Intramolecular Allylstannane Cyclizations in Alkaloid Synthesis: Applications to Pyrrolizidine Alkaloids

Gary E. Keck,* Erik N. K. Cressman, and Eric J. Enholm†

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

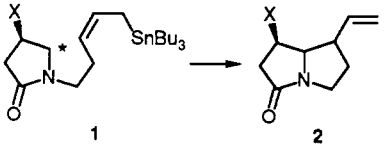
Received March 7, 1989

Syntheses of (±)-isoretronecanol, (±)-supinidine, (−)-dihydroxyheliotridane, and (+)-heliotridine are detailed. The key step in each case involves an intramolecular acyliminium ion cyclization onto a suitably positioned allylstannane for construction of the azabicyclo[3.3.0] ring system. The stereochemistry of the cyclization process, which affords almost exclusively the less stable C_2-endo products, is discussed.

Introduction

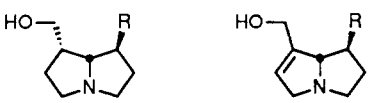
The pyrrolizidine alkaloids are an exceptionally large and diverse group of natural products which exhibit a wide range of biological activities.[1] Due perhaps in part to reports of significant antitumor properties of some members of this class of compounds, such as indicine *N*-oxide,[2] these alkaloids have become popular synthetic targets in recent years.[3] The relatively simple azabicyclo[3.3.0] skeleton common to the materials has also proven popular in testing new synthetic methodology for alkaloid synthesis and has inspired the development of several interesting new methods for its construction.

It occurred to us that one very attractive approach to the construction of such materials would be an intramolecular cyclization reaction of a suitable allylstannane for construction of the C_1–C_2 bond (eq 1). Such a reaction,



(1)

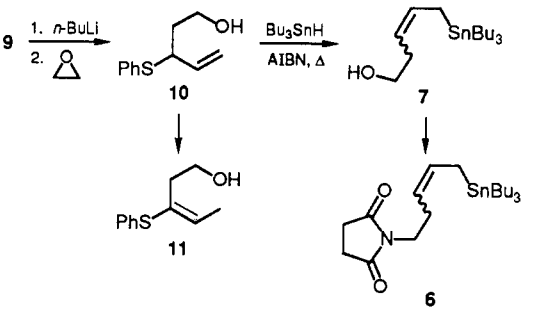
in principle, could be accomplished in two ways due to the versatility of allylstannanes in organic synthesis, specifically, by either cationic or radical pathways. That is, the free valence indicated in **1** could either be a positive charge or a radical center. In either case, the same cyclization would be expected. Moreover, the vinyl unit generated at C_2 appeared to be an ideal latent equivalent for the requisite hydroxymethyl group, and would also allow for convenient introduction of C_2–C_3 unsaturation. Finally, although the stereochemical outcome of such a cyclization process was of intrinsic interest, it appeared that either an exo or endo disposition of the hydroxymethyl group at C_2 could be realized by appropriate manipulations of the aldehyde obtainable from **2** by oxidative cleavage of the vinyl moiety. We record herein the successful application of this approach to total syntheses of (±)-supinidine (**4a**), (−)-dihydroxyheliotridane (**3b**), and (+)-heliotridine (**4b**).



Results

Our studies began with the simplest of the above compounds, isoretronecanol (**3a**). Our approach relies heavily upon close precedent for construction of the C_1–C_2 bond by either radical[4] or acyliminium ion[5] pathways.

Thus, the hydroxy lactam **5**, which could serve as an intermediate in either approach, could be secured by partial reduction of the imide **6**, which should in turn be accessible by Mitsunobu coupling of succinimide with alcohol **7**. Alcohol **7** was prepared in straightforward fashion from alcohol **10**, according to the general procedure of Ueno,[6] as a mixture of cis–trans isomers. Alcohol **10** was in turn prepared from allyl phenyl sulfide (**9**) by metalation and reaction with ethylene oxide.[7] This latter reaction provided quite capricious and in some runs afforded only the rearranged internal olefin **11**. It was found after



considerable experimentation that the alkoxide corresponding to **10** efficiently catalyzes the isomerization of **10** to **11** (both as the corresponding alkoxides). For example, if the alkoxide derived from **10** is allowed to stir at room temperature for 1 h, virtually quantitative isomerization to **11** occurs. However, with careful control of reaction time and internal temperature, good yields of **10** were obtained.

† Present address: Department of Chemistry, University of Florida, Gainesville, FL 32611.

(1) (a) Culvenor, C. C. J.; Bull, L. B.; Dick, A. T. *The Pyrrolizidine Alkaloids*; North-Holland Publishing Co.: Amsterdam, 1968. Atal, C. K. *Lloydia* **1978**, *41*, 312. (b) Mattocks, A. R. *Chemistry and Toxicology of the Pyrrolizidine Alkaloids*; Academic Press: San Diego, 1986.

(2) Zalkow, L. H.; Glinski, J. A.; Gelbaum, L. T.; Fleischmann, T. J.; McGowan, L. S.; Gordon, M. M. *J. Med. Chem.* **1985**, *28*, 687.

(3) For an exhaustive compilation of previous synthetic work, see: Hudlicky, T.; Seoane, G.; Lovelace, T. *J. Org. Chem.* **1988**, *53*, 2094. Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755. For a recent review, see: Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*(6), 1465.

(4) (a) Hart, D. J.; Choi, J. *Tetrahedron* **1985**, 3959. (b) Hart, D. J.; Tsai, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1430. (c) Hart, D. J.; Burnett, D. A.; Choi, J.; Tsai, Y. *J. Am. Chem. Soc.* **1984**, *106*, 8201.

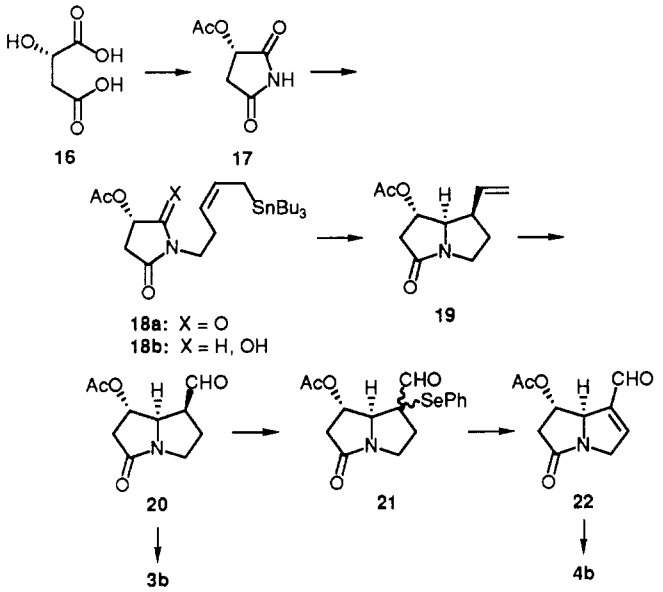
(5) (a) Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1983**, 1407. (b) Chamberlin, A. R.; Chung, J. Y. *J. Org. Chem.* **1985**, *50*, 4225. (c) Hart, D. J.; Yang, T. *J. Org. Chem.* **1985**, *50*, 235. (d) Hiemstra, H.; Speckamp, W. N.; Vijn, R. J.; Sno, M. H. A. M. *J. Org. Chem.* **1985**, *50*, 4014. (e) Chamberlin, A. R.; Chung, J. Y. *Tetrahedron Lett.* **1982**, 2619. (f) Chamberlin, A. R.; Chung, J. Y. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (g) Chamberlin, A. R.; Chung, J. Y.; Nguyen, H. D. *J. Org. Chem.* **1984**, *49*, 1682. (h) Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1985**, *41*(20), 4367.

(6) Ueno, Y.; Aoki, S.; Okawara, M. *J. Am. Chem. Soc.* **1979**, *101*, 5414.

(7) (a) Nederlof, P. J. R.; Moolenar, M. J.; deWaard, E. R.; Huismar, H. O. *Tetrahedron* **1977**, *33*, 579. (b) Brownbridge, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1131.

0022-3263/89/1954-4345$01.50/0

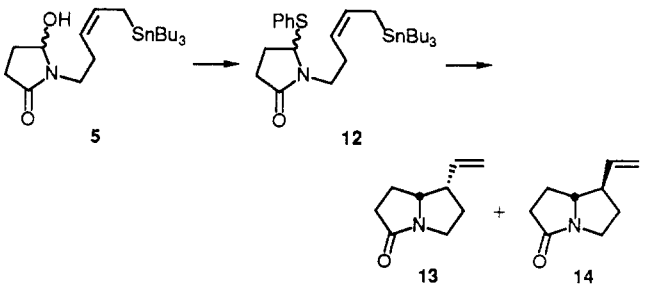
Scheme I



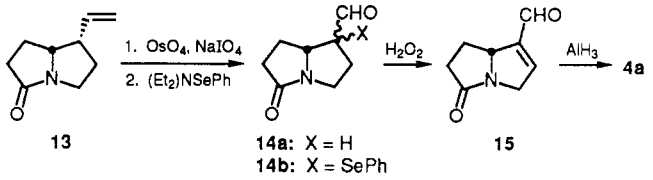
Coupling of alcohol **7** with succinimide according to the general protocol of Mitsunobu[8] proceeded uneventfully to afford **6** in 73% isolated yield. This compound proved quite labile to silica gel chromatography, presumably due to protodestannylation, but was isolable in good yield provided that the silica was deactivated by treatment with methanol.

As has been well documented,[9] the reduction of cyclic imides with $NaBH_4$ can be capricious. In this case, a 10-fold excess of reagent at 0 °C for 5 min afforded optimal results, and gave essentially pure product **5** in virtually quantitative yield, obviating the need for chromatography of this somewhat labile intermediate. This material was then used directly in an acyliminium ion cyclization to afford **2**. Since the allylstannane moiety is acid sensitive, the acyliminium ion cyclization was carried out simply by exposure of **5** to triethylamine and methanesulfonyl chloride at room temperature in dichloromethane. A very rapid (complete within 10 min) cyclization ensued to afford a single isomer of **2** in 77% isolated yield after purification by column chromatography. Although no attempt was made to assign stereochemistry at this point, oxidative cleavage of the vinyl moiety (OsO_4, $NaIO_4$) followed by lithium aluminum hydride reduction afforded (±)-isoretronecanol; thus the intramolecular allylstannane cyclization proceeded with very high stereoselectivity for the production of the less stable endo vinyl compound.

A free-radical version of the same bond construction was also examined, but rapidly discarded as inferior to the very simple acyliminium protocol. Thus, hydroxy lactam **5** was converted to the corresponding thiophenyl derivative **12** by reaction with diphenyl disulfide and tributylphosphine.[10] Irradiation of this material (450-W Hanovia with Pyrex filter) afforded a ca. 10:1 mixture of two cyclization products in 43% isolated yield. The major compound produced was identical with that obtained from the cationic procedure and is therefore assigned as the endo vinyl compound **13**; the minor isomer is thus tentatively assigned as the exo vinyl compound **14**. However, due to the extra step required and the poor yield realized, this approach was not pursued further.



From **13**, introduction of C–C unsaturation to give supinidine proved uneventful.[11] The vinyl compound resulting from acyliminium ion cyclization was again subjected to oxidative cleavage with OsO_4–$NaIO_4$ to give the corresponding aldehyde, which was treated with *N,N*-diethylbenzeneselenamide to yield **14b** as a crystalline solid (but undetermined stereochemistry) in 81% yield. Oxidation and concomitant selnoxide elimination, followed by reduction with allane, then gave (±)-supinidine, although the yield for the reduction step was quite low.



The same procedures were used to gain access to the C_8 oxygenated materials (–)-dihydroxyheliotridane (**3b**) and (+)-heliotridine (**4b**). This route relies heavily upon previous work by Chamberlin,[12] who constructed appropriate precursors for cation–olefin cyclizations from L-malic acid; in his work, ketene dithioacetals were used as terminators for the acyliminium ion-promoted cyclization event. The route employed is outlined in Scheme I and detailed in the Experimental Section. Imide **17** was prepared by treatment of L-malic acid with acetyl chloride, ammonia, and acetyl chloride,[5f] and then coupled as before in a Mitsunobu reaction with **7**. Half-reduction of imide **18a** to hydroxy lactam **18b** required a lower temperature than that used for **5** due to the activating effect of the acetoxy substituent. Cyclization proceeded uneventfully, although at a somewhat slower rate, to give 73% of **19**. Ozonolysis of **19** gave aldehyde **20** in 88% yield, and the aldehyde was then reduced with lithium aluminum hydride to provide dihydroxyheliotridane in 93% yield. Introduction of unsaturation to **20** was accomplished as before by treatment with *N,N*-diethylbenzeneselenamide and oxidation with hydrogen peroxide. Reduction with allane then provided heliotridine in 35% yield.

Both of the intramolecular cyclizations described herein proceed with exceptionally high levels of stereoselectivity for formation of the contrathermodynamic endo product. Although the factors which control stereoselectivity in such reactions are only poorly understood, two independent hypotheses can be advanced to account for the stereochemical outcome of these reactions. One possibility is that a synclinal arrangement of the reacting π systems is preferred over the antiperiplanar alternative, as shown by Denmark[13] for an unrelated carbocyclic intramolecular cyclization process. A second possibility is that a chairlike

(8) (a) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

(9) (a) Speckamp, W. N.; Wijnberg, J. B. P. A.; Schoemaker, H. E. *Tetrahedron* **1978**, 179. (b) Speckamp, W. N.; Wijnberg, J. B. P. A.; Hubert, J. C. *Tetrahedron* **1975**, 1437.

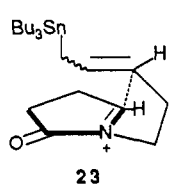
(10) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409.

(11) Reich, H. J.; Renga, J. M. *J. Org. Chem.* **1975**, *40*, 3313.

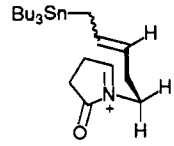
(12) Chamberlin, A. R.; Chung, J. Y. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

(13) Denmark, S. E.; Wilsen, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970.

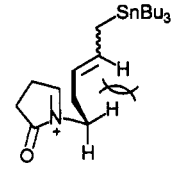
six-atom array is preferred over the boatlike alternative, particularly if the initial approach of the electrophilic iminium carbon is to the center of the π bond in the allylstannane.[14] This latter proposal has been advanced by Hiemstra and Speckamp[15] to rationalize the stereochemistry of intramolecular allylsilane cyclizations. No data is presently available to distinguish between these alternative proposals. Whatever the origin of stereoselectivity in these reactions, the results clearly show that such processes have considerable synthetic potential.



23



24



25

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of nitrogen. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966). Yields were calculated for material judged homogeneous by TLC and NMR. TLC was performed on Merck Kieselgel 60 F_{264} plates, visualizing with a 254-nm UV lamp and staining with an ethanol solution of 12-molybdophosphoric acid. Column chromatography was performed with use of W. G. Grace Davisil 62 silica gel, slurry packed in glass columns. Flash chromatography was performed with use of W. G. Grace Davisil 653 silica gel and adjusted so that the flow rate was approximately 2 in./min. Capillary VPC analyses were carried out on J & W DB-5, DX-4, or DB-1701 columns 30 m in length with a film thickness of 1 μm (DG-5), 0.25 μm (DX-4 and DB-1701), with He as the carrier gas (10 psi) and a flame ionization detector. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Exact mass values were calculated by peak matching with an internal standard whose mass was within ±10% of the unknown compound.

Preparation of 1-(Tri-*n*-butylstannyl)pent-2-en-5-ol (7). To a solution of 3-(phenylthio)penten-5-ol (17.6 g, 90.7 mmol) in 200 mL of toluene was added tri-*n*-butyltin hydride (35 mL, 120 mmol) and AIBN (1.5 g, 9.1 mmol). The reaction vessel was equipped in addition with a stir bar, condenser, and serum cap before being degassed with nitrogen for 40 min. Following this, the reaction mixture was heated at 80 °C overnight in an oil bath. Toluene was removed under reduced pressure, and the resulting material was chromatographed over silica gel (hexanes followed by 10–20% ethyl acetate/hexanes) to render 20 g (60%) of a clear, colorless oil, which was a mixture of cis and trans isomers: R_f = 0.65 in 35% THF/hexanes; IR (neat) 3340, 3010, 2960, 2920, 1650, 1465, 1040, 960, 870 cm^{-1}; 300-MHz ^{1}H NMR ($CDCl_3$) δ 5.65 (m, 1 H), 5.15 (m, 1 H), 3.55 (t, J = 7.6 Hz, 2 H), 2.2 (dt, J = 7, 7.6 Hz, 2 H), 1.6 (d, J = 8.4 Hz, 2 H), 1.4 (m, 18 H), 0.9 (m, 9 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 132.5, 130.6, 120.1, 118.1, 61.9, 35.6, 28.6, 26.8, 13.9, 13.2, 8.6. Anal. Calcd for $C_{17}H_{36}OSn$: C, 54.45; H, 9.60. Found: C, 54.67; H, 9.71.

Preparation of 3-(Phenylthio)penten-5-ol (10). To a solution of allyl phenyl sulfide (34 g, 226 mmol) in 350 mL of THF under nitrogen at −78 °C in a two-neck round-bottom flask was added *n*-butyllithium (170 mL, 238 mmol, 1.4 M solution in hexanes) slowly via syringe. The resulting clear yellow solution was allowed to warm to 0 °C for several min, during which time the color changed to clear orange. The solution was again cooled to −78 °C, and ethylene oxide was added slowly via cannula. Water (10 mL, 50 mL, and then 300 mL) was added, and the aqueous was extracted three times with 100-mL portions of diethyl ether. The organic layers were combined, washed with 100 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography over silica gel (35% ethyl acetate/hexanes) rendered 4 g of allyl phenyl sulfide followed by 33 g (85%) of a clear, yellow oil. Capillary GC indicated a 9:1 ratio of the allylic and vinylic products, respectively: R_f = 0.35 in 35% THF/hexanes; IR (neat, cm^{-1}) 3300, 3100, 2940, 1450, 1040, 940; 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 5.7 (m, 1 H), 4.8 (m, 2 H), 3.7 (m, 3 H), 1.8 (m, 2 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 138.2, 132.7, 128.5, 127.0, 126.2, 115.8, 60.2, 48.9, 36.7. Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.22. Found: C, 67.80; H, 7.45.

Preparation of *N*,*N*-Diethylbenzeneselenamide.[11] To a stirred solution of diphenyl diselenide (3 g, 9.6 mmol) in 60 mL of hexanes under nitrogen was added bromine (0.9 mL, 17.4 mmol) dropwise. The solution was heated to 60 °C, and diethylamine (5 mL, 48 mmol) was added. The dark purple solution turned to clear, pale yellow with concomitant formation of a white precipitate. Heating was continued for approximately 2 h, after which time the solution was filtered and concentrated in vacuo to an orange-red oil. Kugelrohr distillation (75 °C, 0.1 mmHg) gave 2.18 g (50%) of a clear yellow oil: 90-MHz ^{1}H NMR ($CDCl_3$) δ 7.56 (m, 2 H), 7.2 (m, 3 H), 3.0 (q, J = 7 Hz, 4 H), 1.2 (t, J = 7 Hz, 6 H).

Preparation of *N*-[5-(Tri-*n*-butylstannyl)pent-3-enyl]-2,5-pyrrolidinedione (6). To a solution of 1-(tri-*n*-butylstannyl)pent-2-en-5-ol (7, 7.0 g, 18.6 mmol) in 180 mL of THF was added succinimide (2.7 g, 28 mmol), triphenylphosphine (7.3 g, 28 mmol), and diethyl azodicarboxylate (DEAD) (4.8 g, 28 mmol). The last reagent was added dropwise via syringe as a solution in 20 mL of THF. The solution changed from clear and colorless to a clear orange. After 20 min the solution was concentrated under reduced pressure, triturated with a mixture of ethyl acetate and hexanes (3:7), and flash chromatographed through a 3 × 40 cm column of deactivated silica gel (methanol pack, 35% THF/hexanes) to give 6.2 g (73%) of a clear, colorless oil: R_f = 0.4 in 35% THF/hexanes; IR (neat) 3010, 2910, 1700, 1395, 1140, 660 cm^{-1}; 300-MHz ^{1}H NMR ($CDCl_3$) δ 5.6 (m, 1 H), 5.1 (m, 1 H), 3.4 (t, J = 7.6 Hz, 2 H), 2.7 (s, 4 H), 2.2 (dt, J = 7, 7.6 Hz, 2 H), 1.8 (d, J = 8.4 Hz, 2 H), 1.3 (m, 18 H), 0.9 (m, 9 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 176.9, 132.5, 131.4, 120.3, 118.6, 39.0, 38.4, 29.0, 27.3, 25.2, 13.7, 9.3, 9.1. Anal. Calcd for $C_{21}H_{39}NO_2Sn$: C, 55.31; H, 8.55. Found: C, 55.55; H, 8.63.

Preparation of *N*-[5-(Tri-*n*-butylstannyl)pent-3-enyl]-5-hydroxy-2-pyrrolidinone (5). To a cooled solution of the succinimide derivative 6 (6 g, 13 mmol) in 130 mL of methanol at 0 °C was added $NaBH_4$ (3.5 g, 92 mmol) in small portions. TLC analysis of aliquots taken every minute indicated that after 8 min the reaction was complete. It was then quenched by pouring the solution into 200 mL of cold water. The solution was allowed to stir for 10 min, after which time the mixture was extracted with 4 × 200-mL portions of chloroform. The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The clear oil (6 g, 99%) obtained was then used without further purification: R_f = 0.45 in 50% THF/hexanes; IR (neat) 3310, 3040, 2910, 1670, 1450, 1065, 730 cm^{-1}; 300-MHz ^{1}H NMR ($CDCl_3$) δ 5.5 (m, 1 H), 5.2 (m, 2 H), 3.7 (t, J = 7.6 Hz, 2 H), 3.3 (m, 1 H), 2.5 (m, 1 H), 2.2 (m, 4 H), 1.9 (m, 1 H), 1.7 (d, J = 8.4 Hz, 2 H), 1.4 (m, 18 H), 0.9 (m, 9 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 174.5, 132.2, 131.1, 121.4, 119.9, 83.3, 40.5, 31.7, 29.2, 27.3, 28.8, 25.5, 13.7, 9.3, 9.1. Anal. Calcd for $C_{21}H_{41}NO_2Sn$: C, 55.07; H, 8.95. Found: C, 55.02; H, 8.91.

Preparation of 2-Ethylene-5-azabicyclo[3.3.0]octan-6-one (13). To a solution of the hydroxy lactam 5 (6 g, 13 mmol) in 400 mL of methylene chloride was added triethylamine (3.7 mL, 25.6 mmol), followed by methanesulfonyl chloride (2 mL, 25.8 mmol) after 5 min. The clear, colorless solution turned yellow almost immediately, and within 45 s was dark brown. The reaction was complete within 10 min, and the solvent was removed under reduced pressure. The material was dissolved in 100 mL of $CHCl_3$ and 70 mL of H_2O. The aqeuous layer was then extracted with 4 × 100 mL of $CHCl_3$, the organic layers were combined, and the solvent was removed under reduced pressure. Chromatography over silica gel (35–50% THF/hexanes) rendered 1.5 g (77%) of a straw-colored oil. Capillary VPC of the crude reaction mixture indicated a 74:1 ratio of diastereomeric products: R_f = 0.2 in 50% THF/hexanes; IR (neat) 3080, 2950, 1680, 1410, 1280, 915 cm^{-1}; 300-MHz ^{1}H NMR (acetone-d_6) δ 5.6 (m, 1 H), 5.15 (m, 2 H), 4.05 (m, 1 H), 3.6 (m, 1 H), 2.7 (m, 2 H), 2.4 (m, 1 H), 2.25 (m, 1 H),

(14) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
(15) Hiemstra, H.; Speckamp, W. N.; Vijn, R. J. *J. Org. Chem.* **1988**, *53*, 3884.

1.95 (m, 4 H); 75-MHz ^{13}C NMR (acetone-d_6) δ 175.2, 135.5, 117.3, 64.4, 44.1, 40.1, 34.6, 33.1, 21.2; mass spectrum, m/z (relative intensity) 151 (83), 136 (7), 122 (3), 97 (96), 84 (26), 69 (100), 54 (60); exact mass calcd for $C_9H_{13}NO$ 151.094, found 151.097.

Preparation of 2-Formyl-5-azabicyclo[3.3.0]octan-6-one (14a). The olefin **13** (1.40 g, 9.2 mmol) was dissolved in 20 mL of THF, and 10 mL of water was added. Sodium periodate (3.47 g, 16.2 mmol) was then added in one portion, followed by a catalytic amount of osmium tetraoxide. After 20 h TLC analysis indicated consumption of the starting material. The mixture was filtered through Celite and concentrated in vacuo to afford a pale yellow oil. The material was applied to a column of silica gel and eluted with 50% THF/hexanes to give 0.800 g (58%) of an oil: R_f = 0.3 in THF; IR (neat) 1710, 1670 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 9.8 (s, 1 H), 3.7–4.3 (m, 3 H), 2.9–3.2 (m, 2 H), 2.6–2.8 (m, 1 H), 1.9–2.5 (m, 4 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 201.4, 170.5, 62.7, 50.9, 40.7, 34.1, 27.6, 21.9; mass spectrum m/z (relative intensity) 153 (2.8), 136 (4.5), 97 (8.7), 86 (63.8), 84 (100); exact mass calcd for $C_8H_{11}NO_2$ 153.0790, found 153.0777.

Preparation of Isoretronecanol (3a). The aldehyde **14a** (150 mg, 0.98 mmol) was dissolved in 20 mL of THF. To the solution was added lithium aluminum hydride (1 g, 26 mmol), and the solution was allowed to stir for 5 min before being brought to reflux for 30 min. It was then diluted with 50 mL of THF and quenched by the dropwise addition of 3 mL each of water, 1 N NaOH, and water. The mixture was allowed to stir for an additional 15 min before being filtered through Celite, washed with 20 mL each of THF and methanol (stirring the filter cake between washings), and concentrated in vacuo. The crude material was then chromatographed over silica gel eluted with THF followed by 2% NH_4OH in methanol to provide 120 mg (87%) of an oil. R_f = 0 in 2% NH_4OH/MeOH; IR (neat) 3300 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 3.63 (m, 2 H), 3.5 (m, 1 H), 3.15 (m, 1 H), 3.0 (m, 1 H), 2.6 (m, 1 H), 2.45 (m, 2 H), 1.80 (m, 4 H), 1.47 (m, 2 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 66.3, 63.1, 55.6, 54.1, 44.4, 27.3, 26.5, 26.0; mass spectrum m/z (relative intensity) 141 (9.4), 140 (3.6), 124 (6.8), 108 (2.2), 83 (100), 68 (2.3); exact mass calcd for $C_8H_{15}NO$ 141.1153, found 141.11494.

Preparation of *N*-[5-(Tri-*n*-butylstannyl)pent-3-enyl]-5-(phenylthio)-2-pyrrolidinone (12). To a solution of alcohol **5** (448 mg, 0.98 mmol) in CH_2Cl_2 (10 mL) was added diphenyl disulfide (448 mg, 2.05 mmol) followed by tributylphosphine (487 μL, 1.96 mmol), and the solution was then stirred for 16 h at 23 °C. Saturated aqueous $NaHCO_3$ was added, and the resulting mixture was extracted with two 50-mL portions of ether. The combined organic layers were then dried over Na_2SO_4, concentrated, and chromatographed over silica gel to render 253 mg (56%) of a clear oil as a chromatographically homogeneous 3:1 mixture of trans and cis isomers. R_f = 0.58 in 35% THF/hexanes; IR (neat) 2920, 1700, 1400, 740, 690 cm^{-1}; 90-MHz ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 5.62 (m, 1 H), 5.10 (m, 1 H), 4.87 (m, 1 H), 3.70 (m, 1 H), 3.20 (m, 1 H), 2.20 (t, 2 H), 1.95 (m, 2 H), 1.30 (m, 22 H), 0.90 (m, 9 H); mass spectrum m/z (relative intensity) 400.0 (80.1), 398.0 (56.1), 343 (100), 341 (72.9), 339 (42.2), 291.1 (37.2), 289.1 (27.7), 235 (68.2).

Compound 13 via Free-Radical Protocol. A 5-mm thin-walled NMR tube containing sulfide **12** (174 mg, 0.310 mmol) in toluene (2.0 mL) was placed next to a Hanovia photolysis apparatus equipped with a Pyrex filter for 6 h, after which time TLC analysis revealed complete consumption of starting material. The solution was concentrated in vacuo and chromatographed over silica gel to render 20.5 mg (45%) of an oil identical in all respects to **13** produced by the cationic route. Capillary VPC analysis of the crude reaction mixture indicated an 11.3:1 ratio of diastereomeric products.

Preparation of 2-Formyl-2-(phenylselenyl)-5-azabicyclo-[3.3.0]octan-6-one (14b). To a stirred solution of the aldehyde **14a** (300 mg, 1.96 mmol) in 10 mL of THF at room temperature was added *N*,*N*-diethylbenzeneselenamide (1.1 g, 4.4 mmol) in one portion. The solution was allowed to stir for 16 h, after which time concentration in vacuo gave a dark brown oil. Chromatography of this material over silica gel eluted with 20% THF/hexanes gave 488 mg (81%) of an orange crystalline solid (mp 115–117 °C): R_f = 0.3 in 50% THF/hexanes; IR (neat) 1705, 1685 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 9.8 (s, 1 H), 7.4 (m, 5 H), 4.3 (m, 1 H), 3.75 (m, 1 H), 3.15 (m, 1 H), 2.7 (m, 2 H), 2.35 (m, 2 H), 2.15 (m, 1 H), 1.95 (m, 1 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 191.1, 174.3, 137.6, 129.6, 128.0, 119.5, 67.9, 64.1, 40.2, 31.8, 25.6, 22.1; mass spectrum m/z (relative intensity) 309 (2.9), 152 (62.2), 124 (14.8), 97 (61.5), 83 (100), 69 (16.3).

Preparation of 2-Formyl-5-azabicyclo[3.3.0]oct-2-en-6-one (15). The aldehyde **14b** (400 mg, 1.3 mmol) was dissolved in 20 mL of THF. To this was added H_2O_2 (3 mL, 30% solution), and the mixture was allowed to stir overnight. Removal of the solvent gave an orange-red oil, which was chromatographed over silica gel (50% THF/hexanes) to give 185 mg (94%) of the product as an oil: IR (neat) 1710, 1660 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 9.85 (s, 1 H), 6.9 (dd, J = 2, 14 Hz, 1 H), 4.9 (m, 1 H), 4.65 (m, 1 H), 3.9 (m, 1 H), 2.7 (m, 2 H), 2.4 (m, 1 H), 1.9 (m, 1 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 187.1, 178.7, 146.2, 136.9, 66.3, 65.2, 33.5, 29.8; mass spectrum m/z (relative intensity) 151 (76.7), 122 (31.8), 96 (50.2), 68 (58.9), 55 (94.6); exact mass calcd for $C_8H_9NO_2$ 151.0634, found 151.0640.

Preparation of Supinidine (4a). Aldehyde **15** (80 mg, 0.48 mmol) was dissolved in 15 mL of THF and cooled to 0 °C with an ice bath. Allane was added dropwise as a solution (0.588 M, 6 mL) in THF, and the reaction was allowed to stir for 30 min. It was then quenched by the dropwise addition of 1 mL each of water, 1 N NaOH, and water. After 10 min the mixture was filtered through Celite (10 mL each of THF and methanol), concentrated, and chromatographed over 2 g of silica gel (2% NH_4OH/MeOH) to afford 20 mg (30%) of supinidine as an oil: R_f = 0 in 2% NH_4OH/MeOH; IR (neat) 3300, 1050 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 5.5 (s, 1 H), 4.7 (br, 1 H), 4.2 (m, 3 H), 3.9 (m, 1 H), 3.2 (m, 2 H), 2.5 (br, 1 H), 1.7 (m, 4 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 117.1, 66.5, 62.5, 55.2, 47.6, 32.3, 27.9; mass spectrum m/z (relative intensity) 139 (76.4), 122 (55.5), 108 (42.9), 80 (100), 68 (9.3); exact mass calcd for $C_8H_{13}NO$, 139.099, found, 139.0988.

Preparation of *N*-[5-(Tri-*n*-butylstannyl)pent-3-enyl]-3-(*S*)-acetoxy-2,5-pyrrolidinedione (18a). To a solution of **7** (5 g, 13.3 mmol) in 130 mL of THF was added 3(*S*)-acetoxy-2,5-pyrrolidinedione (3.1 g, 19.9 mmol), triphenylphosphine (5.2 g, 19.9 mmol), and diethyl azodicarboxylate (3.6 g, 19.9 mmol). The last reagent was added dropwise over 5 min after the other compounds were in solution. The solution changed from clear and colorless to a clear orange. After 15 min, the solution was concentrated under reduced pressure, triturated with a mixture of ethyl acetate and hexanes (3:7), and flash chromatographed through a 3 × 40 cm column of deactivated silica gel (methanol pack) eluted with 35% ethyl acetate/hexanes to render 5.2 g (75%) of an oil: R_f = 0.6 in 35% ethyl acetate/hexanes; $[\alpha]_D^{21}$ = −14.8° (MeOH, c = 26.5); IR (neat) 3010, 2980, 1790, 1740, 1650, 1410, 1230, 960 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 5.6 (m, 1 H), 5.5 (m, 1 H), 5.1 (m, 1 H), 3.55 (t, J = 7.6 Hz, 2 H), 3.1 (dd, J = 4.8, 18 Hz, 1 H), 2.7 (dd, J = 4.8, 18 Hz, 1 H), 2.25 (dt, J = 7, 7.6 Hz, 2 H), 2.1 (s, 3 H), 1.7 (d, J = 8.3 Hz, 2 H), 1.4 (m, 18 H), 0.9 (m, 9 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 173.0, 172.9, 169.6, 133.1, 131.9, 119.9, 118.2, 67.4, 39.4, 38.8, 35.7, 30.8, 29.1, 27.4, 20.6, 13.1, 9.3. Anal. Calcd for $C_{23}H_{41}NO_4Sn$: C, 53.72; H, 8.04. Found: C, 53.30; H, 8.20.

Preparation of *N*-[5-(Tri-*n*-butylstannyl)pent-3-enyl]-2-hydroxy-3(*S*)-acetoxy-5-pyrrolidinone (18b). To a cooled solution of the succinimide derivative **18a** (4 g, 7.8 mmol) in 100 mL of methanol at −45 °C was added $NaBH_4$ (2.9 g, 76.3 mmol) in one portion. After 5 min the reaction was complete by TLC analysis and was quenched by pouring the reaction mixture into 100 mL of cold water. After 15 min, the aqueous solution was extracted with 5 × 100 mL of $CHCl_3$. The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The material was then flash chromatographed on a 2.5 × 17 cm column of deactivated silica gel (methanol pack) eluted with 35% THF/hexanes. Fractions containing product were combined and concentrated to give 3.23 g (82%) of a clear colorless oil: R_f = 0.35 in 35% ethyl acetate/hexanes; IR (neat) 3310, 3040, 2910, 1760, 1690, 1470, 1240, 960 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 5.6 (m, 1 H), 5.3 (m, 1 H), 5.1 (m, 2 H), 3.5 (t, J = 7.6 Hz, 2 H), 3.3 (m, 1 H), 2.25 (m, 1 H), 2.1 (s, 3 H), 1.7 (d, J = 8.3 Hz, 2 H), 1.4 (m, 18 H), 0.9 (m, 9 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 170.4, 170.1, 132.5, 131.5, 121.1, 119.7, 81.8, 67.9, 40.8, 35.1, 31.3, 29.1, 27.3, 20.8, 13.8, 9.4, 9.2. Anal. Calcd for $C_{23}H_{43}NO_4Sn$: C, 53.51; H, 8.39. Found: C, 53.53; H, 8.63.

Preparation of 2-Ethylene-5-aza-8(*S*)-acetoxybicyclo-[3.3.0]octan-6-one (19). To a solution of the hydroxy lactam **18b** (3.1 g, 6 mmol) in 350 mL of methylene chloride was added triethylamine (2 mL, 13.8 mmol), followed by methanesulfonyl chloride (1 mL, 12.9 mmol) after 5 min. The clear, colorless solution turned yellow almost immediately, and within 45 s was dark brown. The reaction was allowed to stir overnight, after which time the solvent was removed under reduced pressure. The residue was dissolved in 100 mL of chloroform and 100 mL of water, and the aqueous layer was then extracted with 4 × 100-mL portions of chloroform. The organic layers were combined and concentrated, and the material was then chromatographed over silica gel eluting with 50% THF/hexanes. Fractions containing product were combined and concentrated to give 913 mg (73%) of a straw colored oil: R_f = 0.2 in 50% THF/hexanes; $[\alpha]_D^{21}$ = +10.3° (MeOH, c = 16); IR (neat) 3040, 2960, 1740, 1705, 1420, 1230, 920 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 5.6 (m, 1 H), 5.1 (m, 2 H), 3.9 (m, 1 H), 3.6 (m, 1 H), 3.05 (m, 1 H), 2.9 (m, 3 H), 2.7 (m, 2 H), 2.25 (m, 1 H), 2.1 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 173.5, 170.4, 136.3, 117.7, 69.2, 43.6, 41.1, 40.7, 32.3, 30.5, 20.7; mass spectrum m/z (relative intensity) 209 (0.52), 149 (76.55), 95 (18.66), 68 (18.11); exact mass calcd for $C_{11}H_{15}NO_3$ 209.1051, found 209.1052.

Preparation of 2-Formyl-5-aza-8(*S*)-acetoxybicyclo-[3.3.0]octan-6-one (20). The olefin **19** (0.980 g, 4.7 mmol) was dissolved in 40 mL of methanol and cooled to −78 °C. Ozone was then bubbled through the solution until a faint blue color persisted, after which the vessel was purged with oxygen and then nitrogen until the blue color disappeared. Triphenylphosphine (1.2 g, 4.6 mmol) was then added to the solution, and the cold bath was allowed to expire. After 12 h, the mixture was concentrated and flash chromatographed over silica gel eluted with 50% THF/hexanes to give 0.870 g (88%) of an oil: R_f = 0.4 in THF; $[\alpha]_D^{21}$ = −36.4° (MeOH, c = 10.5); IR (neat) 1740, 1690 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 5.3 (ddd, J = 4.3, 6.3, 8.8 Hz, 1 H), 3.92 (m, J = 1, 4.2 Hz, 1 H), 3.56 (ddd, J = 8.3, 8.3, 11.7 Hz, 1 H), 3.33 (dddd, J = 1.6, 3, 4.3, 9 Hz, 1 H), 3.17 (dddd, J = 1.4, 3, 9, 11.7 Hz, 1 H), 2.98 (dd, J = 8.8, 17.3 Hz, 1 H), 2.83 (dddd, J = 1, 1.4, 6.3, 17.3, 1 H), 2.36 (dddd, J = 2, 3, 8, 13.6 Hz, 1 H), 2.22 (ddd, J = 8.3, 8.3, 9, 13.6 Hz, 1 H), 2.1 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 201.1, 172.4, 171.1, 69.7, 68.8, 49.5, 40.36, 40.32, 27.5, 20.8; mass spectrum m/z (relative intensity) 212 (0.7), 151 (49.6), 95 (7.7), 68 (7.9); exact mass calcd for $C_{10}H_{13}NO_4$ 211.0845, found 211.0865.

Preparation of Dihydroxyheliotridane (3b). The aldehyde **20** (263 mg, 1.25 mmol) was dissolved in 10 mL of THF. Lithium aluminum hydride (707 mg, 18.6 mmol) was slowly added; the vessel was equipped with a condenser and was then immersed in an oil bath. The solution was brought to reflux and kept there for 30 min, after which time it was diluted with 50 mL of THF and cooled. The reaction was then quenched by the addition of 1 mL each of water, 1 N NaOH, and water, and after stirring for 15 min the slurry was filtered through Celite. The filter cake was stirred between flushes (10 mL each) of THF and methanol. The solution was then concentrated and chromatographed over 3 g of silica gel eluted first with THF and then 2% NH_4OH/MeOH to give 185 mg (93%) of product as a clear, colorless oil: R_f = 0 in 2% NH_4OH/MeOH; $[\alpha]_D^{21}$ = −22.7° (MeOH, c = 2.6); IR (neat) 3300 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 4.1 (m, 1 H), 3.95 (m, 1 H), 3.8 (m, 1 H), 3.3 (m, 2 H), 2.95 (m, 1 H), 2.55 (m, 3 H), 1.85 (m, 1 H), 1.65 (m, 1 H), 1.35 (m, 1 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 72.1, 70.8, 63.4, 54.7, 53.3, 43.4, 34.4, 26.3; mass spectrum m/z (relative intensity) 157 (3.7), 113 (8.5), 82 (100), 55 (3.1); exact mass calcd for $C_8H_{15}NO_2$ 157.1103, found 157.1084.

Preparation of 2-Formyl-2-(phenylselenyl)-5-aza-8(*S*)-acetoxybicyclo[3.3.0]octan-6-one (21). To a stirred solution of the aldehyde **20** (400 mg, 1.9 mmol) in 20 mL of methylene chloride at room temperature was added *N,N*-diethylbenzeneselenamide (1.1 g, 4.8 mmol) in one portion. The solution was allowed to stir overnight, after which time it was concentrated to a brown oil. The oil was flash chromatographed over 2.5 × 30 cm column of silica gel eluted with THF/hexanes (100 mL each of 10% and 25% v/v, followed by 300 mL of 35% and 250 mL of 50%). Fractions 9–12 (50 mL) were combined and concentrated to give 573 mg (82%) of a reddish oil. ^1H NMR indicated a 4:1 mixture of diastereomers: R_f = 0.35 in 50% THF/hexanes; IR (neat) 1740, 1715, 1685 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 9.79 (s, 0.8 H), 9.45 (s, 0.2 H), 7.3 (m, 5 H), 5.39 (ddd, J = 4.3, 9, 14.6 Hz, 0.8 H), 5.0 (ddd, J = 1.2, 7, 7.2 Hz, 0.2 H), 4.20 (d, J = 3.4 Hz, 0.2 H), 4.17 (d, J = 4.3 Hz, 0.8 H), 3.7 (dt, J = 8.4, 11.5 Hz, 1 H), 3.05 (m, 2 H), 2.80 (dd, J = 6, 17 Hz, 1 H), 2.40 (dt, J = 9.4, 15 Hz, 1 H), 2.19 (m, 1 H), 2.15 (s, 2.5 H), 2.08 (s, 0.5 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 191.8, 173.2, 170.2, 137.4, 129.9, 129.4, 123.4, 73.7, 70.9, 68.7, 63.7, 40.5, 31.3, 20.7; mass spectrum m/z (relative intensity) 368 (30.1), 307 (29.8), 210 (17.1), 168 (19.2), 151 (74.2), 150 (88.9), 122 (12.6), 95 (20.4).

Preparation of 5-Aza-8(*S*)-acetoxy-6-oxobicyclo[3.3.0]-oct-2-ene-2-carboxylic Acid (22). The aldehyde **21** (450 mg, 1.23 mmol) was dissolved in 12 mL of THF, and to this was added H_2O_2 (0.7 mL, 6.1 mmol, 30% solution). The mixture was allowed to stir overnight, after which time the solvent was removed and the residue chromatographed over a 2.5 × 30 cm column of silica gel. Elution was by 100 mL each of 20:77:3 and 30:67:3 THF–hexanes–AcOH followed by 50:47:3 until the product was off the column. Fractions containing product were combined and concentrated to give 158 mg (61%) of an oil: IR (neat) 2580, 1740, 1710, 1670, 1610 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 6.98 (dd, J = 2, 4 Hz, 1 H), 5.47 (ddd, J = 6.5, 8.8, 9 Hz, 1 H), 4.85 (m, 1 H), 4.66 (ddd, J = 2.5, 4, 18 Hz, 1 H), 3.9 (dd, J = 4.5, 18 Hz, 1 H), 2.9 (dd, J = 9.3, 16.6 Hz, 1 H), 2.78 (dd, J = 8.5, 16.6 Hz, 1 H), 2.1 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 174.7, 170.1, 165.8, 142.9, 134.4, 72.7, 70.2, 50.7, 39.7, 20.8; mass spectrum m/z (relative intensity) 225 (1.5), 184 (64.3), 183 (53.7), 166 (16), 149 (34.3), 112 (43.6), 111 (100), 94 (42), 83 (46.6), 81 (48.3), 69 (96), 68 (88.8), 57 (100); exact mass calcd for $C_8H_9NO_4$ ($M^+ - CH_3CO$) 183.0532, found 183.0532.

Preparation of (+)-Heliotridine (4b). The acid **22** (100 mg, 0.44 mmol) was dissolved in 20 mL of THF and cooled to 0 °C by means of an ice bath. Allane (0.558 M, 6 mL) was added dropwise as a solution in THF, and the reaction was allowed to stir for 35 min. The mixture was then quenched by the addition of 1 mL each of water, 1 N NaOH, and water, and allowed to stir for 15 min. The resulting slurry was then filtered through Celite, and the filter cake was stirred and washed with 10 mL each of THF and methanol. The solution was then concentrated and chromatographed over 5 g of silica gel eluted with 40 mL each of 50% THF/hexanes, 50% THF/MeOH, and 100 mL of 2% NH_4OH/MeOH. Fractions containing product were then combined and concentrated to give 24 mg (35%) of an oil: R_f = 0 in 2% NH_4OH/MeOH; $[\alpha]_D^{21}$ = +30° (MeOH, c = 1.5); IR (neat) 3300 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 6.1 (broad s, 2 H), 5.6 (s, 1 H), 4.2 (m, 2 H), 3.85 (d, 1 H), 3.3 (m, 2 H), 2.96 (s, 2 H), 2.70 (m, 1 H), 1.95 (m, 2 H); mass spectrum m/z (relative intensity) 155 (11.9), 136 (3.4), 111 (58), 100 (96), 94 (10.4), 80 (100), 68 (8.2); exact mass calcd for $C_8H_{13}NO_2$, 155.0946, found 155.0970.

Acknowledgment. We thank the National Institutes of Health (Grant No. 2RO1GM 28961-08) for financial support. We also indebted to Professor David Hart of The Ohio State University for samples and spectral data of the pyrrolizidine alkaloids described herein.