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α-ACYLAMINO RADICAL CYCLIZATIONS USING ALLENES AND VINYLSILANES AS ADDENDS: APPLICATIONS TO THE SYNTHESIS OF (+)-HELIOTRIDINE AND (-)-DIHYDROXYHELIOTRIDINE

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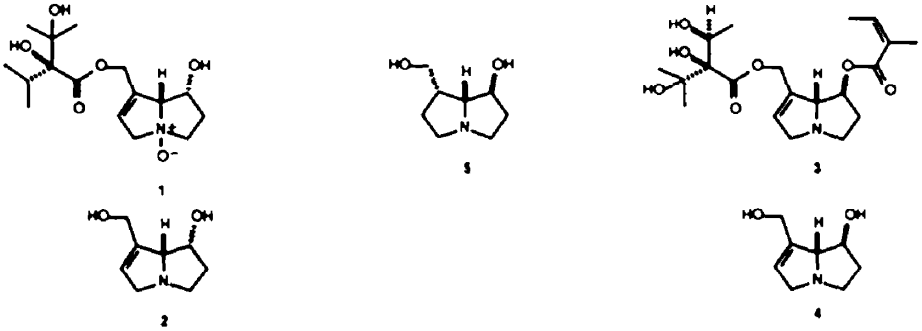
Abstract: Total syntheses of the pyrrolizidine bases (+)-heliotridine (4) and (-)-dihydroxyheliotridane (5) from (*S*)-3-acetoxysuccinimide are described. The syntheses of 4 and 5 revolve around free radical cyclizations involving the use of allenes and vinylsilanes, respectively, as addends.

The pyrrolizidine alkaloids are a large class of naturally occurring compounds isolated primarily from a variety of plant sources throughout the world.[1] These alkaloids exhibit diverse biological activity including antitumor, hypotensive, local anesthetic and antiinflammatory properties.[2] Pyrrolizidine alkaloids are commonly isolated as esters of polyhydroxylated pyrrolizidine or "necine" bases. Several examples are shown in Figure 1. Thus, the antitumor agent indicine-*N*-oxide (1) is derived from retronecine (2) and heliosupine (3) is derived from heliotridine (4). A large number of approaches to optically active necine bases have been developed during the past decade.[3] Carbohydrates and amino acids have been among the chiral educts used in a number of these efforts.[4,5] Our own studies have focused on the use of malic acid as a source of chirality and the development of methods for contruction of the C(7)-C(7a) bond has guided our synthetic efforts.[6-8] We initially used *N*-acyliminium ion cyclizations to construct this bond[6] and later turned to α-acylamino radical cyclizations for the same purpose.[7] This paper describes studies designed to determine the efficacy of allenes and vinylsilanes as addends in α-acylamino radical cyclizations within the context of syntheses of (+)-heliotridine (4)[9] and (-)-dihydroxyheliotridine (5)[10].

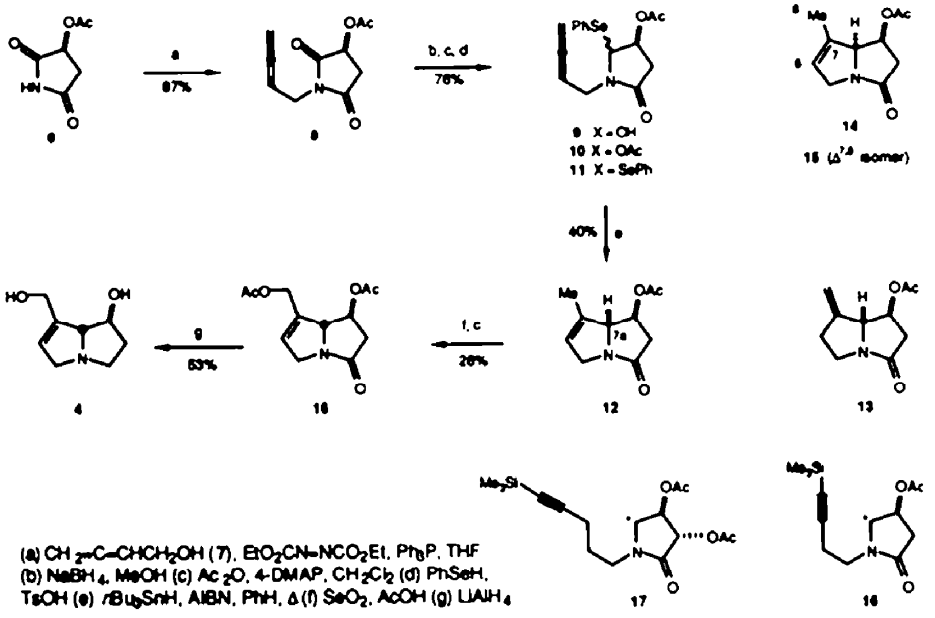
Figure 1



ALLENES AS ADDENDS: SYNTHESIS OF (+)-HELIOTRIDINE (4). Only recently have allenes begun to see use as addends in free radical cyclizations. Pattenden has examined the intramolecular addition of ketyls to allenes within the context of sesquiterpene synthesis.[11] Photochemical variants of this bond construction have also been reported by Cossy and Portella.[12] Tri-*n*-butyltin radical mediated carbon-halogen[13] or carbon-selenium[14] bond homolysis followed by addition of the resulting radical to allenes has been reported by Crandall and ourselves. Early studies from our laboratories demonstrated that such cyclizations could be used to gain rapid entry to both pyrrolizidine and indolizidine ring systems.[14] In an attempt to evaluate stereochemical aspects of these reactions, we undertook the synthesis of (+)-heliotridine shown in Scheme I.

Mitsunobu coupling of (*S*)-3-acetoxysuccinimide (6)[6,8a] with 2,3-butadien-1-ol (7)[15] gave imide 8 in 87% yield.[17] Reduction of 8 using sodium borohydride in methanol[6,8a,15] followed by Steglich acetylation of the resulting alcohol 9 gave lactam 10 in 78% overall yield.[18] Treatment of 10 with selenophenol and a catalytic amount of *p*-toluenesulfonic acid monohydrate gave free radical precursor 11 in 98% yield. Treatment of selenide 11 with tri-*n*-butyltin hydride and azobis(isobutyronitrile) (AIBN) in benzene under reflux afforded a mixture of four cyclization products (12-15). The major product (12), derived from attack of the allene on the radical face opposite the acetoxy group and exocyclic reduction of the resulting allylic radical, was isolated in 40% yield as a crystalline solid after chromatography. The product derived from endocyclic reduction of the same allylic radical (13) was also isolated in 11% yield. Finally, pyrrolizidinone 14 was isolated in 17% yield, contaminated by what appeared to be a small amount of isomeric pyrrolizidinone 15.

Scheme I: Total Synthesis of (+)-Heliotridine (4)

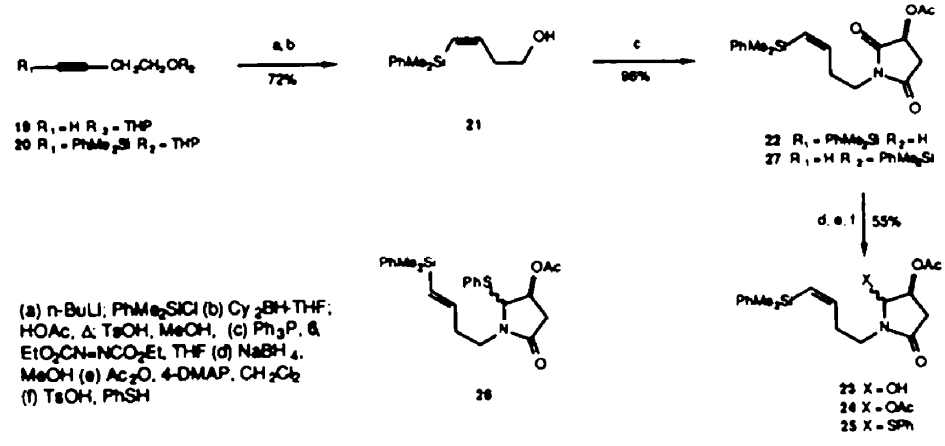


Although the overall yield of cyclization products was acceptable, the diastereoselectivity at C(7a) was disappointing compared to that observed in other cyclization reactions involving attack of α-acylamino radicals at sp-hybridized carbon. For example radical 16 affords an 18:1 ratio of products derived from attack anti or syn to the C(4) acetoxy group, respectively, and 17 affords only indolizidinones derived from attack opposite the C(4) acetoxy group.[7,19] Nonetheless it was possible to prepare gram quantities of 12 via this method.

The synthesis of (+)-heliotridine (4) was completed in three simple steps as outlined in Scheme I. Thus, oxidation of 12 using selenium dioxide followed by acetylation of the resulting mixture of alcohols gave diacetate 18 in 28% yield along with 30% of recovered 12. Treatment of 18 with lithium aluminum hydride afforded a 53% yield of 4, identical in all respects to a sample of the natural product. Although the overall yield of (+)-heliotridine was not high (4.3% from 6), the brevity of the sequence makes it the shortest synthesis of 4 known.

VINYLSILANES AS ADDENDS: SYNTHESIS OF (-)-DIHYDROXYHELIOTRIDANE (5). (-)-Dihydroxyheliotridane (5) is a pyrrolizidine diol that was originally isolated from the hydrogenation of (+)-heliotridine (4) over Raney nickel. This base does not appear to be a natural product although two syntheses of 5 in racemic form have been reported.[20] In earlier radical cyclization studies directed toward the synthesis of simpler pyrrolizidine bases, we described several addends that eventually delivered a hydroxymethyl group to C(7) of the pyrrolizidine nucleus.[21] In an attempt to deliver the ubiquitous C(7)-hydroxymethyl group in a more efficient manner, we decided to examine the use of a vinylsilane as an enol equivalent within the context of a radical cyclization route to 5.

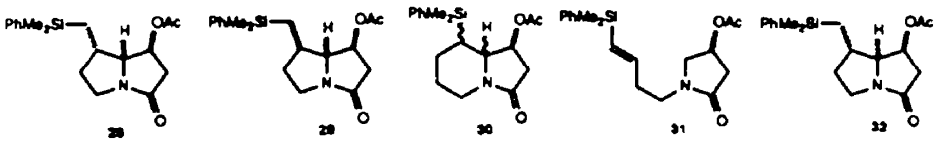
Scheme II



The preparation of the required radical precursor (25) is described in Scheme II. Sequential treatment of acetylene 19[22] with *n*-butyllithium and chlorodimethylphenylsilane afforded silylacetylene 20 in 94% yield. Hydroboration of 20 followed by sequential

treatment of the resulting vinylborane with glacial acetic acid and *p*-toluenesulfonic acid in methanol gave alcohol 21 in 77% yield.[23] Treatment of 21 with imide 6 in the presence of triphenylphosphine and diethyl azodicarboxylate gave a 96% yield of coupling product 22. Regioselective reduction of 22 followed acetylation of the resulting alcohol 23 gave 24 (86%) as a 10:1 mixture of C(5) diastereomers. Treatment of 24 with a limiting amount of thiophenol (0.86 equivalents) and *p*-toluenesulfonic acid gave a 64% yield of radical cyclization precursor 25 (contaminated with 5% of the trans vinylsilane 26) along with 29% of recovered 24. The use of less than one equivalent of thiophenol was important in the conversion of 24 to 25. For example, when 1.5 equivalents of thiophenol was used, a 95% yield of a 1.3:1 mixture of 25 and 26, respectively, was obtained.[24] The isomerization was undoubtedly caused by the excess thiophenol as treatment of cis imide 22 with 0.5 equivalents thiophenol under acidic conditions gave an 82% yield of trans imide 27.

Table I. Products Obtained From Free Radical Cyclizations of 25 and 26



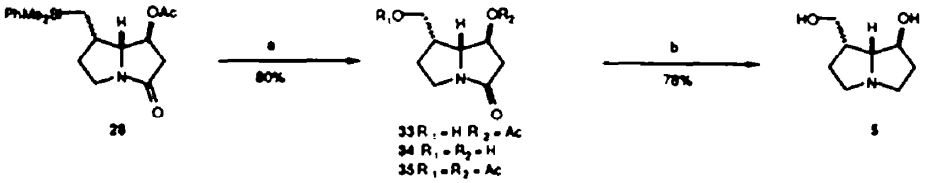
28 29 30 31 32

Radical Precursor	%28	%29	%30	%31	%32
25 + 26 (18:1)	63[a]	10[b]	18[c]	3[d]	-
25 + 26 (1.3:1)	64[a]	11[b]	12[c]	-	4

(a) isolated as a mixture with 29 and 31 (b) isolated as a mixture with 28 and 31
(c) mixture of three diastereomers by GC-MS (d) isolated as a mixture with 28 and 29

We next examined the critical radical cyclization. Treatment of an 18:1 mixture of 25 and 26, respectively, with tri-*n*-butyltin hydride and AIBN in benzene under reflux gave the mixture of the products shown in Table I. Thus, the radical derived from 25 gave a 73% yield of a 6:1 ratio of pyrrolizidinones 28 and 29, respectively, along with 18% of a mixture of isomeric indolizidinones (30) and reduction product 31 (3%). Although the separation of 28 and 29 was difficult, pure 28 for subsequent use in the synthesis was obtained in gram quantities by careful column chromatography. The stereochemical course of this cyclization is notable. First, the 4:1 exo-endo cyclization selectivity (28+29:30) was disappointing in comparison with results obtained with less highly functionalized α-acylamino radicals.[25] Second, within the pyrrolizidinone manifold of products, the 6:1 ratio of 28:29 was consistent with prior observations.[21] Finally, we note that the reduction product (32) was exclusively the trans geometrical isomer. This could be the result of either a pronounced cyclization rate difference between the radicals derived from 25 and 26 or a tri-*n*-butyltin radical mediated olefin isomerization under the reaction conditions. The later explanation seemed reasonable as such olefin isomerizations are well known.[26,27] This observation also suggested that the low exo-endo cyclization ratio might be due to isomerization of 25 to 26 prior to cyclization. Earlier observations in our laboratories suggested that the trans olefin (26) would be expected to exhibit exo-endo selectivity in the observed range.[25] Thus, we examined the cyclization of the aforementioned 1.3:1 mixture of 25 and 26, respectively. In accord with the proposed isomerization, this cyclization provided nearly the same results as those obtained in the cyclization of the 18:1 mixture of 25 and 26.

Scheme III



28 33 R_1 = H R_2 = Ac; 34 R_1 = R_2 = H; 35 R_1 = R_2 = Ac 5

(a) HBF_4-Et_2O, CH_2Cl_2; MCPBA, KF (b) $LiAlH_4$, THF

The synthesis of (-)-dihydroxyheliotridane was completed as outlined in Scheme III. Thus, oxidation of 28 using conditions developed by Fleming gave a separable mixture of alcohol 33 (80%) and diol 34 (9%).[28] Although these compounds were contaminated with *m*-chlorobenzoic acid, their structural relationship was established by independently converting them to diacetate 35. Finally, reduction of 34 with lithium aluminum hydride gave (-)-dihydroxyheliotridane (5) that exhibited spectral and physical properties in agreement with those reported for material derived from hydrogenation of (+)-heliotridine (4).[10] In summary, an enantioselective synthesis of (-)-dihydroxyheliotridane has been accomplished in nine steps from alcohol 19 (seven steps from imide 6) in (16%) overall yield (23% from 6). The synthesis features the use of a vinylsilane as an enol equivalent in a free radical cyclization.

Experimental Section

All melting points are uncorrected as are boiling points. Proton nuclear magnetic resonance spectra were recorded on Varian Associates EM-360, Varian Associates EM-390, Bruker WP-200, Bruker AM-250, Bruker WM-300 or Bruker AM-500 spectrometers and are reported in parts per million from internal tetramethylsilane on the δ scale unless otherwise noted. The ^{1}H NMR spectra are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constant in hertz, integration, interpretation]. ^{13}C NMR spectra were obtained with Bruker WP-60, Bruker AM-250 or Bruker AM-500 spectrometers. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Optical rotation data were obtained using a Perkin-Elmer 241 polarimeter at the sodium D line (1-mL sample cell). Mass spectra were obtained on Kratos MS-30 or Kratos VG70-250s instruments at an ionization energy of 70 eV. Samples on which exact masses were measured exhibited no significant peaks of *m/e* greater than that of the parent. The parent ions of phenylthio lactams, phenylselenenyl lactams and several 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. Gas chromatographic (GC) analyses were performed on a Hewlett-Packard 5890 gas chromatograph using a 25 meter phenylmethylsilicone capillary column and a Hewlett-Packard recording integrator. Gas chromatography-mass spectroscopy was performed on a Finnigan 4021 GC/MS instrument at an ionization potential of 70 eV. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, Delaware.

Solvents and reagents were dried and purified prior to use when deemed necessary: benzene, tetrahydrofuran, and diethyl ether were distilled from Na metal; methanol was distilled from magnesium methoxide; dichloromethane and toluene were distilled from calcium hydride; dimethylformamide was distilled from barium oxide. All reaction temperatures refer to those of the reaction mixture and reactions requiring an inert atmosphere were run under a blanket of argon. Tri-*n*-butyltin hydride was prepared according to a known procedure.[29] Column chromatography was performed over EM Laboratories silica gel (70-230 or 230-400 mesh). Analytical thin-layer chromatography was performed with EM Laboratories 0.25 mm thick precoated silica gel 60F-254 plates. Radial disk chromatography was performed on a Harrison Research Chromatotron using plates coated with silica gel and a $CaSO_4$ binder in thicknesses of 1, 2, or 4 mm. Medium-pressure liquid chromatography (MPLC) was performed on EM Laboratories Lobar prepacked silica gel columns.

3(*S*)-Acetyloxy-1-(2,3-butadienyl)-2,5-pyrrolidinedione (8). To a stirred solution of 7.00 g (44.6 mmol) of imide 6,[8a] 3.39 g (48.4 mmol) of 2,3-butadien-1-ol (7)[16] and 12.7 g (48.4 mmol) of triphenylphosphine in 70 mL of dry tetrahydrofuran, cooled in an ice bath, was added a solution of 8.43 g (48.4 mmol) of diethyl azodicarboxylate over a 45 min period. The resulting solution was stirred at room temperature for 1 h and the solvent was removed in vacuo. The reddish-brown residue was triturated with 90 mL of ethyl acetate-hexane (3:7) and filtered. The filtrate was concentrated in vacuo and the residue (16.9 g) was chromatographed over 200 g of silica gel (CH_2Cl_2) to give 6.60 g (87%) of the allenic imide 8 as a colorless solid: mp 46-48°C; $[\alpha]_D^{20}$ = -23.0° (*c*, 1.76 $CHCl_3$); IR (CCl_4) 1960, 1745, 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3H, CH_3), 2.67 (dd, *J* = 19, 5 Hz, 1H, $COCH_2$), 3.19 (dd, *J* = 19, 9 Hz, 1H, $COCH_2$), 4.12-4.21 (m, 2H, NCH_2), 4.81-4.92 (m, 2H, =CH_2), 5.15-5.28 (m, 1H, =CH), 5.49 (dd, *J* = 9, 5 Hz, 1H, CHOAc); ^{13}C-NMR ($CDCl_3$) δ 20.30 (q), 35.56 (t), 36.87 (t), 67.32 (d), 77.76 (t), 84.92 (d), 169.56 (s), 172.46 (s), 172.73 (s), 208.49 (s); exact mass calcd for $C_{10}H_{11}NO_4$ *m/e* 209.0688, found *m/e* 209.0672.

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.51; H, 5.49; N, 6.82.

(4*S*,5*RS*)-4,5-Diacetyloxy-1-(2,3-butadienyl)-2-pyrrolidinone (10). To a stirred solution of 5.23 g (25.0 mmol) of imide 8 in 200 mL of methanol, cooled to -20°C in a dry ice-acetone bath, was added 3.00 g (81.8 mmol) of sodium borohydride in three equal portions at 15 min intervals while maintaining a bath temperature of -20°C. Fifteen minutes after the addition of the last portion of sodium borohydride, the reaction mixture was poured into a mixture of 40 mL of saturated aqueous sodium bicarbonate, 40 mL of water and 500 mL of dichloromethane. The organic phase was separated and the aqueous layer extracted with two 200-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residual pale yellow oil was dissolved in 50 mL of dichloromethane and 5.05 g (50 mmol) of triethylamine, 5.10 g (50.0 mmol) of acetic anhydride and 20 mg of 4-(*N*,*N*-dimethylamino)pyridine was added in sequence. The mixture was stirred for 45 min and partitioned between 100 mL of dichloromethane and 50 mL of water. The organic phase was washed with two 70-mL portions of saturated aqueous sodium bicarbonate, 100 mL of saturated aqueous sodium chloride, dried ($MgSO_4$) and concentrated in vacuo. The residual oil was chromatographed over 100 g of silica gel (ethyl acetate-hexane, 2:3) to give 4.94 g (78%) of the diacetoxy lactam 10 as a pale yellow oil: IR (neat) 1955, 1745, 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz; major diastereomer) δ 2.07 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.61 (dd, *J* = 16.7, 8.9 Hz, 1H, $COCH_2$), 2.75 (dd, *J* = 16.6, 8.3 Hz, 1H, $COCH_2$), 3.65 (qt, *J* = 15.0, 8.3, 2.7 Hz, 1H, NCH_2), 4.20 (qt, *J* = 15.1, 6.2, 3.3 Hz, 1H, NCH_2), 4.84 (dt, *J* = 6.2, 2.8 Hz, 2H, =CH_2), 5.09 (qu, *J* = 6.3 Hz, 1H, =CH), 5.34 (td, *J* = 8.4, 5.3 Hz, 1H, CHOAc), 6.40 (d, *J* = 5.3 Hz, 1H, NCHOAc); ^{13}C-NMR ($CDCl_3$, peaks due to major diastereomer) δ 20.26 (q), 20.51 (q), 33.80 (t), 39.17 (t), 65.93 (d), 77.11 (d), 81.39 (t), 85.61 (d), 169.61 (s), 169.87 (s), 171.01 (s), 208.96 (s); exact mass calcd for $C_{12}H_{15}NO_5$ *m/e* 253.0950, found *m/e* 253.0949.

(4*S*,5*RS*)-Acetyloxy-1-(2,3-butadienyl)-5-phenylselenyl-2-pyrrolidinone (11). To a stirred solution of 1.18 g (4.66 mmol) of diacetoxy lactam 10 and 0.75 g (4.80 mmol, 0.51 mL) of selenophenol[30] under argon was added 20 mg (0.11 mmol) of *p*-toluenesulfonic acid monohydrate and the resulting mixture was stirred for 55 min. The reaction mixture was chromatographed directly over 50 g of silica gel (ethyl acetate-hexane, 3:7) to afford 1.60 g (98%) of diastereomeric phenylselenenyllactams 11 as a pale yellow oil: IR (neat) 1955, 1745, 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.88-2.52 (m, with two s's at 2.04 and 2.17, 5H, $COCH_2$ and CH_3), 3.56-3.79 (m, 1H, NCH_2), 4.5 (m, 1H, NCH_2), 4.60-5.50 (m, 5H, CHOAc, NCHSe, CH_2=C=CH), 7.23-7.61 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, 25 of 28 signals observed) δ 20.70 (q), 20.83 (q), 34.95 (t), 36.23 (t), 38.78 (t), 39.10 (t), 65.68 (d), 68.23 (d), 68.61 (d), 74.30 (d), 77.05 (t), 85.29 (d), 125.21 (s), 126.49 (s), 128.79 (d), 129.17 (d), 129.43 (d), 136.26 (d), 138.65 (d), 169.80 (s), 170.25

(s), 208.99 (s), 209.15 (s); mass spectrum, *m/e* (relative intensity) 195 (11), 194 (M^+-C_6H_5Se, 88), 142 (37), 134 (59), 100 (16), 82 (87), 43 (100); exact mass calcd for $C_{10}H_{12}NO_3$ (M^+-C_6H_5Se) *m/e* 194.0817, found *m/e* 194.0797.

(1*S-Cis*)-1-Acetyloxy-7-methyl-1,2,5,7a-tetrahydro-3*H*-pyrrolizin-3-one (12), (1*S-Cis*)-1-Acetyloxyhexahydro-7-methylene-3*H*-pyrrolizin-3-one (13) and (1*S-Trans*)-1-Acetyloxy-7-methyl-1,2,5,7a-tetrahydro-3*H*-pyrrolizin-3-one (14). To a solution of 3.95 g (11.3 mmol) of phenylselenyllactam 11 in 105 mL of dry, degassed benzene under reflux was added a solution of 5.00 g (17.2 mmol, 4.6 mL) of tri-*n*-butyltin hydride and 115 mg of AIBN in 115 mL of dry, degassed benzene over a 9 h period. The mixture was warmed under reflux for 2 h, concentrated in vacuo and the residue partitioned between 150 mL of acetonitrile and 150 mL of hexane. The layers were separated and the hexane layer was extracted with 50 mL of acetonitrile. The combined acetonitrile extracts were concentrated in vacuo to afford 3.82 g of a yellow liquid which was chromatographed over a Lobar size C column (ethyl acetate-hexane, 65:35; 400 mL followed by 20 mL fractions). Fractions 28-44 gave 890 mg (40%) of pyrrolizidinone 12 as a white solid after bulb-to-bulb distillation (bp 100°C at 0.35 mm): mp 59.5-61.5°C; $[\alpha]_D^{24}$ = +49.5° (*c*, 1.08 $CHCl_3$). IR (CCl_4) 1745, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.80 (br s, 3H, =CCH_3), 2.11 (s, 3H, $COCH_3$), 2.71 (dd, *J* = 17, 9 Hz, 1H, $COCH_2$), 2.89 (dd, *J* = 17, 8 Hz, 1H, $COCH_2$), 3.68 (br d, *J* = 14 Hz, 1H, NCH_2), 4.30-4.50 (m, 2H, NCH_2 and NCH), 5.19 (dt, *J* = 9, 7 Hz, 1H, CHOAc), 5.49 (br s, 1H, =CH); ^{13}C-NMR ($CDCl_3$) δ 12.43 (q), 20.74 (q), 40.04 (t), 50.10 (t), 73.12 (d), 73.67 (d), 123.25 (d), 137.36 (s), 170.00 (s), 174.15 (s); mass spectrum, *m/e* (relative intensity) 196 (1), 195 (M^+,1), 153 (16), 152 (7), 135 (51), 82 (100), 81 (84); exact mass calcd for $C_{10}H_{13}NO_3$ *m/e* 195.0895, found *m/e* 195.0895.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71. Found: C, 61.22; H, 6.75.

Fractions 45-60 gave 61 mg (3%) of a 5:1 mixture of 12 and 13 by ^{1}H-NMR analysis after bulb-to-bulb distillation (bp 110°C at 0.40 mm). Fractions 61-72 gave 244 mg (11%) of 13 as a colorless oil after bulb-to-bulb distillation (bp 115°C at 0.45 mm); IR (neat) 1745, 1705, 905 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.12 (s, 3H, $COCH_3$), 2.54-3.12 (m, 5H, $NCHCH_2C$=, $COCH_2$), 3.97 (ddd, *J* = 12, 7, 5 Hz, 1H, NCH_2), 4.28 (br s, 1H, NCH), 5.06-5.26 (m, 3H, =CH_2 and CHOAc). ^{13}C-NMR ($CDCl_3$) δ 20.85 (q), 32.67 (t), 40.21 (t), 41.67 (t), 68.44 (d), 73.36 (d), 108.37 (t), 146.18 (s), 170.27 (s), 173.06 (s); mass spectrum, *m/e* (relative intensity) 153 (M^+-C_2H_2O, 25), 135 (72), 82 (100); exact mass calcd for $C_8H_{11}NO_2$ (M^+-C_2H_2O) *m/e* 153.0790, found *m/e* 153.0792.

Fractions 84-116 gave 379 mg (17%) of lactam 14 as a yellow oil after bulb-to-bulb distillation (bp 120°C at 0.45 mm), contaminated with a small amount of material believed to be lactam 15. Lactam 14: IR (neat) 1745, 1705 cm^{-1}; ^{1}H-NMR (CCl_4, 90 MHz) δ 1.73 (br s, 3H, =CCH_3), 2.00 (s, 3H, $COCH_3$), 2.35 (d, *J* = 16 Hz, 1H, $COCH_2$), 2.85 (dd, *J* = 16, 5 Hz, 1H, $COCH_2$), 3.65 (br d, *J* = 15 Hz, 1H, NCH_2), 4.30 (br d, *J* = 15 Hz, NCH_2), 4.62 (br s, 1H, NCH), 5.47-5.67 (m, 2H, =CH and CHOAc); ^{13}C-NMR ($CDCl_3$) δ 12.88 (q), 20.66 (q), 41.80 (t), 49.47 (t), 71.95 (d), 72.85 (d), 123.50 (d), 134.36 (s), 169.82 (s), 174.80 (s); mass spectrum, *m/e* (relative intensity) 153 (19), 135 (36), 134 (11), 82 (100), 81 (58).

(1*S-Cis*)-1-Acetyloxy-7-[(acetyloxy)methyl]-1,2,5,7a-tetrahydro-3*H*-pyrrolizin-3-one (18). To a stirred solution of 1.00 g (5.13 mmol) of acetoxypyrrolizidinone 12 in 10 mL of acetic acid-acetic anhydride (1:1) was added 320 mg (2.88 mmol) of freshly sublimed selenium dioxide and the mixture was heated to 90-95°C under argon for 19.5 h. The resulting brownish-black solution was partitioned between 300 mL of dichloromethane and 100 mL of saturated aqueous sodium bicarbonate. The layers were separated and the bicarbonate layer was extracted with four 100-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered through celite and concentrated in vacuo to afford 1.26 g of a dark brown oil.

The oil was dissolved in 15 mL of dry dichloromethane and stirred for 3 h with 300 mg (2.96 mmol) of triethylamine, 304 mg (2.98 mmol) of acetic anhydride and 30 mg of 4-(*N*,*N*-dimethylamino)pyridine. The mixture diluted with 120 mL of dichloromethane and the organic phase was washed with two 35-mL portions of saturated aqueous sodium bicarbonate and 35 mL of saturated aqueous sodium chloride. The dichloromethane layer was dried ($MgSO_4$), filtered through celite and concentrated in vacuo to afford 1.04 g of a dark brown oil. This material was first chromatographed over 60 g of silica gel (ethyl acetate-hexane, 2:1), followed by a Lobar size B column (ethyl acetate-hexane, 2:1) to give 297 mg (30%) of recovered lactam 12. Continued elution afforded 361 mg (28%) of diacetoxypyrrolizidinone 18 as a brown oil: IR (neat) 1745, 1705 cm^{-1}; $[\alpha]_D^{25}$ = +36.2° (*c*, 1.05 $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.08 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.72 (dd, *J* = 16.4, 9.1 Hz, 1H, $COCH_2$), 2.88 (dd, *J* = 16.5, 8.3 Hz, 1H, $COCH_2$), 3.73 (br d, *J* = 16 Hz, 1H, NCH_2), 4.46 (dq, *J* = 15.9, 2 Hz, 1H, NCH_2) 4.60 (br s, 1H, NCH), 4.74 (AB q, *J* = 14.3 Hz, 2H, CH_2OAc), 5.29 (dt, *J* = 8.6, 6.5 Hz, 1H, CHOAc), 5.69 (br s, 1H, CH=C); ^{13}C-NMR ($CDCl_3$) δ 20.36 (q), 20.47 (q), 39.55 (t), 49.83 (t), 59.45 (t), 71.75 (d), 72.90 (d), 127.68 (d), 136.54 (s), 169.83 (s), 170.05 (s), 173.93 (s); mass spectrum, *m/e* (relative intensity) 251 (5), 211 (7), 193 (M^+-$C_2H_4O_2$, 48), 150 (61), 149 (68), 133 (70), 97 (31), 80 (92), 43 (100); exact mass calcd for $C_{10}H_{11}NO_3$ (M^+-$C_2H_4O_2$) *m/e* 193.0739, found *m/e* 193.0725.

(1*S-Cis*)-2,3,5,7a-tetrahydro-1-hydroxy-1*H*-pyrrolizine-1-methanol [(+)-Heliotridine] (4). To a stirred solution of 209 mg (0.826 mmol) of the diacetoxypyrrolizidinone 18 in 13 mL of dry tetrahydrofuran was added 210 mg (5.54 mmol) of lithium aluminum hydride in small portions over a 5-min period. The resulting greenish-grey suspension was heated to reflux for 35 min. The mixture was cooled in an ice bath, diluted with 30 mL of tetrahydrofuran, followed by the addition of 200 μL of water, 140 μL of 1 N aqueous sodium hydroxide, and 200 μL of water. The resulting suspension was filtered through celite and the filter cake suspended

in 45 mL of tetrahydrofuran and filtered. The filter cake was suspended in 75 mL of methanol-tetrahydrofuran (1:1) and filtered. The combined filtrates were concentrated in vacuo to give 220 mg of a semisolid residue which was chromatographed over 8 g of silica gel (methanol-concentrated ammonium hydroxide, 99:1) to afford 100 mg of a pale yellow solid: mp 104-110°C. This material was further purified by recrystallization from acetone to give 57.0 mg (45%) of 4 as off-white needles. Concentration of the mother liquor afforded 35 mg of an oil which crystallized on standing. Recrystallization of this material from acetone gave an additional 10.7 mg (8%) of (+)-heliotridine: mp 112-114°C (lit.[9a] mp 116.5-118.0°C); $[\alpha]_D^{30}$ = +32.0° (c, 0.22 MeOH) [lit.[9a] $[\alpha]_D^{20}$ = +31.0° (c, 10.0 MeOH)]; IR (KBr) 3350 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.84-1.96 (m, 1H, CH_2), 1.97-2.03 (m, 1H, CH_2), 2.65 (ddd, J = 14.0, 8.0, 6.1 Hz, 1H, NCH_2), 3.12 (br s, 2H, OH), 3.29-3.35 (m, 2H, NCH_2 and NCH_2), 3.88 (dt, J = 15.4, 2.0 Hz, 1H, NCH_2), 3.97 (br s, 1H, NCH), 4.07 (q, J = 5.9 Hz, 1H, CHO), 4.32 (AB q, J = 13.4 Hz, 2H, CH_2O), 5.53 (d, J = 1.5 Hz, 1H, CH=C); mass spectrum, *m/e* (relative intensity) 155 (M^+, 21), 111 (61), 94 (16), 80 (100), 69 (63), 68 (13); exact mass calcd for $C_8H_{13}NO_2$: *m/e* 155.0946, found *m/e* 155.0951.

Anal. Calcd for $C_8H_{11}NO_2$: C, 61.90; H, 8.45. Found: C, 61.88; H, 8.50.

4-(Tetrahydro-2*H*-pyran-2-yloxy)-1-dimethylphenylsilyl-1-butyne (20). To a stirred solution of 5.87 g (37.5 mmol) of 4-(tetrahydro-2*H*-pyran-2-yloxy)-1-butyne (19)[22] in 125 mL of dry tetrahydrofuran, cooled in a dry ice-acetone bath was added 25 mL of a solution of 1.52 N *n*-butyllithium in hexane (38.0 mmol) over a 22-min period. The resulting pale yellow solution was stirred for 30 min followed by the addition of 6.49 g (38.0 mmol) of chlorodimethylphenylsilane over a 30-min period. The mixture was stirred for 1.5 h, the cooling bath was removed and the solution was stirred for an additional 2 h. The solution was diluted with 300 mL of diethyl ether, 75 mL of water and the layers were separated. The aqueous phase was extracted with two 100-mL portions of diethyl ether and the combined organic layers washed with two 150-mL portions of saturated aqueous sodium chloride, dried ($MgSO_4$) and concentrated in vacuo. The residual pale yellow liquid (10.7 g) was purified by chromatography over 150 g of silica gel (ethyl acetate-hexane, 1:5) to give 10.2 g (94%) of the silylacetylene 20 as a pale yellow liquid: IR (neat) 2180 cm^{-1}; ^{1}H-NMR (CCl_4, 90 MHz) δ 0.36 (s, 6H, $SiCH_3$), 1.33-2.17 (br m, 6H, CH_2 manifold), 2.50 (t, J = 7 Hz, 2H, $\equiv CCH_2$), 3.27-3.97 (m, 4H, CH_2O), 4.58 (br s, 1H, OCHO), 7.20-7.72 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ -0.85 (q), 19.10 (t), 21.34 (t), 25.33 (t), 30.36 (t), 61.75 (t), 65.30 (t), 83.40 (s), 98.38 (d), 105.87 (s), 127.63 (d), 129.10 (d), 133.48 (d), 137.19 (s); mass spectrum, *m/e* (relative intensity) 85 (100).

(*Z*)-4-(Dimethylphenylsilyl)-3-buten-1-ol (21). A solution of dicyclohexylborane in tetrahydrofuran was prepared by the addition of 1.21 g (14.8 mmol) of cyclohexene to a solution of 7.0 mL of 1.0 M borane-tetrahydrofuran complex in tetrahydrofuran (7.00 mmol) in 4.8 mL of dry tetrahydrofuran, previously cooled in an ice bath. The resulting white suspension was stirred for 1 h at ice bath temperature. The ice bath was replaced by an ice-salt bath and 2.01 g (6.98 mmol) of acetylene 20 was added. The mixture was stirred for 20 min, the ice bath was removed and the solution was stirred for 1 h. The solvent was removed in vacuo to give a cloudy, viscous oil which was cooled in an ice bath and dissolved in 5 mL of glacial acetic acid. The semisolid mixture was stirred for 5 min in the ice bath and then heated to reflux for 1.5 h. The reaction mixture was carefully poured into 75 mL of ice water, followed by the cautious addition of 10 mL of 3 N aqueous sodium hydroxide and 10 mL of 30% aqueous hydrogen peroxide. The resulting cloudy white emulsion was stirred for 1 h, saturated with solid sodium chloride and 100 mL of dichloromethane was added. The layers were separated and the aqueous phase was extracted with two 100-mL portions of dichloromethane. The combined organic layers were washed with 100 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 2.71 g of material which was shown to be a mixture of the desired alcohol and its tetrahydropyranyl ether.

The crude mixture was dissolved in 50 mL of methanol and was stirred for 2 h with 50 mg of *p*-toluenesulfonic acid monohydrate. The solution was diluted with 25 mL of saturated aqueous sodium bicarbonate and 150 mL of diethyl ether, filtered and washed with two 50-mL portions of saturated aqueous sodium chloride. The ether layer was dried ($MgSO_4$) and concentrated in vacuo. The residual pale yellow liquid (1.87 g) was purified by radial disk chromatography (4 mm thickness; ethyl acetate-hexane, 1:5) to afford 1.11 g (77%) of alcohol 21 as a light yellow oil: IR (neat) 3340, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.47 (s, 6H, $SiCH_3$), 1.26 (br s, 1H, OH), 2.34 (dq, J = 15, 1.6 Hz, 2H, $=CCH_2$), 3.59 (t, J = 6 Hz, 2H, CH_2O), 5.86 (dt, J = 14, 1.2 Hz, 1H, =CHSi), 5.45 (overlapping dt, J = 14, 7 Hz, 1H, SiC=CH), 7.32-7.64 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ -1.00 (q), 36.76 (t), 61.86 (t), 127.72 (d), 128.81 (d), 130.15 (d), 133.60 (d), 139.28 (s), 146.05 (d); mass spectrum, *m/e* (relative intensity) 191 (M^+-CH_3, 34), 188 (1), 173 (13), 163 (33), 145 (43), 137 (72), 135 (44), 130 (11), 129 (16), 121 (34), 113 (100), 75 (94); exact mass calcd for $C_{11}H_{15}OSi$ (M^+-CH_3) *m/e* 191.0892, found *m/e* 191.0897.

(*Z*)-3*S*-Acetyloxy-1-[4-(dimethylphenylsilyl)-3-butenyl]-2,5-pyrrolidinedione (22). To a stirred solution of 1.54 g (7.49 mmol) of alcohol 21, 1.26 g (8.03 mmol) of imide 6, and 2.20 g (8.39 mmol) of triphenylphosphine in 20 mL of dry tetrahydrofuran, cooled in an ice bath, was added dropwise 1.48 g (8.48 mmol) of diethyl azodicarboxylate in 10 mL of dry tetrahydrofuran over a 50-min period. The ice bath was removed 10 min into the addition and the resulting amber-brown solution was stirred for 4 h after the addition was complete. The solvent was removed in vacuo and the dark amber residue was triturated with 50 mL of ethyl acetate-hexane (3:7) and the resulting solid removed by filtration. The filtrate was concentrated in vacuo to give an oily solid which was triturated with the same solvent mixture and filtered. Concentration of the filtrate afforded 4.14 g of a yellow oil which was chromatographed over 80 g of silica gel (dichloromethane) to give 2.52 g (96%) of the imide 22 as a pale yellow oil. IR (neat)

1750, 1715, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.38 (s, 6H, $SiCH_3$), 2.15 (s, 3H, $COCH_3$), 2.39 (dq, J = 7, 1.4 Hz, 2H, $=CCH_2$), 2.55 (dd, J = 18, 5 Hz, 1H, $COCH_2$), 3.02 (dd, J = 18, 9 Hz, 1H, $COCH_2$), 3.57 (t, J = 7 Hz, 2H, NCH_2), 5.29 (dd, J = 9, 5 Hz, 1H, CHOAc), 5.79 (dt, J = 14, 1.1 Hz, 1H, =CHSi), 6.46 (dt, J = 14, 7 Hz, 1H SiC=CH), 7.30-7.58 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ -1.13 (q), 20.31 (q), 31.57 (t), 35.45 (t), 38.13 (t), 67.21 (d), 127.74 (d), 128.83 (d), 130.63 (d), 133.48 (d), 139.00 (s), 144.85 (d), 169.51 (s), 172.84 (s), 173.11 (s); exact mass calcd for $C_{18}H_{23}NO_4Si$ *m/e* 345.1397, found *m/e* 345.1392.

***(Z)*-(4*S*,5*RS*)-4,5-Diacetyloxy-1-[4-(dimethylphenylsilyl)-3-butenyl]-2-pyrrolidinone (24).** To a stirred solution of 2.46 g (7.14 mmol) of imide **22** in 230 mL of methanol, cooled to -4°C with an ice-salt bath, was added 1.51 g (39.9 mmol) of sodium borohydride in one portion and the resulting mixture stirred for 13 min at -3.5 to -5°C. The solution was partitioned between a mixture of 200 mL of dichloromethane, 80 mL of water and 120 mL of saturated aqueous sodium bicarbonate. The layers were separated and the aqueous phase was extracted with five 120-mL portions of dichloromethane. The combined organic layers were washed with 130 mL of saturated aqueous sodium chloride, dried ($MgSO_4$) and concentrated in vacuo.

The resulting pale yellow oil (2.58 g) was dissolved in 35 mL of dry dichloromethane and 1.12 g (11.1 mmol) of triethylamine, 1.12 g (11.1 mmol) of acetic anhydride, and 60 mg of 4-(*N*,*N*-dimethylamino)pyridine were added in sequence. The solution was stirred for 50 min, diluted with 180 mL of dichloromethane and 100 mL of water, and the layers were separated. The aqueous phase was extracted with three 150-mL portions of dichloromethane and the combined organic phases were washed with 200 mL of saturated aqueous sodium bicarbonate and 200 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 2.73 g of a pale yellow semisolid which was chromatographed over 80 g of silica gel (ethyl acetate-hexane, 1:3) to afford 2.40 g (88%) of a roughly 10:1 (^{1}H-NMR) diastereomeric mixture of diacetates **24** as a pale yellow oil: IR (neat) 1750, 1725, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz; peaks due to major diastereomer) δ 0.39 (s, 6H, $SiCH_3$), 2.04 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.23-2.40 (m, 2H, $=CCH_2$), 2.53 (dd, J = 17, 9 Hz, 1H, $COCH_2$), 2.64 (dd, J = 17, 8 Hz, 1H , $COCH_2$), 3.02 (dddd, J = 14, 7.7, 6.3 Hz, 1H, NCH_2), 3.52 (qu, J = 7.5 Hz, 1H, NCH_2), 5.18 (ddd, J = 17, 9, 5 Hz, 1H, CHOAc), 5.80 (dt, J = 14, 1 Hz, 1H, =CHSi), 6.19 (d, J = 5 Hz, 1H, NCHOAc) 6.32 (dt, J = 14, 7 Hz, 1H, SiC=CH), 7.25-7.59 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, peaks due to major diastereomer) δ - 1.19 (q), 20.27 (q), 20.53 (q), 31.90 (t), 33.70 (t), 40.33 (t), 65.89 (d), 82.05 (d), 127.78 (d), 128.87 (d), 130.28 (d), 133.53 (d), 138.96 (s), 145.48 (d), 169.50 (s), 169.69 (s), 171.35 (s); exact mass calcd for $C_{20}H_{27}NO_5Si$ *m/e* 389.1659, found *m/e* 389.1678.

***(Z)*-(4*S*,5*RS*)-Acetyloxy-1-[4-(dimethylphenylsilyl)-3-butenyl]-5-phenylthio-2-pyrrolidinone (25).** To a stirred mixture of 2.33 g (6.00 mmol) of diacetate **24** and 569 mg (5.16 mmol) of thiophenol was added 6 mg of *p*-toluenesulfonic acid monohydrate in one portion. The reaction mixture was stirred for 45 min, diluted with 180 mL of diethyl ether and the ether layer washed with two 150-mL portions of 1 N aqueous sodium hydroxide. The combined base washes were extracted with 175 mL of diethyl ether and the combined ether extracts were washed with two 150-mL portions of saturated aqueous sodium chloride. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow oil which was chromatographed over a Lobar size C column, followed by a Lobar size B column (ethyl acetate-hexane, 2:5). Early fractions gave 1.69 g (64%) of phenylthiolactam **25** (cis:trans = 18:1 by NMR) as an oil: IR (neat) 1745, 1710, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.34-0.40 (2 s's, 6H, $SiCH_3$), 1.80-2.37 (m, with 2 s's at 1.98 and 2.14, 7H, $=CCH_2$, $COCH_3$, and $COCH_2$), 3.07-3.19 (m, 1H, NCH_2), 3.73-3.83 (m, 1H, NCH_2), 4.44-5.13 (m, 1H, NCHS), 5.15-5.27 (m, 1H, CHOAc), 5.70 (m, 1H, =CHSi), 6.24-6.41 (m, 1H, SiC=CH), 7.28-7.56 (m, 10H, ArH); mass spectrum, *m/e* (relative intensity) 330 (M^+-C_6H_5S, 30), 270 (27), 192 (12), 137 (19), 136 (100), 135 (100), 110 (14), 43 (21); exact mass calcd for $C_{18}H_{24}NO_3Si$ (M^+-C_6H_5S) *m/e* 330.1526, found *m/e* 330.1551.

Continued elution afforded 107 mg of a 4:1 mixture (by NMR) of starting diacetate **24** and phenylthiolactam **25**. Later fractions gave 675 mg (29%) of recovered acetate **24**. On one occasion, treatment of 2.52 g (6.48 mmol) of diacetate **24** with 1.07 g (9.72 mmol, 1.5 equivalents) of thiophenol and 12 mg of *p*-toluenesulfonic acid monohydrate gave 2.70 g (95%) of a 1.3:1 mixture (by NMR) of cis olefin **25** and trans olefin **26**. IR and mass spectra of this material were essentially identical those described for **25** above.

***(E)*-3*S*-1-Acetyloxy-1-[4-(dimethylphenylsilyl)-3-butenyl]-2,5-pyrrolidinedione (27). Thiophenol Mediated Isomerization of 22:** To a stirred mixture of 103 mg (0.299 mmol) of imide **22** and 16.5 mg (0.146 mmol) of thiophenol was added 1.0 mg (5.26 μmol) of *p*-toluenesulfonic acid monohydrate and 9.0 mg (0.146 mmol) of acetic acid. The mixture was stirred for 2.5 h, diluted with 15 ml of diethyl ether and the ether layer was washed with two 15-mL portions of 1 N aqueous sodium hydroxide. The aqueous layer was extracted with 20 mL of diethyl ether and the combined organic phases were washed with 10 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a colorless, cloudy oil (91 mg) that was purified by radial disk chromatography (1 mm thickness, ethyl acetate-hexane, 2:5) to afford 85 mg (82%) of imide **27** as a pale yellow oil: IR (neat) 1750, 1715, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.31 (s, 6H, $SiCH_3$), 2.13 (s, 3H, $COCH_3$), 2.39-2.59 (m, with dd at 2.57, J = 18, 5 Hz, 3H, $=CCH_2$ and $COCH_2$), 3.01 (dd, J = 18, 9 Hz, 1H, $COCH_2$), 3.63 (t, J = 7 Hz, NCH_2), 5.30 (dd, J = 9, 5 Hz, 1H, CHOAc), 5.80 (d, J = 18.5 Hz, 1H, =CHSi), 6.00 (dt, J = 18.7, 6.2 Hz, 1H , SiC=CH), 7.27-7.53 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ -2.85 (q), 20.40 (q), 34.46 (t), 35.54 (t), 37.91 (t), 67.29 (d), 127.78 (d), 129.00 (d), 132.06 (d), 133.66 (d), 138.58 (s), 143.50 (d), 169.69 (s), 172.95 (s), 173.20 (s); exact mass calcd for $C_{18}H_{23}NO_4Si$ *m/e* 345.1396, found *m/e* 345.1392. Tri-n-butyltin Hydride

Mediated Isomerization of 22: To a solution of 204 mg (0.59 mmol) of imide 22 in 13 mL of dry benzene under reflux was added a solution of 246 mg (0.845 mmol; 220 μL) of tri-*n*-butyltin hydride and 13.3 mg of AIBN in 2.2 mL of dry benzene over a 21 h period. The mixture was warmed under reflux for an additional 1.5 h and concentrated in vacuo. The semisolid residue was chromatographed over 9 g of silica gel (hexane; then ethyl acetate-hexane, 1:2) to give 239 mg of a colorless oil which was further purified by radial disk chromatography (2 mm thickness; dichloromethane; then dichloromethane-ethyl acetate, 10:1) to afford 170 mg (83%) of imide 27 as a colorless oil. Continued elution afforded 25 mg (14%) of the alcohol derived from hydrolysis of the acetate in 27 as a colorless oil: IR (neat) 3440, 1700, 1615 cm^{-1}; ^1H-NMR ($CDCl_3$, 200 MHz) δ 0.30 (s, 6H, $SiCH_3$), 2.36-2.64 (m, with dd at 2.6, J = 18, 5 Hz, 3H, $=CCH_2$ and $COCH_2$), 2.92 (dd, J = 18, 8 Hz, 1H, $COCH_2$), 3.12 (br s, 1H, OH), 3.61 (t, J = 7 Hz, 2H, NCH_2), 4.44 (dd, J = 8, 5 Hz, 1H, CHO), 5.78 (d, J = 18.5 Hz, 1H, $=CHSi$), 6.00 (dt, J = 18.5, 6Hz, 1H, $SiC=CH$), 7.28-7.53 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ -2.66, -2.62, 34.6, 37.0, 37.7, 66.6, 127.8, 129.0, 132.1, 133.7, 136.5, 143.5, 173.9, 176.2; exact mass calcd for $C_{16}H_{21}NO_3Si$ *m/e* 303.1292, found *m/e* 303.1292.

1*S*-(1α,7β,7aα)-1-(Acetyloxy)-hexahydro-7-[(dimethylphenylsilyl)methyl]-3*H*-pyrrolizin-3-one (28), 1*S*-(1α,7α,7aα)-1-(Acetyloxy)-hexahydro-7-[(dimethylphenylsilyl)methyl]-3*H*-pyrrolizin-3-one (29), 1*S*-(1α,7β,7aβ)-1-(Acetyloxy)-hexahydro-7-[(dimethylphenylsilyl)methyl]-3*H*-pyrrolizin-3-one (32), and 1*S*-(1α, 8aβ, 8aαβ)-1-(Acetyloxy)-8-(dimethylphenylsilyl)-3(2*H*)-indolizinone (30). To a stirred solution of 2.65 g (8.03 mmol) of phenylthiolactams 25 and 26 (1.3:1, respectively) in 118 mL of dry benzene under reflux was added a solution of 2.32 g (7.96 mmol) of tri-*n*-butyltin hydride and 102 mg of AIBN in 21 mL of dry benzene over a 21 h period. The mixture was heated at reflux for 2 h, concentrated in vacuo and the residue was partitioned between 70 mL of acetonitrile and 110 ml of hexane. The layers were separated and the hexane phase was washed with two 70-mL portions of acetonitrile. The combined acetonitrile layers were concentrated in vacuo and the residue was initially chromatographed over 60 g of silica gel (ethyl acetate-hexane, 2:3; then ethyl acetate), followed by MPLC over a Lobar size C column (dichloromethane-ethyl acetate, 3:1) and radial disk chromatography (2 mm thickness; ethyl acetate). MPLC afforded 1.49 g (75%) of a 6:1 mixture (^1H-NMR) of pyrrolizinones 28 and 29 and 239 mg (12%) of an inseparable mixture of indolizinones 30. Radial disk chromatography gave 85 mg (4%) of pure lactam 32 as an oil. On one occasion, chromatography of the major cyclization mixture on a Lobar size C column (dichloromethane-ethyl acetate, 6:1) gave pure lactam 28, as a colorless oil.

Lactam 28: $[\alpha]_D^{20}$ = +48.6° (*c*, 1.33 $CHCl_3$); IR (neat) 1740, 1700 cm^{-1}; ^1H-NMR ($CDCl_3$, 500 MHz) δ 0.32 (s, 3H, $SiCH_3$), 0.35 (s, 3H, $SiCH_3$), 0.44 (dd, J = 14.1, 13.0 Hz, 1H, $SiCH_2$), 0.84 (dd, J = 14.3, 1.6 Hz, 1H, $SiCH_2$), 1.58-1.63 (m, 1H, CH_2), 1.89-1.97 (m, 1H, CH_2), 2.28-2.34 (m, 1H, CH), 2.73 (dd, J = 17.3, 8.5 Hz, 1H, $COCH_2$), 2.89 (dd, J = 17.3, 8.7 Hz, 1H, $COCH_2$), 2.96 (br t, J=11.9 Hz, 1H, NCH_2), 3.45 (dt, J = 11.6, 8.2 Hz, 1H, NCH_2), 3.80 (t, J = 5.0 Hz, 1H, NCH), 5.13-5.17 (m, 1H, CHOAc), 7.34-7.53 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ -2.68 (q), -2.23 (q), 13.52 (t), 20.70 (q), 32.75 (t), 34.39 (d), 39.80 (t), 40.88 (t), 68.44 (d), 71.48 (d), 127.81 (d), 129.03 (d), 133.27 (d), 136.35 (s), 170.37 (s), 172.13 (s); mass spectrum, *m/e* (relative intensity) 273 (18), 272 (78), 243 (26), 194 (8), 137 (18), 136 (21), 135 (100), 96 (24), 43 (24); exact mass calcd for $C_{16}H_{22}NOSi$ (M^+-$C_2H_3O_2$) *m/e* 272.1472, found *m/e* 272.1474.

Lactam 29: ^1H-NMR ($CDCl_3$, 500 MHz; characteristic signals) δ 0.30 (s, $SiCH_3$), 2.09 (s, $COCH_3$), 2.67 (dd, $COCH_2$), 3.08 (br t, J = 12.5 Hz, NCH_2), 5.06 (m, CHOAc); GC-MS data[31] mass spectrum, *m/e* (relative intensity) t_r = 10.48 min: 272 (1), 271 (1), 156 (18), 137 (9), 136 (8), 135 (27), 96 (100), 68 (10), 43 (40).

Lactam 32: $[\alpha]_D^{20}$ = +30.4° (*c*, 1.01 $CHCl_3$); IR (neat) 1740, 1665 cm^{-1}; ^1H-NMR ($CDCl_3$, 500 MHz) δ 0.30 (s, 3H, $SiCH_3$), 0.31 (s, 3H, $SiCH_3$), 0.66 (dd, J = 14.4, 11.2 Hz, 1H, $SiCH_2$), 1.11 (dd, J = 14.4, 3.1 Hz, 1H, $SiCH_2$), 1.61-1.69 (m, 1H, CH_2), 1.90 (s, 3H, $COCH_3$), 1.97-2.05 (m, 1H, CH_2), 2.17-2.22 (m, 1H, CH), 2.37 (d, J = 17.2 Hz, 1H, $COCH_2$), 2.95 (dd, J = 16.7, 5.5 Hz, 1H, $COCH_2$), 3.15 (t, J = 10.0 Hz, 1H, NCH_2), 3.39 (br q, J = 10.6 Hz, 1H, NCH_2), 3.66 (dd, J = 9.3, 4.7 Hz, 1H, NCH), 5.33 (br t, J = 4.9 Hz, 1H, CHOAc), 7.36-7.50 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ -2.49 (q), -2.43 (q), 18.74 (t), 20.62 (q), 33.38 (d), 35.84 (t), 40.66 (t), 42.73 (t), 68.71 (d), 72.89 (d), 127.90 (d), 129.15 (d), 133.40 (d), 138.32 (s), 169.84 (s), 171.07 (s); mass spectrum, *m/e* (relative intensity) 330 (M^+-H, 1), 316 (M^+-CH_3,1), 288 (2), 173 (15), 272 (68), 253 (11), 243 (14), 212 (15), 135 (100), 117 (21), 96 (21), 43 (43); exact mass calcd for $C_{18}H_{24}NO_3Si$ (M^+-H) *m/e* 330.1544, found *m/e* 330.1534.

Indolizidinones 30: IR (neat) 1745, 1700 cm^{-1}; ^1H-NMR ($CDCl_3$, 500 MHz; characteristic signals) δ 0.32-0.38 (4 s's, $SiCH_3$), 1.97-2.15 (3 s's, $COCH_3$), 4.20 (br d, J = 13.1 Hz, NCH_2), 4.70 (dt, J = 8.3, 3.5 Hz, NCH), 5.27 (ddd, J = 6.5, 4.8, 2.0 Hz, CHOAc), 5.54 (dd, J = 10.2, 7.7 Hz, CHOAc); GC-MS data[31] mass spectrum, *m/e* (relative intensity) isomer 1; t_r = 9.02 min: 272 (36), 271 (9), 243 (11), 137 (14), 136 (20), 135 (100), 95 (19), 43 (49); isomer 2, t_r = 9.22 min: 272 (19), 271 (52), 270 (22), 137 (27), 136 (25), 135 (100), 116 (16), 43 (34); isomer 3, t_r =10.10 min: 330 (1), 272 (20), 137 (13), 136 (23), 135 (100), 116 (23), 96 (28), 43 (45). The parent ions for isomers 2 and 3 (*m/e* 331) were observed but were weak.

Treatment of 1.19 g (2.71 mmol) of a mixture of 25 and 26 (18:1, respectively) with a solution of 1.04 g (3.57 mmol) of tri-*n*-butyltin hydride and 56 mg of AIBN in 9.4 mL of dry benzene under identical conditions followed by work-up and chromatography over silica gel gave 297 mg (33%) of pure lactam 28, identical to material described above. Continued elution afforded 384 mg (43%) of a 3.2:1 mixture of lactams 28 and 29, containing about 3% of the reduced lactam 31 (GC-MS). Later fractions gave 160 mg (18%) of

indolizidinones 30, as a mixture of three diastereomers by GC-MS.

1*S*-(1α,7β,7aα)-1-(Acetyloxy)-7-[(acetyloxy)methyl]-hexahydro-3*H*-pyrrolizin-3-one (36). To a stirred solution of 167 mg (0.505 mmol) of pure silane 28 in 500 μL of dichloromethane was added 340 mg (2.09 mmol) of tetrafluoroboric acid-diethyl ether complex in one portion followed by stirring for 13 h. The solvent was removed in vacuo and the residue was dissolved in 2.0 mL of dry *N,N*-dimethylformamide. To this solution was added 142 mg (2.44 mmol) of anhydrous potassium fluoride and 441 mg of 80% *m*-chloroperbenzoic acid in sequence and the resulting solution was stirred for 14 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue (480 mg) was chromatographed over 10 g of silica gel (ethyl acetate; then ethyl acetate-methanol, 9:1) to give 143 mg of hydroxymethyl lactam 33 as an oil and 42 mg of impure material, suspected to be a mixture of dihydroxy lactam 34 and *m*-chlorobenzoic acid, as a white solid. The identity of the latter product was confirmed by acetylation (*vide infra*).

The hydroxylactam 33 was dissolved in 3.0 mL of dry dichloromethane and 100 mg (0.988 mmol) of triethylamine, 100 mg (0.980 mmol) of acetic anhydride and 10 mg of 4-(*N,N*-dimethylamino)pyridine added in sequence. The reaction mixture was stirred for 45 min, diluted with 20 mL of dichloromethane and the dichloromethane was washed with two 10-mL portions of saturated aqueous sodium bicarbonate. The aqueous washes were extracted with two 20-mL portions of dichloromethane and the combined dichloromethane layers were washed with 30 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue (132 mg) was chromatographed over 5 g of silica gel (ethyl acetate-hexane, 9:1) to give 64 mg (50%) of the diacetate 35 as a colorless oil: $[\alpha]_D^{20}$ = +15.4° (*c*, 1.05 $CHCl_3$); IR (neat) 1735, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.95-2.00 (m, 1H, CH_2), 2.06 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.21-2.29 (m, 1H, CH_2), 2.54-2.59 (m, 1H, CH), 2.79 (dd, *J* = 17.3, 6.6 Hz, 1H, $COCH_2$), 2.87 (dd, *J* = 17.3, 8.8 Hz, 1H, $COCH_2$), 3.06 (br t, *J* = 11.3 Hz, 1H, NCH_2), 3.58 (dt, *J* = 11.4, 8.4 Hz, 1H, NCH_2), 3.95 (dd, *J* = 6.2, 4.7 Hz, 1H, NCH), 4.19 (dd, *J* = 5.1, 1.7 Hz, 2H, CH_2OAc), 5.23-5.27 (m, 1H, CHOAc); ^{13}C-NMR ($CDCl_3$) δ 20.69 (q), 20.73 (q), 30.09 (t), 37.06 (d), 40.35 (t), 40.55 (t), 63.70 (t), 68.43 (d), 69.14 (d), 170.51 (s), 170.58 (s), 171.71 (s); mass spectrum, *m/e* (relative intensity) 195 (M^+-$C_2H_4O_2$, 11), 152 (5), 136 (18), 135 (100), 124 (7), 107 (23), 82 (33), 68 (11), 67 (10), 43 (84); exact mass calcd for $C_{10}H_{13}NO_3$ (M^+-$C_2H_4O_2$) *m/e* 195.0896, found *m/e* 195.0904.

1*S*-(1α,7β,7aα)-1-(Acetyloxy)-hexahydro-7-(hydroxymethyl)-3*H*-pyrrolizin-3-one (33) and 1*S*-(1α,7β,7aα)-Hexahydro-1-(hydroxy)-7-(hydroxymethyl)-3*H*-pyrrolizin-3-one (34). To a stirred solution of 679 mg (2.05 mmol) of pure silyl pyrrolizinone 28 in 2.5 mL of dry dichloromethane was added 1.45 g (8.93 mmol) of tetrafluoroboric acid-diethyl ether complex in one portion. The mixture was stirred for 16 h and the solvent removed in vacuo. The residue was dissolved in 8 mL of dry *N,N*-dimethylformamide and 580 mg (9.98 mmol) of anhydrous potassium fluoride and 1.80 g (8.34 mmol) of 80% *m*-chloroperbenzoic acid was added in sequence. The resulting pale yellow suspension was stirred for 14 h, filtered and the filtrate was concentrated in vacuo. The residue (2.34 g) was chromatographed over 60 g of silica gel (ethyl acetate-methanol, 9:1) to give 415 mg (80%) of monoacetate 33 as a pale yellow oil, contaminated with about 16% of *m*-chlorobenzoic acid by ^{1}H-NMR. Lactam 33: IR (neat) 3390 (br) 1790, 1675, cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.92-2.00 (m, 1H, CH_2), 2.10 (s, 3H, $COCH_3$), 2.13-2.23 (m, 1H, CH_2), 2.38-2.44 (m, 1H, CH), 2.77 (dd, *J* = 17.0, 8.2 Hz, 1H, $COCH_2$), 2.88-2.96 (m, 1H, $COCH_2$), 3.03 (br t, *J* = 10.3 Hz, 1H, NCH_2), 3.65 (dd, *J* = 10.9, 4.7 Hz, 1H, CH_2O), 3.71 (dd, *J* = 11.0, 4.7 Hz, 1H, CH_2O), 3.92 (dd, *J* = 6.2, 4.6 Hz, 1H, NCH), 5.42-5.46 (m, 1H, CHOAc); ^{13}C-NMR ($CDCl_3$) δ 20.77 (q), 29.90 (t), 39.56 (d), 40.48 (t), 40.69 (t), 61.90 (t), 68.67 (d), 69.70 (d), 170.66 (d), 172.62 (s); mass spectrum, *m/e* (relative intensity) 154 (13), 153 (100), 97 (35), 82 (25), 68 (31), 67 (29), 42 (23); exact mass calcd for $C_8H_{12}NO_2$ (M^+-$C_2H_3O_2$) *m/e* 154.0869, found *m/e* 154.0852.

Continued elution afforded 49 mg (9%) of material supected to be lactam 34, contaminated with about 35% of *m*-chlorobenzoic acid by ^{1}H-NMR. This material was converted to diacetate 35 as follows. To a stirred solution of 52 mg of impure dihydroxylactam 34 in 2.3 mL of dry dichloromethane was added 130 mg (1.28 mmol) of triethylamine, 130 mg (1.27 mmol) of acetic anhydride and 10 mg of 4-(*N,N*-dimethylamino)pyridine in sequence. The reaction mixture was stirred for 45 min, diluted with 15 mL of dichloromethane and the organic phase was washed with two 10-mL portions of saturated aqueous sodium bicarbonate and 30 mL of saturated aqueous sodium chloride. The organic phase was concentrated in vacuo to afford a yellow oil which was chromatographed over 3 g of silica gel (ethyl acetate-hexane; then ethyl acetate) to give 20 mg of the diacetate 35, identical by TLC and ^{1}H-NMR analysis to material prepared as described previously.

1*S*-(1α,7β,7aα)-Hexahydro-7-hydroxy-1*H*-pyrrolizine-1-methanol [(-)-dihydroxyheliotridane] (5). To a stirred solution of 225 mg (0.887 mmol; 84% purity) of lactam 34 in 10 mL of dry tetrahydrofuran was added 210 mg (5.54 mmol) of lithium aluminum hydride in small portions. The reaction mixture was heated at reflux for 1 h, cooled in a dry ice-acetone bath and 15 drops of water, 15 drops of 1 N aqueous sodium hydroxide and 15 drops of water were added in sequence. The resulting greyish-white gelatinous suspension was filtered through celite and the filter cake was suspended in tetrahydrofuran-methanol (1:1) and filtered. The combined filtrates were concentrated in vacuo to give a yellow residue (478 mg) which was chromatographed over 10 g of silica gel (methanol-concentrated ammonium hydroxide, 50:1) to afford 110 mg (78%) of 5 as an oil which solidified upon drying in vacuo (mp 63-66°C). An analytical sample was prepared by recrystallization from acetone: mp 72.5-74.0°C (lit.[10a] mp 76-77°C); $[\alpha]_D^{20}$ = -

36.0° (c, 0.670 EtOH), [lit.[10a] $[\alpha]_D$ = -34° (c, 3.36 EtOH)]; IR (CH_2Cl_2) 3600, 3540-2300 (br), 1110 cm^{-1}; ^1H-NMR ($CDCl_3$, 500 MHz) δ 1.32-1.40 (m, 1H, CH_2), 1.66 (ddddd, J = 12.4, 6.3, 2.4 Hz, 1H, CH_2), 1.82-1.96 (m, 1H, CH_2), 2.16 (ddddd, J = 12.2, 6.2, 1.6 Hz, 1H, CH_2), 2.53 (ddd, J = 16.5, 10.6, 5.9 Hz, 1H, NCH_2), 2.59-2.66 (m, 2H, NCH_2 and CH), 2.71-3.17 (br s, with ddd at 2.96, J = 16.7, 10.7, 5.9 Hz, 3H, OH and NCH_2), 3.31 (br t, with fine coupling, J = 9.5, 8.1, 1.6 Hz, 1H, NCH_2), 3.80 (t, J = 11.1 Hz, 1H, CH_2O), 3.95 (dd, J = 11.2, 5.5 Hz, 1H, CH_2O), 4.10-4.15 (m, 1H, CHO); ^{13}C-NMR ($CDCl_3$) δ 26.35 (t), 34.32 (t), 43.29 (d), 53.15 (t), 54.53 (t), 63.02 (t), 70.57 (d), 72.11 (d); exact mass calcd for $C_9H_{15}NO_2$ *m/e* 157.1102, found: *m/e* 157.1102.

Treatment of 5 with picric acid provided an analytically pure sample of the corresponding picrate: mp 155.0-156.5°C (lit.[10a] mp 157-158°C).

Anal. Calcd for $C_{14}H_{18}N_4O_9$: C, 43.51; H, 4.70; N, 14.51. Found: C, 43.44; H, 4.57; N, 14.77.

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