m, 1 H), 3.93–3.78 (m, 1 H), 3.62–3.20 (m, 2 H), 2.20–1.93 (m, 2 H), 1.90–1.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.4, 139.5, 138.2, 136.9, 136.4, 131.9, 130.2, 128.8, 128.6, 128.1, 127.5, 125.3, 119.8, 116.5, 67.5, 57.7, 53.2, 50.2, 29.9, 25.8; MS (CI, NH_3) *m/z* (rel int) 499 (MH^+, 17), 471 (100), 455 (6), 437 (5), 361 (13), 335 (10), 255 (8), 229 (14), 175 (9); HRMS calcd for $C_{29}H_{30}N_4O_2H$ (MH^+) 499.2168, found 499.2173.

(6*S*,8a*R*)-3,5,6,7,8,8a-Hexahydro-6-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]-1-(phenylthio)indolizine (21). The azide **20** (0.49 g, 1.0 mmol) was dissolved in $CHCl_3$ (10 mL) in a resealable tube. The tube was degassed with six freeze/thaw cycles and then heated at 110 °C for 24 h. See ref 16d for a complete description of the procedure for these cyclizations. Concentration and chromatography (40% EtOAc/hexane) gave 0.32 g (66%) of **21** as a golden oil, R_f 0.30 (2%, methanol/chloroform): $[\alpha]^{25}_D$ = −19.2° (*c* 3.3, $CHCl_3$); IR (neat) 1697 (s), 1453 (s), 1414 (s), 1251 (s), 1120 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz, carbamate rotamers present) δ 7.45–7.10 (m, 15 H), 5.63 (bs, 1 H), 5.13 (bs, 2 H), 4.45 (bs, 2 H), 4.15–4.05 (m, 1 H), 3.70–3.45 (m, 1 H), 3.30–2.90 (m, 2 H), 2.75–2.50 (m, 1 H), 1.85–1.75 (m, 2 H), 1.75–1.45 (m, 1 H), 1.40–1.20 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.2, 139.1, 138.7, 136.6, 132.9, 131.6, 128.9, 128.3, 127.8, 127.4, 126.9, 67.4, 67.1, 56.7, 53.4, 52.3, 48.2, 27.9, 14.1; MS (EI, 70 eV) *m/z* (rel int) 470 (M^+, 39), 379 (5), 361 (12), 335 (4), 229 (28), 202 (15), 188 (9), 120 (19), 91 (100); HRMS calcd for $C_{29}H_{30}N_2O_2S$ (M^+) 470.2028, found 470.2009.

(6*S*,8a*R*)-Octahydro-6-aminoindolizine (27). W-2 Raney nickel (ca. 1 g, Aldrich) was washed with ethanol and then added to a solution of **21** (148 mg, 0.31 mmol) in ethanol (5 mL). The vessel was evacuated and refilled with N_2 and then evacuated again

and refilled with hydrogen. The mixture was stirred under a balloon of hydrogen for 4 h and then filtered and concentrated to give 22 mg (50%) of **27**, R_f 0.30 (5%, methanol/chloroform, alumina TLC plate): $[\alpha]^{25}_D$ = −2.0° (*c* 0.35, CH_3OH); IR (neat) 3422 (br), 1618 (w), 1545 (w), 1451 (w) cm^{-1}; ^1H NMR (Me_2SO-d_6, 300 MHz), δ 3.22 (dd, *J* = 9.9, 3.4 Hz, H_{5eq}, 1 H), 3.01 (m, H_{6ax} 1 H), 2.90 (td, *J* = 7.8, 2.5 Hz, H_{3eq}, 1 H), 2.22–1.90 (m, H_{3ax}, H_{5ax}, H_{8a}, 3 H), 1.88–1.57 (m, 4 H), 1.40–1.15 (m, 3 H); the NH_2 protons were not assigned. Assignments were made by COSY experiments. NOESY experiments showed that there was no NOE enhancement between H-6 and H-8a, even though H-6 is axial. Assuming a trans ring juncture, H-6 and H-8a are therefore on opposite faces of the ring system. The $w_{1/2}$ of H-6 was 24 Hz, consistent with an axial disposition of H-6, as is the coupling between H-6 and the neighboring hydrogens H_{5eq} and H_{5ax} (J_{H6H5eq} = 10.0 Hz, J_{H6H5ax} = 3.4 Hz). Coupling constants were obtained by decoupling experiments. **27**: ^{13}C NMR (Me_2SO-d_6, 90 MHz) δ 62.5 (C_{8a}), 54.4, 52.8, 47.1 (C_6), 29.3, 28.6, 28.1, 20.9; MS (EI, 70 eV) *m*/*z* (rel int) 140 (M^+, 100), 124 (62), 100 (30), 84 (41); HRMS calcd for $C_8H_{16}N_2$ (M^+) 140.1315, found 140.1310.

(4*S*)-4-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-5-azido-1-cyclopropyl-1-pentanol (28). *t*-BuLi (10 mL of a 1.3 M solution in pentane, 13 mmol) was added to a solution of cyclopropyl bromide (0.98 mL, 12.2 mmol) in Et_2O (120 mL) at −78 °C. After 2 h at −78 °C, a solution of **15** (4.45 g, 12.2 mmol) in Et_2O (10 mL) was added and the mixture was stirred at −78 °C for 30 min. Saturated aqueous NH_4Cl (1.0 mL) was added, and the reaction was warmed to room temperature. The organic phase was dried ($MgSO_4$) and concentrated, and the residue was chromatographed (25% EtOAc/hexane) to give 0.5 g of recovered **15** and 3.9 g of **28** (89% based on recovered starting material) as a mixture of diastereomers which were not separated, R_f 0.24 (25%, EtOAc/hexane): $[\alpha]^{25}_D$ = +7.7° (*c* 1.1, $CHCl_3$); IR (neat) 3462 (br), 2102 (s), 1694 (s), 1453 (s), 1416 (s), 1231 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz, carbamate rotamers present) δ 7.40–7.13 (m, 10 H), 5.22, 5.19 (two bs, 2 H total), 4.65–4.36 (m, 2 H), 4.15–3.85 (m, 1 H), 3.55–3.10 (m, 2 H), 2.75–2.52 (m, 2 H), 1.79–1.29 (m, 5 H), 0.80–0.60 (m, 1 H), 0.42 (bs 2 H), 0.13–0.00 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.2, 138.4, 136.4, 128.4, 128.1, 127.9, 127.8, 127.5, 127.3, 76.2, 75.8, 67.6, 67.3, 57.7, 57.2, 53.6, 53.1, 49.1, 48.7, 33.6, 33.4, 26.4, 17.7, 2.5, 2.4; MS (CI, NH_3) *m*/*z* (rel int) 409 (MH^+, 19), 391 (78), 381 (22), 363 (100), 352 (8), 308 (8), 275 (23), 259 (12), 218 (11), 200 (9); HRMS calcd for $C_{23}H_{28}N_4O_3H$ (MH^+) 409.2240, found 409.2253. Anal. Calcd for $C_{23}H_{28}N_4O_3$: C, 67.63; H, 6.88; N. 13.72. Found: C, 67.30; H, 6.49; N, 13.53.

(*S*)-3-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-4-azidobutyl Cyclopropyl Ketone (29). Dimethyl sulfoxide (1.5 mL, 21.25 mmol) was slowly added to a solution of freshly distilled oxalyl chloride (0.9 mL, 10.6 mmol) in CH_2Cl_2 (20 mL) at −78 °C. After 20 min, a solution of the alcohol **28** (3.9 g, 9.7 mmol) in CH_2Cl_2 (10 mL) was added and the mixture was stirred for 1 h at −78 °C. A solution of triethylamine (6.7 mL, 48.3 mmol) in CH_2Cl_2 (50 mL) was then added, and the reaction was allowed to warm to room temperature over 2 h and then diluted with CH_2Cl_2 (50 mL). The organic phase was washed successively with water, 1 M HCl, 10% Na_2CO_3, and brine and then dried ($MgSO_4$) and concentrated. The residue was filtered through a plug of silica gel, eluting with 15% EtOAc/hexane to give 3.9 g (99%) of **29**, R_f 0.25 (15% EtOAc/hexane): $[\alpha]^{25}_D$ = +11.1° (*c* 2.0, $CHCl_3$); IR (neat) 2101 (s), 1697 (s), 1453 (s), 1231 (s), 1107 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.40–7.10 (m, 10 H), 5.18 (bs, 2 H), 4.62–4.50 (m, 1 H), 4.40–4.36 (m, 1 H), 3.88 (bs, 1 H), 3.56–3.49 (m, 0.8 H), 3.35–3.15 (m, 1.2 H), 2.45–2.15 (m, 2 H), 2.02–1.90 (m, 0.8 H), 1.85–1.55 (m, 2 H), 0.89 (bs, 2 H), 0.78 (bs, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 208.9, 155.6, 137.8, 135.9, 128.2, 128.1, 128.0, 127.6, 127.3, 127.0, 66.9, 56.9, 52.6, 49.3, 39.0, 23.4, 19.8, 10.2; MS (CI, NH_3) *m*/*z* (rel int) 407 (MH^+, 100), 379 (66), 363 (21), 350 (5), 306 (2), 271 (22), 216 (5), 136 (32); HRMS calcd for $C_{23}H_{26}N_4O_3H$ (MH^+) 407.2083, found 407.2064. Anal. Calcd for $C_{23}H_{26}N_4O_3$; C, 67.96; H, 6.45; N, 13.78. Found: C, 67.47; H, 6.52; N, 13.81.

(*S*)-3,4,5,6-Tetrahydro-5-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]-2-cyclopropylpyridine (30). Triphenylphosphine (0.34 g, 1.3 mmol) was added to a solution of **29** (0.50 g, 1.22 mmol) in THF (5 mL) at room temperature. After 18 h, the solution was concentrated and chromatographed on grade III neutral alumina, eluting with 25% EtOAc/hexane to give 0.26 g (60%) of **30** as a clear oil, R_f 0.39 (25% EtOAc/hexane, alumina TLC plate): $[\alpha]^{25}_D$ = +9.1° (*c* 11.4, $CHCl_3$); IR (neat) 1697 (s), 1453 (s), 1242 (s), 1108 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz, carbamate rotamers present) δ 7.40–7.1 (m, 10 H), 5.14 (bs, 2 H), 4.44 (bs, 2 H), 4.30–3.90 (m, 1.2 H), 3.65 (bd, *J* = 16.0 Hz, 1 H), 3.50–3.30 (m, 1 H), 3.0–2.7 (m, 0.8 H), 2.35–2.15 (m, 2 H), 1.80–1.70 (m, 2 H), 1.50–1.49 (m, 1 H), 1.20–0.95 (m, 1 H), 0.80–0.60 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 170.2, 156.2, 139.9, 136.5, 128.6, 128.3, 127.9, 127.7, 127.3, 126.9, 126.7, 67.1, 51.9, 47.8, 29.9, 24.1, 16.2, 7.0, 6.5; MS (EI, 70 eV) *m*/*z* (rel int) 362 (M^+, 16), 347 (5), 285 (8), 271 (15), 241 (9), 186 (6), 122 (38); HRMS calcd for $C_{23}H_{26}N_2O_2$ (M^+) 362.1994, found 362.1976.

(6*S*,8a*R*)-Octahydro-6-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]indolizine (33). A solution of **30** (0.21 g, 0.59 mmol) in xylene (30 mL) containing NH_4Cl (32 mg, 0.59 mmol) was heated to reflux for 4 h. The solvent was removed in vacuo, and the residue was immediately dissolved in acetic acid (2 mL) and cooled to 0 °C. $NaCNBH_3$ (74 mg, 1.2 mmol) was slowly added, and the mixture was allowed to warm to room temperature. After 18 h, the solvent was removed in vacuo, 1 M NaOH was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (5% methanol/chloroform) to give 142 mg (66%) of **33**, R_f 0.30 (5% methanol/chloroform): $[\alpha]^{25}_D$ = −3.0° (*c* 9.4, $CHCl_3$); IR (neat) 1697 (s), 1454 (s), 1414 (s), 1215 (s), 1118 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz, carbamate rotamers present) δ 7.5–7.1 (m, 10 H), 5.30–5.00 (m, 2 H), 4.49 (bs, 2 H), 4.20–3.95 (m, 1 H), 3.30–2.80 (m, 2 H), 2.45–2.20 (m, 1 H), 2.20–2.00 (m, 2 H), 1.80–1.45 (m, 6 H), 1.40–1.1 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.1, 139.1, 136.6, 128.6, 128.3, 127.8, 126.8, 67.0, 63.4, 55.7, 54.9, 53.7, 48.6, 29.6, 28.9, 28.1, 21.3; MS (EI, 70 eV) *m*/*z* (rel int) 364 (M^+, 1), 153 (3), 123 (100), 91 (61), 83 (26); HRMS calcd for $C_{23}H_{28}N_2O_2$ (M^+) 364.2151, found 364.2141.

(6*S*,8a*R*)-Octahydro-6-aminoindolizine (27). Methanol (1 mL) was added to a mixture of **33** (94 mg, 0.26 mmol) and 10% Pd–C (100 mg), and the mixture was stirred under a balloon of hydrogen for 24 h and then filtered and concentrated to give 25 mg (70%) of **27**, which had spectral characteristics consistent with the material reported above.

(3*S*)-2,3,4,5-Tetrahydro-3-[(benzyloxy)methoxy]-2-hydroxyfuran (35). Diisobutylaluminum hydride (15 mL of a 1.5 M solution in toluene, 23 mmol) was added to a solution of **34** (4.2 g, 19 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The resultant mixture was allowed to stir for 30 min and then warmed to room temperature. Solid NH_4Cl (3 g) and five drops of saturated NH_4Cl were added followed by addition of solid $MgSO_4$ (3 g). Filtration, concentration, and chromatography of the residue (50% EtOAc/hexane) provided 2.3 g (53%) of **35** as a clear oil which was a mixture of anomers, R_f 0.33 (50% EtOAc/hexane): $[\alpha]^{25}_D$ = +25.9° (*c* 1.5, $CHCl_3$); IR (neat) 3407 (s), 1497 (w), 1454 (m), 1382 (w), 1168 (m), 1028 (s) cm^{-1}; ^1H NMR ($CDCl_3$; 300 MHz) δ 7.32 (m, 5 H), 5.41 (d, *J* = 2 Hz, 0.5 H), 5.33 (q, *J* = 4 Hz, 0.5 H), 4.8–4.9 (m, 2 H), 4.6–4.7 (m, 2 H), 4.23 (m, 1 H), 4.08 (m, 1.5 H), 3.84 (m, 0.5 H), 3.62 (d, *J* = 7 Hz, 0.5 H), 2.84 (d, *J* = 2 Hz, 0.5 H), 1.9–2.4 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 137.5, 128.5, 128.4, 128.4, 127.8, 127.7, 101.3, 96.4, 94.5, 93.8, 81.8, 70.2, 69.8, 66.8, 64.6, 30.0, 29.9; MS *m*/*z* (rel intensity) 242 (M + NH_4^+, 41), 224 (26), 207 (100), 194 (43), 177 (58), 136 (45), 108 (44), 91 (38); HRMS calcd for $C_{12}H_{14}O_3NH_4$ (M − H_2O + NH_4^+) 224.1287, found 224.1281. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.94; H, 7.03.

(*S*)-3-[(Benzyloxy)methoxy]-4-penten-1-ol (36). *n*-Butyllithium (5.5 mL of a 2.5 M solution in hexane, 25 mmol) was added to a solution of methyltriphenylphosphonium bromide (4.4 g, 12 mmol) in THF (50 mL) at 0 °C. After 30 min, the solution was cooled to −78 °C and a solution of **35** (1.1 g, 4.9 mmol) in THF (5 mL) was added. The mixture was then allowed to stir at room temperature for 14 h and then quenched with saturated aqueous NH_4Cl. Ether was added, and the mixture was washed with brine, dried, ($MgSO_4$) and concentrated in vacuo. Chromatography of the residue (50% EtOAc/hexane) provided 0.79 g of **36** (72%) as a clear oil, R_f 0.57 (50% EtOAc/hexane): $[\alpha]^{25}_D$ = −85.1° (*c* 1.7, $CHCl_3$); IR (neat) 3422 (s), 1451 (m), 1423 (m), 1381 (m), 1165 (m), 1100 (s), 1026 (s), 931 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz)

δ 7.32 (m, 5 H), 5.74 (ddd, J = 17, 10, 8 Hz, 1 H), 5.26 (d, J = 17 Hz, 1 H), 5.23 (d, J = 10 Hz, 1 H), 4.80 (d, part of AB, J = 7 Hz, 1 H), 4.73 (d, part of AB, J = 7 Hz, 1 H), 4.72 (d, part of AB, J = 12 Hz, 1 H), 4.56 (d, part of AB, J = 12 Hz, 1 H), 4.34 (q, J = 7 Hz, 1 H), 3.79 (m, 2 H), 2.38 (bs, 1 H), 1.84 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7, 128.4, 128.4, 127.8, 127.7, 117.3, 92.1, 76.2, 69.8, 59.9, 37.8; MS m/z (rel intensity) 240 ($M + NH_4^+$, 26), 223 ($M + H^+$, 28), 205 (100), 175 (46), 136 (21), 126 (30), 108 (27), 91 (52); HRMS calcd for $C_{13}H_{18}O_3H$ ($M + H^+$) 223.1334, found 223.1334.

(*S*)-3-[(Benzyloxy)methoxy]-5-[(*p*-tolylsulfonyl)oxy]-1-pentene (37). Tosyl chloride (1.4 g, 7.4 mmol) was added to a solution of **36** (1.1 g, 4.9 mmol) in pyridine (1 mL) and $CHCl_3$ (7 mL) at room temperature. After 14 h, the mixture was washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine and dried ($MgSO_4$) and concentrated in vacuo. Chromatography of the residue (20% EtOAc/hexane) provided 1.6 g of **37** (89%) as a clear oil, R_f 0.38 (20% EtOAc/hexane): $[\alpha]^{25}_D$ = −65.2° (c 1.1, $CHCl_3$); IR (neat) 1360 (s), 1189 (s), 1177 (s), 1098 (s), 1038 (s), 991 (m), 917 (m), 816 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, J = 8 Hz, 2 H), 7.33 (m, 5 H), 5.62 (ddd, J = 8, 12, 17 Hz, 1 H), 5.19 (d, J = 12 Hz, 1 H), 5.18 (d, J = 17 Hz, 1 H), 4.73 (d, part of AB, J = 8 Hz, 1 H), 4.62 (d, part of AB, J = 8 Hz, 1 H), 4.59 (d, part of AB, J = 11 Hz, 1 H), 4.48 (d, part of AB, J = 11 Hz, 1 H), 4.18 (m, 3 H), 2.41 (s, 3 H), 1.42 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6, 137.8, 137.1, 133.4, 129.8, 127.9, 127.7, 118.2, 92.1, 73.7, 69.7, 67.0, 34.8, 21.5; MS m/z (rel intensity) 394 ($M + NH_4^+$, 100), 274 (8), 246 (21), 218 (13), 136 (6); HRMS calcd for $C_{20}H_{24}O_5SNH_4$ ($M + NH_4^+$) 394.1688, found 394.1677. Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43. Found: C, 64.27; H, 6.47.

(*S*)-5-Azido-3-[(benzyloxy)methoxy]-1-pentene (38). Sodium azide (1.0 g, 13 mmol) was added to a solution of **37** (1.6 g, 4.3 mmol) in DMSO (14 mL) at room temperature. After 14 h, the mixture was poured into water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (10% EtOAc/hexane) gave 0.85 g (79%) of **38** as a clear oil, R_f 0.36 (10% EtOAc/hexane): $[\alpha]^{25}_D$ = −86.1° (c 2.2, $CHCl_3$); IR (neat) 2096 (s), 1454 (w), 1265 (m), 1166 (m), 1101 (w), 1037 (s), 932 (w), 737 (m), cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (m, 5 H), 5.69 (ddd, J = 17, 11, 7 Hz, 1 H), 5.28 (d, J = 17 Hz, 1 H), 5.25 (d, J = 11 Hz, 1 H), 4.81 (d, part of AB, J = 7 Hz, 1 H), 4.73 (d, part of AB, J = 7 Hz, 1 H), 4.69 (d, part of AB, J = 12 Hz, 1 H), 4.56 (d, part of AB, J = 12 Hz, 1 H), 4.22 (q, J = 7 Hz, 1 H), 3.41 (t, J = 7 Hz, 1 H), 1.87 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.9, 137.4, 128.4, 127.8, 127.7, 118.0, 92.1, 74.7, 69.8, 47.8, 34.6; MS m/z (rel intensity) 265 ($M + NH_4^+$, 70), 248 ($M + H^+$, 19), 220 (23), 136 (100), 112 (6); HRMS calcd for $C_{13}H_{17}O_2N_3H$ ($M + H^+$) 248.1399, found 248.1399.

(*S*)-4,5-Dihydro-3-[(benzyloxy)methoxy]-2-methyl-3*H*-pyrrole (39). A solution of **38** (0.92 g, 3.7 mmol) in $CHCl_3$ (18 mL) was heated to 120 °C for 3 h. Evaporation of the solvent and chromatography (5% MeOH/$CHCl_3$) gave 0.72 g (89%) of **39** as a clear oil, R_f 0.58 (10% MeOH/$CHCl_3$): $[\alpha]^{25}_D$ = +7.47° (c 0.75, $CHCl_3$); IR (neat) 1652 (m), 1497 (w), 1454 (m), 1436 (w), 1379 (m), 1163 (m), 1110 (s), 1047 (s), 751 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 5 H), 4.84 (s, 2 H), 4.66 (m, 3 H), 3.9 (m, 1 H), 3.67 (m, 1 H), 2.29 (m, 1 H), 2.1 (t, J = 2 Hz, 3 H), 1.82 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1, 137.5, 128.5, 127.8, 127.8, 94.3, 84.1, 69.8, 58.2, 30.8, 17.1; MS m/z (rel intensity) 220 ($M + H^+$, 100), 136 (33); HRMS calcd for $C_{13}H_{17}NO_2H$ ($M + H^+$) 220.1338, found 220.1337.

(1*S*,8a*S*)-Octahydro-1-[(benzyloxy)methoxy]-6-methyleneindolizidine (40). *n*-Butyllithium (0.68 mL of a 2.2 M solution in hexane, 1.5 mmol) was added to a solution of **39** (0.33 g, 1.5 mmol) in THF (6 mL) at −78 °C. After 15 min, 3-chloro-2-(chloromethyl)propene (0.19 g, 1.5 mmol) was added. After the solution was warmed to room temperature, the solvent was evaporated and methanol (6 mL) and $NaBH_4$ (0.068 g, 1.8 mmol) were then added to the mixture. After 1 h, the mixture was poured into saturated $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (2% MeOH/$CHCl_3$) gave 0.35 g (85%) of **40** as a yellow oil, R_f 0.48 (10% MeOH/$CHCl_3$): $[\alpha]^{25}_D$ = +27.2° (c 1.8, $CHCl_3$); IR (neat) 1655 (w), 1497 (w), 1454 (m), 1440 (m), 1380 (w), 1312 (m), 1167 (s), 1121 (s), 1051 (s), 896 (m), 734 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.35 (m, 5 H), 4.79 (s, 2 H), 4.76 (d, part of AB, J = 7 Hz, 1 H), 4.70 (d, part of AB, J = 7 Hz, 1 H), 4.62 (d, part of AB, J = 12 Hz, 1 H), 4.55 (d, part of AB, J = 12 Hz, 1 H), 4.22 (m, 1 H), 3.55 (d, J = 12 Hz, 1 H), 3.17 (t, J = 8 Hz, 1 H), 2.58 (d, J = 12 Hz, 1 H), 2.41 (m, 1 H), 1.68–2.2 (m, 7 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 143.8, 138.0, 128.4, 127.9, 127.6, 109.7, 93.0, 77.2, 69.3, 67.6, 59.7, 52.8, 32.3, 30.8, 25.8; MS m/z (rel intensity) 273 (M^+, 24), 182 (34), 167 (21), 152 (100), 110 (20), 109 (41), 108 (20), 91 (25); HRMS calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1734.

(*S*)-4,5-Dihydro-3-[(*tert*-butyldimethylsilyl)oxy]-2-[4-chloro-3,3-(ethylenedioxy)butyl]-3*H*-pyrrole (43). A solution of **42** (0.91 g, 2.6 mmol) in benzene (20 mL) was heated to 120 °C for 3 h. Evaporation of solvent gave 0.83 g (100%) of **43** which was not purified further. Partial spectral data: ^{1}H NMR (benzene-d_6, 300 MHz) δ 4.32 (t, J = 7 Hz, 1 H), 3.85 (m, 1 H), 3.50 (m, 4 H), 3.32 (s, 2 H), 2.77 (m, 1 H), 2.37 (m, 4 H), 1.8 (m, 1 H), 1.49 (m, 1 H), 0.94 (s, 9 H), 0.05 (s, 6 H).

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[4-chloro-3,3-(ethylenedioxy)butyl]pyrrolidine (45). Sodium borohydride (82 mg, 2.2 mmol) was added to a solution of **43** (0.56 g, 1.8 mmol) in MeOH (9 mL) at room temperature. After 1 h, the mixture was poured into saturated $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.50 g (89%) of **45**, which was not purified further. Partial spectral data: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.12 (m, 1 H), 3.7–4.0 (m, 4 H), 3.56 (s, 2 H), 2.94 (m, 1 H), 2.68 (m, 1 H), 1.3–2.0 (m, 6 H), 0.85 (s, 9 H), 0.05 (s, 6 H).

(*S*)-(*Z*)-7-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-8-azido-3-octen-1-ol (47). A solution of $KN(SiMe_3)_2$ (64 mL of a 0.5 M solution in toluene, 32 mmol) was added to a suspension of (3-hydroxypropyl)triphenylphosphonium bromide[43] (6.42 g, 16 mmol) in THF (80 mL) at 0 °C. After 2 h, the mixture was warmed to room temperature for 20 min, and then the deep red solution was recooled to 0 °C and treated with freshly distilled trimethylsilyl chloride (2.0 mL, 16 mmol). After 20 min, the mixture was cooled to −78 °C and the aldehyde **15** (5.87 g, 16 mmol) was added. After 1 h, the mixture was warmed to room temperature and stirred for 1 h. A 1 M solution of HCl (100 mL) was then added, and the mixture was stirred for 1 h and then extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (25% EtOAc/hexane) to give 1.78 g of **15** and 3.33 g (80% yield based on recovered **15**) of **47** as a clear oil, R_f 0.43 (50% EtOAc/hexane): $[\alpha]^{25}_D$ = +7.0° (c 3.9, $CHCl_3$); IR (neat) 3445 (br), 2100 (s), 1698 (s), 1454 (s), 1417 (w), 1231 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.45–7.15 (m, 10 H), 5.42. 5.10 (m, 4 H), 4.54, 4.37 (AB quartet, J_{AB} = 16 Hz, 2 H), 4.00–3.80 (m, 1 H), 3.60–3.40 (m, 2.5 H), 3.32 (dd, J = 12.3, 5.4 Hz, 1 H), 3.18–2.05 (m, 0.5 H), 2.30–1.40 (m, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.1, 138.3, 136.3, 130.8, 128.4, 128.0, 127.5, 127.3, 126.7, 67.3, 61.9, 57.3, 53.0, 49.5, 30.7, 30.0, 24.0; MS (CI, NH_3) m/z (rel int) 409 (MH^+, 56), 381 (73), 365 (4), 308 (4), 275 (6), 218 (2), 140 (9), 136 (49); HRMS calcd for $C_{23}H_{28}N_4O_3H$ (MH^+) 409.2240, found 409.2241. Anal. Calcd for $C_{23}H_{28}N_4O_3$: C, 67.63; H, 6.91; N, 13.72. Found: C, 67.87; H, 6.97; N, 13.73.

(3*S*,4*R*,7*S*)-7-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-8-azido-3,4-epoxy-1-octanol (48) and (3*R*,4*S*,7*S*)-7-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-8-azido-3,4-epoxy-1-octanol (49). *m*-Chloroperbenzoic acid (1.74 g, 8.1 mmol) was added to a solution of **47** (3.3 g, 8.1 mmol) in CH_2Cl_2 (25 mL) at room temperature. After 2 h, the mixture was washed with 1 M NaOH and brine and then dried (Na_2SO_4) and concentrated to give 3.11 g (91%) of **48** and **49** in a 1:1 ratio. This mixture was separated by preparative HPLC (silica gel column), eluting with 15% *i*-PrOH/hexane at 15 mL/min to give 1.40 g (41%) of **48** and 1.38 g (40%) of **49** as clear oils.

Data for 48: t_R = 7.0 min (15% *i*-PrOH/hexane, silica, 2 mL/min); R_f 0.40 (75% EtOAc/hexane); $[\alpha]^{25}_D$ = +3.8° (c 1.3, $CHCl_3$); IR (neat) 3458 (br), 2100 (s), 1694 (s), 1454 (s), 1417 (s), 1230 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.45–7.15 (m, 10 H), 5.18 (s, 2 H), 4.60, 4.37 (AB quartet, J_{AB} = 15.7 Hz, 2 H), 3.90–3.55 (m, 2.8 H), 3.40–3.15 (m, 1.2 H), 2.97 (bs, 1 H), 2.75–2.55 (two bs, 1 H total), 2.28 (bs, 2 H), 2.0–1.8 (m, 0.8 H), 1.75–1.10 (m, 5.2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

155.8, 138.0, 136.3, 128.5, 128.1, 127.9, 127.5, 67.3, 60.2, 58.2, 56.1, 54.8, 53.0, 50.6, 30.5, 26.9, 24.9; MS (CI, NH_3) m/z (rel int) 425 (MH^+, 66), 397 (100), 379 (7), 368 (2), 353 (2), 324 (3), 289 (4), 259 (10), 180 (3), 144 (17), 136 (64); HRMS calcd for $C_{23}H_{28}N_4O_4H$ (MH^+) 425.2189, found 425.2169. Anal. Calcd for $C_{23}H_{28}N_4O_4$: C, 65.08; H, 6.65; N, 13.20. Found: C, 65.41; H, 6.95; N, 13.01.

Data for 49: t_R = 7.7 min (15% *i*-PrOH/hexane, silica, 2 mL/min); R_f 0.40 (75% EtOAc/hexane); $[\alpha]^{25}_D$ = +16.7° (*c* 3.3, $CHCl_3$); IR (neat) 3438 (br), 2100 (s), 1693 (s), 1454 (s), 1415 (s), 1230 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.40–7.15 (m, 10 H), 5.17 (s, 2 H), 4.60, 4.32 (AB quartet, J_{AB} = 15.7 Hz, 2 H), 4.05–3.85 (m, 1 H), 3.90–3.65 (m, 2 H), 3.62–3.48 (m, 0.8 H), 3.35–3.02 (m, 1.2 H), 3.01–2.90 (m, 1 H), 2.76 (bs, 0.8 H), 2.66 (bs, 0.2 H), 2.40 (bs, 1 H), 1.81–1.20 (m, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.1, 138.1, 136.1, 128.5, 128.0, 127.4, 67.4, 60.1, 57.2, 55.7, 54.1, 53.0, 49.5, 30.5, 27.0, 24.6; MS (CI, NH_3) m/z (rel int) 425 (MH^+, 100), 397 (71), 353 (3), 324 (4), 289 (2), 259 (2), 136 (33); HRMS calcd for $C_{23}H_{28}N_4O_4H$ (MH^+) 425.2189, found 425.2171. Anal. Calcd for $C_{23}H_{28}N_4O_4$: C, 65.08; H, 6.65; N, 13.20. Found: C, 64.69; H, 6.53; N, 13.38.

(3*S*,4*R*,7*S*)-7-[*N*-Benzyl-*N*-(benzyloxycarbonyl)-amino]-8-azido-3,4-epoxy-1-[(*p*-tolylsulfonyl)oxy]octane (50). A solution of **48** (0.54 g, 1.3 mmol), pyridine (0.21 mL, 2.5 mmol), and DMAP (16 mg, 0.1 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −15 °C, and *p*-toluenesulfonyl chloride (0.36 g, 1.90 mmol) was added. After 24 h at −15 °C, the mixture was diluted with Et_2O (20 mL) and washed with water, 1 M HCl, and 5% $NaHCO_3$ and then dried ($MgSO_4$) and concentrated. The residue was chromatographed (25% EtOAc/hexane) to give 0.63 g (86%) of **50** as a clear oil, R_f 0.20 (25% EtOAc/hexane): $[\alpha]^{25}_D$ = −1° (*c* 2.3, EtOH); IR (neat) 2100 (s), 1696 (s), 1453 (s), 1416 (s), 1228 (s), 1176 (s) cm^{-1}; ^1H NMR $CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.78 (d, J = 8.3 Hz, 2 H), 7.40–7.15 (m, 12 H), 5.18 (bs, 2 H), 4.59, 4.34 (AB quartet, J_{AB} = 15.7 Hz, 2 H), 4.12–4.00 (m, 2 H), 3.85–3.65 (m, 1 H), 3.65–3.50 (m, 0.8 H), 3.33–3.21 (m, 1.2 H), 2.88–2.75 (m, 1 H), 2.70–2.50 (m, 1 H), 2.42 (s, 3 H), 1.88–0.90 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 144.9, 136.3, 132.9, 129.9, 128.5, 127.8, 127.5, 67.5, 57.9, 56.1, 50.3, 27.5, 26.9, 24.8, 21.4; MS (CI, NH_3) m/z (rel int) 579 (MH^+, 8), 551 (8), 379 (30), 291 (5), 280 (100), 259 (30), 136 (27); HRMS calcd for $C_{30}H_{34}N_4O_6SH$ (MH^+) 579.2277, found 579.2279. Anal. Calcd for $C_{30}H_{34}N_4O_6S$: C, 62.27; H, 5.92; N, 9.68. Found: C, 62.51; H, 6.08; N, 10.02.

(3*R*,4*S*,7*S*)-7-[*N*-Benzyl-*N*-(benzyloxycarbonyl)-amino]-8-azido-3,4-epoxy-1-[(*p*-tolylsulfonyl)oxy]octane (51). A solution of **49** (0.76 g, 1.8 mmol), pyridine (0.29 mL, 3.6 mmol), and DMAP (22 mg, 0.2 mmol) in CH_2Cl_2 (2.0 mL) was cooled to −10 °C, and *p*-toluenesulfonyl chloride (0.52 g, 2.7 mmol) was added. After 10 h at −10 °C the reaction was diluted with Et_2O (20 mL) and washed with water, 1 M HCl, and 5% $NaHCO_3$ and then dried ($MgSO_4$) and concentrated. The residue was chromatographed (25% EtOAc/hexane) to give 0.85 g (81%) of **51** as a clear oil, R_f 0.20 (25% EtOAc/hexane): $[\alpha]^{25}_D$ = +10.7° (*c* 2.8, $CHCl_3$); IR (neat) 2101 (s), 1696 (s), 1453 (s), 1414 (w), 1359 (s), 1229 (s), 1176 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz, carbamate rotamers present) δ 7.79 (d, J = 8.2 Hz, 2 H), 7.42–7.15 (m, 12 H), 5.18 (bs, 2 H), 4.60, 4.32 (AB quartet, J_{AB} = 15.8 Hz, 2 H), 4.14–4.05 (m, 2 H), 4.02–3.85 (m, 1 H), 3.62–3.48 (m, 0.6 H), 3.38–3.15 (m, 1.4 H), 2.88–2.76 (m, 1 H), 2.75–2.65 (m, 0.6 H), 2.65–2.55 (m, 0.4 H), 2.44 (s, 3 H), 1.83–1.50 (m, 4 H), 1.40–1.05 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.0, 138.2, 136.3, 132.9, 129.8, 128.5, 128.0, 127.8, 127.6, 127.4, 67.4, 57.1, 55.8, 49.2, 27.6, 27.4, 26.8, 24.5, 21.5; MS (CI, NH_3) m/z (rel int) 579 (MH^+, 55), 551 (22), 522 (16), 478 (26), 425 (45), 397 (26), 381 (100), 291 (38), 280 (51), 242 (34), 174 (34); HRMS calcd for $C_{30}H_{34}N_4O_6SH$ (MH^+) 579.2277, found 579.2271. Anal. Calcd for $C_{30}H_{34}N_4O_6S$: C, 62.27; H, 5.92; N, 9.68. Found: C, 61.79; H, 5.83; N, 9.95.

(1*S*,6*S*,8a*S*)-Octahydro-1-hydroxy-6-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]indolizine (52). The azide **50** (0.54 g, 0.93 mmol) and 10% Pd–C (27 mg) in 95% EtOH (1 mL) were stirred under a balloon of hydrogen for 22 h. The mixture was filtered through Celite, washing with EtOH. The filtrate was diluted to a volume of 90 mL with EtOH, K_2CO_3 (0.69 g, 5.0 mmol) was added, and the mixture was heated at reflux for 20 h. The mixture was then concentrated, dissolved in $CHCl_3$, filtered, and concentrated again. Chromatography of the residue (5% $CH_3OH/CHCl_3$) gave 0.26 g (75%) of **52** as a yellow oil, R_f 0.26 (10% methanol/chloroform): $[\alpha]^{25}_D$ = +17.9° (*c* 1.8, $CHCl_3$); IR (neat) 3441 (br), 1691 (s), 1452 (w), 1413 (w), 1338 (w), cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz, carbamate rotamers present) δ 7.40–7.00 (m, 10 H), 5.25–5.05 (m, 3 H), 4.86 (d, J = 16.7 Hz, 1 H), 4.35–4.25 (m, 1 H), 4.05–3.98 (m, 1 H), 3.15 (bd, J = 12 Hz, 1 H), 2.92 (td, 1 H, J = 8.9, 2.8 Hz), 2.36–2.06 (m, 4 H), 1.95–1.88 (m, 1 H), 1.85–1.72 (m, 1 H), 1.67–1.52 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.9, 140.7, 136.8, 128.3, 127.9, 126.2, 73.0, 67.5, 67.2, 54.9, 52.2, 50.4, 48.6, 33.2, 28.4, 21.1; MS (EI, 70 eV) m/z (rel int) 380 (M^+, 4), 362 (3), 273 (1), 245 (2), 139 (100), 122 (7), 91 (44); HRMS calcd for $C_{23}H_{28}N_2O_3$ (M^+) 380.2100, found 380.2102. Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.99; H, 7.60; N, 7.41.

(1*R*,6*S*,8a*R*)-Octahydro-1-hydroxy-6-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]indolizine (53). The azide **51** (0.21 g, 0.36 mmol) and 10% Pd–C (13 mg) in 95% EtOH (1 mL) were stirred under a balloon of hydrogen for 20 h. The mixture was filtered through Celite, washing with EtOH. The filtrate was diluted to a volume of 36 mL with EtOH, K_2CO_3 (0.25 g, 1.8 mmol) was added, and the mixture was heated at reflux for 20 h. The mixture was then concentrated, dissolved in $CHCl_3$, filtered, and concentrated again. Chromatography of the residue (5% $CH_3OH/CHCl_3$) gave 0.11 g (81%) of **53** as a yellow oil, R_f 0.44 (10% methanol/chloroform): $[\alpha]^{25}_D$ = −15.5° (*c* 3.8, $CHCl_3$); IR (neat) 3442 (br), 1694 (s), 1453 (s), 1416 (s), 1249 (s), 1217 (s), 1122 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.42–7.10 (m, 10 H), 5.25–5.05 (m, 2 H), 4.47 (bs, 2 H), 4.10–3.95 (m, 2 H), 3.12–2.95 (m, 2 H), 2.72–2.50 (m, 1 H), 2.23–2.05 (m, 2 H), 2.03–1.88 (m, 1 H), 1.76–1.62 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.7, 139.3, 136.8, 128.5, 127.9, 127.0, 72.3, 67.7, 67.2, 56.0, 54.9, 52.2, 48.6, 33.8, 28.0, 23.8; MS (EI, 70 eV) m/z (rel int) 380 (M^+, 5), 362 (2), 245 (2), 224 (2), 153 (2), 153 (5), 139 (100), 122 (8); HRMS calcd for $C_{23}H_{28}N_2O_3$ (M^+) 380.2100, found 380.2081. Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61, H. 7.42; N, 7.36. Found: C, 72.22; H, 7.71; N, 7.39.

(1*S*,6*S*,8a*S*)-Octahydro-1-acetoxy-6-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]indolizine (54). The alcohol **52** (0.19 g, 0.49 mmol) was dissolved in pyridine (0.50 mL, 6.2 mmol), and acetic anhydride (0.5 mL, 5.3 mmol) was added. After 18 h at room temperature, the solvent was removed in vacuo and the residue was filtered through a plug of silica gel (0.6 mm × 30 mm), eluting with 2.5% methanol/chloroform to give 0.19 g (90%) of **54** as a light gold oil, R_f 0.46 (5% methanol/chloroform): $[\alpha]^{25}_D$ = +10.1° (*c* 2.4, $CHCl_3$); IR (neat) 1736 (s), 1695 (s), 1452 (s), 1413 (s), 1243 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.42–7.08 (m, 10 H), 5.26–5.00 (m, 5 H), 4.36–4.20 (m, 1 H), 3.15–2.95 (m, 1 H), 2.92–2.83 (m, 1 H), 2.38–1.98 (m, 5 H), 1.99 (s, 3 H), 1.81–1.51 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 156.6, 130.5, 136.6, 128.2, 128.1, 127.6, 126.2, 74.1, 66.9, 65.5, 54.2, 52.3, 50.0, 48.6, 40.5, 30.4, 27.9, 21.1, 20.8; MS (EI, 70 eV) m/z (rel int) 422 (M^+, 11), 363 (10), 181 (100), 142 (9), 121 (43), 91 (52); HRMS calcd for $C_{25}H_{30}N_2O_4$ (M^+) 422.2206, found 422.2186. Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.07; H, 7.16; N, 6.63. Found: C, 71.02; H, 7.28; N, 6.79.

(1*R*,6*S*,8a*R*)-Octahydro-1-acetoxy-6-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]indolizine (55). The alcohol **53** (75 mg, 0.20 mmol) was dissolved in pyridine (0.20 mL, 1.9 mmol), and acetic anhydride (0.2 mL, 1.9 mmol) was added. After 18 h at room temperature, the solvent was removed in vacuo and the residue was filtered through a plug of silica gel (0.6 mm × 30 mm), eluting with 2.5% methanol/chloroform to give 75 mg (90%) of **55** as a light gold oil, R_f 0.60 (5% methanol/chloroform): $[\alpha]^{25}_D$ = +9.8° (*c* 3.8, $CHCl_3$); IR (neat) 1736 (s), 1697 (s), 1453 (s), 1415 (s), 1241 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.42–7.15 (m, 10 H), 5.25–5.10 (m, 3 H), 4.54, 4.43 (AB quartet, J_{AB} = 15.0 Hz, 2 H), 4.15–3.82 (m, 1 H), 3.17–3.02 (m, 2 H), 2.40–2.15 (m, 2 H), 2.03 (s, 3 H), 2.03–1.40 (m, 7 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 156.2, 139.0, 136.6, 128.4, 127.9, 127.0, 74.1, 67.1, 66.5, 55.3, 52.5, 49.1, 40.5, 30.9, 27.5, 23.9, 20.9; MS (EI, 70 eV) m/z (rel int) 422 (M^+, 9), 363 (37), 181 (100), 142 (9), 121 (41), 91 (55); HRMS calcd for $C_{25}H_{30}N_2O_4$ (M^+) 422.2206, found 422.2201.

(1*S*,6*S*,8a*S*)-Octahydro-1-acetoxy-6-aminoindolizine (Slaframine) (1). The acetate **54** (44 mg, 0.10 mmol) and 10% Pd–C (44 mg) in 95% EtOH (1 mL) was stirred under a balloon

of hydrogen for 4 h. The mixture was filtered through Celite and concentrated to yield 16 mg (78%) of **1**, which was pure by NMR, R_f 0.50 (5% methanol/chloroform, alumina TLC plate): $[\alpha]^{25}_D$ = -33° (*c* 1.6 $CHCl_3$) [lit.[15] $[\alpha]^{25}_D$ = -38° (*c* = 0.16, $CHCl_3$)]; IR ($CHCl_3$) 1731 (s), 1377 (s), 1254 (s), 1109 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.19 (ddd, *J* = 7.6, 4.9, 2.2 Hz, 1 H), 4.22 (bs, 2 H), 3.21 (bs, 1 H), 3.15–3.02 (m, 2 H), 2.29–2.07 (m, 1 H), 2.13 (dd, *J* = 11.4, 2.2 Hz, 1 H), 2.05 (s, 3 H), 2.05–1.97 (m, 1 H), 1.90–1.81 (m, 2 H), 1.79–1.60 (m, 2 H), 1.58–1.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 170.8, 74.9, 67.4, 58.7, 52.9, 45.8, 30.5, 30.1, 21.0, 19.7; MS (EI, 70 eV) *m/z* (rel int) 198 (M^+, 6), 181 (2), 155 (46), 138 (54), 122 (10), 111 (16), 100 (17), 96 (20), 82 (19), 70 (58), 56 (17), 43 (100).

(1*S*,6*S*,8a*S*)-Octahydro-1-acetoxy-6-(*N*-acetylamino)-indolizine (*N*-Acetylslaframine). The amine **1** (16 mg, 0.08 mmol) was dissolved in pyridine (0.5 mL, 6.2 mmol), and then acetic anhydride (0.5 mL, 5.3 mmol) was added and the mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was filtered through a plug of silica gel (0.6 mm × 30 mm) eluting with 5% methanol/chloroform to give 15 mg (75%) of the title compound, R_f 0.50 (5% methanol/chloroform), mp 139–141 °C, $[\alpha]^{25}_D$ = -11.2° (*c* = 1.45, EtOH) [lit.[4,46] mp 140–142 °C, $[\alpha]^{25}_D$ = -15.9° (*c* = 5, EtOH)]: IR ($CDCl_3$) 1738 (s), 1660, 1530, 1430, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.3 (bs, 1 H), 5.22 (ddd, *J* = 7.7, 5.0, 2.2 Hz, 1 H), 4.16 (td, *J* = 8.3, 2.7 Hz, 1 H), 3.12–2.96 (m, 2 H), 2.32–2.18 (m, 1 H), 2.16 (dd, *J* = 11.4, 2.6 Hz, 1 H), 2.06 (s, 3 H), 2.06–1.69 (m, 4 H), 1.61–1.39 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 169.2, 74.8, 67.4, 57.5, 53.1, 43.9, 30.6, 28.2, 23.5, 21.0, 20.6.

(1*R*,6*S*,8a*R*)-Octahydro-1-acetoxy-6-aminoindolizine (1,8a-Diepislaframine) (56). The acetate **55** (51 mg, 0.12 mmol) and 10% Pd–C (50 mg) were in 95% EtOH (1 mL) was stirred under a balloon of hydrogen for 6 h. The reaction was filtered through Celite and concentrated to yield 15 mg (64%) of **56**, which was pure by NMR, R_f 0.50 (5% methanol/chloroform, alumina TLC plate): $[\alpha]^{25}_D$ = +20° (*c* 0.5, EtOH); IR (neat) 1731 (s), 1466 (w), 1378 (s), 1098 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.20 (ddd, *J* = 7.6, 4.7, 2.0 Hz, 1 H), 3.24 (ddd, *J* = 10.3, 4.3, 1.7 Hz, 1 H), 3.12 (td, *J* = 8.9, 1.8 Hz, 1 H), 2.99–2.85 (m, 1 H), 2.36–2.20 (m, 1 H), 2.05 (s, 3 H), 2.05–1.92 (m, 2 H), 1.88–1.78 (m, 2 H), 1.75–1.65 (m, 2 H), 1.58–1.40 (m, 1 H), 1.43 (bs, 2 H), 1.15–1.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.6, 73.6, 66.3, 55.0, 52.1, 47.9, 30.8, 28.4, 22.8, 20.9.

(*S*)-(*Z*)-7-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-8-azido-1-[(*p*-tolylsulfonyl)oxy]oct-3-ene (57). Pyridine (0.65 mL, 8.0 mmol) and DMAP (50 mg, 0.4 mmol) were added to a solution of **47** (1.63 g, 4.0 mmol) in CH_2Cl_2 (4.0 mL), followed by *p*-toluensulfonyl chloride (1.14 g, 6.0 mmol). After 6 h at room temperature, the mixture was diluted with Et_2O (20 mL) and washed successively with water, 1 M HCl, and 5% $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was chromatographed (20% EtOAc/hexane) to give 1.51 g (67%) of **57** as a clear oil, R_f 0.40 (25% EtOAc/hexane): $[\alpha]^{25}_D$ = +3.7° (*c* 7.5, $CHCl_3$); IR (neat) 2100 (s), 1698 (s), 1454 (s), 1415 (s), 1359 (s), 1229 (s), 1188 (s), 1176 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, carbamate rotamers present) δ 7.78 (d, *J* = 8.3 Hz, 2 H), 7.40–7.15 (m, 12 H), 5.40–5.15 (m, 4 H), 4.60, 4.38 (AB quartet, J_{AB} = 15.9 Hz, 2 H), 4.00–3.85 (m, 3 H), 3.65–3.55 (m, 0.75 H), 3.48–3.22 (m, 1.25 H), 2.44 (s, 3 H), 2.35–2.2 (m, 2 H), 1.83–1.40 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 144.6, 138.3, 136.4, 133.3, 131.9, 129.8, 128.5, 128.0, 127.8, 127.4, 124.0, 69.4, 67.3, 57.4, 53.0, 49.7, 29.9, 27.0, 24.1, 21.5; MS (CI, NH_3) *m/z* (rel int) 563 (MH^+, 11), 535 (5), 468 (12), 408 (18), 391 (20), 363 (94), 318 (8), 280 (24), 259 (60); HRMS calcd for $C_{30}H_{34}N_4O_5SH$ (MH^+) 563.2328, found 563.2341. Anal. Calcd for $C_{30}H_{34}N_4O_5S$: C, 64.04; H, 6.09; N, 9.96. Found: C, 63.65; H, 6.06; N, 10.03.

(3*S*,4*R*,7*S*)-7-[*N*-Benzyl-*N*-(benzyloxycarbonyl)-amino]-8-azido-3,4-epoxy-1-[(*p*-tolylsulfonyl)oxy]octane (50) and (3*R*,4*S*,7*S*)-7-[*N*-Benzyl-*N*-(benzyloxycarbonyl)-amino]-8-azido-3,4-epoxy-1-[(*p*-tolylsulfonyl)oxy]octane (51). *m*-Chloroperbenzoic acid (430 mg, 2.0 mmol) was added to a solution of **57** (1.1 g, 2.0 mmol) in CH_2Cl_2 (5 mL). After 2 h at room temperature, the mixture was washed with 1 M NaOH and brine and then dried (Na_2SO_4) and concentrated to give 1.03 g (90%) of **50** and **51** in a 1:1 ratio. The spectral data of the mixture were consistent with those reported above.

(1*S*,6*S*,8a*S*)-Octahydro-1-hydroxy-6-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]indolizine (52) and (1*R*,6*S*,8a*R*)-Octahydro-1-hydroxy-6-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]indolizine (53). The mixture of azides **50** and **51** (1.03 g, 1.78 mmol) from above and 10% Pd–C (51 mg) in 95% EtOH (5 mL) were stirred under a balloon of hydrogen for 22 h. The mixture was filtered through Celite, washing with EtOH. The filtrate was diluted to a volume of 90 mL with EtOH, K_2CO_3 (0.69 g, 5.0 mmol) was added, and the mixture was heated at reflux for 20 h. The mixture was concentrated, dissolved in $CHCl_3$, filtered, and reconcentrated. The residue was chromatographed, eluting first with 5% $CH_3OH/CHCl_3$ and then with 10% $CH_3OH/CHCl_3$ to give 0.20 g (30%) of **52** (fraction 1) and 0.24 g (36%) of **53** (fraction 2), each with spectral characteristics consistent with those reported above.

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Supplementary Material Available: ^1H NMR spectra of synthetic (-)-slaframine (**1**), (-)-*N*-acetylslaframine, (-)-1,8a-diepislaframine (**56**), and the compounds which had no elemental analysis: **20**, **21**, **27**, **30**, **33**, **36**, **38**, **39**, **40**, **43**, **45**, and **55**. Note that the resonances in the spectra for compounds **20**, **21**, **30**, **33**, **55** are broadened due to slow rotation of the tertiary carbamate groups (21 pages). This material is contained in many 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.