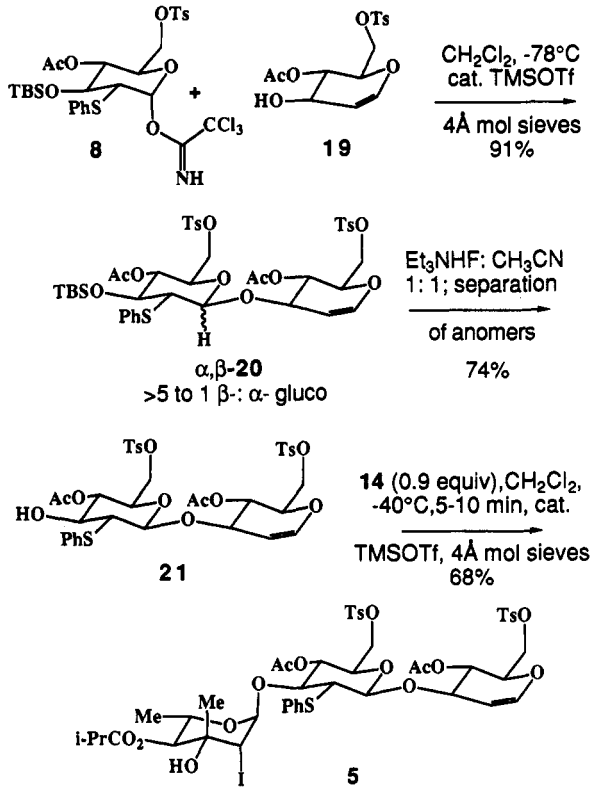

olivin derivative, glycal **19**[21] was glycosylated with **8** (0.8 equiv of **8**, CH_2Cl_2, -78 °C, 4-Å molecular sieves, 0.2 equiv of TMSOTf, 5 min) to give glycal disaccharide **α,β-20** as a mixture of anomers (>5:1; β:α) in 91% combined yield.[22] The mixture was desilylated (Et_3NHF–CH_3CN, 23 °C) and, after separation of the α-anomer by flash silica gel chromatography, C–D disaccharide **21** was obtained as a single diastereomer in 74% yield. Glycosylation of **21** with **14** as before (0.9 equiv of **14**, 0.3 equiv of TMSOTf, -40 °C, CH_2Cl_2, 4-Å molecular sieves, 5 min) gave C–D–E trisaccharide **5** in 68% yield, along with 16% of recovered **21**.

Further elaborations of trisaccharide **5** and studies on the glycosidation of the aglycon are currently under investigation. Progress along these lines will be reported in due course.

Acknowledgment. We gratefully acknowledge support provided by a grant from the National Institute of General Medical Sciences (GM 38907).

Supplementary Material Available: Experimental procedures, tabulated spectral data, and ^1H and ^{13}C NMR spectra for **8**, **11**, **16**, and **19** and ^1H NMR spectra for the β-gluco isomer of **10**, **α,β-12**, the α-gluco isomer of **13**, **α,β-20**, and the α-gluco isomer of **21** (25 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.

(21) Glycal **19** was prepared from **6** by treatment with Et_3NHF–CH_3CN (1:1), 23 °C (75%).

(22) To the best of our knowledge, Danishefsky was the first to employ glycal alcohols as acceptors in glycosidation reactions: (a) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (b) Halcomb, R. L.; Danishefsky, S. J. *Ibid.* **1989**, *111*, 6661.

Articles

Radical Routes to Indolizidines. Synthesis of (-)-Slaframine

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The synthesis of (-)-slaframine (**5**) was executed in 11 steps and 25% overall yield from resolved 3(*S*)-hydroxy-4-pentenamide (**22**). Two cyclization reactions were used to form the indolizidine skeleton and also to provide the necessary stereocontrol at C-8a and C-6 of the natural product. "Iodolactamization" of **22** gave selectively the *cis*-pyrrolidinone **21**. Later in the synthesis, a silane-mediated radical cyclization of the phenylseleno lactam **33** gave selectively the 6α-hydroxyindolizidinone **35a**, an event predictable from model studies such as **14c** → **15c**. Replacement of hydroxy with azido and reduction of the lactam carbonyl gave "slaframine azide", **38**, a stable and easily convertible immediate precursor to **5**.

Iodolactams can be made by iodocyclization of unsaturated amides, as for **1** → **2**.[1-3] Although N-substituted amides do not give high yields in this cyclization reaction, N-substituted lactams can be made by alkylation of **2**, or better, the derived phenylselenolactam **3**, as previously reported.[4] Such N-alkylated lactams are useful as substrates for free-radical-initiated cyclization,[4] and several indolizidine derivatives **4** have been prepared in this way. These examples feature some novel radical acceptor groups: bromoalkene, chloroalkene, and (ethoxymethoxy)alkene. The cyclizations are also notable for the predominance of six-membered rig formation, in contrast

(1) Knapp, S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803.
(2) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.
(3) Knapp, S.; Gibson, F. S. *Org. Synth.* **1991**, *70*, 101.
(4) Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *38*, 5397.

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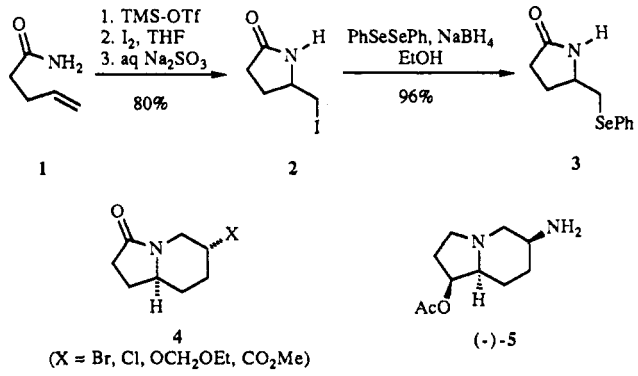
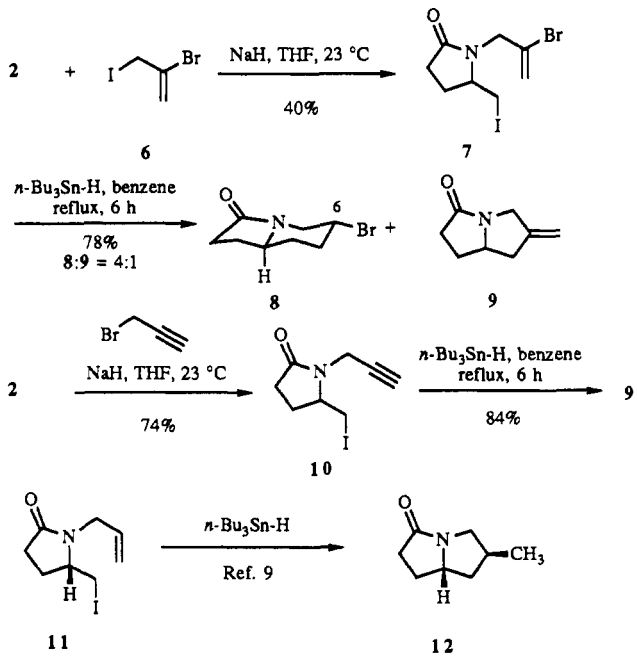
to the five-membered cyclizations usually seen for simpler 5-hexenyl radicals.[5] The structural similarities between the indolizidinone models and the alkaloid slaframine (5) suggest that 5 might be synthesized by an "iodolactamization"/radical cyclization approach. We report the completion of an efficient, stereocontrolled total synthesis of 5 that incorporates both of these ring-forming methods. Experimental details for the alkylation and cyclization reactions leading to model indolizidinones 4 are also included.



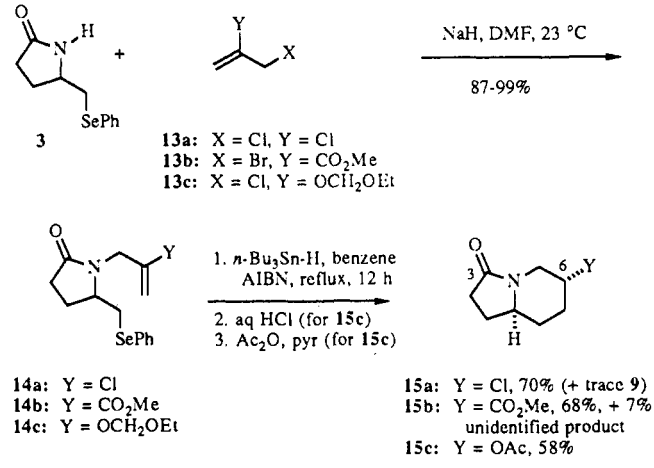
Indolizidine Model Studies. The simplest approach to the indolizidine skeleton involved directed alkylation of 2 with 2-bromo-3-iodopropene (6) to give the *N*-(bromallyl) derivative 7 and then tri-*n*-butyltin hydride mediated radical ring closure to the bicyclic bromo lactam 8. *N*-bromoindolizidin-3-one (8) and the alkene 9 occurred with good efficiency, 4:1 site selectivity favoring the six-membered ring and >20:1 stereoselectivity favoring the 6α-bromo, or "6-*exo*-bromo", isomer. Assignment of structure to the bromoindolizidinone (8) is based on its ^1H NMR spectrum, particularly the large ^1H–^1H coupling constant (12.1 Hz) between vicinal pseudodiaxial protons on C-5 and C-6, suggestive of a pseudoequatorial position for the 6-bromo substituent. The alkene 9, the product of 5-*exo-trig* radical cyclization[5] and loss of Br•, was independently prepared by N-alkylation of 2 with propargyl bromide and then 5-*exo-dig* radical cyclization of the iodo lactam 10, as shown below.



Deprotonation of iodolactams gives an unstable anion that can only be intercepted by reactive alkylating agents—if alkylation on nitrogen is a slow reaction, the sodium or potassium salt of 2 decomposes instead to a polymeric material.[2] Thus with 6 as the electrophile, the best yield for alkylation of 2, though modest, was achieved in tetrahydrofuran solution by using sodium hydride as the base. Less reactive alkylating agents, such as 1-iodobutane, gave no alkylated product at all. The *N*-(bromallyl) lactam 7 was then treated with tri-*n*-butyltin hydride under standard conditions for generating the carbon-centered radical: benzene solution, azobis(isobutyronitrile) as initiator, reflux for 6–8 h.[6] Cyclization to a mixture of the

The prodominance of six-membered ring formation may be attributed to the difference in steric hindrance between the terminal (methylidene) carbon where C–C bond closure to the indolizidinone product 8 occurs and the internal alkene carbon bearing two substituents.[7-9] By comparison, the simpler substrate *N*-allyl-5-(iodomethyl)pyrrolidin-2-one (11), which lacks the bromo substituent, cyclizes with high site selectivity to the pyrrolizidin-3-one product 12, despite the greater strain of the [3.3.0] ring system.[9] From these two examples, and the three given below, one can infer that the mode of cyclization (five-membered ring vs six), although delicately balanced, is relatively insensitive to the effect of the alkene substituent on the energy of the alkene LUMO.[10] The preferred formation of 8 as the 6α-bromo isomer suggests that the hydrogen atom transfer from tri-*n*-butyltin hydride to the α-bromo radical intermediate occurs in a pseudoaxial fashion, the kinetically-favored mode for such processes in cyclohexyl radicals,[11] to produce the pseudoequatorial bromide 8.

The problematic lactam N-alkylation step was improved considerably by replacing iodo with phenylseleno (2 → 3). N-Alkylation of 3 was successful for a variety of allylic halides 13, as illustrated below. Furthermore, treatment



of the N-alkylated phenylseleno lactams 14 with tri-*n*-butyltin hydride as described for 7 → 8 gave analogous cyclization to indolizidin-3-one products 15. The bulky substituent (Cl, CO_2Me, or OCH_2OEt) at C-2 of the N-allyl group directs preferential formation of the indolizidinone

(5) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(6) Curran, D. P. *Synthesis* **1988**, 417.

(7) The 5-methyl-5-hexenyl radical shows a slight preference for 6-*endo-trig* cyclization (for discussion see ref 5). Two groups (see refs 8 and 9) studying radical cyclization in lactam systems find preferred 6-*endo* cyclization where steric factors contribute.

(8) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959 and references cited therein.

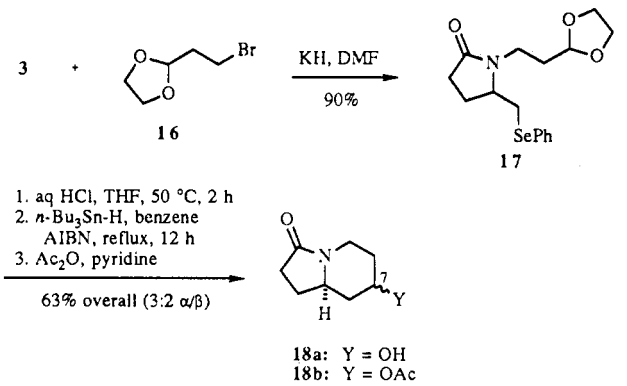
(9) (a) Keusenkothen, P. F.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3369. (b) Keusenkothen, P. F.; Smith, M. B. *Tetrahedron*, in press.

(10) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753.

(11) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969.

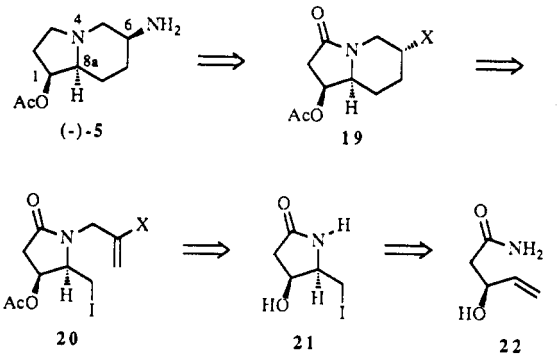
ring system, as for **8**. The stereochemical result, preferential hydrogen atom abstraction at C-6 to give the (pseudoequatorial) 6α-substituent, is also analogous. It is noteworthy that the phenylseleno group is abstracted from the starting material **14a** without competitive removal of the chloro substituent in either starting material or product (**15a**). This may be the result of the difference in bond dissociation energies (65 kcal/mol for $PhSe-CH_2$, 79–88 kcal/mol for Cl–C), which could override the kinetic preference sometimes observed for abstraction of monovalent atoms over divalent ones.[12]

An additional indolizidin-3-one ring system **18a** was prepared by radical cyclization of the phenylseleno aldehyde derived[13] from acetal **17**, which in turn is available by alkylation of **3** with 2-(2-bromoethyl)-1,3-dioxolane (**16**).

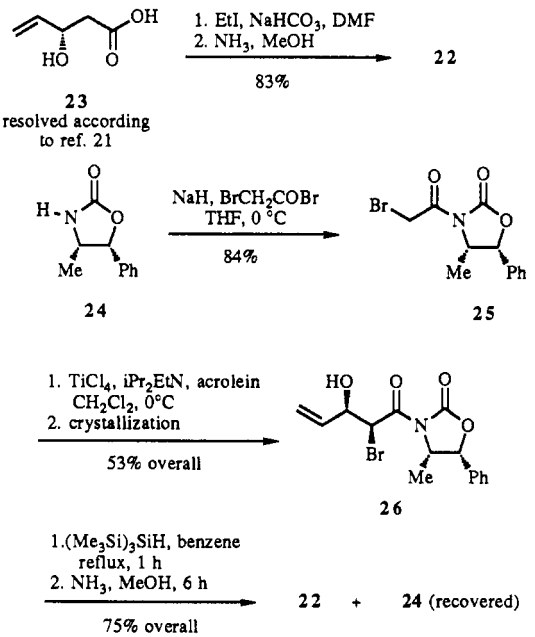


The 3:2 mixture of products was analyzed as the acetate derivatives **18b** by 400-MHz ^1H NMR, and stereochemistry was assigned based on the magnitude of coupling of H-7 with the four neighboring protons [pseudoequatorial H-7 of 7α-acetoxy (major) isomer: 5.18 (app quintet, J = 2.8 Hz); pseudoaxial H-7 of 7β-acetoxy (minor) isomer: 4.84 (tt, J = 11.4, 4.0 Hz)]. No clear stereochemical preference was exhibited for the intramolecular addition of alkyl radical to aldehyde carbonyl, which is in accord with earlier observations for this type of cyclization.[14]

Synthesis of (–)-Slaframine. Slaframine (**5**) is an indolizidine alkaloid thought to cause excessive salivation in ruminants affected by a fungal infection known as "black patch".[15] In light of the model studies and literature precedent, an "iodolactamization"/radical cyclization approach to the synthesis of **5** seemed feasible. We planned to displace a leaving group X from a radical cyclization product **19** with a nitrogen nucleophile to set the stereochemistry at C-6. In turn, **19** would arise by cyclization of an N-alkylated lactam **20**, and **20** could be made by iodocyclization and N-alkylation of 3(*S*)-hydroxy-4-pentenamide (**22**), which we hoped to prepare in optically pure form. Studies of iodolactonization[16] and related reactions[17,18] had already established the preference for cis stereochemistry for halocyclizations such as **22** → **21**. The synthesis as planned would address some of the shortcomings of previously published syntheses of **5**,[15] including the difficulty of controlling the relative stereochemistry at the remote centers C-8a and C-6, the difficulty of a late O-acetylation step, and the problems of carrying a basic nitrogen at N-4 or C-6 through more than a step or two. In addition, we hoped to match the excellent management of stereochemistry in the recent Cha synthesis[19] and the advantages of a stable and easily convertible immediate precursor to **5** as advocated by Pearson.[20]



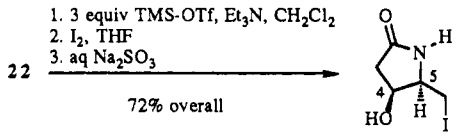
3-Hydroxy-4-pentoic acid (**23**) has been prepared and resolved using quinine and quinidine, ultimately providing the pure 3*S* enantiomer.[21] This preparation was reproduced, and the resolved **23** was converted to 3(*S*)-hydroxy-4-pentenamide (**22**) as shown below. Direct asymmetric synthesis of **22** was also accomplished by a modification of the Evans asymmetric aldol procedure.[22–24] Oxazolidinone **24** was N-acylated to give the bromoacetyl derivative **25**. By using titanium tetrachloride and diisopropylethylamine, **25** was condensed with acrolein to give **26** (>19:1 stereoselectivity), which was purified by crystallization, and converted to **22** by tris(trimethylsilyl)silane-mediated free-radical reduction,[25–27] followed by am-

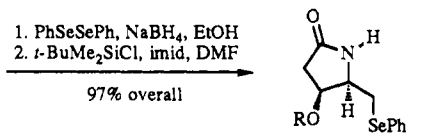


(12) Laird, E. R.; Jorgensen, W. L. *J. Org. Chem.* **1990**, *55*, 9.
(13) Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, 499.
(14) Fraser-Reid, B.; Vite, G. D.; Yeung, B.-W. A.; Tsang, R. *Tetrahedron Lett.* **1988**, *29*, 1645.
(15) Elbein, A. D.; Molyneux, R. J. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley and Sons: New York, 1987; Vol. 5, pp 1–49.
(16) Chamberlain, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819.
(17) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monohan, R. *J. Org. Chem.* **1987**, *52*, 4191.
(18) Takahata, H.; Takamatsu, T.; Yamazaki, T. *J. Org. Chem.* **1989**, *54*, 4812.
(19) Choi, J.-R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469.
(20) (a) Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1991**, *56*, 1976. (b) Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.*, in press.
(21) Nakanimami, G.; Shioi, S.; Sugiyama, Y.; Isemura, S.; Shibuya, M.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2624.
(22) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(23) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151.
(24) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

inolysis of the chiral auxiliary.

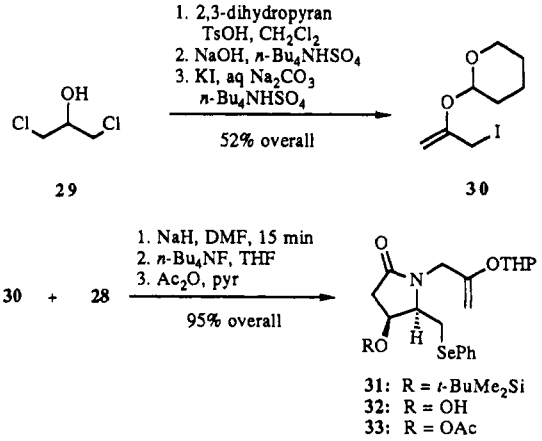
Iodolactamization of **22** was carried out according to the usual protocol,[2,3] but with sufficient trimethylsilyl trifluoromethanesulfonate to silylate nitrogen and both oxygens, and with THF as the solvent. After sulfite quench, the required 4(*S*)-hydroxy-5(*R*)-(iodomethyl)-2-pyrrolidinone (**21**) was isolated in good yield by chromatography and crystallization. According to NMR analysis, a small amount (<5%) of the C-5 epimer was formed during the cyclization, but was removed during purification of **21**. Attempts to directly N-alkylate **21**, or O-protected derivatives of **21**, with 3-chloro-2-(ethoxymethoxy)propene (**13c**) were unsuccessful. However, prior replacement of iodo with phenylseleno as for **2** → **3**, and hydroxyl protection as the *tert*-butyldimethylsilyl ether, gave a lactam **28** that could be N-alkylated in high yield with a variety of alkylating reagents, including **13c**. A more direct precursor to **19**, the C-4 *O*-acetate derivative of alcohol **27**, was deacetylated during attempted N-alkylation and therefore could not be used.

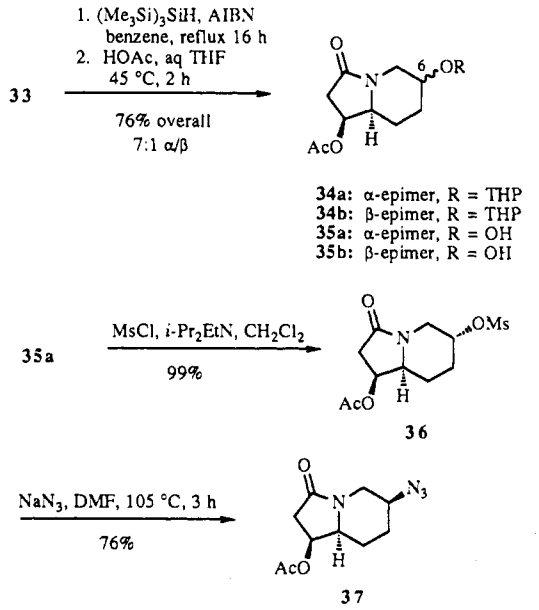




At this point in the synthesis the choice of "X" (see **19** and **20**) in the alkylating agent was given more consideration. An important feature of the route as outlined was to be early introduction of the *O*-acetate at C-1. This dictates the use of a group "X" that can be converted to the C-6 amino without disturbing the C-1 acetoxy substituent. Model studies on chloroindolizidinone **15a** showed that S_N2 displacement of chloride by azide is difficult. An ethoxymethyl protecting group (from **13c**) on the C-6 hydroxyl might be difficult to hydrolyze without cleaving an acetate at C-1. A more acid-labile hydroxyl protecting group seemed to offer an advantage, so the new alkylating agent 3-iodo-2-(2-tetrahydropyranyloxy)propene (**30**) was prepared from 1,3-dichloro-2-propanol (**29**) as shown below. N-Alkylation of the lactam **28** with **30** was rapid and nearly quantitative. Likewise, removal of the silyl protecting group at C-1 (**31** → **32**) and installation of the acetate was very efficient. The required substrate for free-radical-initiated cyclization, **33**, could thus be prepared by a high yielding route, the major drawbacks of which are the necessity of introducing phenylseleno and of protecting the C-4 hydroxyl.

Free-radical-initiated cyclization of **33** was carried out as in the model studies, but with substitution of the new reagent tris(trimethylsilyl)silane[25-27] for the tributyltin hydride. In our experience with indolizidinone formation by radical cyclization, use of the silane led to essentially the same products and yields as the tin reagent, but simplified the workup considerably. The cyclized product

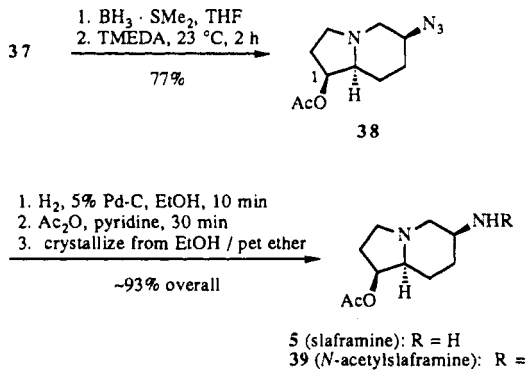




consisted of two pairs of diastereomers (due to the THP): the higher R_f indolizidinone **34a** was hydrolyzed to a single C-6 alcohol that was assigned structure **35a** based on coupling constants and comparison with **15c**; the lower R_f indolizidinone likewise produced an epimeric alcohol, **35b**. The 6α-hydroxy isomer **35a** predominated by ~7:1. Conversion of **35a** to its methanesulfonyl ester **36**, followed by S_N2 displacement of the mesylate with azide, gave the azidoindolizidinone **37**. Very little β-elimination[2] accompanied the displacement, perhaps as a consequence of the pseudoequatorial position of the leaving group.

Reduction of the lactam was carried out in the presence of the C-1 acetoxy by using the borane–dimethyl sulfide complex.[28] After liberation of the free amine with tetramethylethylenediamine,[29] the indolizidine **38** was isolated in good yield. "Slaframine azide" **38** was obtained in analytically pure form, and proved to be stable to storage and handling. It was rapidly and efficiently converted to slaframine **5** by catalytic hydrogenation. The 400-MHz ^1H NMR spectrum of synthetic **5** prepared in this way matched the spectrum of the natural product and also the synthetic **5** prepared by Pearson.[20] The optical rotation, $[\alpha] = -32.3°$, also matched the reported values (lit.[20] $[\alpha] = -33°$, lit.[19] $[\alpha] = -38°$). Acetylation of **5** gave the known *N*-acetylslaframine (**39**), whose mp (140–141 °C (lit.[30] mp

(25) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3642.
(26) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678.
(27) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681.
(28) Reymond, J. L.; Pinkerton, A. A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128.
(29) Brown, H. C.; Choi, Y. M.; Narasimhan, N. *J. Org. Chem.* **1982**, *47*, 3153.



140–142 °C, lit.[20] mp 139–141 °C, lit.[19] mp 136–138 °C), optical rotation $[\alpha] = -14.6°$ (lit.[30] $[\alpha] = -15.9°$, lit.[20] $[\alpha] = -11.2°$, lit.[19] $[\alpha] = -18.8°$), and ^1H NMR spectrum matched those reported previously.

In summary, a stereoselective synthesis of (−)-slaframine (**5**) has been accomplished in 11 steps, 25% overall yield, from resolved 3(*S*)-hydroxy-4-pentenamide (**22**). Literature precedent for cis halocyclization of 3-hydroxy-4-pentenyl systems was sustained in the iodolactamization reaction **22** → **21**. The indication from model studies that the 6α-substituted indolizidinone would predominate in the radical cyclization was borne out in the conversion of **33** to **34**. Finally, "azidoslaframine" **38** proved to be a convenient precursor for rapid and efficient conversion to slaframine.

Experimental Section

Apparatus and Reagents. Melting points were determined on an Electrothermal apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 727B spectrophotometer or Mattson Instruments Expert-FT-IR instrument (selected absorption maxima are reported in cm^{-1}). Proton nuclear magnetic resonance (NMR) spectra were obtained with a Varian Associates XL-400 instrument in deuteriochloroform solutions. Chemical shifts are reported in parts per million downfield from tetramethylsilane, and coupling constants are reported in hertz. Elemental analyses were performed by Robertson Laboratories (Madison, NJ). Chemical ionization mass spectra (CI-MS) were obtained on a VG Analytical Model 7070 EQ spectrometer by using isobutane as the carrier gas. Specific rotations $[\alpha]$ were determined on a Perkin-Elmer Model 241 polarimeter at the sodium D line at 25 °C.

Precoated silica gel plates (Baker Si250F) were used for analytical thin-layer chromatography (TLC). Macherery Nagel silica gel 60 (230–400 mesh) was employed for column chromatography. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl; dichloromethane, pyridine, *N,N*-dimethylformamide (DMF), triethylamine, diisopropylamine, benzene, and pentane were distilled from calcium hydride. 2-(Ethoxymethoxy)-3-chloropropene was prepared according to a literature procedure for 2-(methoxymethoxy)-3-chloropropene.[31] 2-Bromo-3-iodopropene was prepared from 2,3-dibromopropene by reaction with sodium iodide in acetone solution (23 °C, 4 h). Other reagents were obtained commercially and used as received unless otherwise specified. Organic solutions were dried over anhydrous sodium sulfate. All moisture- or air-sensitive reactions were carried out under a static argon atmosphere.

5-[(Phenylseleno)methyl]-2-pyrrolidinone (3). A suspension of 2.09 g (6.6 mmol) of diphenyl diselenide in 20 mL of anhydrous ethanol was stirred and cooled to 0 °C. Sodium borohydride was added in small portions until the solution was colorless. Iodo lactam **2**[2] (1.5 g, 6.6 mmol) was added in one portion, and the reaction was allowed to stir at room temperature for 3 h. The reaction mixture was concentrated, and the residue was dissolved in ethyl acetate, which was washed twice with saturated aqueous sodium bicarbonate and dried. The solvent was removed, and the residue was chromatographed by using ether as the eluant to afford 1.63 g (96%) of **3**, mp 77–78 °C (from ethyl acetate/hexane): NMR 1.72–1.80 (m, 1 H), 2.20–2.41 (m, 3 H), 2.81 (dd, 1 H, J = 8.4, 12.4), 3.01 (dd, 1 H, J = 5.2, 12.8), 3.70–3.78 (m, 1 H), 5.91 (br s, 1 H), 7.22–7.51 (m, 5 H); IR 3344, 3257, 1693. Anal. Calcd for $C_{11}H_{13}NOSe$: C, 51.67; H, 5.15; N, 5.51. Found: C, 51.47; H, 5.02; N, 5.32.

General Procedure for N-Alkylation of Lactams. A solution of 0.5 mmol of the iodo (**2**) or phenylseleno (**3**) lactam and 2.5 mmol of the alkylating agent in 4 mL of DMF (or THF as indicated) was treated with 0.55 mmol of sodium hydride and stirred until disappearance of starting material, typically 2–4 h. The reaction mixture was chromatographed by using ether/petroleum ether mixtures as the eluant to give pure N-alkylated lactam.

General Procedure for Radical Cyclizations. A solution of 0.5 mmol of N-alkylated lactam in 12 mL of dry benzene was heated at reflux for 10 min. Tributyltin hydride (0.55 mmol) was added by syringe, followed by 4 mg of azobis(isobutyronitrile). The reaction was heated at reflux until the starting material disappeared (typically ~6 h for iodides, ~12 h for selenides), cooled, concentrated, and chromatographed by using ether/petroleum ether mixtures as the eluant to give the cyclized product.

1-(2-Bromo-2-propenyl)-5-(iodomethyl)-2-pyrrolidinone (7). Alkylation of **2** with 2-bromo-3-iodopropene using THF as the reaction solvent gave **7** (42%) as a pale yellow oil: NMR 1.80–1.89 (m, 1 H), 2.23–2.30 (m, 1 H), 2.42 (ddd, 1, H, J = 5.6, 10.1, 17.0), 2.53–2.63 (m, 1 H), 3.26 (dd, 1 H, J = 6.3, 10.7), 3.36 (dd, 1 H, J = 2.6, 10.8), 3.65 (d, 1 H, J = 16.1), 3.63–3.69 (m, 1 H), 4.70 (d, 1 H, J = 16.1), 5.61 (s, 1 H), 5.82 (s, 1 H); IR 3078, 1691; CI-MS 344 ($M^+ + 1$).

6α-Bromo-(8aα-H)-3-indolizidinone (8). Cyclization of **7** by the general procedure afforded **8** (63%) as a pale yellow oil: NMR 1.31–1.40 (m, 1 H), 1.58–1.64 (m, 1 H), 1.82–1.99 (m, 2 H), 2.19–2.30 (m, 1 H), 2.42 (t, 1 H, J = 8.2), 2.39–2.46 (m, 2 H), 2.89 (t, 1 H, J = 11.8), 3.45–3.52 (m, 1 H), 3.78–3.86 (m, 1 H), 4.51 (ddd, 1 H, J = 1.9, 5.1, 13.0); IR 1695. Anal. Calcd for $C_8H_{12}NBrO$: C, 44.06; H, 5.54; N, 6.42. Found: C, 44.66; H, 5.40; N, 6.14. Pyrrolizidinone **9** was also isolated as a minor product (15%) of lower R_f.

6-Methylidene-3(3*H*)-pyrrolizidinone (9). Cyclization of **10** by using the general procedure gave **9** (84%) as an oil: NMR 1.75–1.86 (m, 1 H), 2.13–2.20 (m, 1 H), 2.36–2.42 (m, 1 H), 2.46 (dd, 1 H, J = 2.2, 9.7), 2.68–2.78 (m, 2 H), 3.60 (dt, 1 H, J = 15.9, 2.0), 3.98–4.05 (m, 1 H), 4.25 (d, 1 H, J = 15.9), 5.04 (d, 2 H, J = 20.3); IR 3078, 1691; CI-MS 138 ($M^+ + 1$). The same experiment run at shorter reaction times gave varying amounts of 6-(iodomethylene)hexahydro-3(3*H*)-pyrrolizidinone, the product of an atom-transfer process.[4,32] Further reduction fully converted this intermediate to **9**.

5-(Iodomethyl)-1-(2-propynyl)-2-pyrrolidinone (10). Alkylation of **2** by the general procedure with propargyl bromide and using THF as the reaction solvent afforded **10** (74%) as a pale yellow oil: NMR 1.79–1.88 (m, 1 H), 2.21–2.29 (m, 2 H), 2.39 (ddd, 1 H, J = 6.3, 10.5, 17.1), 2.52–2.61 (m, 1 H), 3.38 (dd, 1 H, J = 5.9, 11.0), 3.46 (dd, 1 H, J = 2.5, 10.6), 3.66 (dd, 1 H, J = 1.7, 17.2), 3.79–3.84 (m, 1 H), 4.61 (dd, 1 H, J = 2.7, 18.0); IR 3290, 3232, 2117, 1687; CI-MS 164 ($M^+ + 1$). Anal. Calcd for $C_8H_{10}NIO$: C, 36.52; H, 3.83; N, 5.32. Found: C, 37.66; H, 3.80; N, 5.16.

1-(2-Chloro-2-propenyl)-5-[(phenylseleno)methyl]-2-pyrrolidinone (14a). Alkylation of **3** by the general procedure with 2,3-dichloropropene (**13a**) afforded **14a** (87%) as a white solid, mp 35–36 °C (from ether/hexane): NMR 1.83–1.92 (m, 1 H), 2.21–2.29 (m, 1 H), 2.38 (ddd, 1 H, J = 5.6, 10.1, 17.0), 2.50–2.59 (m, 1 H), 2.89 (dd, 1 H, J = 8.2, 12.6), 3.14 (dd, 1 H, J = 3.0, 8.2), 3.46 (d, 1 H, J = 15.8), 3.83–3.89 (m, 1 H), 4.39 (d, 1 H, J = 15.8), 5.20 (s, 1 H), 5.26 (s, 1 H), 7.23–7.51 (m, 5 H); IR 3053, 1693. Anal. Calcd for $C_{14}H_{16}NClOSe$: C, 51.15; H, 4.91; N, 4.26. Found: C, 51.42; H, 4.82; N, 4.47.

1-[2-(Methoxycarbonyl)-2-methylideneethyl]-5-[(phenylseleno)methyl]-2-pyrrolidinone (14b). Alkylation of **3** by the

(30) Gardiner, R. A.; Rinehart, K. L.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639.
(31) Gu, X.-P.; Nishida, N.; Ikeda, I.; Okahara, M. *J. Org. Chem.* **1987**, *52*, 3192.
(32) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140 and references cited therein.

general procedure with methyl 2-(bromomethyl)acrylate (**13b**) gave **14b** (93%) as an oil: NMR 1.73–1.91 (m, 1 H), 2.10–2.61 (m, 3 H), 2.91 (dd, 1 H, J = 8.2, 12.6), 3.13 (dd, 1 H, J = 2.9, 12.6), 3.65 (d, 1 H, J = 16.3), 3.70 (s, 3 H), 3.75–3.88 (m, 1 H), 4.26 (d, 1 H, J = 16.3), 5.58 (s, 1 H), 6.23 (s, 1 H), 7.20–7.48 (m, 5 H); IR 3070, 1735, 1697. Anal. Calcd for $C_{16}H_{19}NO_3Se$: C, 54.55; H, 5.44; N, 3.98. Found: C, 54.29; H, 5.17; N, 3.84.

1-[2-(Ethoxymethoxy)-2-propenyl]-5-[(phenylseleno)methyl]-2-pyrrolidinone (14c). Alkylation of **3** by the general procedure with 3-chloro-2-(ethoxymethoxy)propene (**13c**) gave **14c** (99%) as a colorless oil: NMR 1.19 (t, 3 H, J = 5.0), 1.83–1.90 (m, 1 H), 2.18–2.26 (m, 1 H), 2.36 (ddd, 1 H, J = 5.8, 10.2, 17.0), 2.49–2.59 (m, 1 H), 2.91 (dd, 1 H, J = 8.7, 12.5), 3.25 (dd, 1 H, J = 2.9, 12.6), 3.30 (d, 1 H, J = 15.1), 3.55–3.61 (m, 2 H), 3.84–3.90 (m, 1 H), 4.10 (d, 1 H, J = 2.4), 4.29 (d, 1 H, J = 2.3), 4.30 (d, 1 H, J = 15.3), 4.90–4.95 (m, 2 H), 7.23–7.51 (m, 5 H); IR 3065, 1695. Anal. Calcd for $C_{17}H_{23}NO_3Se$: C, 55.43, H, 6.29; N, 3.80. Found: C, 55.57; H, 6.20; N, 3.61.

6α-Chloro-(8aα-H)-3-indolizidinone (15a). Radical cyclization of **14a** by the general procedure afforded **15a** (70%) as a colorless oil: NMR 1.25–1.38 (m, 1 H), 1.51–1.80 (m, 3 H), 1.95–2.18 (m, 1 H), 2.20–2.38 (m, 2 H), 2.40 (t, 1 H, J = 7.3), 2.71 (t, 1 H, J = 12.5), 3.43–3.50 (m, 1 H), 3.68–3.78 (m, 1 H), 4.43 (ddd, 1 H, J = 2.0, 5.1, 12.9); IR 1695. Anal. Calcd for $C_8H_{12}NClO$: C, 55.34; H, 6.96; N, 8.07. Found: C, 55.51; H, 7.13; N, 7.81. A trace of pyrrolizidinone **9** was detected in the crude product by NMR but was not isolated.

3-Oxo-(8aα-H)-indolizidine-6α-carboxylic Acid, Methyl Ester (15b). Cyclization of **14b** by the general procedure gave 76% yield of an inseparable mixture (~10:1) of **15b** and an unidentified minor product containing a methyl ester (δ 3.73): NMR of **15b** (in mixture) 1.21 (app dq, 1 H, J = 3.5, 11.4), 1.56–1.70 (m, 2 H), 1.96 (dq, 1 H, J = 13.0, 3.4), 2.15–2.28 (m, 2 H), 2.38–2.43 (m, 3 H), 2.73 (t, 1 H, J = 12.4), 3.41 (m, 1 H), 3.69 (s, 3 H), 4.37 (ddd, 1 H, J = 1.8, 6.7, 13.3); IR 1735, 1695. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.66; N, 7.10. Found: C, 59.81; H, 7.44; N, 6.56.

6α-Acetoxy-(8aα-H)-3-indolizidinone (15c). Cyclization of **14c** by the general procedure gave a single protected-carbinol product. Treatment of this product with 1 N aqueous hydrochloric acid, followed by acetic anhydride and pyridine, gave **15c** (58% from **14c**) as a crystalline solid, mp 39–41 °C: NMR 1.28–1.32 (m 1 H), 1.40–1.51 (m, 1 H), 1.55–1.65 (m, 1 H), 1.91–1.97 (m, 1 H), 2.03 (s, 3 H), 2.14–2.25 (m, 2 H), 2.38–2.41 (m, 2 H), 2.55 (t, 1 H, J = 11.7), 3.36–3.41 (m, 1 H), 4.30 (ddd, 1 H, J = 1.5, 5.4, 12.5), 4.62 (ddd, 1 H, J = 4.8, 10.6, 15.7); IR 1741, 1693. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.66; N, 7.10. Found: C, 60.57; H, 7.48; N, 6.83.

1-[2-(1,3-Dioxolan-2-yl)ethyl]-5-[(phenylseleno)methyl]-2-pyrrolidinone (17). Alkylation of **3** with 2-(2-bromoethyl)-1,3-dioxolane (**16**) by the general procedure afforded **17** (90% yield) as a colorless oil: NMR 1.70–1.88 (m, 3 H), 2.10–2.22 (m, 1 H), 2.26 (ddd, 1 H, J = 5.2, 10.0, 16.4), 2.38–2.48 (m, 1 H), 2.80–2.90 (m, 2 H), 3.16 (dd, 1 H, J = 2.8, 12.4), 3.61–3.68 (m, 1 H), 3.72–3.78 (m, 2 H), 3.79–3.84 (m, 1 H), 3.85–3.89 (m, 2 H), 4.78 (t, 1 H, J = 4.4), 7.19–7.51 (m, 5 H); IR 1695. Anal. Calcd for $C_{16}H_{21}NO_3Se$: C, 54.24; H, 5.97; N, 3.95. Found: C, 53.97; H, 5.70; N, 3.72.

7-Acetoxy-3-indolizidinone (18b). Acetal **17** was dissolved in a 1:1 THF/1 N aqueous hydrochloric acid mixture and heated at 50 °C for 2 h. The mixture was cooled, concentrated, and extracted with ethyl ether, and then the organic extract was dried and concentrated. The resulting crude aldehyde was cyclized by the general procedure to give crude carbinol **18a**. This material was treated with acetic anhydride and pyridine and chromatographed by using ether as the eluant to give **18b** (63% overall from **17**) as a 3:2 α-acetoxy/β-acetoxy mixture: Partial NMR of mixture 2.04 (s, $COCH_3$ minor), 2.08 (s, $COCH_3$ major), 2.70 (td, J = 13, 2, H-5_{ax} minor), 2.93 (td, J = 14, 2, H-5_{ax} major), 3.50–3.67 (m, H-8a minor), 3.71–3.80 (m, H-8a major), 4.01 (dd, J = 13, 5.5, H-5_{eq} major), 4.18 (ddd, J = 13, 5.2, 2.1, H-5_{eq} minor), 4.84 (tt, J = 11.4, 4.0, H-7_{ax} minor), 5.18 (app quintet, J = 2.8, H-7_{eq} major); IR 1732, 1672. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.66; N, 7.10. Found: C, 60.72; H, 7.62; N, 6.95.

3(*S*)-Hydroxy-4-pentenamide (22). A mixture of 0.69 g (5.9 mmol) of resolved[21] 3(*S*)-hydroxy-4-pentenoic acid (**23**), 0.74 g (8.9 mmol) of sodium bicarbonate, 3.68 g (23.6 mmol) of ethyl iodide, and 4 mL of DMF was stirred for 5 h. The reaction mixture was filtered, and the solvents were removed to give 0.85 g (100%) of the ethyl ester as a clear oil. A solution of 608 mg (5.28 mmol) of this product and 25 mL of methanol was saturated with anhydrous ammonia gas at 0 °C. The reaction flask was sealed at 0 °C and was stirred at 23 °C for 4 days. The reaction mixture was concentrated and chromatographed by using 5% methanol/ether as the eluant to give 403 mg (83%) of **22**, mp 88–89 °C: [α] = +10.3° (c = 4, ethanol); NMR 2.42 (dd, 1 H, J = 8.6, 15.6), 2.51 (dd, 1 H, J = 3.3, 5.6), 3.36 (s, 1 H), 4.56 (s, 1 H), 5.18 (dt, 1 H, J = 10.5, 1.3), 5.35 (dt, 1 H, J = 17.2, 1.4), 5.45 (br s, 1 H), 5.80 (br s, 1 H), 5.90 (ddd, 1 H, J = 5.6, 10.5, 18.1); IR 3355, 3185, 1678. Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.19; H, 7.76; N, 11.97.

Amide **22** was also obtained by direct asymmetric synthesis. A solution of 6.0 g (39.7 mmol) of (1*S*,2*R*)-norephedrine in 50 mL of toluene was added to 70 mL of a 3.4 M aqueous potassium hydroxide solution. The mixture was cooled to 0 °C, and then 61 mL of a 1.9 M phosgene solution in toluene was added dropwise over 15 min. After the addition was complete the reaction mixture was stirred for an additional 15 min. The layers were separated, and about 30 mL of hexane was added to the toluene layer to induce crystallization. The product was collected by filtration and dried in vacuo to give 6.05 g (86%) of **24** as a white crystalline solid.

Sodium hydride (0.75 g of a 60% oil dispersion, 1.1 equiv) was added slowly to a solution of 3 g (17 mmol) of **24** in 25 mL of dry THF at 0 °C. The reaction mixture was stirred for 15 min and then cooled to −78 °C. Bromoacetyl bromide (1.63 mL, 1.1 equiv) was added dropwise, and the resulting orange solution was allowed to warm to room temperature. After an additional 30 min, the reaction was quenched with 3 mL of methanol, concentrated, and chromatographed by using 1:1 ether/petroleum ether as the eluant. Bromoacetyl derivative **25** (4.27 g, 84%) was obtained as a viscous oil.[23]

A solution of 3.2 mL of a 1 M solution of titanium tetrachloride[24] in dichloromethane was added slowly over 5 min to a solution of 0.9 g (3 mmol) of **25** in 15 mL of dry dichloromethane at 0 °C. This mixture was allowed to stir for 5 min, and then 0.63 mL (3.3 mmol) of diisopropylethylamine was added. The resulting dark solution was allowed to stir at 0 °C for 1.5 h. The solution was cooled to −78 °C, and then 0.2 mL (6 mmol) of acrolein was added. This mixture was stirred an additional 0.5 h at −78 °C and then allowed to warm to 0 °C over 1 h. The reaction was quenched with 25 mL of saturated aqueous ammonium chloride and extracted with two 50-mL portions of ether. The ether extracts were dried, concentrated, and chromatographed by using 1:1 ether/petroleum ether as the eluant, and then the product was crystallized from about 20 mL of ether/petroleum ether to give 0.57 g (53%) of **26** as a light brown crystalline solid, mp 90–91 °C: NMR 0.94 (d, 3 H, J = 6.5), 3.11 (br s, 1 H), 4.61–4.64 (m, 1 H), 4.79–4.85 (m, 1 H), 5.33 (dt, 1 H, J = 10.5, 1.3), 5.47 (dt, 1 H, J = 17.2, 1.4), 5.75–5.79 (m, 2 H), 5.89 (ddd, 1 H, J = 5.6, 10.5, 18.1), 7.30–7.50 (m, 5 H); IR 3500, 1790, 1710.

Tris(trimethylsilyl)silane (0.26 mL, 1.1 equiv) was added to a solution of 0.27 g (0.76 mmol) of **26** is 6 mL of dry benzene, and the solution was brought to reflux. Azobis(isobutyronitrile) (1 mg) was added, and the solution was heated at reflux for 1 h. The solution was cooled and concentrated. The crude product was dissolved in 15 mL of saturated ammoniacal methanol. After 6 h, the solvents were removed and the oily residue was chromatographed by using 1:19 methanol/ether as the eluant. The resulting amide **22** (66 mg, 75%) was identical to the material obtained by resolution, according to analysis by NMR and TLC, and showed comparable [α] (+10.8°).

4(*S*)-Hydroxy-5(*R*)-(iodomethyl)-2-pyrrolidinone (21). Trimethylsilyl trifluoromethanesulfonate (3.9 mL, 20.4 mmol) was added dropwise to a vigorously stirred suspension of 0.778 g (6.8 mmol) of **22**, 2.8 mL (20.4 mmol) of triethylamine, and 10 mL of dry pentane. The reaction was allowed to stir for 20 min, during which time the suspended amide completely dissolved. The stirring was stopped, and the two layers were allowed to separate. The top (pentane) layer was transferred under argon by cannula to a dry flask, concentrated to one fourth the volume, and then cooled to 0 °C. A solution of 3.8 g (15 mmol) of iodine in 15 mL

of dry THF was added rapidly, and the reaction mixture was stirred vigorously for 5 min. The cooling bath was removed and the reaction quenched by the cautious addition of 25 mL of saturated aqueous sodium sulfite followed by 25 mL of saturated aqueous sodium bicarbonate. The reaction mixture was extracted with three 100-mL portions of ethyl acetate. The combined extracts were washed with 50 mL of saturated aqueous sodium bicarbonate, dried, and concentrated. The crude product was chromatographed by using 1:19 methanol/ether as the eluant to afford 1.51 g (72%) of **21**, mp 123–124 °C (from THF/petroleum ether); $[\alpha]$ = +21.7° (c = 0.23, methanol); NMR 2.05 (d, 1 H, J = 5.6), 2.47 (dd, 1 H, J = 2.8, 17.2), 2.71 (dd, 1 H, J = 6.4, 17.6), 3.21–3.25 (dd, 1 H, 7.6, 9.6), 3.38 (dd, 1 H, J = 6.4, 10.0), 3.96–4.01 (m, 1 H), 4.56–4.60 (m, 1 H), 5.80 (br s, 1 H); IR 3560, 3322, 1705. Anal. Calcd for $C_5H_8INO_2$: C, 24.91; H, 3.34; N, 5.81. Found: C, 24.94, H, 3.06; N, 5.57.

4(*S*)-Hydroxy-5(*R*)-[(phenylseleno)methyl]-2-pyrrolidinone (27). Sodium borohydride was added slowly in small portions to a stirred suspension of 1.60 g (5.1 mmol) of diphenyl diselenide in anhydrous ethanol at 0 °C until the solution became colorless. The cooling bath was removed, and 1.24 g (5.1 mmol) of **21** was added in one portion. After 4 h, the reaction mixture was concentrated and chromatographed by using 3% methanol/ether as the eluant to give 1.44 g (98%) of **27**, mp 109–110 °C (from THF/hexane): $[\alpha]$ = +15.8° (c = 0.4, ethanol); NMR 2.11 (d, 1 H, J = 5.5), 2.38 (dd, 1 H, J = 2.3, 7.3), 2.65 (dd, 1 H, J = 6.3, 17.4), 3.00 (dd, 1 H, J = 8.3, 12.7), 3.18 (dd, 1 H, J = 6.0, 12.6), 3.78 (dt, 1 H, J = 9.8, 5.3), 4.50–4.55 (m, 1 H), 5.81 (br s, 1 H), 7.25–7.56 (m, 5 H); IR 3575, 1703. Anal. Calcd for $C_{11}H_{13}NO_2Se$: C, 48.89; H, 4.85; N, 5.18. Found: C, 49.06; H, 4.74; N, 5.05.

4(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-5(*R*)-[(phenylseleno)methyl]-2-pyrrolidinone (28). Imidazole (0.44 g, 6.4 mmol) and *tert*-butyldimethylsilyl chloride (0.96 g, 6.4 mmol) were added to a solution of 1.16 g (4.3 mmol) of **27** in 8 mL of dry DMF. The reaction mixture was allowed to stir overnight, and then it was directly chromatographed by using 3:1 petroleum ether/ether as the eluant, giving 1.617 g (99%) of **28** as a white solid, mp 95–96 °C (from ether/hexane): $[\alpha]$ = −42.4° (c = 0.37, dichloromethane); NMR 0.03 (s, 6 H), 0.85 (s, 9 H), 2.31 (dd, 1 H, J = 4.0, 16.8), 2.53 (dd, 1 H, J = 6.4, 16.8), 2.90 (dd, 1 H, J = 9.6, 12.8), 3.15 (dd, 1 H, J = 4.0, 12.8), 3.72 (dt, 1 H, J = 9.6, 5.2), 4.41–4.46 (m, 1 H), 5.85 (br s, 1 H), 7.22–7.49 (m, 5 H); IR 3311, 3115, 1710, 1666. Anal. Calcd for $C_{17}H_{27}NO_2SeSi$: C, 53.11; H, 7.08; N, 3.64. Found: C, 52.99; H, 6.95; N, 3.59.

3-Iodo-2-(2-tetrahydropyranyloxy)propene (30). 1,3-Dichloro-2-propanol **29** (10 g, 0.078 mmol), and 2,3-dihydropyran (13.1 g, 0.156 mol) were dissolved in 150 mL of dry dichloromethane. Upon addition of 10 mg of *p*-toluenesulfonic acid, the reaction mixture turned deep purple. After 3 h, the reaction mixture was washed with two 50-mL portions of saturated aqueous sodium bicarbonate and the solvents were evaporated. The crude product was distilled (104 °C, 1 mm) to give 14.0 g (85%) of the THP acetal as a clear liquid. This material was heated with 3.17 g (0.079 mol) of powdered sodium hydroxide and 1.1 g (3.3 mmol) of tetra-*n*-butylammonium hydrogen sulfate under reduced pressure to afford 10.1 g (87%) of the allylic chloride as a clear distillate (bp 80 °C, 1 mm). A mixture of 10.1 g (0.057 mol) of the allylic chloride, 19.0 g (0.114 mol) of potassium iodide, 6.1 g (0.057 mol) of sodium carbonate, 0.97 g (2.9 mmol) of tetra-*n*-butylammonium hydrogen sulfate, and 50 mL of water was heated at 80 °C for 3 h. The reaction was cooled and extracted with three 50-mL portions of ether. The combined organic extracts were dried and concentrated to afford 13.75 g of **30** as a dark brown oil. The product was distilled in a Kugelrohrofen (90 °C, 1 mm) to give **30** as a clear yellow oil (12.70 g, 61% overall yield from the THP acetal): NMR 1.40–1.95 (m, 6 H), 3.50–4.00 (m, 3 H), 4.31 (d, 1 H, J = 2.5), 4.40 (d, 1 H, J = 2.4), 4.70–4.74 (m, 1 H), 5.19 (m, 1 H); IR 1626.

4(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-5(*R*)-[(phenylseleno)methyl]-1-[2-(2-tetrahydropyranyloxy)-2-propenyl]-2-pyrrolidinone (31). Lactam **28** (0.754 g, 1.9 mmol) was added to a stirred solution of 2.1 g (7.8 mmol) of iodide **30** in 10 mL of dry DMF. Sodium hydride (0.052 g, 2.1 mmol) was added slowly over a 5-min period. After 15 min, the reaction was directly chromatographed by using 2:1 petroleum ether/ether as the eluant to afford 1.020 g (99%) of **31** as a clear oil that was used as obtained for the next step.

4(*S*)-Acetoxy-5(*R*)-[(phenylseleno)methyl]-1-[2-(2-tetrahydropyranyloxy)-2-propenyl]-2-pyrrolidinone (33). Tetra-*n*-butylammonium fluoride (7.6 mL of a 1 M THF solution, 7.6 mmol) was added to a solution of 1.00 g (1.9 mmol) of **31** in 8 mL of THF, and the solution was allowed to stir for 1 h. The reaction mixture was concentrated, and the residual syrup (crude **32**, IR 3400, 1695) was dissolved in 4 mL of pyridine. Acetic anhydride (4.0 mmol, 0.8 mL) was added, and the mixture was stirred overnight. The reaction mixture was concentrated to a viscous oil, which was chromatographed by using 1:1 ether/hexane as the eluant to give 0.825 g (96%) of **33** as a thick pale yellow oil: IR 1740, 1700, 1640. Anal. Calcd for $C_{21}H_{27}NO_5Se$: C, 56.48; H, 5.97; N, 3.09. Found: C, 56.75; H, 6.12; N, 2.93.

1(*S*)-Acetoxy-6(*R*)-hydroxy-(8a*S*)-indolizidin-3-one (35a). Lactam **33** (0.21 g, 0.46 mmol) was dissolved in 11 mL of dry benzene. The solution was heated at reflux for 10 min, and then 156 μL (0.51 mmol) of tris(trimethylsilyl)silane was added, followed by 5 mg of azobis(isobutyronitrile). The solution was heated at reflux for 16 h and then cooled to room temperature. The benzene was evaporated, and the oily yellow residue was chromatographed by using ether as the eluant. The product of R_f = 0.4 (ether) was collected and concentrated, giving 95 mg of the 6α indolizidinone **34a**. The THP protecting group was removed by heating a solution of **34a** in 4 mL of a 1:1:1 mixture of acetic acid/water/THF at 45 °C for 2 h. The reaction was cooled, and the solvents were evaporated. The residue was chromatographed by using 3% methanol/ether as the eluant to give 68 mg (69% overall yield from **33**) of indolizidinone alcohol **35a** as an oil: $[\alpha]$ = −25.0° (c = 0.3, methanol); NMR 1.48–1.52 (m, 2 H), 1.70–1.73 (m, 1 H), 2.00 (s, 3 H), 2.10–2.13 (m, 2 H), 2.41–2.51 (m, 2 H), 2.79 (ddd, 1 H, J = 1.6, 7.5, 17.9), 3.60–3.66 (m, 2 H), 4.30 (ddd, 1 H, J = 1.8, 5.2, 12.5), 5.41 (ddd, 1 H, J = 2.7, 6.1, 8.8); IR 3450, 1745, 1695. Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.35; H, 7.09; N, 6.57. Found: C, 56.11; H, 7.05; N, 6.72.

Material corresponding to two lower spots (**34b**, $R_f \approx 0.3$) from the radical cyclization was collected and hydrolyzed as above to give 10 mg of **35b** as a crystalline solid, mp 48–49 °C: NMR 1.49 (dq, 1 H, J = 13.2, 3.6), 1.63 (tdd, 1 H, J = 13.6, 2.4, 3.6), 1.90–2.18 (m, 6 H), 2.50 (dd, 1 H, J = 3.6, 18.0), 2.78 (ddd, 1 H, J = 1.6, 8.0, 18.0), 2.86 (d, 1 H, J = 14.4), 3.72 (ddd, 1 H, J = 3.6, 6.4, 11.6), 4.08 (br s, 1 H), 4.15 (dt, 1 H, J = 14.0, 2.0), 5.44 (ddd, 1 H, J = 2.7, 6.1, 8.8); IR 3450, 1745, 1695.

1(*S*)-Acetoxy-6(*R*)-[(methanesulfonyl)oxy]-(8a*S*)-indolizidin-3-one (36). Methanesulfonyl chloride (18 μL, 0.24 mmol) was added to a stirred solution of 26 mg (0.12 mmol) of alcohol **35a** and 42 μL (0.24 mmol) of diisopropylethylamine in 3 mL of dry dichloromethane at 0 °C. After 30 min, the reaction mixture was concentrated and chromatographed by using 5% methanol/ether as the eluant to afford 35 mg (99%) of **36** as a white crystalline solid, mp 168–170 °C dec. Anal. Calcd for $C_{11}H_{17}NO_6S$: C, 45.35; H, 5.88; N, 4.81. Found: C, 45.63; H, 5.96; N, 4.51.

1(*S*)-Acetoxy-6(*S*)-azido-(8a*S*)-indolizidin-3-one (37). A solution of 35 mg (0.12 mmol) of mesylate **36** and 78 mg (1.2 mmol) of sodium azide in 1 mL of dry DMF was heated at 105 °C for 3 h. The reaction was cooled, and the DMF was removed under reduced pressure. The residue was chromatographed by using ethyl acetate as the eluant to give 22 mg (76%) of **37** an oil: $[\alpha]$ = −28.6° (c = 0.1, dichloromethane); NMR 1.51 (dt, 1 H, J = 12.8, 3.2), 1.70–1.88 (m, 2 H), 2.10–2.14 (m, 4 H), 2.50 (dd, 1 H, J = 3.2, 17.6) 2.77 (ddd, 1 H, J = 1.6, 7.6, 18.0), 2.87 (dt, 1 H, J = 14.0, 2.4), 3.69 (ddd, 1 H, J = 3.6, 6.0, 11.2), 3.87 (t, 1 H, J = 2.4), 4.25 (dt, 1 H, J = 14.0, 2.4), 5.43 (ddd, 1 H, J = 3.2, 7.6, 9.6); IR 2110, 1740, 1695. Anal. Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.12; H, 5.79; N, 23.21.

1(*S*)-Acetoxy-6(*S*)-azido-(8a*S*)-indolizidine, "Slaframine Azide" (38). Borane–methyl sulfide (0.3 mL of a 2 M toluene solution) was added dropwise to a stirred solution of 14 mg (0.06 mmol) of indolizidinone **37** in 1 mL of dry THF. After 16 h, the reaction was quenched by the dropwise addition of 2 mL of methanol. Solvents were evaporated, and the residue was chromatographed by using 1:1 ether/petroleum ether as the eluant to give 12 mg of the amine–borane complex (IR 2400). This material was dissolved in 2 mL of tetramethylethylenediamine and stirred at room temperature for 2 h. The solvent was

evaporated, and the residue was chromatographed by using 1:1 ether/petroleum ether as the eluant, resulting in 10 mg (77%) of slaframine azide **38** as a colorless oil: $[\alpha] = -29.3°$ ($c = 0.04$, dichloromethane); NMR 1.50–1.65 (m, 3 H), 1.71–1.79 (m, 1 H), 1.82–1.90 (m, 1 H), 2.02–2.07 (m, 2 H), 2.08 (s, 3 H), 2.15–2.19 (m, 1 H), 2.21–2.30 (m, 1 H), 3.15 (td, 1 H, $J = 7.2, 2.0$), 3.23 (dd, 1 H, $J = 2.4, 12.0$), 3.82 (br s, 1 H), 5.22 (ddd, 1 H, $J = 2.0, 4.8, 7.2$); IR 2110, 1740. Anal. Calcd for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.18; N, 24.98. Found: C, 53.80; H, 7.21; N, 24.79.

1(*S*)-Acetoxy-6(*S*)-amino-(8a*S*)-indolizidine, Slaframine (5). A mixture of 4 mg (0.018 mmol) of azido acetate **38**, 5 mg of 5% palladium-on-carbon, and 1 mL of ethanol was stirred under an atmosphere of hydrogen gas for 10 min. The mixture was filtered through Celite, and the ethanol was evaporated to give approximately 3 mg of slaframine (**5**) which showed $[\alpha] = -32.3°$ ($c = 0.3$, chloroform): NMR 1.54–1.60 (m, 2 H), 1.65–1.82 (m, 2 H), 1.87–1.96 (m, 2 H), 2.02–2.05 (m, 1 H), 2.08 (s, 3 H), 2.14–2.30 (m, 2 H), 2.75 (br s, 2 H), 3.07–3.18 (m, 2 H), 3.28 (br s, 1 H), 5.20 (ddd, 1 H, $J = 2.3, 4.9, 7.4$); IR 3500–3400, 1735.

A solution of slaframine as obtained above in 1 mL of pyridine and 0.5 mL of acetic anhydride was stirred for 0.5 h. The solvents were evaporated, and the product was crystallized from petroleum ether/ethanol to give 4 mg of *N*-acetylslaframine (**39**) as tiny white needles, mp 140–141 °C: $[\alpha] = -14.6°$ ($c = 0.3$, ethanol); NMR 1.40–2.12 (m, 2 H), 2.18 (dd, 1 H, $J = 2.7, 11.5$), 2.25–2.31 (m, 1 H), 3.03 (dt, 2 H, $J = 11.5, 2.1$), 3.08 (td, 1 H, $J = 9.2, 2.1$), 4.19 (dt, 1 H, $J = 8.4, 2.8$), 5.25 (ddd, 1 H, $J = 2.0, 4.8, 7.2$), 6.33 (br d, 1 H, $J = 6.0$); IR 3350, 1735, 1665.

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Porphyrins with Exocyclic Rings. 1. Chemistry of 4,5,6,7-Tetrahydro-1*H*-indoles: Synthesis of Acetoxy Derivatives, Dihydroindoles, and Novel Porphyrins with Four Exocyclic Rings[1,2]

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A variety of 4,5,6,7-tetrahydro-1*H*-indoles (THI's) and 4-oxo-4,5,6,7-tetrahydro-1*H*-indoles (4-oxoTHIs) have been synthesized from cyclohexanone and 1,3-cyclohexanedione, respectively. The THI's reacted regioselectively with lead tetraacetate in acetic acid to give the 7-acetoxy derivatives. The isomeric 4-acetoxyTHI's were prepared by first reducing the corresponding 4-oxoTHI's with sodium borohydride and then reacting the resulting hydroxyTHI's with acetic acid–pyridine. Both series of acetoxyTHI's underwent elimination of acetic acid when heated with pyridine–acetic anhydride to give dihydroindoles. The 7-acetoxyTHI's were hydrolyzed with potassium hydroxide in methanol–water and carefully neutralized with hydrochloric acid to give the corresponding hydroxyTHI carboxylic acids. Treatment with potassium ferricyanide in refluxing acetic acid gave good yields of tetrapropanoporphyrins when 3-methyl-, 3-ethyl-, or 3-*n*-propyl substituents were present. The 3-phenylTHI gave variable yields of the corresponding tetraphenylporphyrin. The 3-isopropylTHI gave only trace amounts of porphyrin under these conditions, and the 3-*tert*-butylTHI failed to give any porphyrin product. THI's with 6-methyl or 6,6-dimethyl substituents were prepared in two steps from 5-methyl-1,3-cyclohexanedione or dimedone, respectively. These compounds also reacted smoothly with lead tetraacetate to give the 7-acetoxy derivatives in high yield. Attempts to convert the 6,6-dimethylTHI's into symmetrical porphyrins were unsuccessful, although the 6-methylTHI gave a mixture of porphyrin stereoisomers in low yield. The influence of alkyl substituents and carbocyclic rings on the cyclotetramerization of THI's is discussed.

Introduction

Complex mixtures of metalloporphyrins are present[3] in organic-rich sediments such as oil shales, petroleum, bitumens, and coal. These compounds are believed to be the degradation products from biological pigments such as the chlorophylls. The peripheral substituents of these "molecular fossils" have undergone considerable modification, and the analysis of metalloporphyrins from a given organic sediment can give information about its geochemical history (depositional environment, thermal maturity, etc.). Since sedimentary porphyrins differ structurally from biological tetrapyrroles, the terms "petroporphyrin" and "geoporphyrin" have been coined[4] to describe these compounds. Over the last 10 years, individual petroporphyrins have been isolated and characterized by mass spectrometry and proton NMR spectroscopy.[5] Two major

(1) Preliminary communication: Lash, T. D.; Bladel, K. A.; Johnson, M. C. *Tetrahedron Lett.* **1987**, *28*, 1135.

(2) Results presented, in part, at the Tenth International Congress of Heterocyclic Chemistry, University of Waterloo, Ontario, Canada, Aug 1985 (Abstract: Lash, T. D. *Book of Abstracts*, P5-164); 193rd National American Chemical Society Meeting, Denver, Colorado, April 1987 (Abstract: Bladel, K. A.; Lash, T. D. *Book of Abstracts*, CHED 78); 82nd Annual Meeting of the Illinois State Academy of Science, Loyola University, Chicago, Illinois, Oct. 1989 (Abstract: Shiner, C. M.; Lash, T. D. *Trans. Ill. St. Acad. Sci.* **1989**, *Suppl. to Vol. 82*, 43).

(3) Baker, E. W.; Palmer, S. E. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 1, pp 486–552.

(4) Eglinton, E.; Calvin, M. *Sci. Am.* **1967**, *216*, 32.

(5) (a) Filby, R. H.; Van Berkel, G. J. In *Metal Complexes in Fossil Fuels. Geochemistry, Characterization, and Processing*. Filby, R. H., Branthaver, J. F., Ed.; American Chemical Society: Washington DC, pp 2–37. (b) Chicarelli, M. I.; Kaur, S.; Maxwell, J. R. *Ibid.* pp 40–67. (c) Ocampo, R.; Callot, H. J.; Albrecht, P. *Ibid.* pp 68–73.

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