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FREE RADICAL CYCLIZATIONS IN ALKALOID SYNTHESIS: (+)-HELIOTRIDINE AND (+)-HASTANECINE

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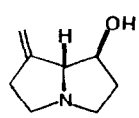
Summary: Treatment of phenylthiolactams **5a-5f** with tri-n-butyltin hydride and AIBN affords mixtures of reduction and cyclization products. Cyclization products partition between indolizidinones and pyrrolizidinones depending on the terminal alkyne substituent. When the terminal substituent is a trimethylsilyl group, synthetically useful yields of pyrrolizidinones are obtained. Applications of this chemistry to the synthesis of (+)-heliotridine (**2**) and (+)-hastanecine (**3**) via the key intermediates **37** and **38** are described.

The pyrrolizidine alkaloids have attracted the attention of synthetic organic chemists for several decades.[1,2] This interest has in part been due to the potentially useful biological properties of several members of this family of natural products.[3] A more likely reason for the widespread interest in pyrrolizidine alkaloids, however, is that their deceptively simple structures provide a testing ground for procedures which may be of general interest in the area of alkaloid synthesis. We recently reported a new route to the pyrrolizidine nucleus via the intramolecular addition of α-acylamino radicals to alkynes.[4] This article presents the details of these studies and describes the application of this chemistry to the enantioselective synthesis of the (-)-dehydrohastanecine (**1**),[5] (+)-heliotridine (**2**)[6] and (+)-hastanecine (**3**).[7]



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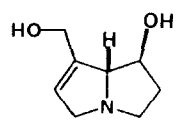

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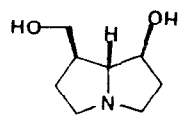

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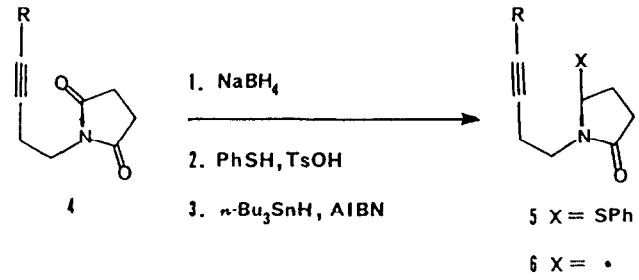
Results and Discussion

Preliminary Studies: Pyrrolizidinone vs. Indolizidinone Formation. We began our studies by examining radicals **6a-6f**. These were generated from phenylthiolactams **5a-5f** which were prepared from imides **4a-4f** as outlined in Table I. The required imides were prepared by Mitsunobu coupling[8] of succinimide with the appropriate homopropargylic alcohols. For the sake of clarity, the behavior of radicals **6a-6f** will be discussed individually.

Treatment of **5a** with tri-n-butyltin hydride and AIBN gave **7** (61%) and **8** (27%) as shown in Scheme I. It was surprising to find that **8** was the only cyclization product since all 5-hexynyl radical cyclizations reported previously had afforded only alkylidene cyclopentanes.[9] To confirm our structure assignment, **8** was converted to a separable mixture of the known indolizidinones **9** and **10** upon hydrogenation over palladium on charcoal.[10]

The Eleaocarpus alkaloids are a large family of natural products which structually resemble **8**.[11] To see if this reaction would provide an entry to these alkaloids, we next examined radical **5b**. The results of this study are shown in Scheme II. Once again we were surprised to find that pyrrolizidinone **11**, formed as a separable 1.7:1 mixture of geometrical isomers, was the sole

TABLE I



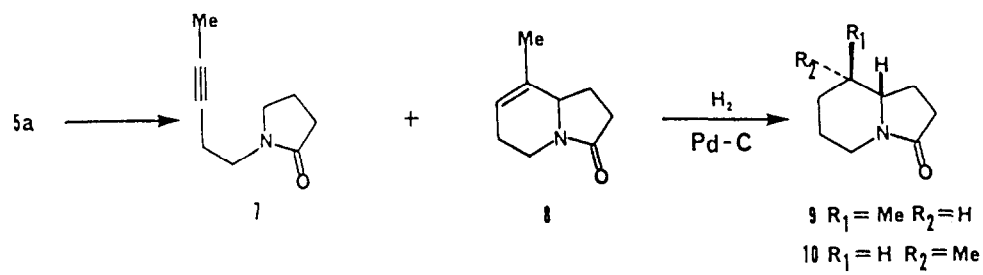
a R=H b R=$SiMe_3$ c R=t-Bu d R=$C(CH_3)_2OMe$

e R=i-Pr f R=n-Pr

Entry	R	%4	%5
1	Me	85	76
2	Me_3Si	84	83
3	tBu	87	34
4	$C(Me)_2OMe$	84	94
5	iPr	88	85
6	nPr	91	77

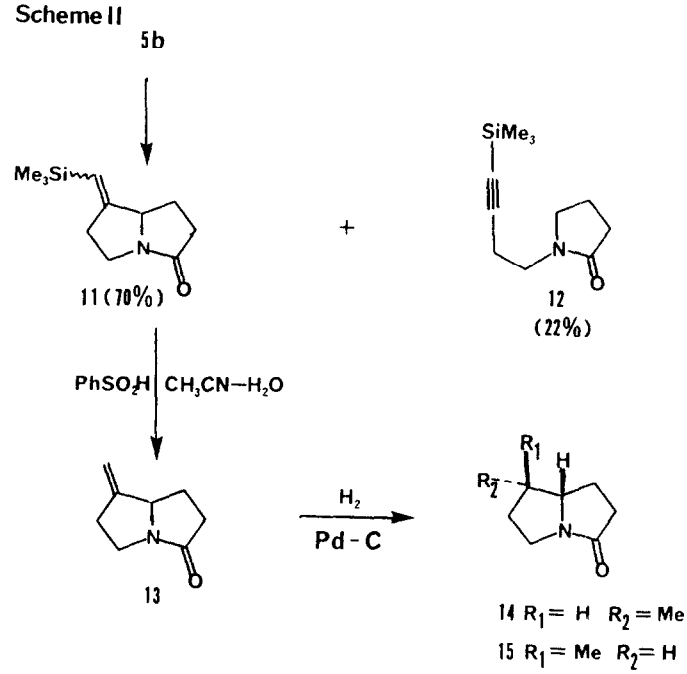
cyclization product. The structure of **11** was proven by conversion to a separable mixture of the known pyrrolizidinones **14** and **15** by sequential protodesilylation and hydrogenation of the resulting olefin **13**.[12] Therefore, the effects of changing the terminal alkyne substituent from a methyl (**6a**) to a trimethylsilyl (**6b**) group were two-fold. First, the regiochemical course of the cyclization was changed from that of an endo (**6a**) to an exo (**6b**) process. Second, the cyclization-reduction ratio became preparatively valuable.

Scheme I

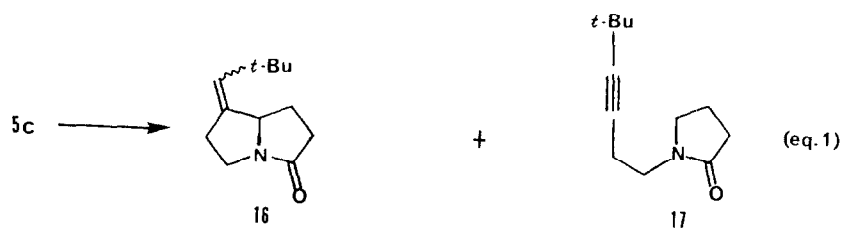


Although the effect of moving from terminal methyl to trimethylsilyl substitution was dramatic, the experiments shown in Eq. 1 reveal that similar changes are observed with terminal t-butyl substitution. Thus, treatment of **5c** with tri-n-butyltin hydride and AIBN gave pyrrolizidinone **16** (49%) as a 2.2:1 mixture of geometrical isomers along with reduction product **17** (35%).[13] Although the structure of **16** was not proven rigorously, a comparison of spectral data with those of **8** and **11** supported the structural assignment. For example, the vinylic proton in **8** appeared as a broad doublet (J=4.5 Hz) and the vinylic protons of both isomers of **11** and **16** appeared as quartets (J=2-2.5 Hz).

Scheme II

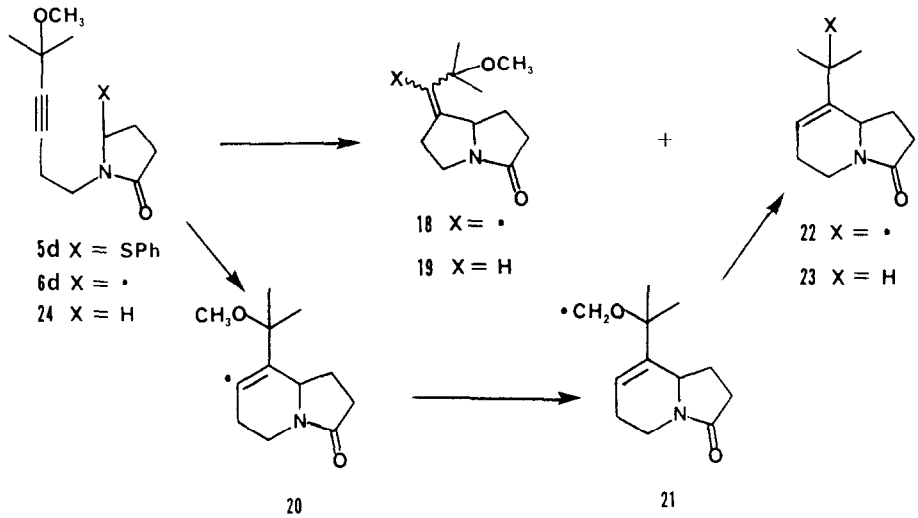


In addition to terminal trimethylsilyl (**6b**) and t-butyl (**6c**) groups, one other bulky substituent was examined. Thus, generation of **6d** from **5d** gave an 89% yield of lactams **19**, **23**, and **24** in a 23:4:62 ratio, respectively (Scheme III).[14] All of the structure assignments were based on spectral data and additional support for structure **23** was obtained by an independent synthesis (vide infra). Once again, the major pathway involved exo cyclization of **6d** to afford pyrrolizidinone **19** as a 1:4:1 mixture of geometrical isomers. In this case, however, a small amount of endo cyclization was detected. We imagine that indolizidinone **23** was formed by cyclization of **6d** to vinyl radical **20** followed by sequential hydrogen atom transfer (**20** → **21**), fragmentation (**21** → **22**), and trapping of the resulting allylic radical (**23**) with tri-n-butyltin hydride.

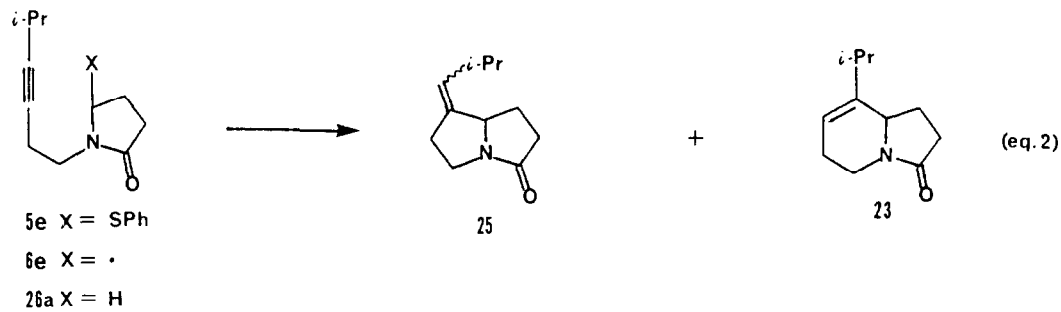


The substituent studies described above suggested that steric effects played a major role in determining the regiochemical course of these radical cyclizations. Therefore two systems which fall between the extremes represented by **6a** and **6b-6d** were examined. The results of these studies are shown in Eq. 2 and 3. Consistent with the view that steric effects were important, radicals **6e** and **6f** gave mixture of cyclization products upon treatment with tri-n-butyltin hydride and AIBN. Thus, **6e** gave a 73% yield of **26a**, **25** and **23** in a 33:26:14 ratio, respectively.[15] Phenylthiolactam **5f** gave a 93% yield of **26d-29** in a 59:19:11:4 ratio, respectively.[16] The formation of enamide **29** from **5f** can be rationalized by the sequence of events outlined in Eq. 4. This mechanism is

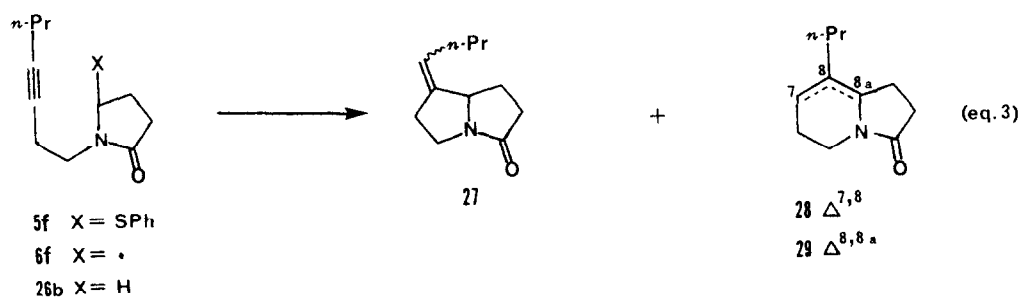
Scheme III

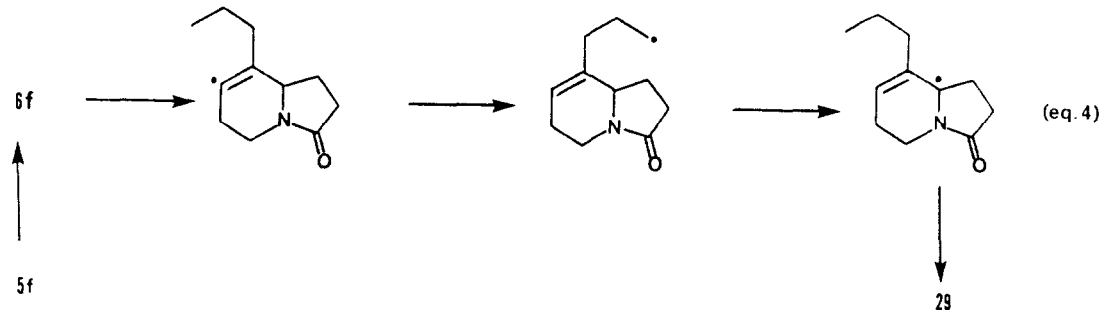


consistent with the formation of **23** from **5d** and explains the absence of enamide formation in the endo cyclizations of **5a** and **5e**.



In summary, radicals of type **6** cyclize to form indolizidinones and pyrrolizidinones. The regiochemical course of the cyclizations depend on the nature of the terminal acetylene substituent. It is clear that the larger the substituent, the more pyrrolizidinone formation is observed. Thus steric effects appear to play an important role in the partitioning process. It is noted, however, that the formation of <u>any</u> endo cyclization product (indolizidinone) is unusual in a 5-hexynyl radical cyclization. Perhaps geometrical factors due to the insertion of an sp^2-hybridized nitrogen atom in the chain linking the radical and unsaturated moieties are responsible for the unusual partitioning observed here. Finally, a lack of information regarding reversibility of these cyclizations renders further mechanistic interpretations speculative at best.



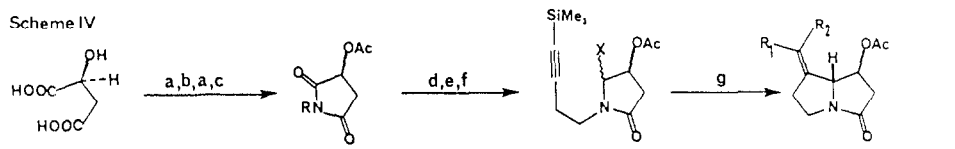


(eq. 4)

From the standpoint of organic synthesis, the reactions described above are plagued by competitive reduction of the initially formed free radical. It is possible that the use of cyclization media free of hydrogen atom donors will remove this problem. The following studies, however, will focus on the cyclization of terminal trimethylsilyl acetylenes as the preliminary studies showed that they had some synthetic potential.[17]

Synthesis of Pyrrolizidine Alkaloids. Earlier studies in these[6b,7b] and other[6c] laboratories had shown that malic acid (**30**) was an excellent starting material for enantioselective syntheses of pyrrolizidine alkaloids via routes involving C(1)-C(8) bond construction. Therefore we began by modifying our preliminary studies (Scheme II) as shown in Scheme IV. Sequential treatment of (S)-malic acid with acetyl chloride, ammonia, and acetyl chloride gave crystalline imide **31** in a 50% overall yield. Mitsunobu coupling of **31** with 4-trimethylsilyl-3-butyn-1-ol[16] afforded imide **32** (97%). Regioselective reduction of **32** with sodium borohydride in methanol at -30°C gave a 59% yield of carbinol amide **33**. Only a small amount of the regioisomeric carbinol amide was obtained. Acetylation of **33** followed by acetoxy-thiophenoxy exchange proceeded smoothly to afford radical precursor **35** (98%). Treatment of **35** with tri-n-butyltin hydride and AIBN in benzene using high dilution conditions gave reduction product **36** (18%) and geometrical isomers **38** (56%) and **37** (15%) after separation by column chromatography over silica gel. Therefore the cyclization proceeded with excellent diastereoselectivity at C(8) as only 3-5% of materials suspected to be diastereomeric at that center were isolated.

Scheme IV



30

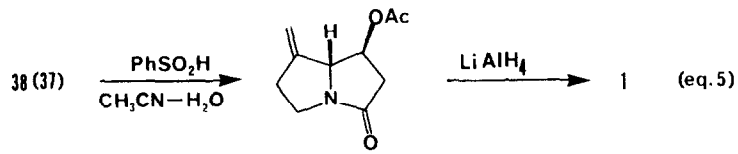
31 R = H
32 R = $CH_2CH_2C{\equiv}CSiMe_3$

33 X = OH
34 X = OAc
35 X = SPh
36 X = H

37 R_1 = SiMe$_3$, R_2 = H
38 R_1 = H R_2 = SiMe$_3$

(a) AcCl (b) NH_3 (c) Ph_3P, $EtO_2CN{=}NCO_2Et$, $Me_3SiC{\equiv}CCH_2CH_2OH$ (d) $NaBH_4$ (e) Ac_2O, Et_3N, 4-DMAP (f) PhSH, TsOH (g) nBu_3SnH, AIBN, 80°C, PhH

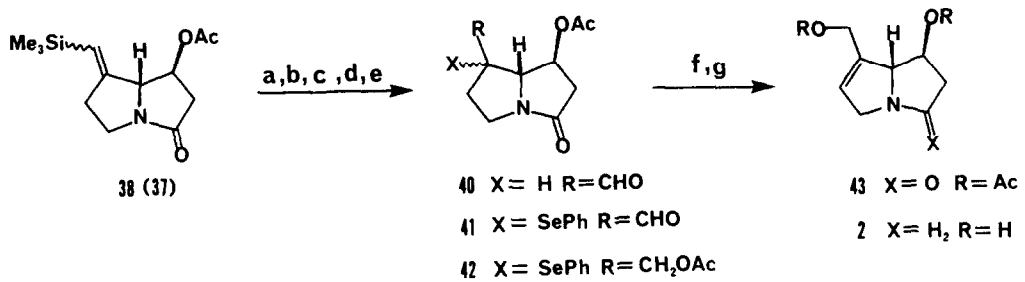
The structures of **37** and **38** were proven as shown in Eq. 5.[19a] The relationship between **37** and **38** was established by independent protodesilylation[19b] to afford the same olefin **39** (81%) which was converted to pyrrolizidine **1** (90%) upon reduction with lithium aluminum hydride. In fact, **1** is the enantiomer of the natural product (+)-dehydrohastanecine.[5] Therefore a comparison of specific rotation data collected on **1** with those reported for the natural product and its C(8) diastereomer fully established the structure of **1** and its precursors.



39

We feel that **37** (**38**) should serve as a useful intermediate in the synthesis of a number of pyrrolizidine alkaloids. The conversion of **37** and **38** to (+)-heliotridine (**2**) illustrates that point (Scheme V). Sequential treatment of **37** and **38** with m-chloroperbenzoic acid and warm 90% aqueous formic acid gave aldehyde **40** (90%) as a 4:1 mixture of C(7) diastereomers.[20] Treatment of this mixture with phenylselenenyldiethylamine gave diastereomeric selenides **41**.[21] Reduction of the aldehyde **41** with sodium borohydride followed by acetylation[22] of the resulting alcohol gave diastereomeric acetates **42**. Oxidation of **42** with hydrogen peroxide gave allylic acetate **43** in a 48% overall yield from **40**. Finally, treatment of **43** with lithium aluminum hydride, as previously reported for its enantiomer,[6b] afforded (+)-heliotridine (**2**).

Scheme V



38 (37)

40 X= H R=CHO

41 X= SePh R=CHO

42 X= SePh R=CH_2OAc

43 X=O R=Ac

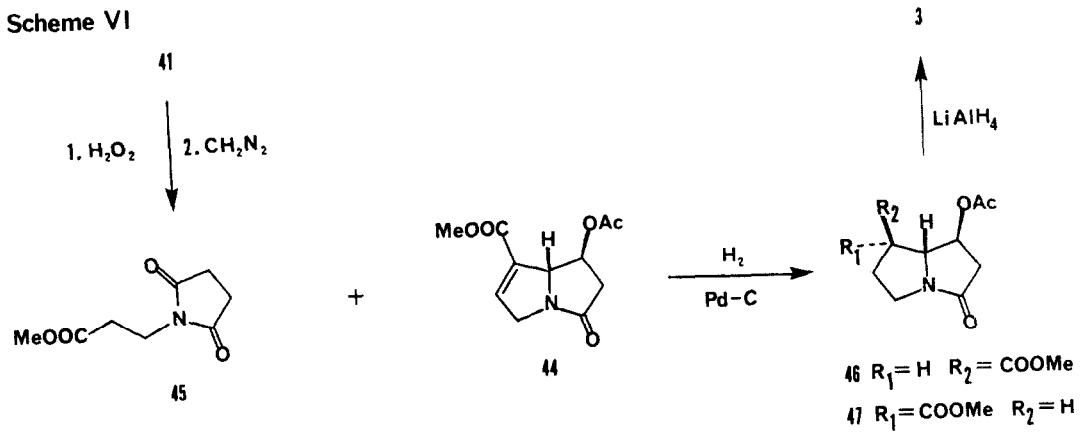
2 X=H_2, R=H

(a) MCPBA (b) HCOOH, H_2O (c) $PhSeNEt_2$ (d) $NaBH_4$ (e) Ac_2O, Et_3N, 4-DMAP (f) H_2O_2 (g) $LiAlH_4$

Several approaches to hastanecine (**3**) were also pursued. A sequence which afforded pure **3** is outlined in Scheme VI.[23] Oxidation of selenide **41** with hydrogen peroxide followed by treatment of the crude reaction mixture with diazomethane gave unsaturated ester **44** (59%) along with 21% of imide **45**.[24] Catalytic hydrogenation of **44** gave a quantitative yield of 3:1 mixture of **46** and **47**, respectively, from which pure **46** could be crystallized in a 39% yield. Treatment of **46** with lithium aluminum hydride gave (+)-hastanecine (**3**) in 95% yield.

In conclusion, it has been shown that 2-aza-5-hexynyl radical cyclizations can be used to prepare pyrrolizidine bases in a manner which competes well with other approaches to these alkaloids. Given the importance of C-C(N) bond construction in alkaloid biosynthesis in general, we hope that this type of reaction will find use in the synthesis of other alkaloid families.

Scheme VI



Experimental

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are boiling points. ^1H and ^{13}C NMR spectra were recorded on Varian Associates EM-390 and Bruker WP-200 spectrometers and 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, m=multiplet), integration, coupling constants, interpretation]. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were recorded on AE1-MS9 or Kratos DS-55 spectrometers at an ionization energy of 70 eV. Samples on which exact mass were measured exhibited no significant peaks at m/e greater than that of the parent. The parent ions of phenylthiolactams and a few other compounds were 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, Delaware.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran (distilled from sodium); benzene, hexane, dichloromethane (distilled from calcium hydride). Reactions requiring an inert atmosphere were run under a blanket of argon. Tri-n-butyltin hydride,[25] 2-methoxy-2-methyl-3-butyne[26] and N,N-diethylphenylselenamide[21] were prepared according to known procedures. 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 was performed using EM Laboratories Lobar prepacked silica gel columns. Gas chromatographic analyses were done on a Varian Aerograph Series 1400 instrument equipped with a thermal conductivity detector.

(3S)-3-Acetoxy-1-(4-trimethylsilyl-3-butynyl)-2,5-pyrrolidindione (32). To 11.17 g (71.1 mmol) of imide **31**,[6c] 10.11 g (71.1 mmol) of 4-trimethylsilyl-3-butyn-1-ol[18] and 19.2 g (73.2 mmol) of triphenylphosphine in 144 mL of tetrahydrofuran was added dropwise 13.5 g (95%, 73.6 mmol) of diethyl azodicarboxylate in 16 mL of tetrahydrofuran with cooling in an ice-water bath over a 15 min period. The resulting solution was stirred at room temperature for 1 h and concentrated in vacuo. The residue was dissolved in 50 mL of ethyl acetate followed by addition of 100 mL of hexane. The resulting crystals were collected and rinsed with 100 mL of ethyl acetate-hexane (1:2). The filtrate was concentrated in vacuo and the residue was chromatographed over 200 g of silica gel (eluted with ethyl acetate-hexane, 1:3) to give 19.37 g (97%) of imide **32** as an oil: IR(CCl_4) 2190, 1760, 1730 cm^{-1}; NMR(CCl_4) δ 0.13(s, 9H, $SiCH_3$), 2.17(s, 3H, $COCH_3$), 2.56(t, 2H, J=6 Hz, $CH_2C\equiv$), 2.63(dd, 1H, J=6, 17 Hz, $COCH_2$), 3.18(dd, 1H, J=8, 17 Hz, $COCH_2$), 3.70(t, 2H, J=6 Hz NCH_2), 5.48(dd, 1H, J=6, 8 Hz, CHOAc); exact mass Calcd for $C_{13}H_{19}NO_4Si$ m/e 281.1083, Found m/e 281.1099; $[\alpha]_D^{25}$ = -17.4° ($CHCl_3$, c=1.00).

(4S,5S)-4-Acetoxy-5-hydroxy-1-(4-trimethylsilyl-3-butynyl)-2-pyrrolidinone (33). To 2.00 g (7.11 mmol) of imide **32** in 150 mL of methanol was added portionwise 3.36 g (88.8 mmol) of sodium borohydride at -26°C to -28°C over 30 min period. The resulting suspension was stirred for 10 min at -27°C to -30°C and poured into 200 mL of water. The resulting solution was extracted with eight 50-mL portions of dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give 1.74 g of a solid mixture. Crystallization from 50 mL of ethyl acetate-hexane (1:6) afforded 0.96 g of crystalline carbinol lactam **33**: mp 134-134.5°C; IR(CH_2Cl_2) 3300, 2190, 1740, 1715 cm^{-1}; NMR($CDCl_3$) δ 0.16(s, 9H, $SiCH_3$), 2.15(s, 3H, $COCH_3$), 2.54(t, 2H, J=6.2 Hz, $CH_2\equiv$), 2.67(m, 2H, $COCH_2$), 3.08(d, 1H, J=7.2 Hz, OH), 3.46(dt, 1H, J=6.5, 13.7 Hz, NCH_2), 3.58(dt, 1H, J=6.5, 13.7 Hz, NCH_2), 5.20(m, 1H, J=5.5, 7.2Hz, CHOAc), 5.44(dd, 1H, J=5.5, 7.3 Hz, CHOH); exact mass Calcd for $C_{13}H_{21}NO_4Si$ m/e 283.1240, Found m/e 283.1231; $[\alpha]_D^{25}$ = -82.1° (EtOH, c = 1.00).

Anal. Calcd for $C_{13}H_{21}NO_4Si$: C, 55.10; H, 7.47. Found: C, 55.04; H, 7.51.

The mother liquor was concentrated and the residue was chromatographed over silica gel (Lobar size B column, eluted acetate-hexane, 1:1) under medium pressure. Initial fractions (180-200 mL) gave 0.178 g (9%) of recovered imide **32**. Following fractions (420-580 mL) gave 0.337 g (17%) of the (4S,5R)-isomer of **33** and the regioisomeric carbinol lactam in a 5:3 ratio by 200 MHz NMR. Repeated fractional crystallization of this mixture from ethyl acetate-hexane gave 78 mg (4%) of the (4S,5R)-isomer of **33**; mp 110-111°C; IR($CHCl_3$) 3450, 2160, 1730, 1690 cm^{-1}; NMR($CDCl_3$) δ 0.17(s, 9H, $SiCH_3$), 2.14(s, 3H, $COCH_3$), 2.34(dd, 1H, J=2.0, 18 Hz, $COCH_2$), 2.58(t, 2H, J=6.5 Hz, $CH_2C\equiv$), 2.96(dd, 1H, J=7.0, 18 Hz, $COCH_2$), 3.38(dt, 1H, J=6.7, 13.5 Hz, NCH_2), 3.68(dt, 1H, J=6.7, 13.5 Hz, NCH_2), 3.90(broad s, 1H, OH), 5.03(dd, 1H, J=2.0, 7.0 Hz, CHOAc), 5.19(s, 1H, CHOH); exact mass Calcd for $C_{13}H_{21}NO_4Si$ m/e 283.1240, Found m/e 283.1242. Final fractions (600-800 mL) afforded 0.21 g of additional (4S,5S)-**33** (59% overall). For practical purposes, the crude product can be used directly without purification.

(4S,5S)-4,5-Diacetoxy-1-(4-trimethylsilyl-3-butynyl)-2-pyrrolidinone (34). To 7.23 g (25.5 mmol) of carbinol lactam **33** in 60 mL of dichloromethane was added 31 mg of 4-dimethylaminopyridine and 3.87 g (38.2 mmol) of triethylamine. The resulting solution was cooled in an ice-water bath followed by addition of 5.22 g (51.1 mmol) of acetic anhydride. The resulting solution was stirred at room temperature for 30 min and diluted with 250 mL of ether. The solution was washed with 20 mL of water, 20 mL of 0.3 N hydrochloric acid, 20 mL of water, 20 mL of saturated aqueous sodium bicarbonate and 20 mL of saturated aqueous sodium chloride, dried (Na_2SO_4) and concentrated in vacuo to give 8.30 g (100%) of diacetoxylactam **34** as a viscous oil: IR(neat) 2180, 1752, 1730 cm^{-1}; NMR(CCl_4) δ 0.13(s, 9H, $SiCH_3$), 2.03(s, 3H, $COCH_3$), 2.07(s, 3H, CH_3CO), 2.33-2.75(m, 4H, $COCH_2$, $CH_2C\equiv$), 3.23(dt, 1H, J=7, 13.5 Hz, NCH_2), 3.58(dt, 1H, J=7, 13.5 Hz, NCH_2), 5.33(ddd, 1H, J=5.5, 9.0, 9.0 Hz, C4-H), 6.47(d, 1H, J=5.5 Hz, NCHOAc); exact mass Calcd for $C_{15}H_{23}NO_5Si$ m/e 325.1346, Found m/e 325.1340. This material was used in subsequent reactions without further purification.

Similar treatment of the (4S,5R)-isomer of **33** gave the (4S,5R)-isomer of **34**: IR($CHCl_3$) 2180, 1750, 1725 cm^{-1}; NMR(CCl_4) δ 0.14(s, 9H, $SiCH_3$), 2.07(s, 3H, $COCH_3$), 2.10(s, 3H, $COCH_3$), 2.46(m, 3H, $CH_2C\equiv$, COCH), 2.82(dd, 1H, J=7.0, 17 Hz, $COCH_2$), 3.43(dt, 1H, J=6.8, 13.5 Hz, NCH_2), 3.67(dt, J=6.8, 13.5 Hz, NCH_2), 5.03(d, 1H, J=5 Hz, CHOAc), 6.33(s, 1H, NCHOAc); exact mass Calcd for $C_{15}H_{23}NO_5Si$ m/e 325.1346, Found m/e 325.1348.

(4S,5RS)-4-Acetoxy-5-phenylthio-1-(4-trimethylsilyl-3-butynyl)-2-pyrrolidinone (35). To 8.52 g (26 mmol) of diacetoxylactam **34** was added 50 mg of p-toluenesulfonic acid monohydrate and 4.29 g (39 mmol) of thiophenol with cooling in an ice-water bath. The resulting solution was stirred at room temperature for 1.5 h, diluted with 100 mL of ether, washed with two 40-mL portions of 1 N aqueous sodium hydroxide, 40 mL of water and 40 mL of saturated aqueous sodium chloride. The combined aqueous phases were extracted with 50 mL of ether. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give 9.43 g (97%) of phenylthiolactam **35** as a viscous oil: IR(CCl_4) 2190, 1750, 1720 cm^{-1}; NMR(CCl_4) δ 0.10(s, 5.1 H, $SiCH_3$), 0.16(s, 3.9H, $SiCH_3$), 1.97(m, 2H, CH_2CO), 2.00(s, 1.7H, $COCH_3$), 2.09(s, 1.3H, $COCH_3$), 2.52(t, 2H, J=6.8 Hz, $CH_2C\equiv$), 3.33(m, 1H, NCH_2), 3.83 (m, 1H, NCH_2), 5.03(s, 0.57H, CHSPh), 5.10(m, 1.4H, CHOAc, CHSPh), 7.34(m, 5H, ArH); mass spectrum m/e (relative intensity) 266(M^+-PhS, 70), 224(35), 206(9), 181(11), 131(19), 117(16), 109(19), 73 (50), 69(100); exact mass Calcd for $C_{13}H_{20}NO_3Si$ ($M-C_6H_5S$) m/e 266.1212, Found m/e 266.1206. This material was used directly in subsequent reactions. Similar treatment of the (4S,5R)-isomer of **34** afforded the same mixture of phenylthiolactams **35**.

(Z)-(1S,7aR)-1-Acetoxyhexahydro-7-trimethylsilylmethylene-3H-pyrrolizin-3-one (38), (E)-(1S,7aR)-1-Acetoxyhexahydro-7-trimethylsilylmethylene-3H-pyrrolizin-3-one (37), and (4S)-4-Acetoxy-1-(4-trimethylsilyl-3-butynyl)-2-pyrrolidinone (36). To 8.51 g (22.7 mmol) of phenylthiolactam **35** in 430 mL of benzene under reflux was added 8.60 g (29.6 mmol) of tri-n-butyltin hydride and 226 mg of AIBN (1.38 mmol) in 80 mL of benzene via syringe pump over an 18 h period. The resulting solution was heated under reflux for 2 h and concentrated in vacuo. The residue was chromatographed over 200 g of silica gel (eluted with ethyl acetate-hexane, 1:1) and collected in three fractions. Each fraction was further separated by medium pressure liquid chromatography (Lobar size C, eluted with ethyl acetate-hexane, 1:1) to afford the following compounds.

Pyrrolizidinone **38**: 3.77 g (56%); mp 65.5-66.5°C; IR(CCl_4) 1750, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09(s, 9H, $SiCH_3$), 2.07(s, 3H, $COCH_3$), 2.44(dd, 1H, J=5.3, 13 Hz, $COCH_2$), 2.58(m, 2H, $=CCH_2$), 2.90(m, 1H, NCH_2), 2.99(dd, 1H, J=6.2, 13 Hz, $COCH_2$), 4.05(dd, 1H, J=8.6, 12.1 Hz, NCH_2), 4.49(dt, 1H, J=3.8, 6.5 Hz, NCH), 4.99(dt, 1H, J=6.5, 7.9 Hz, CHOAc), 5.73(m, 1H, =CH); ^{13}C NMR($CDCl_3$) δ -0.50(q), 20.9(q), 38.1(t), 40.4(t), 42.6(t), 65.5(d), 75.1(d), 125.7(d), 155.2(s), 169.9(s), 173.4(s); mass spectrum m/e (relative intensity) 267(M^+, 0.5), 252(41), 225(53), 207(89), 196(38), 154(40), 117(33), 75(59), 73(57), 43(100); $[\alpha]_D^{25}$ = -94.7° (EtOH, c=1.17), -88.0° ($CHCl_3$, c=1.11).

Anal Calcd for $C_{13}H_{21}NO_4Si$: C, 58.39; H, 7.92. Found: C, 58.65; H, 7.87.

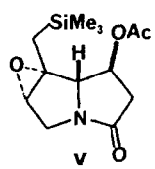
Pyrrolizidinone **37**: 1.00 g (15%); IR(neat) 1749, 1715, 1635, 840 cm^{-1}; ^1H NMR($CDCl_3$) δ 0.08 (s, 9H, $SiCH_3$), 2.08(s, 3H, $COCH_3$), 2.50-2.68(m, 3H, COCH, $=CCH_2$), 2.91(dd, 1H, J=9.1, 18.3 Hz, COCH), 3.03(dd, 1H, J=1.7, 8.1 Hz, NCH_2), 4.01(ddd, 1H, J=5.1, 6.9, 12 Hz, NCH_2), 4.22(dd, 1H, J=2.4, 3.3 Hz, NCH), 5.08(ddd, 1H, J=3.3, 5.1, 8.5 Hz, CHOAc), 5.67(dd, 1H, J=2.4, 3.0 Hz, =CH); ^{13}C NMR($CDCl_3$) δ -0.81(q), 20.8(q), 32.1(t), 40.1(t), 41.7(t), 70.0(d), 73.4(d), 121.9(d), 154.0 (s), 170.2(s), 173.2(s); mass spectrum m/e (relative intensity) 225(13), 207(48), 196(15), 154(29), 117(17), 75(51), 73(48), 43(100); exact mass Calcd for $C_{11}H_{19}NO_2Si$ ($M-C_2H_2O$) m/e 225.1185, Found m/e 225.1168; $[\alpha]_D^{25}$ = -4.1° (c=1.18, $CHCl_3$).

Pyrrolidinone **36**: 1.22 g (18%); IR(neat) 2180, 1745, 1705 cm^{-1}; NMR(CCl_4) δ 0.13(s, 9H, $SiCH_3$), 2.08(s, 3H, $COCH_3$), 2.45(m, 1H, $COCH_2$), 2.48(t, 2H, J=7 Hz, $CH_2C\equiv$), 2.82(dd, 1H, J=7.5, 15 Hz, $COCH_2$), 3.49(t, 2H, J=7 Hz, NCH_2CH_2), 3.55(m, 1H, NCH_2CHOAc), 3.88(dd, 1H, J=6, 11 Hz, NCH_2CHOAc), 5.33(m, 1H, CHOAc); exact mass Calcd for $C_{13}H_{21}NO_3Si$ m/e 267.1290, Found m/e 267.1305; $[\alpha]_D^{25}$ = -25.4° (c=2.73, $CHCl_3$).

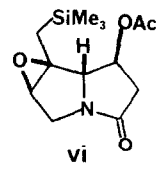
(1S,7aR)-1-Acetoxyhexahydro-7-methylene-3H-pyrrolizin-3-one (39). A solution of 1.26 g (4.71 mmol) of vinylsilane **38** and 147 mg (0.94 mmol) of p-toluenesulfinic acid in 12.6 mL of acetonitrile containing 2% of water was heated under reflux for 18 h and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexane, 1:1). Fractions from 170-270 mL gave 109 mg (10%) of allylic silane **iv** as an oil: IR(neat) 1740, 1705 cm^{-1}; NMR(CCl_4) δ 0.03(s, 9H, $SiCH_3$), 1.63(broad s, 2H, CH_2Si), 2.07(s, 3H, $COCH_3$), 2.63(m, 2H, $COCH_2$), 3.56(m, 1H, NCH_2), 4.30(m, 2H, NCH, NCH_2), 5.13(dt, 1H, J=6, 9 Hz, CHOAc), 5.30(broad s, 1H, =CH); exact mass Calcd for $C_{13}H_{21}NO_3Si$ m/e 267.1290, Found m/e 267.1311. Fractions from 270-650 mL gave 625 mg of pyrrolizidinone **39** as a light yellow oil: IR(neat) 1745, 1710, 910 cm^{-1}; NMR($CDCl_3$) δ 2.18(s, 3H, CH_3), 2.35-3.10(m, 5H, $COCH_2$, $NCHCH_2$), 3.85(m, 1H, J=5.7 Hz, NCH_2), 4.18(broad s, 1H, NCH), 4.93-5.34(m with d at 5.10 and d at 5.24, 3H, J=2 Hz, $=CH_2$, CHOAc); mass spectrum m/e (relative intensity) 153(M^+-C_2H_2O, 45), 135(81), 124(43), 107(19), 82(100), 80(19); exact mass Calcd for $C_8H_{11}NO_2$(M-C_2H_2O) m/e 153.0790, Found m/e 153.0798. Continued elution with 200 mL of ethyl acetate afforded 199 mg of crude desacetyl-**39** as an oil. This alcohol was converted to acetate **39** as follows. To 199 mg of crude alcohol in 2mL of dichloromethane was added 102 mg (1.0 mmol) of acetic anhydride, 102 mg (1.0 mmol) of triethylamine and a catalytic amount of 4-dimethylaminopyridine. The resulting solution was stirred at room temperature for 30 min and concentrated in vacuo. The residue was chromatographed over 12 g of silica gel (eluted with ethyl acetate-hexane, 1:1) to give 123 mg of acetate **39** (81% overall). Similar treatment of vinyl silane **37** afforded the same acetate **39**.

(-)-Dehydrohastanecine (1). To 154 mg (0.79 mmol) to pyrrolizidinone **39** in 10 mL of tetrahydrofuran was added 120 mg (3.2 mmol) of lithium aluminum hydride in one portion and the resulting mixture was heated under reflux for 30 min. To the mixture was added sequentially 0.10 mL of water, 0.15 mL of 1 N aqueous sodium hydroxide and 0.10 mL of water. The resulting suspension was concentrated in vacuo and the residue was suspended in 50 mL of methanol and filtered through a pad of celite. The filtrate was concentrated in vacuo and the residue was chromatographed over 20 g of silica gel (eluted with 1% concentrated ammonium hydroxide in methanol) to give 88 mg (80%) of (-)-dehydrohastanecine (**1**) as colorless oil: IR(neat) 3370, 1661, 890 cm^{-1}; NMR($CDCl_3$) δ 1.79(m, 1H, $OCHCH_2$), 2.08(m, 1H, $OCHCH_2$), 2.48(m, 3H, $=CCH_2$, OH), 2.68(m, 2H, NCH_2), 3.10(dt, 1H, J=10.4, 6.9 Hz, NCH_2), 3.29(dt, 1H, J=11.0, 7.0 Hz, NCH_2), 3.76(broad s, 1H, NCH), 4.16(m, 1H, CHO), 5.00(m, 2H, $=CH_2$); exact mass Calcd for $C_8H_{13}NO$ m/e 139.0997, Found m/e 139.1002; $[\alpha]_D^{25}$ = -37.2° (c=1.83, EtOH) [lit.[5] +36.1° (c=1.39, EtOH) for its enantiomer].

(1S,7RS,7aR)-1-Acetoxy-7-formylhexahydro-3H-pyrrolizin-3-one (40). A. From **38**: To 500 mg (1.87 mmol) of vinylsilane **38** in 5 mL of dichloromethane was added 484 mg (85%, 2.38 mmol) of m-chloroperbenzoic acid in one portion. The resulting solution was stirred at room temperature for 12 h. The resulting suspension was filtered and the filtrate was diluted to 25 mL with dichloromethane, washed with 10 mL of saturated aqueous sodium bicarbonate and 10 mL of water, dried (Na_2SO_4) and concentrated in vacuo and the residue was separated by medium pressure chromatography (Lobar size C, eluted with ethyl acetate-hexane, 1:1). Fractions from 1200-1700 mL gave 313 mg (59%) of α-epoxide **v**: mp 112-113°C; IR(KBr) 3025, 1760, 1725, 1250, 860 cm^{-1}; NMR($CDCl_3$) δ 0.16(s, 9H, $SiCH_3$), 1.51(dd, 1H, J=5.3, 13 Hz, α-NCH_2CH_2), 2.07(s, 3H, CH_3CO), 2.15(ddd, 1H, J=7.9, 12, 13 Hz, β-NCH_2CH_2), 2.49(s, 1H, epoxide), 2.51(dd, 1H, J=1.0, 9.3, 16 Hz, α-$COCH_2$), 3.02(dd, 1H, J=7, 16 Hz, β-$COCH_2$), 3.11(ddd, 1H, J=1.0, 5.3, 12 Hz, α-NCH_2), 3.85(d, 1H, J=7.7 Hz, NCH), 4.08(dd, 1H, J=7.9, 12 Hz, β-NCH_2), 4.96(dt, 1H, J=7.7, 9.3 Hz, CHOAc); mass spectrum m/e (relative intensity) 240(M^+-Ac, 6.6), 223(36), 195(21), 170(26), 149(18), 117(32), 75(63), 73(100); exact mass Calcd for $C_{11}H_{18}NO_3Si$ ($M-C_2H_3O$) m/e 240.1056, Found m/e 240.1042; $[\alpha]_D^{25}$ = +3.72° (c=3.26, $CHCl_3$). Fractions from 1850-2140 mL afforded 194 mg (38%) of β-epoxide **vi** as an oil: IR(neat) 1750, 1715, 850 cm^{-1}; NMR($CDCl_3$) δ 0.16(s, 9H, $SiCH_3$), 2.03(dd, 1H, J=12, 15 Hz, α-NCH_2CH_2), 2.05(s, 3H, $COCH_3$), 2.32 (ddd, 1H, J=4.8, 8.3, 15 Hz, β-NCH_2CH_2), 2.46(s, 1H, epoxide), 2.50(ddd, 1H, J=1.0, 5.1, 16.6 Hz, α-$COCH_2$), 3.04(dd, 1H, J=8.8, 17 Hz, β-$COCH_2$), 3.10(dt, 1H, J=1.0, 8.3 Hz, α-NCH_2), 4.04(ddd, 1H, J=4.8, 8.3, 12 Hz, β-NCH_2), 4.10(d, 1H, J=4.3 Hz, NCH), 5.05(ddd, 1H, J=4.3, 5.1, 8.8 Hz, CHOAc); mass spectrum m/e (relative intensity) 240(M^+-Ac, 5.9) 223(40), 195(23), 170(25), 149(16), 117(33), 110(18), 75(59), 73(100); exact mass Calcd for $C_{13}H_{22}NO_4Si$ (M+H) m/e 284.1318, Found m/e 284.1366.



v



vi

A solution of 1.60 g (5.65 mmol) of a mixture of epoxysilanes (3:2 by NMR) in 15 mL of 90% formic acid was heated under reflux for 30 min and concentrated in vacuo. The residue was chromatographed over 60 g of silica gel (eluted with ethyl acetate). Fractions from 220-720 mL gave 1.09 g (91%) of aldehydes **40** as a 5:1 mixture of inseparable isomers determined by 200 MHz NMR: IR(neat) 1740, 1700 cm^{-1}; NMR($CDCl_3$) δ 2.10(s, 3H, CH_3), 2.25(m, 2H, NCH_2CH_2), 2.95(m with d at 2.88, 4H, J=8.5 Hz, $COCH_2$, NCH_2, CHCHO), 3.88(m with dd at 3.88, 1H, NCH_2), 4.08(m with dd at 4.06, 1H, J=4.9, 8.8 Hz, NCH), 5.08(dt, 0.84H, J=4.9, 8.8 Hz, CHOAc), 5.18(dt, 0.16H, J=4.9, 8.8 Hz, CHOAc), 9.76(d, 0.84H, J=1.8 Hz, CHO) 9.88(d, 0.16H, J=1.2 Hz, CHO); exact mass calcd for $C_{10}H_{13}NO_4$ m/e 211.0844, Found m/e 211.0853.

B. From **37**: To 700 mg (2.62 mmol) of vinylsilane **37** in 7 mL of dichloromethane was added 630 mg of m-chloroperbenzoic acid (85%, 3.1 mmol) and 122 mg (0.10 mL; 2.6 mmol) of formic acid and the resulting solution was stirred at room temperature for 1.5 h. The resulting suspension was dissolved in 30 mL of ether and the solution was washed with two 15-mL portions of saturated aqueous sodium bicarbonate. The combined aqueous layers were extracted with 10 mL of ether. The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo to give 825 mg of crude epoxides contaminated with some m-chlorobenzoic acid as an oily solid. The residue was dissolved in 8 mL of 95% of formic acid and the resulting solution was heated under reflux for 30 min and concentrated in vacuo. The residue was chromatographed over 25 g of silica gel (eluted with ethyl acetate). Fractions from 120-300 mL gave 396 mg (72%) of aldehydes **40** as an oil. The material obtained from this sequence was identical to that obtained from vinylsilane **38**.

(1S,7RS,7aS)-1-Acetoxy-7-formylhexahydro-7-phenylseleno-3H-pyrrolizin-3-one (41). To 498 mg (2.31 mmol) of aldehyde **40** in 15 mL of dry dichloromethane was added 694 mg (3.04 mmol) of N,N-diethylphenylselenylamine[21] in one portion and the resulting solution was stirred at room temperature for 2.5 h, and concentrated in vacuo. The resulting dark brown oil was chromatographed over 40 g of silica gel (eluted with ethyl acetate-hexane, 1:1). The fractions from 320-870 mL gave 753 mg (89%) of selenide **41** as a 5:1 mixture of inseparable isomers by 200 MHz NMR (a reddish-yellow oil): IR(neat) 1755, 1715, 1695 cm^{-1}; NMR($CDCl_3$) δ 2.08(s, 0.5H, CH_3), 2.13(s, 2.5H, CH_3), 2.20(m, 1H, NCH_2CH), 2.40(dt, 1H, J=9.1, 14.6 Hz, $COCH_2$), 2.80(dd, 1H, J=6.0, 17.3 Hz, NCH_2CH), 2.94-3.28(m with dd at 3.13, 2H, J=8.9, 17.5 Hz, NCH_2, $COCH_2$), 3.70(dt, 1H, J=8.4, 11.5 Hz, NCH_2), 4.15(d, 0.82H, J=4.3 Hz, NCH), 4.20(dd, 0.18H, J=1.4, 3.4 Hz, NCH), 5.05(ddd, 0.18H, J=1.1, 6.7, 7.2 Hz, CHOAc), 5.38(ddd, 0.82H, J=4.3, 9.1, 14.6 Hz, CHOAc), 7.4(m, 5H, ArH), 9.46(d, 0.18H, J=1.1 Hz, CHO), 9.77(s, 0.82H, CHO); mass spectrum m/e (relative intensity) 368(M^+, 3.4), 351(6), 226(7), 215(8), 214(81), 210(6.8), 195(49), 168(73), 167(73), 152(31), 151(32), 140(31), 139(39), 122(100), 114(41), 98(33), 96(56), 95(54).

(1S,7RS,7aS)-1-Acetoxy-7-acetoxymethylhexahydro-7-phenylseleno-3H-pyrrolizin-3-one (42). To 410 mg (1.12 mmol) of selenides **41** in 30 mL of ethanol was added 82 mg (2.2 mmol) of sodium borohydride in one portion and the resulting suspension was stirred for 30 min and concentrated in vacuo. To the residue was added 0.2 mL of water and 30 mL of dichloromethane. The turbid mixture was dried (Na_2SO_4) and the supernatant was decanted. The residue was washed with four 20-mL portions of dichloromethane an two 20-mL portions of ethyl acetate. The combined organic phases were concentrated in vacuo to give 378 mg of sticky solid residue. The residue was suspended in 10 mL of dichloromethane followed by addition of 220 mg (2.2 mmol) of triethylamine, 330 mg (3.2 mmol) of acetic anhydride and a catalytic amount of 4-dimethylaminopyridine. The resulting solution was stirred at room temperature for 1.5 h followed by addition of 73 mg (0.72 mmol) of triethylamine and 110 mg (1.1 mmol) of acetic anhydride. The mixture was stirred at room temperature for 2 h, diluted with ether to 60 mL, washed with two 10-mL portions of water, 10 mL of 1 N hydrochloric acid, 10 mL of water, 10 mL of saturated sodium bicarbonate solution and 10 mL of water. The combined aqueous phases were extracted with 20 mL of ether and the ethereal layer was washed with 10 mL of water, 10 mL of 1 N hydrochloric acid, 10 mL of saturated aqueous sodium bicarbonate and 10 mL of water. The combined organic phases were washed with 20 mL of saturated sodium chloride solution, dried (Na_2SO_4) and concentrated in vacuo to give 368 mg of a reddish yellow oil. The oil was chromatographed over 30 g of silica gel (eluted with ethyl acetate-hexane, 2:1) to give 318 mg (69%) of the diacetate **42** as a colorless oil: IR(neat) 1740, 1700 cm^{-1}; NMR(CCl_4) δ 1.87(m, 2H, NCH_2CH_2), 2.02(s, 3H, $COCH_3$), 2.06(s, 3H, $COCH_3$), 2.51(dd, 1H, J=5, 16 Hz, $COCH_2$), 3.00(m, 2H, $COCH_2$, NCH_2), 3.39(m, 1H, NCH_2), 3.81(d, 1H, J=3 Hz, NCH), 4.15(d, 1H, J=11 Hz, CH_2OAc), 4.53(d, 1H, J=11 Hz, CH_2OAc), 5.27(m, 1H, CHOAc), 7.31(m, 3H, ArH), 7.60(m, 2H, ArH); mass spectrum m/e (relative intensity) 411(M^+, 1.1), 351(19), 292(9), 254(5), 212(13), 194(100), 152(48), 134(61), 43(93).

(1S,7aS)-1-Acetoxy-7-acetoxymethyl-1,2,3,7a-tetrahydro-3H-pyrrolizin-3-one (43). To 220 mg (0.536 mmol) of diacetate **42** in 10 mL of tetrahydrofuran was added 0.055 mL (0.54 mmol) of 30% hydrogen peroxide. The resulting solution was stirred at room temperature for 1.5 h followed by addition of 0.033 mL (0.32 mmol) of 30% hydrogen peroxide. The resulting mixture was stirred at room temperature for 2 h, concentrated in vacuo and the residue was suspended in 2.5 mL of ethyl acetate-hexane (1:1). The supernatant was chromatographed over 13 g of silica gel (eluted with ethyl acetate-hexane, 1:1) to give 156 mg of an oily residue. Since the residue still contained starting material, it was dissolved in 5 mL of tetrahydrofuran followed by addition of 0.022 mL (0.22 mmol) of 30% hydrogen peroxide. The resulting solution was stirred at room temperature for 2 h and concentrated in vacuo. The residue was chromatographed as above to give 131 mg (97%) of allylic acetate **43** as a colorless oil: IR(neat) 1747, 1715 cm^{-1}; NMR($CDCl_3$) δ 2.07(s, 3H, $COCH_3$), 2.12(s, 3H, $COCH_3$), 2.73(dd, 1H, J=9, 17 Hz, $COCH_2$), 2.90(dd, 1H, J=9, 17 Hz, $COCH_2$), 3.73(broad d, 1H, J=15.5

Hz, NCH_2), 4.40-5.00(m with d at 4.75, 4H, J=7 Hz, CH_2OAc, NCH_2, NCH), 5.28(dt, 1H, J=7, 9 Hz, CHOAc), 5.90(s, 1H, =CH); mass spectrum m/e (relative intensity) 211(4.6), 193(36), 150(43), 149 (88), 133(50), 97(20), 80(100); exact mass Calcd for $C_{10}H_{11}NO_3$(M-C_2H_4O) m/e 193.0743, Found m/e 193.0739.

(+)-Heliotridine (2). Allylic acetate **43** afforded (+)-heliotridine (**2**) upon treatment with lithium aluminum hydride, as previously reported[6b] for its enantiomer: mp 115-116°C (lit.[6a] 117.5-118°C); IR(CH_2Cl_2) 3300 cm^{-1}; NMR($CDCl_3$) δ 1.95(m, 2H, NCH_2CH_2), 2.70(m, 1H, NCH_2CH_2), 2.96(s, 2H, OH's), 3.35(m, 2H, NCH_2CH_2, CHOH), 3.94(d, 1H, NCH), 4.11(m, 2H, NCH_2C=), 4.22(s, 2H, CH_2O), 5.62(s, 1H, =CH); mass spectrum m/e (relative intensity) 155(M^+, 21), 138(3), 124(2), 111(67), 94(16), 80(100), 68(13); exact mass calcd for $C_8H_{13}NO_2$ m/e 155.0946, Found m/e 155.0939; $[\alpha]_D^{25}$ = +32.1° (c=0.45, MeOH) [lit.[16] $[\alpha]_D^{25}$ = +32.1° (c=10.0, MeOH)].

Methyl 3-[(3S)-3-Acetoxy-2,5-pyrrolidindion-1-yl]-propionate (45) and Methyl (1S,7aR)-1-Acetoxy-1,2,5,7a-tetrahydro-3H-pyrrolizin-3-one-7-caboxylate (44). To 1.02 g (2.78 mmol) of selenides **41** in 20 mL of tetrahydrofuran was added dropwise 1.48 mL (14.5 mmol) of 30% hydrogen peroxide with cooling in an ice-water bath. The resulting solution was stirred for 3 h with cooling and the mixture was concentrated in vacuo to give 1.19 g of solid residue. The residue was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexane-formic acid, 49:49:2) to give 591 mg of crude acid. To the crude acid in 20 mL of tetrahydrofuran was added dropwise a dichloromethane solution of diazomethane with cooling in an ice-water bath until a slight yellow color persisted. The resulting solution was concentrated in vacuo and the residue was chromatographed over 13 g of silica gel (eluted with ethyl acetate-hexane, 1:1). Initial fractions gave 114 mg (21%) of imide **45**: IR($CHCl_3$) 1780(w), 1730, 1715 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.16(s, 3H, $COCH_3$), 2.66(t, 2H, J=6.9 Hz, CH_2CO_2), 2.68(dd, 1H, J=6, 18 Hz, $NCOCH_2$), 3.12(dd, 1H, J=9, 18 Hz, $NCOCH_2$), 3.67(s, 3H, OCH_3), 3.74 (t, 2H, J=6.9 Hz, NCH_2), 5.38(dd, 1H, J=6, 9 Hz, CHOAc); ^{13}C NMR($CDCl_3$) δ 20.3(q), 31.5(t), 34.8(t), 35.6(t), 51.7(q), 67.5(d), 169.4(s), 170.6(s), 172.5(s), 172.7(s); mass spectrum m/e (relative intensity) 212(M^+-OMe, 4.4), 211(6), 183(14), 151(9), 55(24), 43(100); exact mass Calcd for $C_9H_{10}NO_5$(M-OCH_3) m/e 212.0561, Found m/e 212.0559. Later fractions gave 397 mg (59%) of ester **44** as white crystals: mp 100-102°C; IR(CCl_4) 1740, 1712, 1630 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.12(s, 3H, CH_3CO), 2.72(d, 1H, J=3 Hz, $COCH_2$), 2.82(d, 1H, J=2 Hz, $COCH_2$), 3.71(s, 3H, CO_2CH_3), 3.87(m, 1H, NCH_2), 4.47(m, 1H, NCH_2), 4.72(m, 1H, NCH), 5.35(m, 1H, J=7.5, 8.4 Hz, CHOAc), 6.77(d, 1H, J=2 Hz, =CH); ^{13}C NMR($CDCl_3$) δ 20.9(q), 39.8(t), 50.6(t), 52.0(q), 70.5(d), 72.9(d), 134.8(s), 140.7(d), 162.5(s), 169.9(s), 174.5(s); exact mass Calcd for $C_{11}H_{13}NO_5$ m/e 239.0796, Found m/e 239.0793; $[\alpha]_D^{25}$ = +16.4° (c=1.02, $CHCl_3$).

Methyl (1S,7R,7aS)-1-Acetoxyhexahydro-3H-pyrrolizin-3-one-7-carboxylate (46) and Methyl (1S,7S,7aS)-1-Acetoxyhexahydro-3H-pyrrolizin-3-one-7-carboxylate (47). A mixture of 395 mg (1.65 mmol) of ester **44** and 100 mg of 5% palladium on carbon in 25 mL of ethanol was hydrogenated under 60 psi of hydrogen for 18 h and filtered. The filtrate was concentrated in vacuo to give 395 mg (100%) of a 3:1 mixture of esters **46** and **47**, respectively. This mixture was crystallized from ethyl acetate-hexane to afford 155 mg (39%) of pure ester **46** as colorless leaflets: mp 96.5-97.5°C; IR($CHCl_3$) 1740, 1700 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.08(s, 3H, CH_3CO), 2.31(m, 2H, NCH_2CH_2), 2.76(dd, 1H, J=9, 18 Hz, $COCH_2$), 2.85(d, 2H, J=9 Hz, $COCH_2$, $CHCO_2$), 3.18(m, 1H, NCH_2), 3.70(m, 1H, NCH_2), 3.74(s, 3H, OCH_3), 4.06(dd, 1H, J=5, 9 Hz, NCH), 5.14(dt, 1H, J=5, 9 Hz, CHOAc); ^{13}C NMR($CDCl_3$) δ 20.6(q), 30.7(t), 40.1(t), 41.2(t), 47.5(d), 52.1(q), 69.7(d), 72.0(d), 170.3(s), 171.7(s), 172.4(s); mass spectrum m/e (relative intensity) 198(M^+-Ac,1.0), 181(100), 168(27), 138(70), 128(42), 100(22), 95(18), 67(34); exact mass Calcd for $C_9H_{12}NO_4$(M-Ac,1.0) m/e 198.0767, Found m/e 198.0767. The presence of ester **47** was apparent from the NMR spectrum of crude mixture. For example, the acetyl groups appeared as singles at δ 2.08 (**46**) and δ 2.09 (**47**).

(+)-Hastanecine (3). To 97 mg (0.40 mmol) of ester **46** in 6.5 mL of tetrahydrofuran was added 100 mg (2.6 mmol) of lithium aluminum hydride in one portion and the resulting mixture was heated under reflux for 40 min. To the mixture was added 0.1 mL of water, 0.1 mL of 1 N aqueous sodium hydroxide and 0.1 mL of water. The resulting suspension was concentrated in vacuo and the residue was chromatographed over 10 g of silica gel (eluted with methanol containing 1% concentrated ammonia solution) to give 58 mg (92%) of (+)-hastanecine (**3**). An analytical sample was obtained by crystallization from acetone: mp 111-112°C (lit.[7a] 113-114°C); IR(CH_2Cl_2) 3300 cm^{-1}; NMR($CDCl_3$) δ 1.69(m, 1H, CH_2), 1.96(m, 1H, CH_2), 2.13(m, 1H, CH_2), 2.52(m, 4H, NCH_2, OH, CH_2), 2.68(m, 1H, NCH_2) 3.27(m, 3H, NCH, NCH_2), 3.59(dd, 1H, J=8, 11 Hz, OCH_2), 3.86(dd, 1H, J=8, 11 Hz, OCH_2), 4.12(m, 1H, OCH); mass spectrum m/e (relative intensity) 157(M^+, 8), 113(18), 82(100); exact mass Calcd for $C_8H_{15}NO_2$ m/e 157.1103, Found m/e 157.1108; $[\alpha]_D^{25}$ = +10.0° (c=0.48, EtOH) [lit.[7a] $[\alpha]_D^{25}$ = -10.0° (c=0.43, EtOH)].

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12. Both geometrical isomers of **11** independently gave **13** upon protodesilylation. The overall yield of **13** from **5b** was 50%. Isomers **14** and **15** were obtained as a 3.5:1 mixture, respectively, in a 95% yield and were separated by GC (see ref. 10).

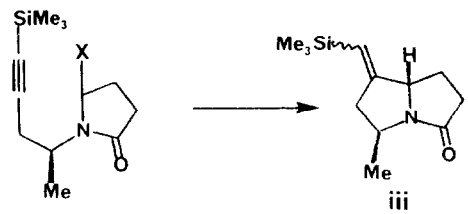
13. Pure samples of **17** and each geometrical isomer of **16** were obtained by a combination of LC and GC.

14. Products ratios were obtained by NMR. Pure samples of **19**, **23** and **24** were obtained by a combination of GC and LC.

15. Pure samples of **23**, **25** (1:1) and **26a** were obtained by GC.

16. Pure samples of **26b**, **29** and one isomer of **27** were obtained by LC and GC. The other isomers of **27** and **28** were analyzed as a mixture.

17. An additional substituent effect study showed that phenylthiolactam **i** gave **ii** (12%) and **iii** (63%, 2:1 mixture of geometrical isomers) upon treatment with tri-n-butyltin hydride and AIBN. The diastereoselectivity observed here is notable and can be attributed to allylic strain phenomena: Hart, D. J. J. Am. Chem. Soc. **1980**, 102, 397. The details of this experiment including structure proofs appear in the Ph.D. Thesis of J.-K. Choi, The Ohio State University, 1985.



i X=SPh
ii X=H
iii

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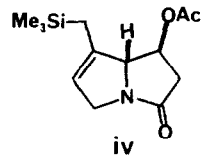

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23. Treatment of **40** or **44** with lithium aluminum hydride gave inseparable mixtures of **3** (major) and its C(1)-diastereomer, dihydroxyheliotridane, in high yields.

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