apparatus from the furnace to the trap. At a pyrolysis temperature of 570 °C, a 13% yield of **4** was detected in the NMR tubes at temperatures below −70 °C, along with ca. 1% of the [4 + 2] dimer **10**. At 0 °C the product solution consisted of [4 + 2] dimer **10** (12% from **8**; 91.3% from **4**) and a small amount of white, insoluble, polymeric material. The products were identified from the following data.

Furanoradialene (4) [2,3,4,5-tetramethylene-2,3,4,5-tetrahydrofuran]: ^{1}H NMR (1:1 $CS_2/CDCl_3$; −78 °C) δ 5.55 (s, 2 H), 5.52 (s, 2 H), 4.59 (d, J = 3 Hz, 2 H), 4.52 (d, J = 3 Hz, 2 H); ^{13}C NMR (1:1 $CS_2/CDCl_3$; −78 °C) δ 156.08 (s), 135.76 (s), 105.97 (t, J = 162 Hz), 81.86 (t, J = 162 Hz); [lit.[29] ^{1}H NMR ($CDCl_3$; −50 °C) δ 5.59 (br s, 4 H), 4.61 (AB quartet, J = 2.5 Hz, 4 H); ^{13}C NMR ($CDCl_3$; −60 °C) δ 160.5, 156.6, 106.2, 81.8].

[4 + 2] Dimer 10: ^{1}H NMR (1:1 $CS_2/CDCl_3$) δ 5.5 (s, 1 H) (H_a), 4.92 (s, 1 H) (H_b), 4.54 (d, J = 2.5 Hz, 1 H) (H_c), 4.46 (d, J = 2.5 Hz, 4 H) (H_d, $H_{d'}$, $H_{d''}$, $H_{d'''}$), 4.09 (m, 2 H) (H_e, $H_{e'}$), 3.94 (d, J = 2.5 Hz, 1 H) (H_f), 2.55–2.27 (m, 4 H) ($H_{g'}$, $H_{g''}$), 1.88–1.65 (m, 2 H) (H_h); ^{13}C NMR (1:1 $CS_2/CDCl_3$) δ 165.72, 160.95, 160.79, 156.99, 146.76, 134.79, 133.76, 106.72, 82.62, 81.48, 81.05, 80.83, 45.02, 33.26, 30.23, 18.09.

Pyrolysis of 3,4-Bis(benzoyloxymethyl)-2,5-dimethylfuran (9). A 0.439-g (1.21 mmol) quantity of **9** was pyrolyzed at 610 °C by using the general procedure. ^{1}H and ^{13}C NMR analyses at −70 °C indicated that furanoradialene (**4**) and [4 + 2] dimer **10** were the only major products formed from **9**, aside from benzoic acid and a substantial amount of white, polymeric material. Quantitative ^{1}H NMR analysis at −78 °C indicated that the product mixture consisted of 0.359 mmol of **4** (30%) and 0.211 mol of **10** (35%). The ^{1}H and ^{13}C NMR spectra of **4** formed from dibenzoate **9** matched the spectra of **4** formed from diacetate **8**. Upon warming the samples above −50 °C, **4** rapidly dimerized forming [4 + 2] dimer **10**. The ^{1}H and ^{13}C NMR of **10** matched the spectra of **10** obtained from diacetate **8**. ^{1}H NMR analysis using a 1,1,2,2-tetrachloroethane internal standard indicated that a quantitative yield of **10** was formed from **4** (69% yield from dibenzoate **9**).

3,4-Bis[acetoxydideuteriomethyl]-2,5-dimethylfuran (8-d_4). To a stirred slurry of lithium aluminum deuteride (3.41 g; 81.2 mmol) in 5 mL of dry ether ($LiAlH_4$) at 0 °C was added dropwise a solution of 5.489 g (22.8 mmol) of diethyl 2,5-dimethyl-3,4-furandicarboxylate (**7**) in 20 mL of dry ether. After the mixture was stirred for 7 h at room temperature, a standard workup[45] yielded 2.88 g (17.98 mmol; 79%) of **6-d_4**: IR ($CHCl_3$) 3605, 3400, 2260–2050, 1612, 1276, 995, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.75 (br s, 2 H), 2.18 (s, 6 H). A solution of 1.554 g (19.8 mmol) of acetyl chloride in 10 mL of dry ether was added dropwise over a 15-min period to a stirred solution of 2.88 g (18.0 mmol) of **6-d_4** and 2.517 g (24.9 mmol) of triethylamine in 15 mL of dry ether. After the mixture was stirred for 20 h at room temperature, 10 mL of water was added and the products were isolated by using the method described for preparation of diacetate **8**. The crude product (3.068 g; 12.6 mmol; 70%) was purified by short-path distillation, yielding 2.529 g (10.4 mmol; 58% isolated yield) of **8-d_4**: bp 80–81 °C (0.005 mm); IR (thin film) 2280–2040, 1735, 1610, 1255, 1155, 1045, 1015, 925 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6 H), 2.05 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.92, 149.63, 114.52, 20.97, 11.48; high-resolution mass spectrum calcd for $C_{12}H_{12}D_4O_5$ 244.12489, measured 244.12465. ^{1}H NMR spectral analysis of **8-d_4** showed no evidence for any deuterated species other than **8-d_4**.

Pyrolysis of 8-d_4. A 0.422-g quantity of **8-d_4** was pyrolyzed at 600 °C by using the general procedure. The pyrolyzate was collected in 4 mL of 1:1 $CS_2/CDCl_3$ and NMR spectral data were recorded at low temperature for 3,4-dimethylene-d_2-2,5-dimethylene-2,3,4,5-tetrahydrofuran (**4-d_4**): ^{1}H NMR (1:1 $CS_2/CDCl_3$; −60 °C) δ 4.61 (d, J = 2.5 Hz, 2 H), 4.52 (d, J = 2.5 Hz, 2 H); ^{13}C NMR (1:1 $CS_2/CDCl_3$; −60 °C) δ 156.08, 135.60, 81.80. Upon warming the samples to room temperature, **4-d_4** was cleaning converted to [4 + 2] dimer **10-d_8**: ^{1}H NMR (1:1 $CS_2/CDCl_3$) δ 4.53 (d, J = 2.5 Hz, 1 H) (H_a), 4.45 (d, J = 2.5 Hz, 4 H) (H_b, $H_{b'}$, $H_{b''}$, $H_{b'''}$), 4.09 (m, 2 H) (H_c, $H_{c'}$), 3.92 (d, J = 2.5 Hz, 1 H) (H_d); ^{13}C (1:1 $CS_2/CDCl_3$) δ 165.42, 160.64, 160.31, 156.57, 146.53, 134.65, 133.58, 82.51, 81.64, 8' 21, 80.99, 44.89. The signals for the CD_2 carbons were not observed fter 25 000 scans (pulse width = 2.0 μs). NMR analysis of the pyrolysis product mixtures formed from **8-d_4** showed no evidence for any deuterated species other than **4-d_4** and **10-d_8**.

Acknowledgment. This work was supported by the U.S. Department of Energy, Office of Basic Energy Sciences, Chemical Sciences Division, under contract W-7405-ENG-82.

Registry No. 4, 75075-85-3; **4-d_4**, 92009-82-0; **6**, 90199-61-4; **6-d_4**, 91994-43-3; **7**, 19434-69-6; **8**, 91994-45-5; **8-d_4**, 91994-44-4; **9**, 91994-46-6; **10**, 91994-47-7; **10-d_8**, 92009-83-1.

Pyrrolizidinone and Indolizidinone Synthesis: Generation and Intramolecular Addition of α-Acylamino Radicals to Olefins and Allenes

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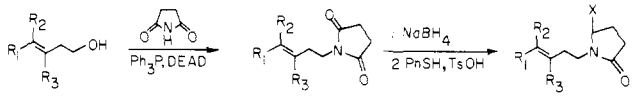
Abstract: α-Acylamino radicals can be generated by treatment of phenylthio, methylthio, or phenylselenenyl lactams of type **7**, **8**, and **17** with tri-*n*-butyltin hydride in the presence of AIBN. The radicals add intramolecularly to olefins and allenes to give indolizidinones and pyrrolizidinones. The product distribution depends on the substitution patterns of the unsaturated moiety and the length of the chain connecting the radical and olefinic centers. Product ratios appear to reflect the kinetic partitioning of the radical between cyclization pathways. These reactions are potentially useful in the area of pyrrolizidine alkaloid synthesis. The conversion of cyclization products **50** and **51** to (±)-supinidine (**1**) serves as an example.

During studies directed toward a synthesis of structures related to the Dendrobatid alkaloid GTX-223AB, we encountered a situation in which a 5-hexenyl radical cyclization was used to provide evidence for a stereochemical assignment.[4] From a synthetic standpoint, we were struck by the ease with which this reaction allowed the preparation of a reasonably complicated tricyclic compound. Provided with this stimulus, we decided to embark on studies designed to develop and apply free radical cyclizations to natural product synthesis. A literature survey revealed that although much was known about carbon–carbon bond-forming free radical cyclizations, there had been relatively few attempts to design syntheses which relied on their use.[5-8] In

(1) Alfred P. Sloan Foundation Fellow, 1983–1985.
(2) McPherson-Evans Scholar, 1981–1982.
(3) Taken in part from: Tsai, Y.-M., Ph.D. Thesis Ohio State University, 1983.
(4) Hari, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1982**, *47*, 4403.
(5) For an excellent review of radical cyclizations, see: Surzer, J.-M. In "Reactive Intermediates"; Abramovitch, A. R., Ed.; Plenum Press: New York, 1980; Vol. I.

0002-7863/84/1506-8201$01.50/0

Table I. Preparation of Radical Precursors 7



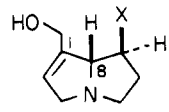
3 4 5 X = OH; 6 X = Cl; 7 X = SPh; 8 X = SePh; 9 X = •

a $R_1 = R_2 = R_3 = H$; b $R_1 = Me$, $R_2 = R_3 = H$; c $R_2 = Me$, $R_1 = R_3 = H$; d $R_1 = R_2 = Me$, $R_3 = H$; e $R_1 = R_2 = H$, $R_3 = Me$

entry[a]	starting alcohol	% imide 4	% lactam 7
1	3a	96	88
2	3b	85	88
3	3c	92	89
4	3d	86	93
5	3e	87	83

[a] See Experimental Section for conditions and representative procedures.

particular, there had been no serious attempts to use such reactions in alkaloid synthesis. Therefore our initial studies were devoted to this area. Pyrrolizidine alkaloids such as supinidine (**1**) and heliotridine (**2**) were selected as initial targets for several reasons.



1 X = H

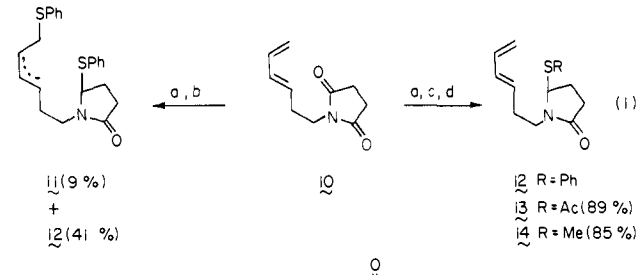
2 X = OH

Since a large number of syntheses of these compounds had been reported, any new strategy we adopted could be compared to other approaches. In addition, these alkaloids provided an opportunity to develop a new series of cyclizations based on α-acylamino radicals. This article presents the details of our initial studies.[9]

Results and Discussion

Preparation of Radical Precursors. Our approach to the pyrrolizidine nucleus focused on construction of the C(1)–C(8) bond via cyclization of the radical **9** derived from homolysis of the C–X bond in compounds of type **6–8**. At the onset of this work, several entries to α-acylamino radicals had been described.[10,11] Of these, tri-*n*-butyltin radical mediated homolysis of a carbon–halogen bond was best suited to our objective.[11] It was not surprising to find that α-chlorolactams of type **6** were unmanageable, and we quickly turned to sulfides of type **7**. The required sulfides were prepared as outlined in Table I. Thus, the imides **4** were prepared via Mitsunobu coupling of the alcohols **3** with succinimide.[12] Treatment of these imides with sodium borohydride[13,14] afforded the carbinolamides **5** which were converted to lactams **7** upon treatment with an equivalent of thiophenol and a catalytic amount of *p*-toluenesulfonic acid. In all cases, purification of the intermediate carbinolamide was unnecessary.

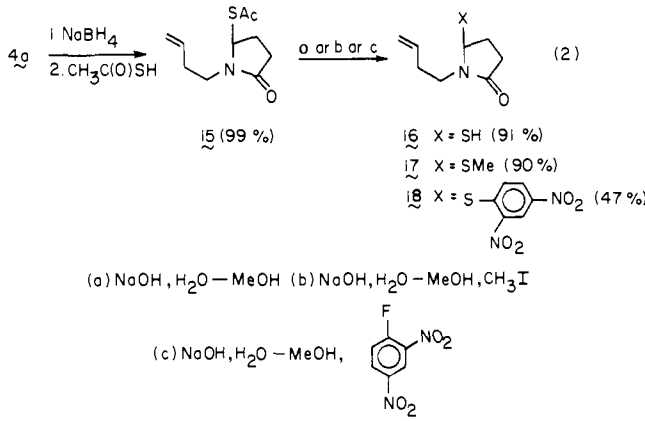
The only problem we encountered with this procedure was that, on occasion, free radical addition of thiophenol to the unsaturated component of the carbinolamide was observed. For example, treatment of the carbinolamide derived from reduction of dienoic imide **10** with thiophenol and acid gave annoying amounts of addition products **11** (9%) along with a modest yield of exchange product **12** (41%). Treatment of the same carbinolamide with



11 (9%) + 12 (41%); 10; 12 R = Ph; 13 R = Ac (89%); 14 R = Me (85%)

(a) $NaBH_4$ (b) PhSH (1 equiv), TsOH (c) CH_3CSH (d) NaOH, H_2O–MeOH, CH_3I

thiolacetic acid, however, gave **13** (89%) without complications resulting from addition to the diene moiety. Treatment of **13** with sodium hydroxide followed by iodomethane gave methylthiolactam **14** in an 85% yield. Although addition of thiophenol to the terminal double bond did not cause problems in this case, this reaction sequence was also applied to imide **4a** to prepare imides **15–18** for evaluation as radical precursors (vide infra).



15 (99%); 16 X = SH (91%); 17 X = SMe (90%); 18 X = S–(2,4-$(NO_2)_2$C$_6$H$_3$) (47%)

(a) NaOH, H_2O–MeOH (b) NaOH, H_2O–MeOH, CH_3I

(c) NaOH, H_2O–MeOH, 2,4-dinitrofluorobenzene

Radical Cyclizations. Our initial studies focused on the generation of radical **9a** by treatment of lactams **7a** and **15–18** with tri-*n*-butyltin hydride and AIBN in benzene under reflux. Thioacetate **15** was stable to these conditions (10 h) while **16** and **18** gave a myriad of products.[15,16] Lactam **7a**, however, was well-behaved and gave the products shown in eq 3.[17] Isomeric lactams **19–22** could only be partially separated with difficulty. Reduction product **19** (12%) was separated from **20–22** (72%) by silica gel chromatography. A pure sample of **20** was obtained

(6) The Julia group has investigated certain intramolecular carbon–carbon bond-forming reactions in depth. Although Julia has shown that a number of carbocyclic ring systems common to terpenoids can be constructed via radical processes, this chemistry has not been exploited in natural product synthesis. For an overview of contributions of the Julia group see: Julia, M. *Rec. Chem. Prog.* **1964**, *25*, 1. Julia, M. *Pure Appl. Chem.* **1967**, *15*, 167. Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386. Julia, M. *Pure Appl. Chem.*, **1974**, *40*, 553.

(7) For two notable applications of radical cyclizations to sesquiterpene synthesis see Bakuzis, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261. Büchi, G.; Wüest, H. *J. Org. Chem.* **1979**, *44*, 546.

(8) For an overview of recent contributions to the use of radical carbon–carbon bond-forming reactions in synthesis, see: Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883.

(9) For a preliminary account of a portion of this work, see: Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430.

(10) Friedman, L.; Shechter, H. *Tetrahedron Lett.* **1961**, 238. Nikishin, G. I.; Mustafaev, R. I. *Dokl. Akad. Nauk SSR* **1964**, *158*, 1127. Elad, D.; Sinnreich, J. *Tetrahedron* **1968**, *24*, 4509.

(11) Whitesitt, C. H.; Herron, D. K. *Tetrahedron Lett.* **1978**, 1737.

(12) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

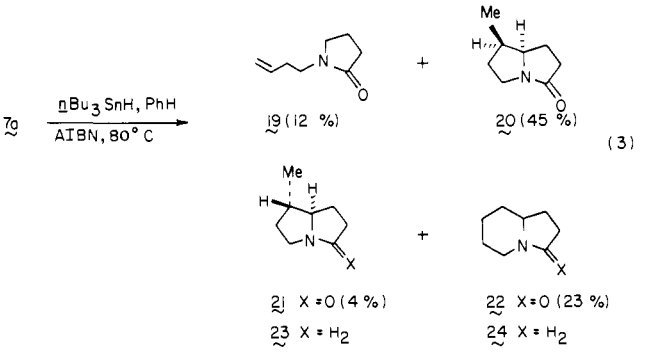
(13) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(14) The Speckamp procedure requires that acid be added to ethanolic solutions of sodium borohydride and the imide. We (Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135) and others (Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, 2619) have noticed that the use of methanol as a solvent eliminates the need for acid. This has some operational advantages on occasion. The Experimental Section provides representative examples of both procedures.

(15) Vedejs, E.; Powell, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 2046.

(16) Treatment of **16** with triethyl phosphite also gave a myriad of products: Walling, C.; Pearson, M. S. *J. Am. Chem. Soc.* **1964**, *86*, 2262.

(17) After the completion of our initial studies, the method of α-acylamino radical generation developed herein was reported by: Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, 2693.



by preparative gas chromatography. Lactams **21** and **22** could not be separated and were analyzed as a mixture. The structures of **19–22** were all proven by independent syntheses which are outlined in the supplementary material. Further proof of the assignments for **21** and **22** was obtained by their conversion to heliotridane (**23**) and δ-coniceine (**24**), respectively. Thus, treatment of a mixture of **21** and **22** with lithium aluminum hydride gave a mixture of **23** and **24** (32%). The presence of **23** and **24** was confirmed by comparison of the ^{1}H NMR spectrum of the mixture with spectra of authentic samples prepared by alternate routes.[18,19] Furthermore, when the apparent difference in basicity between **23** and **24** was relied upon, pure samples of the corresponding picrates were obtained from the aforementioned mixture. Once again, these were identical with authentic samples.

When methylthiolactam **17** was used as the radical precursor, the same product distribution (**19–22**) was obtained. The rate of radical generation, however, was qualitatively slower than from **7a**, and conversion of **17** to products was incomplete. Therefore we prefer to use phenylthiolactams **7** as radical precursors whenever possible.

One of the most striking aspects of the reaction shown in eq 3 was the 2:1 ratio of exo (**20** + **21**) and endo (**22**) cyclization products.[20] The experiments outlined in Scheme I suggest that this ratio reflects the kinetic partitioning of **7a** between the exo and endo cyclization paths. Thus, xanthates **25b** and **26b** were prepared from the corresponding alcohols. Treatment of **25b** and **26b** with tri-*n*-butyltin hydride under the conditions used to generate **9a** gave **20** (61%) and **22** (78%), respectively.[21] No evidence for the formation of **9a** (**19**) or crossover between **25c** and **26c** was obtained. The reasons for the unusually small exo–endo ratio in the kinetic partitioning of **9a** are uncertain.[22]

Another noteworthy aspect of the cyclization shown in eq 3 is the high diastereoselectivity of the exo cyclization. The origin of this selectivity also remains uncertain. Nonetheless, our results are consistent with those obtained in a related carbocyclic system.[23]

From a synthetic standpoint, the results presented in eq 3 were encouraging. Based on Julia's substituent effect studies performed with hydrocarbon systems, we felt that the small exo–endo cyclization ratio obtained with **7a** would translate to exclusive pyrrolizidinone or indolizidinone formation if substituents were placed appropriately on the olefin.[24] Therefore radicals **9b–e** were generated from phenylthiolactams **7b–e**, and the resulting product mixtures were analyzed. The results are documented in Chart I and Table II. Once again, the reduction products (**27**) were separable from the cyclization products (**28–30**) by chromatography over silica gel. In most cases, pure samples of cyclization products were isolated by chromatography although **28b** and **29b** were analyzed as a mixture. The structures of cyclization products were based on spectral data with the exception of **30b** which was prepared via an alternate synthesis (vide infra). The stereochemical assignments of pyrrolidizidinones **28** and **29** were based on spectral data. Of diagnostic importance for pyrrolizidinones of type **28** was a signal at δ 3.9–4.1 due to H_8 in their ^{1}H NMR spectra. In addition, pyrrolizidinones of type **29** all displayed a broadened triplet centered at δ 3.05–3.20 due to one of the C(3) hydrogens.

Scheme I

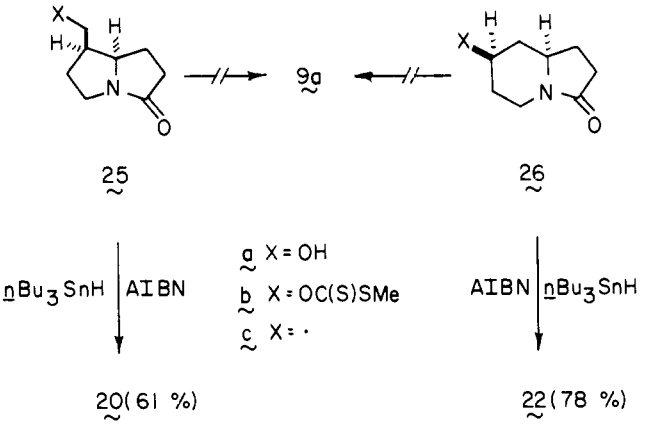
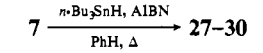


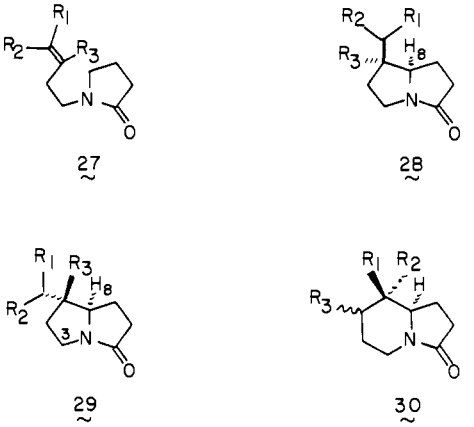
Table II. Generation and Cyclization of Radicals **9**



entry[a]	radical precursor	% 27[b]	% 28[c]	% 29[c]	% 30[c]
1	**7a**	12	45	4	24
2	**7b**[d]	13[e]	42	5	22
3	**7c**[d]	25[f]	45	7	4[g]
4	**7d**[h]	12	60	15	0
5	**7e**[i]	12	7	0	63

[a] All reactions were run under identical conditions. See the Experimental Section for details. [b] Isolated. [c] Based on VPC and 300-MHz ^{1}H NMR data collected on purified mixtures of cyclization products. [d] Pure **30b** was obtained by VPC. Lactams **28b** and **29b** were analyzed as a pure mixture. [e] Contaminated with 8% of **27c** by VPC. [f] Contaminated with 15% of **27b** by VPC. [g] Only **30b** was obtained in this experiment. [h] Pure samples of **29d** and **30d** were obtained by chromatography. [i] The structure of **28e** is tentative. Lactam **30e** was a separable 3.7:1 mixture of diastereomers. Pure samples were obtained by VPC.

Chart I. Radical Cyclization Products



a $R_1 = R_2 = R_3 = H$ b $R_1 = Me, R_2 = R_3 = H$ c $R_2 = Me, R_1 = R_3 = H$
d $R_1 = R_2 = Me, R_3 = H$ e $R_1 = R_2 = H, R_3 = Me$

(18) A sample of heliotridane (**23**) was prepared via the method of: Schweizer, E. E.; Light, K. K. *J. Org. Chem.* **1966**, *31*, 870.

(19) δ-Coniceine (**24**) was prepared by treatment of **22** with lithium aluminum hydride.

(20) For a summary of regiochemical guidelines for radical cyclizations, see: Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482.

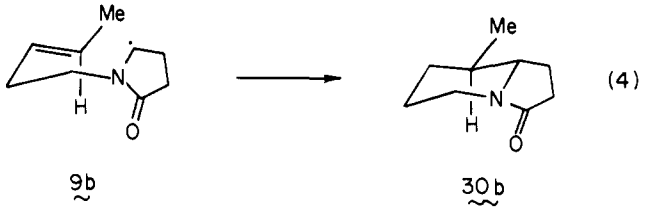
(21) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(22) It is possible that bond angle widening due to insertion of an sp^2-hybridized nitrogen in the chain connecting the olefin and radical centers is partially responsible for this observation.

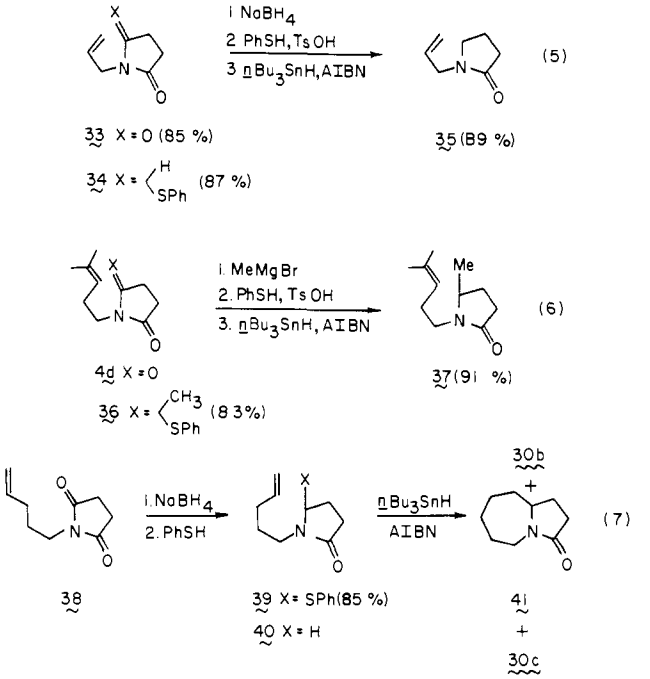
(23) Agosta, W. C.; Wolff, S. *J. Chem. Res. Synop.* **1981**, 78.

(24) Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 1737.

The results shown in Table II provide some important information about the cyclization process. Entry 2 shows that terminal *E*-methyl substitution has little effect on the cyclization regiochemistry (compare with entry 1). The formation of **30b** as the only endo cyclization diastereomer supports the notion that this reaction proceeds via a transition state which resembles a chair piperidine (eq 4). Entry 3 shows that terminal *Z*-methyl substitution affords predominantly pyrrolizidinones. This result is in accord with Julia's studies[24] and is probably due to a decrease in the rate of the endo cyclization process.[25] Entry 4 shows that introducing two methyl groups at the olefin terminus gives only pyrrolizidinones. Internal olefin substitution (entry 5) leads to predominantly indolizidinone formation. Finally, it is noted that all of the exo cyclizations proceed with good diastereoselectivity.[26]

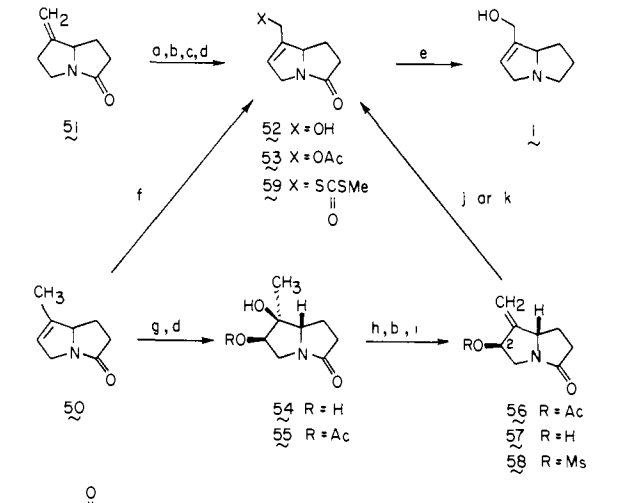


In an attempt to further define the scope of the α-acylamino radical cyclizations, phenylthiolactams **34**, **36**, and **39** were prepared as outlined in eq 5–7. Although **34** and **36** were merely



reduced to **35** and **37**, respectively, upon treatment with tri-*n*-butyltin hydride and AIBN, phenylthiolactam **39** gave reduction

Scheme II

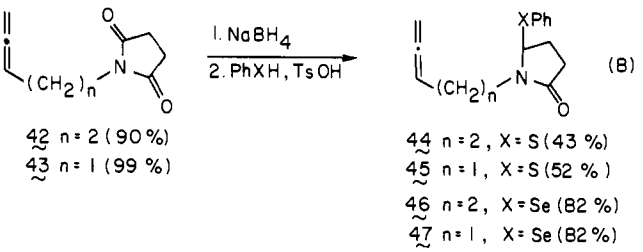


(a) $PhSeOCCF_3$ (b) $NaHCO_3, H_2O$ (c) H_2O_2 (d) Ac_2O, Et_3N, DMAP (e) $LiAlH_4$ (f) SeO_2, AcOH (g) OsO_4, Me_3NO (h) $Ph_2S[OC(CF_3)_2Ph]_2$ (i) MsCl, Et_3N (j) AcOH, Δ (k) NaH, CS_2, CH_3I

product **40** (8%) along with cyclization products **30b**, **30c**, and **41** in 24%, 30%, and 21% yields, respectively. The indolizidinone stereochemical assignments were based on H_4–H_5 coupling constants of 9 and 3.7 Hz in **30b** and **30c**, respectively. Once again, a drop in the exo–endo ratio (2.5:1) was observed compared to the 6:1 ratio reported for the 6-heptenyl radical.[27]

The aforementioned studies gave us some insight into what to expect from various α-acylamino radicals. With this background, we began to investigate cyclizations which had more direct bearing on projected pyrrolizidine alkaloid syntheses. Supinidine (**1**) and heliotridine (**2**), two of our targets, had $\Delta^{1,2}$ unsaturation that was absent in the pyrrolizidine products we had prepared. Therefore we examined allenes as the unsaturated components of the cyclizations.[28,29]

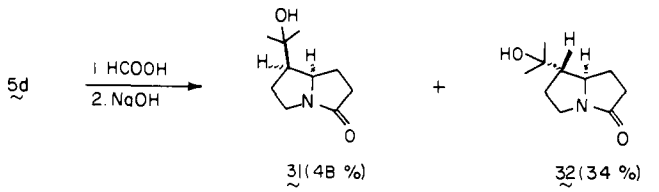
We began by preparing radical precursors **44** and **45** (eq 8) by using the procedures discussed previously. Treatment of either



44 or **45** with tri-*n*-butyltin hydride and AIBN, however, failed to generate the desired radicals. Instead, products derived from addition of tri-*n*-butyltin radicals to the allene were obtained.[30] Therefore selenophenol was substituted for thiophenol in the exchange reaction to afford phenylselenenyllactams **46** and **47**. Both **46** and **47** served admirably as radical precursors and gave the cyclization products shown in eq 9 and 10, respectively.[31] Stereoisomeric indolizidinones **49** could not be separated by chromatographic techniques. The presence of the $\Delta^{7,8}$ isomer as

(25) It is notable that a minor amount of olefin isomerization was observed in the reduction products (**27b,c**). This isomerization may have occurred during the preparation of **7b** and **7c** from the corresponding imides via a thiophenoxy radical addition–fragmentation process. An alternative explanation involves addition–fragmentation of tri-*n*-butyltin radicals during the cyclization reaction. (Kuivila, H. G.; Sommer, R. *J. Org. Chem.* **1968**, *33*, 802.) With this in mind, we suggest that most of the **30b** observed in entry 3 actually comes from cyclization of **9b** rather than **9c**.

(26) We note that the cyclization of radical **9d** is more stereoselective than the corresponding acyliminium ion cyclization shown below.



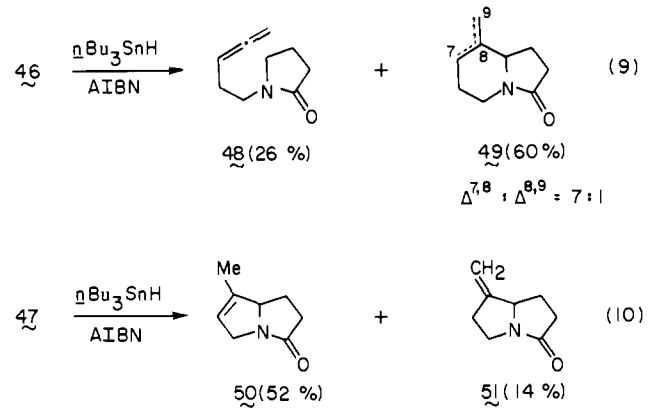
(27) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472.

(28) For an account of the occurrence, chemistry, and pharmacology of pyrrolizidine alkaloids, see: Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North-Holland Publishing Co.: Amsterdam, 1968.

(29) For recent accounts of pyrrolizidine alkaloid syntheses, see: Robins, D. J. *Adv. Heterocycl. Chem.* **1979**, *24*, 247–291. Robins, D. J. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 115–203.

(30) Kuivila, H. G.; Rahman, W.; Fish, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 2835.

(31) Clive, D. L. J.; Chittattu, G.; Wong, C. K. *J. Chem. Soc., Chem. Commun.* **1978**, *41*. Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884.



the major component, however, was easily discernible by comparing the ^{1}H NMR spectrum of the mixture with that of an authentic sample.[32] The presence of small amounts of the $\Delta^{8,9}$ isomer was apparent from the appearance of methylidene resonances at δ 4.8 and 4.9. Pyrrolizidinones **50** and **51** were separable by silica gel chromatography, and their structures were assigned on the basis of spectral data and comparison with an authentic sample in the case of **51**.[32] These results indicate that allenes are promising as the unsaturated components of radical cyclizations.

Synthesis of Supinidine (1). Both **51** and **50** could be converted to supinidine as outlined in Scheme II. Treatment of **51** with phenylselenenyl trifluoroacetate[33] gave a mixture of regioisomeric addition products. Hydrolysis of the trifluoroacetate, oxidation to the selenoxide, and subsequent elimination of phenylselenenic acid gave a mixture of products which included allylic alcohol **52**. Acetylation of this mixture using Steglich's procedure[34] followed by chromatography over silica gel gave allylic acetate **53** in a 41% overall yield from **51**. Reduction of **53** with lithium aluminum hydride gave supinidine (93%). Although this hardly represents a superior synthesis of **1**, it is noted that **51** is available via a more efficient route involving a 2-aza-5-hexynyl radical cyclization.[32,35]

The major cyclization product (**50**) was converted to **53** in a single step by oxidation with selenium dioxide (23%). Because of the low yield in this reaction, alternate procedures were sought. Although none of these efforts were very successful, a few of the more interesting observations are included in Scheme II. Treatment of **50** with osmium tetroxide and trimethylamine oxide gave a single diol which was tentatively assigned structure **54**.[36] Acetylation of the secondary alcohol gave **55** in an 80% overall yield. Dehydration of **55** with Martin's reagent afforded allylic acetate **56** in a 70% yield.[37] A number of less exotic dehydration conditions were examined, none of which gave any **56**. We had hoped to rearrange **56** to **53** by using a palladium catalyst, but this met with failure.[38] Solvolysis of mesylate **58**, derived from **56** via alcohol **57** (89% overall), in acetic acid did give **52** in a disappointing 40% yield along with **56** (7%) and its C(2) stereoisomer (16%). Although other schemes for converting **56** into **53** were investigated, none of them met with success. It is noted, however, that attempts to convert **57** to the corresponding xanthate led to efficient formation of dithiocarbonate **59** (77%), a potential precursor of 9-thiapyrrolizidine alkaloid analogues.[39,40]

(32) Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1982**, 4765.
(33) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1974**, 100. Reich, H. J. *J. Org. Chem.* **1974**, *39*, 428. Sharpless, K. B.; Lauer, R. H. *J. Org. Chem.* **1974**, *39*, 429.
(34) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(35) For other syntheses of supinidine, see: Macdonald, T. L.; Narayanan, B. A. *J. Org. Chem.* **1983**, *48*, 1129 and references cited therein.
(36) VanRheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.
(37) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327. We thank Professor Martin for kindly supplying a sample of $Ph_2S[OC(CF_3)_2Ph]_2$ for our initial studies.
(38) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, *321*.
(39) Taguchi, T.; Kawazoe, Y.; Yoshihira, K.; Kanayama, H.; Mori, M.; Tabata, K.; Harano, K. *Tetrahedron Lett.* **1965**, 2717.
(40) Studies designed to use allene cyclizations in a synthesis of heliotridine (**2**) are in progress.

Experimental Section

Introduction. Only a portion of the reactions reported above appear in this section. These experiments should provide the reader with representative procedures. The compounds reported here are **4d**, **7a**, **15–24**, **31**, **32**, **43**, **47**, and **50–59**. Procedures for the preparation of all other new compounds (**4c**, **7b–e**, **10–14**, **25b**, **26b**, **27b–e**, **28b–e**, **29b–e**, **30b–e**, **34–41**, **44–46**, **48**, and **49**) are presented in the Supplementary Material. Many of these experiments resemble procedures appearing in *this* section and thus are presented in abbreviated form. Compounds **4a**,[41] **4b**,[41] **4e**,[41] **25a**,[42] **26a**,[41] **33**,[43] and **44**[43] were prepared by known procedures.

General. All melting points are uncorrected as are boiling points. ^{1}H NMR spectra are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constants in hertz, integration, interpretation]. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were recorded at an ionization energy of 70 eV. Samples on which exact masses were measured exhibited no significant peaks at *m/e* greater than those of the parent. The parent ions of phenylthiolactams (e.g., **7a**) and a few other compounds are too small for exact mass measurements to be obtained. In these cases, the fragmentation patterns were in accord with the assigned structures. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl ether (distilled from Na metal); benzene, dimethyl sulfoxide, pyridine, toluene (distilled from calcium hydride); methanol (distilled from magnesium methoxide); chloroform, dichloromethane (passed through activity I alumina). All reaction temperatures refer to those of the reaction mixture. Reactions requiring an inert atmosphere were run under a blanket of nitrogen or argon. Tri-*n*-butyltin hydride was prepared according to a known procedure.[45] Analytical thin-layer chromatography was performed with EM Laboratories 0.25 mm thick precoated silica gel 60 F-254 plates. Column chromatography was performed over EM Laboratories silica gel (70–230 mesh). Medium-pressure liquid chromatography (MPLC) was performed by using EM Laboratories Lobar prepacked silica gel columns.

1-(4-Methyl-3-pentenyl)-2,5-pyrrolidinedione (4d). To a mixture of 1.38 g (13.8 mmol) of 4-methyl-3-penten-1-ol,[46] 1.37 g (13.8 mmol) of succinimide, and 3.62 g (13.8 mmol) of triphenylphosphine in 20 mL of dry tetrahydrofuran under argon was added a solution of 2.40 g (13.8 mmol) of diethyl azodicarboxylate[46] in 5.8 mL of dry tetrahydrofuran over a period of 1 h. The resulting solution was stirred at room temperature for 3 h, and the solvent was removed in vacuo. The resulting residue was triturated with 30 mL of ethyl acetate–hexane (3:7) and filtered. The filter cake was triturated again with 20 mL of the same solvent pair. The combined extracts were concentrated in vacuo. The residue was mixed with 30 mL of ethyl acetate–hexane (3:7) and filtered. The filtrate was concentrated in vacuo to give 4.50 g of pale-yellow oil. The oil was chromatographed over 50 g of silica gel (dichloromethane) to afford 2.14 g (86%) of imide **4d** as a colorless liquid which solidified on standing to give a white solid: mp 42.5–43.5 °C; IR (KBr) 1705 cm^{-1}; NMR (CCl_4) δ 1.60 (br s, 3 H, CH_3), 1.69 (br s, 3 H, CH_3), 2.22 (br q, J = 7 Hz, 2 H, CH_2C=), 2.60 (s, 4 H, $COCH_2$), 3.39 (br t, J = 7 Hz, 2 H, NCH_2), 5.03 (br t, J = 7 Hz, 1 H, =CH); mass spectrum, *m/e* (rel intensity) 181 (17), 113 (4), 112 (2), 100 (36), 82 (100), 69 (25), 67 (51). Exact mass calcd for $C_{10}H_{15}NO_2$: *m/e* 181.1103. Found: *m/e* 181.1107.

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34. Found: C, 66.46; H, 8.20.

1-(3-Butenyl)-5-(phenylthio)-2-pyrrolidinone (7a). To a solution of 1.50 g (9.80 mmol) of imide **4a** in 60 mL of absolute ethanol cooled in an ice–water bath under argon was added 1.10 g (29.1 mmol) of sodium borohydride. A 1.94 N solution of hydrogen chloride in absolute ethanol was added at a rate of 2 drops every 5 min over a period of 2 h and 15 min. The reaction mixture was then acidified with 1.94 N hydrogen chloride in absolute ethanol (about 14 mL) to approximately pH 3. The resulting mixture was stirred at 0 °C for 15 min and basified with 1% potassium hydroxide in absolute ethanol (about 30 mL) to approximately pH 9. Throughout the whole process, the reaction temperature was kept below 5 °C. The reaction mixture was partitioned between 100 mL of

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(42) Prepared by hydrolysis of the corresponding acetate: Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.*, following paper in this issue.
(43) Rossi, P. F.; Barolo, P. *Ann. Chim. (Rome)* **1968**, *48*, 1416.
(44) Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, 3289.
(45) Kuivila, H. G. *Synthesis* **1970**, 499.
(46) Purchased for Aldrich Chemical Company.

water and 100 mL of dichloromethane. The aqueous phase was extracted with four 100-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 1.75 g of crude ethoxylactam as a colorless liquid. This material was dissolved in 10 mL of thiophenol followed by the addition of 72 mg (0.38 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting solution was stirred at room temperature for 10 min and partitioned between 110 mL of 1 N sodium hydroxide solution and 100 mL of dichloromethane. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 2.30 g of a white turbid liquid. This material was chromatographed over 50 g of silica gel (ethyl acetate–hexane, 2:8, followed by ethyl acetate–hexane, 4:6) to yield 2.14 g (88%) of thiophenoxylactam **7a** as a colorless liquid: IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 1.43–2.70 (m, 6 H, CH_2 manifold), 3.20 (td, J = 13, 6 Hz, 1 H, NCH), 3.78 (td, J = 13, 6 Hz, 1 H, NCH), 4.75–5.20 (m, with dd, J = 7, 3 Hz, at 4.80, 3 H, $=CH_2$ and SCH), 5.47–6.00 (m, 1 H, =CH), 7.33 (br s, 5 H, ArH); mass spectrum, *m/e* (rel intensity) 218 (16), 138 (M^+ – SPh, 100), 110 (31), 109 (19), 96 (25), 84 (12).

1-(3-Butenyl)-5-(thioacetoxy)-2-pyrrolidinone (15). Imide **4a**[41] (1.0 g, 6.54 mmol) was reduced with 726 mg (19.1 mmol) of sodium borohydride, and the resulting crude carbinolamide was stirred with 3.5 mL of thiolacetic acid at room temperature for 20 min. The resulting solution was partitioned between 100 mL of dichloromethane and 70 mL of saturated sodium bicarbonate solution. The aqueous phase was extracted with two 100-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil which was chromatographed over 40 g of silica gel (ethyl acetate–hexane, 2:8, followed by ethyl acetate–hexane, 4:6) to yield 1.38 g (99%) of **15** as a yellow oil: IR (neat) 1710 cm^{-1}; NMR (CCl_4) δ 1.90–3.08 (m with s at 2.31, 10 H, CH_3, NCH and CH_2 manifold), 3.61 (td, J = 12, 7 Hz, 1 H, NCH), 4.81–5.25 (m, 2 H, $=CH_2$), 5.25–6.05 (m, 2 H, NCHS and =CH); mass spectrum, *m/e* (rel intensity) 213 (M^+, 0.6), 172 (10), 138 (M^+ – $SCOCH_3$, 100), 127 (8), 130 (11), 101 (14), 96 (24), 84 (28).

1-(3-Butenyl)-5-mercapto-2-pyrrolidinone (16). To 149 mg (0.70 mmol) of lactam thioacetate **15** under argon was added 1.6 mL of a 0.86 N solution of sodium hydroxide in aqueous methanol (H_2O–MeOH, 1:5). The resulting solution was stirred at room temperature for 10 min and acidified with 1 N hydrogen chloride solution to pH 1. The resulting mixture was partitioned between 5 mL of water and 20 mL of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to yield 109 mg (91%) of **16** as a pale-yellow oil: NMR (CCl_4) δ 1.80–2.73 (m, 7 H, SH and CH_2 manifold), 3.00 (td, J = 14, 7 Hz, 1 H, NCH), 3.67 (td, J = 14, 7 Hz, 1 H, NCH), 4.50–5.20 (m, 3 H, $=CH_2$ and NCHS), 5.70 (tdd, J = 16, 10, 6 Hz, 1 H, =CH). Since further purification via column chromatography led to decomposition, this material was used directly in subsequent reactions.

1-(3-Butenyl)-5-(methylthio)-2-pyrrolidinone (17). To 232 mg (1.09 mmol) of lactam thioacetate **15** under argon was added in a single portion 2.9 mL of 0.85 N solution of sodium hydroxide in aqueous methanol (H_2O–MeOH, 1:5). The resulting solution was stirred at room temperature for 15 min followed by the addition of 0.39 mL (6.3 mmol) of methyl iodide. The reaction mixture was stirred for another hour and partitioned between 20 mL of dichloromethane and 5 mL of water. The aqueous phase was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 190 mg of a pale-pink liquid. This material was chromatographed over 5 g of silica gel (ethyl acetate–hexane, 45:55) to yield 181 mg (90%) of **17** as a colorless liquid: IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 1.97 (s, 3 H, CH_3), 2.00–2.70 (m, 6 H, CH_2 manifold), 3.10 (td, J = 14, 7 Hz, 1 H, NCH), 3.70 (td, J = 14, 7 Hz, 1 H, NCH), 4.60 (dd, J = 7, 5 Hz, 1 H, NCHS), 4.90–5.20 (m, 2 H, $=CH_2$), 5.80 (tdd, J = 16, 10, 6 Hz, 1 H, =CH); mass spectrum, *m/e* (rel intensity) 138 (M^+ – SCH_3, 100), 96 (15), 84 (27).

1-(3-Butenyl)-5-((2,4-dinitrophenyl)thio)-2-pyrrolidinone (18). To 199 mg (0.934 mmol) of lactam thioacetate **15** under argon was added 0.65 mL of a 1.50 N sodium hydroxide solution in aqueous methanol (H_2O–MeOH, 1:5). The resulting brownish solution was stirred at room temperature for 5 min followed by the addition of 177 mg (0.950 mmol) of 2,4-dinitrofluorobenzene[46] in a single portion. The resulting mixture was stirred for 5 min to give a solution with a yellow solid suspension. This mixture was partitioned between 5 mL of water and 20 mL of dichloromethane. The aqueous phase was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford a yellow solid. This material was chromatographed over 13 g of silica gel (ethyl acetate–hexane, 1:1, followed by ethyl acetate–hexane, 7:3) to yield a yellow solid which was recrystallized from ethyl acetate (3 mL) and hexane (5 mL) to give 148 mg (47%) of **18** as a yellow crystalline solid: mp 134–135 °C; IR (KBr) 1695, 1590, 1510, 1345 cm^{-1}; NMR ($CDCl_3$) δ 2.10–2.87 (m, 6 H, CH_2 manifold), 3.13 (td, J = 14, 7 Hz, 1 H, NCH), 3.83 (td, J = 14, 7 Hz, 1 H, NCH), 4.87–6.00 (m, 4 H, CH=CH_2 and NCHS), 7.47 (d, J = 9 Hz, 1 H, ArH(5)), 8.32 (dd, J = 9, 3 Hz, 1 H, ArH(6)), 9.00 (d, J = 3 Hz, 1 H, ArH(3)).

Anal. Calcd for $C_{14}H_{15}N_3O_5S$: C, 49.84; H, 4.48. Found: C, 50.12; H, 4.70.

1-(3-Butenyl)-2-pyrrolidinone (19), *rel*-(1*R*,7a*R*)-Hexahydro-1-methyl-1*H*-pyrrolizin-5-one (20), *rel*-(1*S*,7a*R*)-Hexahydro-1-methyl-1*H*-pyrrolizin-5-one (21), and Hexahydro-2*H*-indolizin-3-one (22). To a solution of 1.00 g (4.05 mmol) of thiophenoxylactam **7a** in 50 mL of dry benzene heated to reflux under argon was added a solution of 1.50 mL (5.68 mmol) of tri-*n*-butyltin hydride and 40.1 mg (0.244 mmol) of AIBN in 40 mL of dry benzene over a period of 5 h. The resulting solution was heated at the same temperature for another 2 h, and the solvent was removed in vacuo to give a white turbid oil (2.74 g). This material was chromatographed over 35 g of silica gel (ethyl acetate–hexane, 7:3, followed by ethyl acetate) and again over a Lobar size **B** column (ethyl acetate–hexane, 7:3, followed by ethyl acetate) to yield 68.6 mg (12%) of the less polar lactam **19** as a colorless oil: IR (CCl_4) 1690 cm^{-1}; NMR (CCl_4) δ 1.80–2.40 (m, 6 H, CH_2 manifold), 3.30 (overlapping t's, J = 7 Hz, 4 H, CH_2NCH_2), 4.90–5.20 (m, 2 H, $=CH_2$), 5.50–6.00 (m, 1 H, =CH). Exact mass calcd for $C_8H_{13}NO$: *m/*E 139.0997. Found: *m/e* 139.1002. Further elution gave 405 mg (72%) of a mixture of lactams **20**, **21**, and **22** (58:7:35, respectively, by NMR) as a pale-yellow oil. A pure sample of **21** was obtained by GLC (10% OV-101, column temperature = 148 °C, 30 mL He min^{-1}): t_R = 6.0 min; IR (CCl_4) 1705 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.04 (d, 3 H, J = 6 Hz, CH_3), 1.59–1.81 (m, 2 H), 2.18–2.38 (m, 3 H), 2.45 (m, 1 H, COCH), 2.68 (m, 1 H, COCH), 3.15 (br t, 1 H, J = 10.5 Hz, NCH), 3.37 –3.54 (m, 2 H, NCH). Exact mass calcd for $C_8H_{13}NO$: *m/e* 139.0997. Found: *m/e* 139.1002.

Lactams **20** and **22** could not be separated by GLC (t_R = 7.0 min) but were identified by the following characteristic signals in the 300-MHz NMR spectrum of the mixture. Lactam **20**: NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, J= 7.4 Hz, 3 H, CH_3), 2.40 (ddd, J = 16.6, 9.4, 2.8 Hz, 1 H, COCH), 2.70 (td, J = 17, 9 Hz, 1 H, COCH), 3.05 (br t, J = 10.7 Hz, 1 H, NCH), 3.49 (td, J = 11.3, 7.6 Hz, 1 H, NCH), 4.00 (dt, J = 7.7, 5.5 Hz, 1 H, NCH). Lactam **22**: NMR ($CDCl_3$, 300 MHz) δ 4.12 (br d, J = 13.6 Hz, 1 H, equatorial NCH). Full spectral data for **20** and **22** are presented elsewhere (vide infra).

Heliotridane (23) and δ-Coniceine (24). To a mixture of 101 mg (2.66 mmol) of lithium aluminum hydride in 20 mL of dry ether under argon was added dropwise a solution of 98.6 mg (0.71 mmol) of the cyclized products **20a–22a** obtained from thiophenoxylactam **7a** in 2 mL of dry ether over a period of 10 min. The resulting mixture was heated to reflux for 6 h and cooled to room temperature. Water (0.3 mL) was added slowly followed by the addition of magnesium sulfate. After the solution was stirred for 20 min, the reaction mixture was filtered through magnesium sulfate. The solvent was removed by distillation first at atmospheric pressure and then at 160 mmHg to give 44.8 mg of a pale-yellow oil. This material was bulb-to-bulb distilled (oven temperature at 100 °C at 30 mmHg) to afford 28.2 mg (32%) of a mixture of (±)-δ-coniceine (**24**) and (±)-heliotridane (**23**) as a colorless liquid. This material was dissolved in 1.5 mL of absolute ethanol and treated with 18.5 mg (0.081 mmol) of picric acid. The resulting mixture was heated to give a clear solution and cooled slowly to room temperature. The resulting yellow crystals (12.5 mg) were collected: mp 235–242 °C, dec. A portion of this solid (11.5 mg) was further recrystallized from 1 mL of absolute ethanol to yield 6 mg of pure picrate of amine **23** as yellow crystals: mp 240–243 °C, dec (lit.[18] mp 248–250 °C, lit.[47] mp 243–244 °C). This material was identical with an authentic sample by virtue of its ^1H NMR, IR, and mixed melting point data: IR (CH_2Cl_2) 3100–2200 (br), 1610, 1320 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, J = 6.7 Hz, 3 H, CH_3), 1.60–1.81 (m, 2 H), 2.01–2.29 (m, 4 H), 2.64 (octet, J = 6.7 Hz, 1 H), 2.72–2.88 (m, 1 H), 3.12 (dd, J = 11.6, 7.3 Hz, 1 H), 3.70 (sextet, J = 6.2 Hz, 1 H), 3.90–4.08 (m, 1 H), 4.24–4.35 (m, 1 H), 8.89 (s, 2 H, ArH), 11.49 (br s, 1 H).

The mother liquor from the first recrystallization was concentrated in vacuo, dissolved in 1.5 mL of absolute ethanol, and treated with 34.4 mg of picric acid. The resulting mixture was heated to give a clear solution and cooled slowly to room temperature to yield 3 mg of the picrate of amine **24** as a yellow solid; mp 224–229 °C, dec (lit.[48] mp 227–231 °C, lit.[49] mp 224–228 °C). This material was identical with an authentic sample by virtue of its ^1H NMR, IR, and mixed melting

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point data: IR (CH_2Cl_2) 3100–2200 (br), 1615, 1320 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.40–2.35 (m, 10 H). Signals due to the major diastereomer: NMR ($CDCl_3$, 300 MHz) δ 2.59–2.84 (m, 3 H), 3.80–3.94 (m, 2 H), 8.89 (s, 2 H, ArH), 10.28 (br s, 1 H). Signals due to the minor isomer: NMR ($CDCl_3$, 300 MHz) δ 3.10–3.30 (m, 2 H), 3.39–3.50 (m, 1 H), 3.59–3.70 (m, 1 H), 8.89 (s, 2 H, ArH), 10.95 (br s, 1 H).

***rel*-(1*R*,7a*R*)-Hexahydro-1-methyl-1*H*-pyrrolizin-5-one (20) from Xanthate 25b.** To a solution of 87.1 mg (0.37 mmol) of xanthate **25b** in 4.7 mL of dry benzene heated at 80 °C under argon was added a solution of 0.15 mL (0.57 mmol) of tri-*n*-butyltin hydride and 3.8 mg (0.023 mmol) of AIBN in 3.3 mL of dry benzene over 2 h and 20 min. The resulting solution was stirred at 80 °C for another 70 min. The solvent was removed in vacuo, and the residue (235 mg) was chromatographed first over 6 g of silica gel (ethyl acetate) and then over a Lobar size A column (ethyl acetate) to give 32 mg (61%) of **20** as a colorless liquid. The 200-MHz ^1H NMR spectrum of this material compared favorably with that synthesized from the cyclization route and was free of **22**: IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, J = 7 Hz, 3 H, CH_3), 1.65–2.32 (m, 5 H, CH_2 manifold and CH), 2.40 (ddd, J = 17, 9.3 Hz, 1 H, COCH), 2.70 (td, J = 17, 9 Hz, 1 H, COCH), 3.05 (br t, J = 11 Hz, 1 H, NCH), 3.49 (td, J = 11, 8 Hz, 1 H, NCH), 4.00 (dt, J = 7.7, 5.5 Hz, 1 H, angular NCH). Exact mass calcd for $C_8H_{13}NO$: m/e 139.0997. Found: m/e 139.1002.

Hexahydro-2*H*-indolizin-3-one (22).[48] To a solution of 117 mg (0.48 mmol) of xanthates **26b** in 5.6 mL of benzene under reflux was added 209 mg (0.72 mmol) of tri-*n*-butyltin hydride and 5 mg (0.03 mmol) of AIBN in 4 mL of dry benzene over a 5.8-h period. After the solution was heated for another 1.5 h, the solvent was removed in vacuo to give 236 mg of a pale-yellow liquid. This material was chromatographed over 6 g of silica gel (ethyl acetate followed by ethyl acetate–methanol, 19:1) and again over a Lobar size A column (ethyl acetate) to yield 46 mg (69%) of **22** as a colorless liquid: NMR ($CDCl_3$, 300 MHz) δ 1.08–1.75 (m, 5 H), 1.81–1.95 (m, 2 H), 2.15–2.27 (m, 1 H), 2.33–2.41 (m, 2 H), 2.62 (dt, J = 12.7, 3.3 Hz, 1 H, axial NCH), 3.40 (dtd, J = 10.8, 7.2, 3.4 Hz, 1 H, angular NCH), 4.12 (br d, J = 13.6 Hz, 1 H, equatorial NCH). This material and the crude reaction mixture did not contain any **19**, **20**, or **21** by NMR or GC analysis.

***rel*-(1*R*,7a*R*)- and *rel*-(1*S*,7a*R*)-Hexahydro-1-(2-hydroxyprop-2-yl)-1*H*-pyrrolizin-5-one (31 and 32).** Crude carbinolamide **5d** (0.9 g, 5.3 mmol), prepared from **4d** as described above, was dissolved in 9.8 mL of formic acid, stirred at 0 °C for 5 min, and then stirred at room temperature for 45 min. The resulting solution was dissolved in 50 mL of dichloromethane and washed with 30 mL of water. The aqueous phase was extracted with 50 mL of dichloromethane. The combined organic layers were washed with 50 mL of saturated sodium bicarbonate solution. The base wash was extracted with 50 mL of dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to afford 1.04 g of a pale-yellow oil. The oil was mixed with a 0.89 N solution of sodium hydroxide in aqueous methanol (H_2O–MeOH, 1:5) and stirred at room temperature for 30 min. The resulting mixture was diluted with 200 mL of dichloromethane, dried ($MgSO_4$), and concentrated in vacuo to give 0.977 g of a pale-yellow oil. The oil was chromatographed over a Lobar size B column (5% methanol in ethyl acetate) to yield 418 mg (48%) of the less polar **31** as a white solid: mp 110.5–111.5 °C; IR (CH_2Cl_2) 3600, 3400 (br), 1680 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.28 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.70–2.62 (m, 8 H, CH_2 manifold and OH), 2.86 (dt, J = 11, 6 Hz, 1 H, NCH), 3.88 (ddd, J = 11, 7, 2 Hz, 1 H, NCH), 4.08 (dt, J = 9, 5.5 Hz, 1 H, angular NCH). Exact mass calcd for $C_{10}H_{17}NO_2$: m/e 183.1259. Found: m/e 183.1264.

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35. Found: C, 65.56; H, 9.49.

Continued elution gave 297 mg (34%) of **32** as a white solid: mp 55–58 °C; IR (CCl_4) 3400 (br), 1670 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.67–1.91 (m, 2 H), 1.96 (br, s, 1 H, OH), 2.01–2.25 (m, 2 H), 2.26–2.40 (m, 1 H), 2.48 (ddd, J = 16, 9, 2 Hz, 1 H, COCH), 2.75 (td, J = 16, 9 Hz, 1 H, COCH), 3.15 (br *t*, J = 11 Hz, 1 H, NCH), 3.57 (td, J = 11, 8 Hz, 1 H, NCH), 3.94 (q, J = 6 Hz, 1 H, angular NCH). Exact mass calcd for $C_{10}H_{17}NO_2$: m/e 183.1259. Found: m/e 183.1264.

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35. Found: C, 65.20; H, 9.51.

1-(2,3-Butadienyl)-2,5-pyrrolidinedione (43). To an ice–water bath cooled mixture of 0.989 g (14.1 mmol) of 2,3-butadien-1-ol,[50] 1.54 g (15.5 mmol) of succinimide, and 4.08 g (15.6 mmol) of triphenylphosphine in 19 mL of dry tetrahydrofuran was added dropwise under argon a solution of 2.71 g (15.6 mmol) of diethyl azodicarboxylate in 6 mL of dry tetrahydrofuran over a period of 50 min. The resulting solution was stirred at room temperature for 1.5 h. The solvent was removed in vacuo, and the residue was triturated with 40 mL of ethyl acetate–hexane (3:7) and filtered. The filtrate was concentrated in vacuo to afford 5.41 g of a yellow oil which was chromatographed over 55 g of silica gel (dichloromethane) to give 2.01 g (99%) of imide **43** as a yellow oil: IR (CCl_4) 1960, 1780, 1710 cm^{-1}; NMR (CCl_4) δ 2.60 (s, 4 H, $COCH_2$), 3.93 (td, J = 6, 3 Hz, 2 H, NCH_2), 4.60–4.87 (m, 2 H, $=CH_2$), 5.07 (qu, J = 6 Hz, 1 H, =CH). Exact mass calcd for $C_8H_9NO_2$: m/e 151.0633. Found: m/e 151.0633.

1-(2,3-Butadienyl)-5-(phenylseleno)-2-pyrrolidinone (47). To a solution of 9.73 g (64.4 mmol) of imide **43** in 150 mL of absolute ethanol cooled in an ice–water bath under argon was added 6.45 g (170 mmol) of sodium borohydride. A 1.49 N solution of hydrogen chloride in absolute ethanol was added at a rate of 5 drops every 5 min over 2 h. The resulting mixture was stirred at 0 °C for another 20 min and partitioned between 75 mL of water, 75 mL of saturated sodium chloride solution, and 200 mL of dichloromethane. The aqueous layer was extracted with three 150-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 9.47 g of crude carbinollactam as a pale-yellow oil. The oil was stirred with 152 mg (0.80 mmol) of *p*-toluenesulfonic acid monohydrate and 6.55 mL (62.0 mmol) of selenophenol under argon at room temperature for 3 h and chromatographed directly over 250 g of silica gel (ethyl acetate–hexane, 2:8, followed by ethyl acetate–hexane, 4:6) to yield 15.5 g (82%) of selenophenoxylactam **47** as a yellow oil: IR (CCl_4) 1950, 1700 cm^{-1}; NMR (CCl_4) δ 1.20–2.90 (m, 4 H, $COCH_2CH_2$), 3.30–3.82 (m, 1 H, NCH), 4.10–5.20 (m, 5 H, CH_2=C=CH, NCH, and SeCHN), 7.05–7.50 (m, 5 H, ArH); mass spectrum, m/e (rel intensity) 170 (9), 158 (20), 152 (25), 136 (M^+ – SePh, 86), 126 (19), 114 (19), 96 (51), 84 (86), 78 (59), 68 (89), 55 (63), 41 (100).

5,6,7,7a-Tetrahydro-1-methyl-3*H*-pyrrolizin-5-one (50) and Hexahydro-1-methylene-1*H*-pyrrolizin-5-one (51). To a solution of 15.5 g (53.1 mmol) of selenophenoxylactam **47** in 800 mL of dry benzene heated to reflux under argon was added a solution of 21.0 mL (79.6 mmol) of tri-*n*-butyltin hydride and 307 mg (1.87 mmol) of AIBN in 200 mL of dry benzene over a period of 15 h. The solvent was removed in vacuo, and the residue was dissolved in 200 mL of hexane and extracted with four 50-mL portions of acetonitrile. The combined acetonitrile layers were concentrated in vacuo and distilled to yield 5.04 g of **50** and **51** as a pale-yellow liquid (bp 87 °C at 1.65 mmHg). The distillate was first chromatographed over 60 g of silica gel (ethyl acetate–hexane, 7:3, followed by ethyl acetate) and then over a Lobar size C column (ethyl acetate–hexane, 9:1), and the overlapping portions were chromatographed again over Lobar size C column (ethyl acetate–hexane, 65:35, followed by ethyl acetate–hexane, 7:3) to yield a total of 3.67 g (52%) of the less polar **50** as a colorless liquid: IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 1.60–1.83 (m, 3 H, CH_3), 1.83–2.90 (m, 4 H, $COCH_2CH_2$), 3.20–3.80 (m, 1 H, NCH), 3.95–4.55 (m, 2 H, NCH), 5.29 (br s, 1 H, =CH). Exact mass calcd for $C_8H_{11}NO$: m/e 137.0841. Found: m/e 137.0807 and 1.04 g (14%) of **51** as a colorless liquid: IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 1.30–3.50 (m, 7 H, CH_2 manifold and NCH), 3.78 (td, J = 10, 5 Hz, 1 H, NCH), 4.17 (br t, J = 6 Hz, 1 H, NCH), 4.72–4.98 (a six line AB multiplet, 2 H, $=CH_2$). Exact mass calcd for $C_8H_{11}NO$: m/e 137.0841. Found: m/e 137.0844.

1-(Acetoxymethyl)-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-5-one (53) from Olefin 50. To a solution of 72 mg (0.53 mmol) of **50** in 1.0 mL of acetic acid–acetic anhydride (1:1) was added 31 mg (0.28 mmol) of freshly sublimed selenium dioxide. The resulting mixture was stirred at 90 °C for 19.5 h and partitioned between 30 mL of dichloromethane and 10 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three 10-mL portions of dichloromethane. The combined dichloromethane layers were dried ($MgSO_4$), filtered through celite, and concentrated in vacuo. The resulting black residue was bulb-to-bulb distilled to afford 38 mg of a colorless liquid which was a 29:8 mixture by weight of **50** and **53**, respectively, by ^1H NMR (bp 95–100 °C at 0.6 mm). The residue was chromatographed over 7 g of silica gel (ethyl acetate) to give an additional 14 mg of **53** as a pale-yellow oil: IR (CH_2Cl_2) 1740, 1695 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.81–2.01 (m, 1 H), 2.09 (s, 3 H, CH_3), 2.26–2.50 (m, 2 H), 2.60–2.82 (m, 1 H, COCH), 3.72 (br d, J = 16 Hz, 1 H, NCH), 4.42 (br d, J = 16 Hz, 1 H, NCH), 4.65 (m, 1 H, NCH), 4.70 (br s, 2 H, OCH_2), 5.81 (br s, 1 H, =CH); mass spectrum m/e (rel intensity) 195 (7), 178 (5), 149 (8), 136 (34), 135 (100), 134 (71), 122 (30), 106 (28), 97 (25), 80 (75), 55 (62).

1-(Acetoxymethyl)-4,5,6,7a-tetrahydro-3*H*-pyrrolizin-5-one (53) from Olefin 51. To a suspension of 225 mg (1.02 mmol) of silver trifluoroacetate in 3 mL of tetrahydrofuran was added at room temperature 168 mg (0.877 mmol) of phenylselenyl chloride in 1.5 mL of tetrahydrofuran. The resulting yellow suspension was stirred at room temperature for 10

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min followed by dropwise addition of 100 mg (0.729 mmol) of alkene **51** at −10 °C. The resulting mixture was stirred at room temperature for 2 h and centrifuged. The supernatant was removed, and the residue was rinsed with two 5-mL portions of ether. The combined supernatants were concentrated in vacuo to give 340 mg of a mixture of trifluoroacetoxy selenides as a red oil. The oil was dissolved in 6 mL of methanol–water (3:1), and 123 mg (1.46 mmol) of sodium bicarbonate was added to the resulting suspension. The suspension was stirred at room temperature for 2 h and diluted with 20 mL of water. The resulting turbid solution was extracted with five 10-mL portions of methylene chloride. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give 253 mg of a mixture of hydroxy selenides as an oil. To the hydroxy selenides in 2 mL of tetrahydrofuran was added dropwise 0.30 mL (2.9 mmol) of 30% hydrogen peroxide with cooling in an ice–water bath. The resulting solution was stirred for 10 min in an ice–water bath and for 2.5 h at room temperature and concentrated in vacuo. The residue chromatographed over 20 g of silica gel (methanol–ethyl acetate, 1:2) to afford 46 mg of allylic alcohol **52** as an oil: NMR ($CDCl_3$) δ 1.75–3.04 (m, 5 H), 3.80 (broad s, 1 H, NCH_2), 4.29 (t, 2 H, J = 2 Hz, CH_2O), 4.48 (m, 1 H, NCH), 4.80 (m, 1 H, NCH), 5.77 (broad s, 1 H, =CH). The allylic alcohol was dissolved in 1 mL of dichloromethane, and 66 mg (0.65 mmol) of acetic anhydride, 44 mg (0.43 mmol) of triethylamine, and a catalytic amount of 4-(dimethylamino)pyridine were added. The resulting solution was stirred at room temperature for 30 min, diluted to 10 mL with dichloromethane, and washed with two 5-mL portions of water and 5 mL of saturated sodium bicarbonate solution. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give 57 mg (41%) of allylic acetate **53** as an oil, identical with the material prepared from **50**.

(±)-Supinidine (1). A mixture of 75 mg (0.38 mmol) of acetate **53** and 75 mg (1.84 mmol) of lithium aluminum hydride was warmed under reflux for 30 min. To the resulting solution was sequentially added 70 μL of water, 70 μL of 3 N aqueous sodium hydroxide, and 100 μL of water. The mixture was filtered, and the filtrate was dried ($MgSO_4$) and concentrated in vacuo to give 49 mg (93%) of supinidine as a pale-yellow oil: mp (picrate) 124.5–125 °C (lit.[51] 124–126 °C); IR (CH_2Cl_2) 3300 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 2.45–2.61 (m, 1 H), 2.69–2.81 (m, 2 H, CH_2), 2.89–3.06 (m, 1 H), 2.54 (td, J = 10, 6.5 Hz, 1 H, CHN), 3.08 (td, J = 10, 6.5 Hz, 1 H, CHN), 3.31 (br d with fine coupling, J = 15 Hz, 1 H, NCHC=), 3.88 (m with two br d's at 3.88 and 4.16, J = 15, 7 Hz, 5 H, OH, NCH, NCHC=, and OCH_2), 5.48 (br, d, J = 1.6 Hz, 1 H, =CH). Exact mass calcd for $C_8H_{13}NO$: m/e 139.0997. Found: m/e 139.1002.

***rel*-(1*S*,2*R*,7a*S*)-2-Acetoxy-1-hydroxy-1-methylhexahydro-1*H*-pyrrolizin-5-one (55).** To a solution of 1.50 g (10.9 mmol) of olefin **50** in 3 mL of acetone, 7.5 mL of water, and 1.5 mL of *tert*-butyl alcohol was added 94 mg (0.37 mmol) of osmium tetroxide followed by 1.57 g of trimethylamine oxide dihydrate. the resulting black solution was stirred at 70 °C for 25 min, and another 208 mg (16.0 mmol total) of the *N*-oxide was added. The mixture was warmed for another 35 min, cooled to room temperature, diluted with dichloromethane, saturated with sodium chloride, stirred with magnesium sulfate for 2.5 h, and filtered. The filtrate was concentrated in vacuo. The residual brownish solid (2.14 g) was stirred with 12 mL of dichloromethane, 4.78 mL of triethylamine, and 3.09 mL of acetic anhydride at room temperature for 1.5 h and directly chromatographed over 100 g of silica gel (ethyl acetate–hexane, 9:1) to give a brown oil. The oil was crystallized from ethyl acetate–hexane (40:120 mL) to give 1.95 g (83%) of hydroxy acetate **55** as white needles: mp 132–133 °C; IR (KBr) 3300, 1750, 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (s, 3 H, CH_3), 1.80–2.70 (m, with s at 2.13, 8 H, CH_3, OH, and CH_2 manifold), 3.30–3.75 (m, 3 H, NCH_2 and NCH), 5.07 (t, J = 7 Hz, 1 H, OCH). Exact mass calcd for $C_{10}H_{15}NO_4$: m/e 213.1001. Found: m/e 213.1038.

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09. Found: C, 56.43; H, 7.02.

***rel*-(2*S*,7a*S*)-2-Acetoxy-1-methylindenehexahydro-1*H*-pyrrolizin-5-one (56).** To a solution of 1.84 g (8.64 mmol) of hydroxy acetate **55** in 18 mL of dichloromethane was added a solution of 7.75 g (11.85 mmol) of Martin's sulfurane[37] in 18 mL of dichloromethane via syringe over a 5-min period. The solution was stirred at room temperature for 2.5 h and chromatographed directly over 80 g of silica gel (ethyl acetate followed by ethyl acetate–methanol, 95:5) to give 1.17 g (70%) of **56** as a pale-yellow oil: IR (CCl_4) 1750, 1715 cm^{-1}; NMR (CCl_4) δ 1.50–2.70 (m with s at 1.99, 7 H, CH_3 and CH_2), 3.10 (dd, J = 14, 5 Hz, 1 H, NCH), 3.86 (br d, J = 14 Hz, 1 H, NCH), 4.32 (br t, J = 6 Hz, 1 H, NCH), 5.10–5.55 (m, 3 H, OCH and $=CH_2$); mass spectrum, m/e (rel intensity) 196 (M^+ + 1, 1), 153 (18), 152 (23), 136 (77), 135 (M^+ − AcOH, 100), 134 (68), 125 (11), 124 (14), 110 (18), 106 (11), 98 (87), 80 (70), 67 (23), 55 (33). Later fractions gave 130 mg (8%) of recovered **55** (mp 125–128 °C).

***rel*-(2*S*,7a*S*)-1-Methylidenehexahydro-1*H*-pyrrolizin-5-on-2-yl Methanesulfonate (58).** To 101 mg (0.52 mmol) of acetate **56** was added 0.8 mL of a 1 N solution of sodium hydroxide in water–methanol (1:5). The solution was stirred at room temperature for 10 min and poured into 200 mL of dichloromethane. The resulting mixture was saturated with sodium chloride, dried with $MgSO_4$ for 2 h, filtered, and concentrated in vacuo.

To the residual oil (76 mg) and 80 μL (0.57 mmol) of triethylamine in 0.6 mL of dichloromethane cooled in an ice–water bath was added a solution of 67 mg (0.59 mmol) of methanesulfonyl chloride in 0.6 mL of dichloromethane over a 2-min period. The resulting solution was stirred at 0 °C for 10 min and at room temperature for 1.5 h followed by the addition of another 80-μL portion of triethylamine. The resulting mixture was stirred for 1.5 h and chromatographed directly over 14 g of silica gel (ethyl acetate–methanol, 9:1) to give 106 mg (89%) of mesylate **58** as a white solid: mp 92–93 °C; IR (CH_2Cl_2) 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.70–2.87 (m, 4 H, CH_2 manifold), 3.03 (s, 3 H, CH_3), 3.27 (dd, J = 14, 4 Hz, 1 H, NCH), 4.10–4.60 (br d, J = 14 Hz at 4.21 with overlapping br t, J = 7 Hz, at 4.41, 2 H, NCH and NCH), 5.40–5.85 (m, 3 H, CHOMs and $=CH_2$). Exact mass calcd for $C_9H_{13}NO_4S$: m/e 231.0565. Found: m/e 231.0619.

Acetolysis of Mesylate 58. A solution of 83 mg (0.38 mmol) of mesylate **58** in 1.0 mL of acetic acid was warmed at 90 °C for 5.5 h. The resulting dark brown solution was concentrated in vacuo, and the residue was chromatographed over 7 g of silica gel (ethyl acetate–methanol, 9:1) to give 76 mg of a mixture of products. Further chromatography over a Lobar size A column (ethyl acetate–hexane, 4:1) gave 12 mg (16%) of the C(2) isomer of **56** as a colorless oil: IR (CCl_4) 1740, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.50–3.13 (m with s at 2.04, 8 H, NCH, CH_3, and $COCH_2CH_2$), 4.17 (dd, J = 12, 7 Hz, NCH), 4.43 (br t, J = 6 Hz, 1 H, NCH), 5.00–5.35 (m, 2 H, $=CH_2$), 5.53 (br t, J = 6 Hz, 1 H, CHOAc). Continued elution gave 35 mg of a 40:7 mixture of **53** and **56**, respectively, by NMR integration.

***S*-(5,6,7,7a-Tetrahydro-3*H*-pyrrolizin-5-on-1-yl)methyl *S*-Methyl Dithiocarbonate (59).** A mixture of 146.5 mg (0.75 mmol) of allylic acetate **56** and 1.2 mL of 1 N sodium hydroxide in methanol–water (5:1) was stirred at room temperature for 10 min. The resulting solution was diluted with 120 mL of dichloromethane, saturated with sodium chloride, stirred over magnesium sulfate for 1 h, filtered, and concentrated in vacuo. The residue (112 mg) was stirred with 3.1 mg (0.046 mmol) of imidazole and 73.7 mg (3.07 mmol) of sodium hydride in 3.3 mL of tetrahydrofuran at 60 °C for 30 min. To the mixture was added 0.3 mL (5.0 mmol) of carbon disulfide. The mixture was warmed at 60 °C for 5 min, and 0.3 mL of iodomethane (4.82 mmol) was added. The mixture was warmed for 5 min, poured into 5 mL of water, and extracted with three 25-mL portions of dichloromethane. The extracts were dried ($MgSO_4$) and concentrated in vacuo. The residual orange oil was chromatographed over 9 g of silica gel (ethyl acetate–hexane, 3:1, followed by ethyl acetate) to give 142 mg (77%) of **59** as a yellow oil: IR (CCl_4) 1705, 1650 cm^{-1}; NMR (CCl_4) δ 1.60–2.70 (m with s at 2.41, 7 H, SCH_3 and CH_2 manifold), 3.30–3.80 (m with br s at 3.68, 3 H, NCH and SCH_2), 4.05–4.80 (m, 2 H, NCH), 5.70 (br s, 1 H, $=CH_2$); mass spectrum, m/e (rel intensity) 168 (M^+ − $COSCH_3$, 2), 137 (13), 136 (M^+ − $SCOSCH_3$, 100), 135 (40), 122 (21), 106 (10), 80 (59), 55 (44).

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Registry No. (±)-**1**, 23185-51-5; **3d**, 763-89-3; **4a**, 58805-10-0; **4b**, 58805-11-1; **4c**, 92721-22-7; **4d**, 92721-23-8; **4e**, 58804-92-5; (±)-**5d**, 92721-62-5; (±)-**7a**, 80664-38-6; (±)-**7a** (X = OEt), 80664-37-5; (±)-**7b**, 80664-43-3; (±)-**7c**, 80664-44-4; (±)-**7d**, 92721-24-9; (±)-**7e**, 80664-42-2; **10**, 92721-25-0; (±)-**10** (hydroxy lactam), 92721-63-6; (±)-**12**, 92721-26-1; (±)-**13**, 92721-27-2; (±)-**14**, 92721-28-3; (±)-**15**, 92721-29-4; (±)-**16**, 92721-30-7; (±)-**17**, 92721-31-8; (±)-**18**, 92721-32-9; **19**, 52132-72-6; (±)-**20**, 80664-40-0; (±)-**21**, 80664-41-1; (±)-**21**, 71779-55-0; (±)-**23**, 17463-81-9; (±)-**24**, 62279-67-8; (±)-**25a**, 92721-64-7; (±)-**25b**, 92721-33-0; (±)-**26a**, 92721-65-8; (±)-**26b**, 92721-34-1; **27b**, 80664-46-6; **27c**, 80664-47-7; **27d**, 92721-35-2; **27e**, 80664-45-5; (±)-**28b**, 80664-49-9; (±)-**28d**, 92721-36-3; (±)-**28e**, 92721-38-5; (±)-**29b**, 80664-48-8; (±)-**29d**, 92721-37-4; (±)-**30b**, 80664-59-1; (±)-**30c**,

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80664-52-4; (±)-*cis*-**30e**, 80664-51-3; (±)-*trans*-**30e**, 80664-50-2; (±)-**31**, 92721-39-6; (±)-**32**, 92721-40-9; **33**, 2555-14-8; (±)-**34**, 92721-41-0; **35**, 2687-97-0; (±)-**36**, 92721-42-1; (±)-**36** (X = CH_3, OH), 92721-43-2; (±)-**37**, 92721-44-3; **38**, 92721-45-4; (±)-**39**, 80664-60-4; **40**, 80664-61-5; (±)-**41**, 92721-46-5; **43**, 92721-47-6; (±)-**43** (hydroxy lactam), 92721-59-0; (±)-**44**, 92721-48-7; (±)-**45**, 92721-49-8; (±)-**46**, 92721-50-1; (±)-**47**, 92762-55-5; **48**, 92721-51-2; (±)-$\Delta^{7,8}$-**49**, 92721-52-3; (±)-**50**, 92721-53-4; (±)-**51**, 92721-54-5; (±)-**52**, 92721-60-3; (±)-**53**, 83004-66-4; (±)-**55**, 92721-55-6; (±)-**56**, 92721-56-7; (±)-**57**, 92721-61-4; (±)-**58**, 92721-57-8; (±)-**59**, 92721-58-9; PhSH, 108-98-5; PhSeH, 645-96-5; 2,4-$(NO_2)_2C_6H_3F$, 70-34-8; CH_2=C=$CHCH_2OH$, 18913-31-0; PhSeCl, 5707-04-0; CH_2=$CHCH$=$CH(CH_2)_2OH$, 5747-07-9; succinimide, 123-56-8; 1-(3-pentynyl)-2,5-pyrrolidinedione, 63838-13-1.

Supplementary Material Available: Experimental procedures for the preparation of **4c**, **7b–e**, **10–14**, **25b**, **26b**, **27b–e**, **28b–e**, **29b–e**, **30b–e**, **34–41**, **44–46**, **48**, and **49** (17 pages). Ordering information is given on any current masthead page.

α-Acylamino Radical Cyclizations: Syntheses of Isoretronecanol

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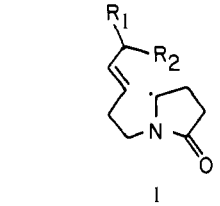
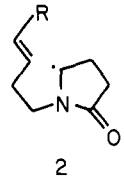
Abstract: α-Acylamino radicals **1–3** can be generated by tri-*n*-butyltin radical mediated cleavage of a carbon–sulfur bond. These radicals cyclize with good regio- and stereoselectivity to afford pyrrolizidinones. Cyclization products **12a** and **23a** were converted to the alkaloid isoretronecanol (**4**).

In the preceding paper in this issue we reported a new entry to pyrrolizidinones and indolizidinones by the cyclization of *N*-acyl-2-aza-5-hexenyl radicals.[4] Our initial studies showed that by placing methyl groups appropriately on the double bond, one could direct the regiochemical course of cyclization toward either pyrrolizidinone or indolizidinone formation. In subsequent studies, with an eye on using this methodology in pyrrolizidine alkaloid synthesis, we have focused on olefin substitution patterns which permit the introduction of the C(1)-hydroxymethyl group which appears in many of these natural products.[5] Specifically, this article describes the behavior of α-acylamino radicals **1–3** within the context of syntheses of the pyrrolizidine base isoretronecanol (**4**). For the sake of clarity, the synthesis and properties of radicals **1–3** will be discussed individually.



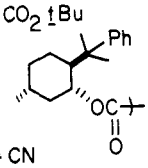
1

a R_1 = Me, R_2 = OAc
b R_1 = H, R_2 = OAc
c R_1 = R_2 = H

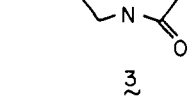


2

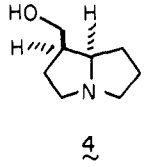
a R = CO_2 t-Bu
b R =



c R = CN

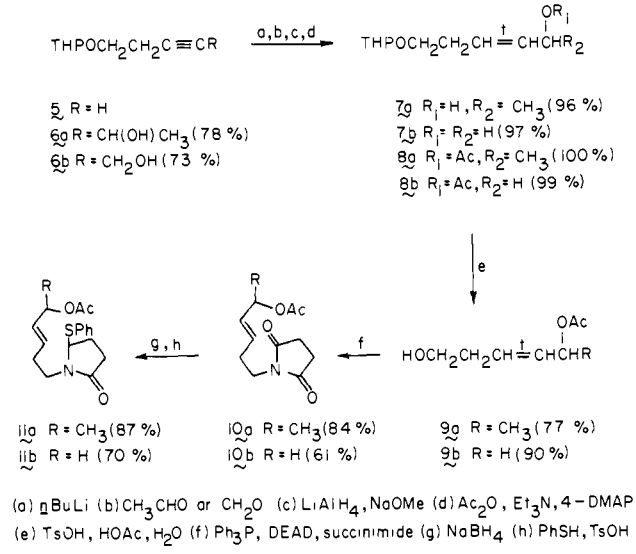


3



4

Scheme I



Results and Discussion

Generation and Cyclization of 1. The precursors of radicals **1a,b** were prepared in a straightforward manner as outlined in Scheme I. Sequential treatment of terminal acetylene **5**[6] with *n*-butyllithium and acetaldehyde gave alcohol **6a** (78%) which was reduced with lithium aluminum hydride–sodium methoxide to give trans allylic alcohol **7a** (96%).[7] The alcohol was acetylated by using the Steglich procedure,[8] and the resulting acetate **8a** (100%) was converted to alcohol **9a** upon treatment with aqueous acetic acid in tetrahydrofuran (77%). Coupling of **9a** with succiminide using the Mitsunobu procedure[9] gave imide **10a** (84%) which was converted to radical precursor **11a** by sequential reduction with sodium borohydride[10] and hydroxy–thiophenoxy exchange (87%).[4] Lactam **11b**, the precursor of **1b**, was prepared by using a similar

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(2) McPherson-Evans Scholar, 1981–1982.
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