Anal. Calcd for $C_{12}H_{19}F_3O$: C, 60.90; H, 8.09. Found: C, 61.10; H, 8.20.

4-Phenyl-1,1,1-trifluorobut-3-yn-2-ol (35): ^1H NMR (CCl_4) δ 3.60 (s, OH), 4.86 (q, 1 H), 7.36 (m, 5 H); ^{19}F NMR (CCl_4) δ -80.0 (d); IR (neat) (cm^{-1}) 3300, 2200, 1130. Anal. Calcd for $C_{10}H_7F_3O$: C, 60.00; H, 3.53. Found: C, 59.95; H, 3.51.

1,1,1-Trifluorooct-3-yn-2-ol (36): ^1H NMR (CCl_4) δ 0.93 (t, 3 H), 1.53 (m, 4 H), 2.26 (t, 2 H), 3.76 (br s, OH), 4.6 (q, 1 H); ^{19}F NMR (CCl_4) δ -81.66 (d); IR (neat) (cm^{-1}) 3300, 2200, 1150. Anal. Calcd for $C_8H_{11}F_3O$: C, 53.32; H, 6.17. Found: C, 53.41; H, 6.14.

1-Phenyl-3-(trifluoromethyl)hexadec-1-yn-3-ol (37): ^1H NMR (CCl_4) δ 0.96 (t, 3 H), 1.26 (m, 22 H), 1.80 (t, 2 H), 2.50 (s, OH), 7.30 (m, 5 H); ^{19}F NMR (CCl_4) δ -86.30 (s); IR (CCl_4) (cm^{-1}) 3440, 2230, 1150. Correct combustion analysis not obtained.

4,4-Diphenyl-1,1,1-trifluorobut-3-en-2-one (38): ^1H NMR (CCl_4) δ 6.80 (s, 1 H), 6.98-7.53 (m, 10 H); ^{19}F NMR (CCl_4) δ -79.67 (s); IR (neat) (cm^{-1}) 1700, 1560, 1130. Anal. Calcd for $C_{16}H_{11}F_3O$: C, 69.56; H, 4.01. Found: C, 69.35; H, 4.12.

2,4-Diphenyl-1,1,1-trifluorobut-3-yn-2-ol (39): ^1H NMR (CCl_4) δ 2.93 (br s, OH), 6.67-7.93 (m, 10 H); ^{19}F NMR (CCl_4) δ -82.10 (s); IR (neat) (cm^{-1}) 3500, 2240, 1170. Anal. Calcd for $C_{16}H_{11}F_3O$: C, 69.56; H, 4.01. Found: C, 69.41; H, 4.05.

1-Phenyl-3-(trifluoromethyl)pent-4-en-1-yn-3-ol (40): ^1H NMR (CCl_4) δ 3.20 (s, OH), 5.27-5.67 (m, 2 H), 5.86-6.16 (m, 1 H), 7.07-7.67 (m, 5 H); ^{19}F NMR (CCl_4) δ -81.07 (s); IR (neat) (cm^{-1}) 3420, 2240, 1140. Anal. Calcd for $C_{12}H_9F_3O$: C, 63.71; H, 4.01. Found: C, 63.62; H, 4.05.

Acknowledgment. We would like to thank the NCS-U-NIH (Biomedical Research Support Grant RR7071), the United States Department of Agriculture (Grant 87-CRCR-1-2417), and the Herman Frasch Foundation (Grant 0145 HF) for financial support and Dr. R. van Breemen for the exact mass measurements.

α-Acylamino Radical Cyclizations: Application to the Synthesis of (-)-Swainsonine

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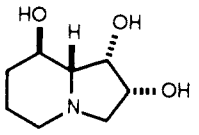
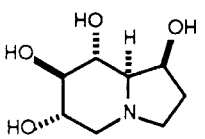
Free-radical precursor **21** was prepared in six steps from D-tartaric acid. Treatment of **21** with tri-*n*-butyltin hydride and AIBN gave a mixture of **23** and **24** in 81% yield. Ozonolysis of these isomeric olefins followed by the reduction of the resulting ketone gave indolizidinone **5**, which was converted to (-)-swainsonine (**1**) via a nine-step sequence that featured a sterically demanding alcohol inversion.

Swainsonine (**1**) is a polyhydroxylated indolizidine alkaloid first isolated from the fungus *Rhizoctonia leguminicola*[1] and later found in the legume *Swainsona canescens*[2] and the spotted locoweed *Astragalus lentiginosus*.[3] This simple base is believed to be responsible for locoism, a disease frequently contracted by range animals upon ingestion of the aforementioned plants.[3] Several years ago it was suggested that the physiological effects of swainsonine may in part be due to its ability to inhibit various mannosidases, enzymes involved in the processing of certain carbohydrates and glycoproteins. More recently it has been reported that swainsonine exhibits interesting immunoregulatory activity.[4] Although the structurally related glucosidase inhibitor castanospermine (**2**)[5] has received more attention as an immunoregulatory substance, the synthesis and biological evaluation of swainsonine and analogues thereof have been the focus of a number of research programs. A total of seven enantioselective syntheses of swainsonine have been reported. Given the structural relationship of swainsonine to mannose and glucose, it is not surprising that five of the syntheses use these carbohydrates as starting materials.[6-10] One of the remaining syntheses uses glutamic acid as a point of departure,[11] and the other synthesis relies on a series of enantioselective epoxidations to control asymmetry.[12]



1



2

As part of a program designed to explore the use of α-acylamino radical cyclizations in alkaloid synthesis, we

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(2) (a) Dorling, P. R.; Huxtable, C. R.; Vogel, P. *Neuropath. Appl. Neurobiol.* **1978**, *4*, 285. (b) Colgate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257.

(3) For reviews that focus upon the polyhydroxylated indolizidine alkaloids, see: Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1986; Vol. 26, Chapter 3. Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical And Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1. See also: Molyneux, R. J.; James, L. F. *Science (Washington, D.C.)* **1982**, *216*, 190.

(4) Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 926. Kino, T.; Inamura, N.; Nakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 936.

(5) Isolation: Hohenschutz, L. D.; Bell, E. B.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811. Biologial activity: Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature (London)* **1987**, *330*, 74. See also: Dagani, R. *Chem. Eng. News* **1987**, *65* (June 29), 25-27.

(6) (a) Bashyal, B. P.; Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083. (b) Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, *25*, 1853.

(7) (a) Ali, M. H.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 447. (b) Ali, M. H.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1985**, *136*, 225.

(8) (a) Suami, T.; Tadano, K.-I.; Iimura, Y. *Chem. Lett.* **1984**, 513. (b) Suami, T.; Tadano, K.-I.; Iimura, Y. *Carbohydr. Res.* **1985**, *136*, 67.

(9) Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1984**, 1201.

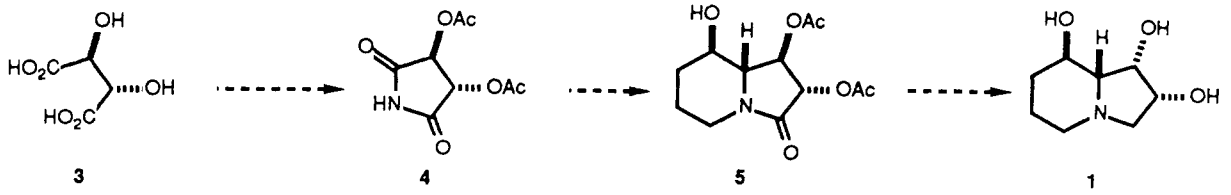
(10) Setoi, H.; Takeno, H.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 3948.

(11) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1987**, *35*, 2140.

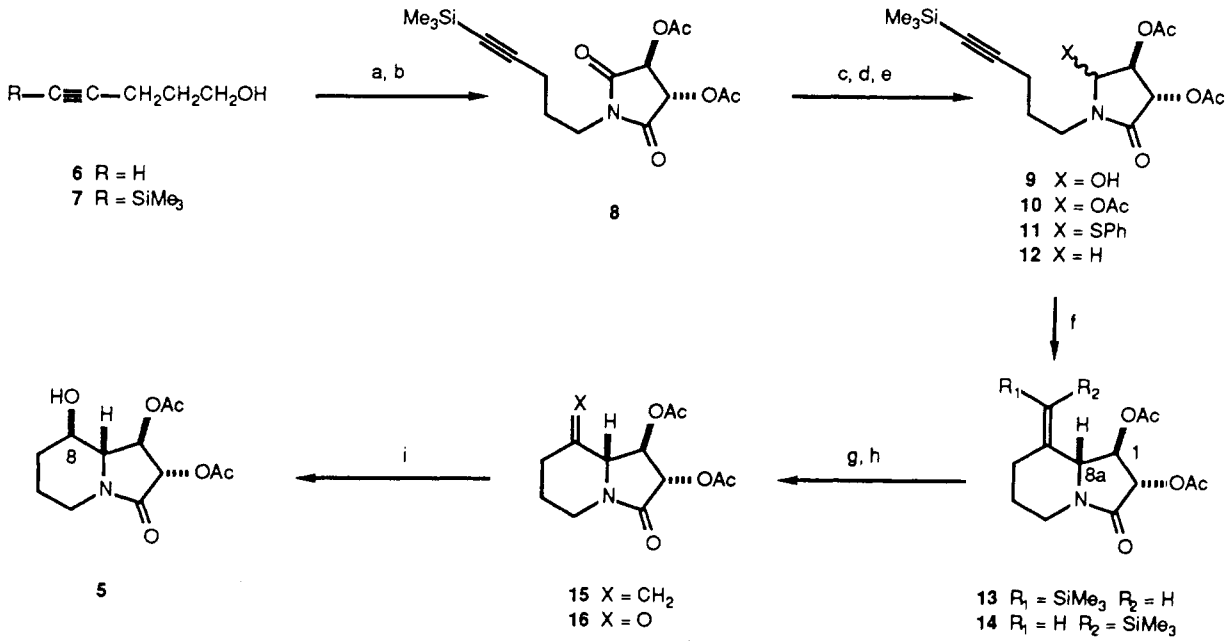
(12) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420.

0022-3263/88/1953-6022$01.50/0

Scheme I



Scheme II[a]



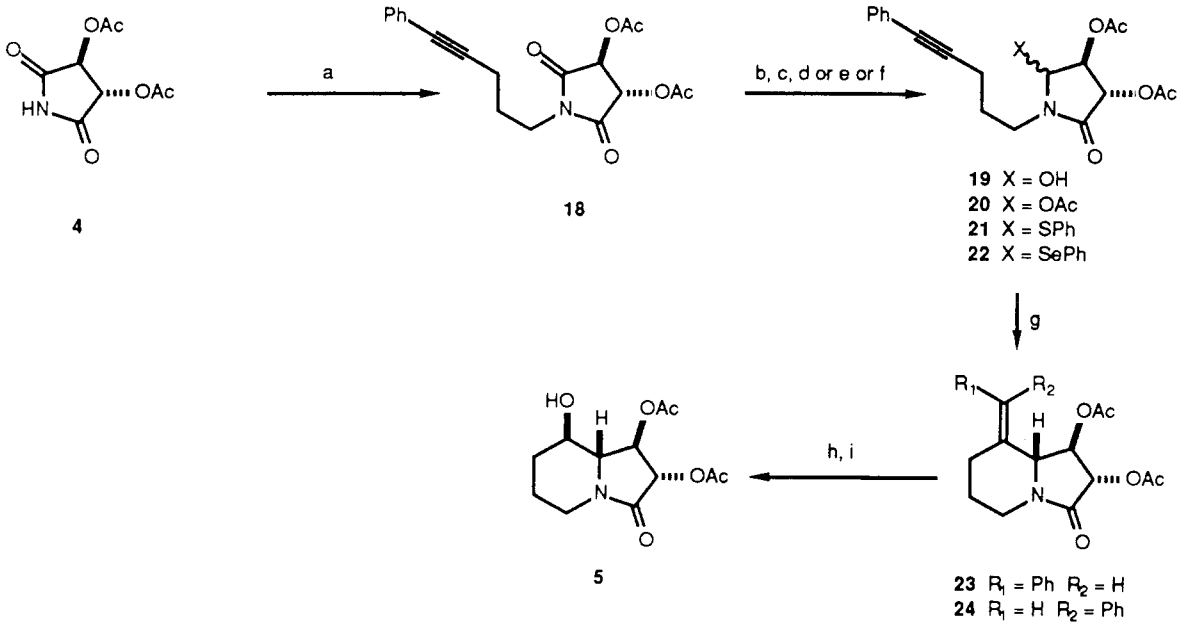
[a] (a) *n*-BuLi (2 equiv); Me_3SiCl (2 equiv); H_2O, HCl. (b) Ph_3P, $EtO_2CN{=}NCO_2Et$, **4**, THF. (c) $NaBH_4$, MeOH. (d) Ac_2O, Et_3N, 4-DMAP, CH_2Cl_2. (e) PhSH, TsOH (cat.). (f) *n*-Bu_3SnH, AIBN, PhH, Δ. (g) *p*-$MeC_6H_4SO_2H$, CH_3CN, H_2O. (h) O_3, CH_2Cl_2; Me_2S. (i) $NaBH_4$, MeOH.

undertook a synthesis of swainsonine according to the general plan outlined in Scheme I.[13,14] We felt that several features of this plan were attractive. For example, the use of tartaric acid (**3**) as a starting material would provide access to either enantiomer of swainsonine as well as a variety of stereoisomers of **1**. In addition, our past experience in the area of pyrrolizidine alkaloid synthesis gave us confidence that a 2-aza-6-heptynyl radical cyclization followed by an appropriate degradation would allow us to graft the required four-carbon fragment onto tartarimide **4**.[15] Our major concern revolved around the inversion of C(1) stereochemistry that would have to be accomplished en route from **5** to **1**.

Our first approach to projected indolizidinone intermediate **5** is outlined in Scheme II. We had previously reported a synthesis of pyrrolizidinones that revolved around the cyclization of a 2-aza-6-(trimethylsilyl)-5-hexynyl radical.[15] Thus, we felt that cyclization of the 2-aza-7-(trimethylsilyl)-6-heptynyl radical derived from **11** would provide an indolizidinone suitable for conversion to **5**. Imide **4** and acetylene **7**, the compounds needed to assemble radical precursor **11**, were prepared in a straightforward manner. Thus, sequential treatment of D-tartaric acid with acetyl chloride, ammonia, and acetyl chloride again gave crystalline imide **4** in 48% yield. Sequential treatment of 4-pentyn-1-ol (**6**) with 2 equiv of *n*-butyllithium and chlorotrimethylsilane followed by aqueous acid gave acetylene **7** in 92% yield.[16] Mitsunobu coupling of **4** and **7** afforded imide **8** in 86% yield.[17] Reduction of **8** with sodium borohydride followed by acetylation of the resulting alcohol **9** gave triacetate **10** in 62% yield.[18,19] Finally, treatment of **10** with thiophenol and a catalytic amount of *p*-toluenesulfonic acid gave radical precursor **11** (92%).[13] As anticipated, treatment of **11** with tri-*n*-butyltin hydride[20] and azobis(isobutyronitrile) in benzene under reflux gave indolizidinones **13** (31%) and **14** (39%) along with reduction product **12** (11%). The stereochemistry at C(8a) in cyclization products **13** and **14** was based on the expectation that cyclization would occur opposite the C(1) acetoxy group,[13,15] and olefin geometry was assigned on the basis of NOE experiments that established the relationship between the vinylic and C(1) hydrogens. Although it was possible to obtain pure samples of **13** and **14**, it was op-

(13) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430.
(14) For reviews of radical chemistry, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417, 489. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883. (e) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. (f) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.
(15) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959.
(16) Cochrane, J. S.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 361.
(17) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(18) For reduction of tartarimide derivatives similar to the ones described, see: (a) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115. (b) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1987. Also see ref 13.
(19) Steglich, W.; Hofle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(20) For excellent general reviews of tin hydride chemistry, see: (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987; Chapters 3–7. (b) Neumann, W. P. *Synthesis* **1987**, 665.

Scheme III[a]



[a] (a) Ph_3P, $EtO_2CN{=}NCO_2Et$, $PhC{\equiv}CCH_2CH_2CH_2OH$ (17), THF. (b) $NaBH_4$, MeOH. (c) Ac_2O, Et_3N, 4-DMAP, CH_2Cl_2. (d) PhSH, TsOH (cat.). (e) n-Bu_3P, PhSSPh. (f) PhSeH, TsOH. (g) n-Bu_3SnH, AIBN, PhH, Δ. (h) O_3, MeOH; Me_2S. (i) $NaBH_4$, MeOH.

erationally most convenient to continue with the mixture of products obtained from the aforementioned radical cyclization. Thus, protodesilylation of a mixture of **12**–**14** using p-toluenesulfinic acid in aqueous acetonitrile gave olefin **15** (58% based on **13** + **14**), which was easily separated from unchanged **12** by using column chromatography.[21] Finally, ozonolysis of **15** followed by reduction of the resulting crude ketone **16** completed the synthesis of **5** in 68% yield. The stereochemical course of the reduction (**16** → **5**) is consistent with the propensity of sodium borohydride to reduce unhindered cyclohexanones with "axial" delivery of hydride and was confirmed by the appearance of the C(8) hydrogen as a doublet of a doublet of doublets (J = 13.5, 9.4, 4.4 Hz) at δ 3.54 in the ^{1}H NMR spectrum of **5**.[22]

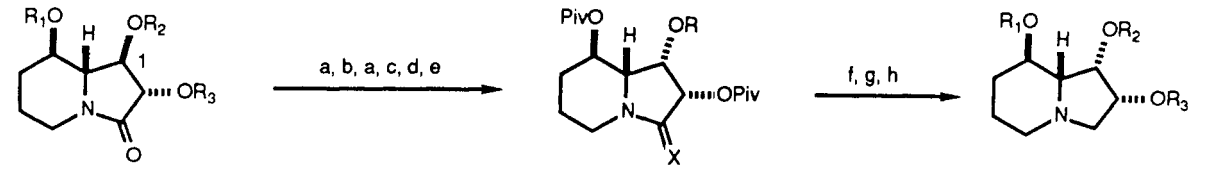
Although the synthesis of **5** described in Scheme II did provide gram quantities of material, we were disappointed in the overall yield for the degradation of the alkylidene moiety to a hydroxyl group (**13** + **14** → **5**). Ample literature precedent suggested that use of an aryl group in place of the trimethylsilyl group would improve the radical cyclization and also streamline the degradation process.[23] This expectation was realized as outlined in Scheme III. Acetylenic alcohol **17** was prepared from iodobenzene and **6** in 76% yield by using a palladium-catalyzed coupling reaction.[24] Imide **4** was then alkylated with **17** to afford tartarimide **18** in 96% yield.[17] Reduction of **18** by using sodium borohydride gave carbinol lactam **19** (91%) as a mixture of diastereomers.[18] Acetylation of **19** followed by acetoxy–thiophenoxy exchange gave radical precursor **21** in 79% overall yield. Addition of thiophenol to the triple bond was frequently observed during the exchange reaction (**20** → **21**). This problem could be avoided by treating carbinol **19** with diphenyl disulfide in the presence of tri-n-butylphosphine to afford **21** directly in 77% yield.[25] Another alternative involved treating triacetate **20** with selenophenol and p-toluenesulfonic acid. This procedure gave radical precursor **22** in 86% overall yield from **19**.

When thioether **21** was subjected to typical radical cyclization conditions, an 80–85% yield of a mixture of indolizidinones **23** and **24** was obtained.[26] The ratio of these geometrical isomers varied from one run to another, but the major product was always **23**.[27] Similar exposure of selenide **22** to cyclization conditions gave a mixture of **23** and **24** (85–92%) in which **24** always predominated.[28] Mechanistic reasoning predicts that the stereochemical course of these reactions (**21** or **22** → **23** + **24**) should be identical. Perhaps some entity, produced in the cyclization of thioether **21** but absent in the cyclization of **22**, catalyzes the isomerization of **24** to **23**.[29] According to our expectations, the conversion of **23** and **24** to **5** was superior to the preparation of this alcohol from vinylsilanes **12** and **13**. Thus, ozonolysis of **23** + **24** in methanol followed by sequential treatment of the reaction mixture with dimethyl sulfide and sodium borohydride gave **5** in 74% overall yield.[30]

Having accomplished the well-precedented portion of our plan, we were faced with the task of inverting stereo-

(21) Buchi, G.; Wuest, H. *Tetrahedron Lett.* **1977**, 4305.
(22) The stereochemical course of metal hydride reduction of cyclic ketones has been reviewed: Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.
(23) For examples of phenylacetylenes as addends in radical cyclizations, see: (a) Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313. (b) Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1982**, *23*, 2505. (c) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841.
(24) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
(25) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409. Other research groups have prepared phenylthio lactams via this method: Kano, S.; Yuasa, Y.; Asami, K.; Shibuya, S. *Chem. Lett.* **1986**, 735. Keck, G. E.; Enholm, E. J. *Tetrahedron Lett.* **1985**, *26*, 3311.
(26) This material was contaminated with about 10% of a mixture of other compounds. A pure sample of **23** was isolated by chromatography.
(27) The ratio of **23** to **24** varied from 5.6:1 to 1.4:1.
(28) This material was contaminated with about 10% of a mixture of other products. A pure sample of **24** was isolated by chromatography. The ratio of **23** to **24** was typically in the range of 1:6.
(29) Diphenyl disulfide or an alternate source of phenylthiyl radicals is one possibility. We did show that tri-n-butyltin radicals would isomerize **24** to **23**. Thus, treatment of a sample of **24** (71% pure by GC) with 10 equiv of tin hydride and a small amount of AIBN in benzene under reflux gave a 5.3:1 mixture of olefins **23**:**24** in 66% yield. It is clear, however, that this is not the major factor underlying the difference in behavior of **21** and **22**.
(30) Ozonolysis of vinylsilanes does not normally lead to double bond cleavage: Buchi, G.; Wuest, H. *J. Am. Chem. Soc.* **1978**, *100*, 294.

Scheme IV[a]



5 $R_1 = H$ $R_2 = R_3 = Ac$
25 $R_1 = Piv$ $R_2 = R_3 = Ac$
26 $R_1 = Piv$ $R_2 = R_3 = H$
27 $R_1 = R_3 = Piv$ $R_2 = H$
28 $R_1 = R_2 = R_3 = Piv$
30 $R_1 = R_3 = Piv$ $R_2 = Ac$

29 X = O R = Ac
31 X = S R = Ac

Piv = Me_3CCO

32 $R_1 = R_3 = Piv$ $R_2 = Ac$
1 $R_1 = R_2 = R_3 = H$

[a] (a) Me_3CCOCl, 4-DMAP, pyridine. (b) NH_3, MeOH. (c) Tf_2O. (d) KOAc, 18-crown-6, DMF. (e) Ac_2O, Et_3N, 4-DMAP. (f) (p-$MeOC_6H_4PS_2)_2$, $PhCH_3$, Δ. (g) Raney Ni, EtOH. (h) $MeNH_2$.

chemistry at C(1). This was accomplished as outlined in Scheme IV. Treatment of alcohol **5** with pivaloyl chloride gave **25** in 93% yield. Ammonolysis of the acetates was accomplished by using methanolic ammonia, and the resulting crude diol **26** was acylated by using pivaloyl chloride to afford diester **27** (67%) and triester **28** (20%), easily separable by column chromatography. The regiochemical course of the monoesterification was determined by the multiplicity of the C(1) proton, which appeared as a triplet (J = 5.8 Hz) at δ 4.12 in the ^1H NMR spectrum of **27**. This selectivity was a welcome surprise. Having appropriately adjusted the blocking groups on the indolizidinetriol nucleus, we attempted the inversion of stereochemistry. A number of methods met with failure,[31] but the desired transformation was eventually accomplished by exposing **27** to triflic anhydride followed by treating the resulting triflate with anhydrous potassium acetate and 18-crown-6 in *N,N*-dimethylformamide.[32] Acetylation of the resulting crude product gave acetate **29** in 85% yield. To establish that inversion of stereochemistry had in fact been accomplished, alcohol **27** was acetylated to afford isomeric acetate **30** (89%), clearly different than **29**.

The synthesis of swainsonine (**1**) was completed in a straightforward manner. Treatment of lactam **29** with Lawesson's reagent gave thiolactam **31** (97%).[33] Desulfurization of **31** using Raney nickel afforded **32** in 96% yield.[34] Finally, the three acyl groups were removed by using methylamine to afford swainsonine (**1**) in 63% yield after purification by recrystallization. In summary, a total synthesis of (−)-swainsonine has been accomplished in 15 steps and 14% overall yield from imide **4** and alcohol **17**. The synthesis features a stereoselective free-radical cyclization and a stereochemically demanding alcohol inversion. Finally, slight modifications of this route should provide access to a number of stereoisomeric indolizidinetriols.[35]

Experimental Section

All melting points are uncorrected as are boiling points. Mass spectra were obtained 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, phenylseleno 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 by using a 25-m phenylmethylsilicone capillary column.

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.[36] 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 chromtography 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*,4*S*)-3,4-Diacetoxy-2,5-pyrrolidinedione (4). A slurry of 100 g of D-tartaric acid (**3**) and 400 mL of acetyl chloride was stirred under reflux for 30 h, during which the solution became homogeneous. Excess acetyl chloride was removed by distillation at 1 atm, and trace amounts were removed under high vacuum.

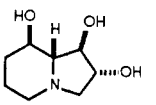
(31) For example, alcohol **27** was inert to Mitsunobu inversion conditions: Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783. When treated with either sodium or potassium acetate and 18-crown-6 in DMF, the mesylate derived from **27** gave several products, none of which corresponded to acetate **29**.

(32) This method is essentially a hybrid of several reported inversion sequences. For related examples, see: (a) Hoppe, D.; Tarara, G.; Wilchens, M.; Jones, P. G.; Schmidt, D.; Stezowski, J. J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1034. (b) Ranganathan, R.; Larwood, D. *Tetrahedron Lett.* **1978**, 4341. (c) Ranganthan, R. *Tetrahedron Lett.* **1977**, 1291. For the increased nucleophilicity of potassium acetate in the presence of 18-crown-6, see: Liotta, C. L.; Harris, H. P.; McDermott, M.; Gonzalez, T.; Smith, K. *Tetrahedron Lett.* **1974**, 2417. Durst, H. D. *Tetrahedron Lett.* **1974**, 2420.

(33) (a) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158. (b) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

(34) Mozingo, R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 181. For reviews of the synthetic applications of Raney nickel, including reduction of sulfur compounds, see: (a) Pizey, J. S. In *Synthetic Reagents*; Ellis Horwood: Chichester, 1974; Vol. 2, Chapter 4. (b) Pettit, G. R.; van Tamelen, E. E. *Org. React. (N.Y.)* **1962**, *12*, 356.

(35) For example, reduction of **5** using lithium aluminum hydride gave a 25% yield of indolizidinetriol **i** (Ikota, N.; Hanaki, A. *Heterocycles* **1987**,



i

26, 2369): mp 120–121 °C; IR (CH_2Cl_2) 3400 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 1.26 (qd, J = 12.2, 4.0 Hz, 1 H, CH_2); 1.55 (qt, J = 13.0, 4.0 Hz, 1 H, CH_2), 1.70–1.78 (m, 1 H, CH_2), 1.88 (t, J = 9.0 Hz, 1 H, CH_2), 1.96–2.10 (m, 2 H, NCH_2 and NCH), 2.68 (dd, J = 10.8, 6.8 Hz, 1 H, NCH_2), 2.86–2.94 (m, with d at 2.87, J = 10.8 Hz, 2 H, NCH_2), 3.58 (ddd, J = 13.5, 9.5, 4.0 Hz, 1 H, CHO), 3.93 (dd, J = 6.8, 3.2 Hz, 1 H, CHO), 4.08 (m, 1 H, CHO); ^{13}C NMR (D_2O) δ 25.2, 34.9, 53.7, 62.2, 73.3, 75.9, 78.9, 84.8; exact mass calcd for $C_8H_{15}NO_3$ m/e 173.1053, found 173.1058.

(36) Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81.

The residue was recrystallized from dichloromethane to give 133 g (93%) of (3*S-trans*)-3,4-diacetoxydihydro-2,5-furandione: mp 133–135 °C (lit.[37] mp 133–134 °C for its enantiomer); $[\alpha]^{20}_D$ = −89.3° (*c* 2.21, $CHCl_3$) [lit.[37] $[\alpha]^{20}_D$ = +97.2° (*c* 0.47, $CHCl_3$), for its enantiomer]; IR (CH_2Cl_2) 1890, 1810, 1765, 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.18 (s, 6 H, $COCH_3$), 5.62 (s, 2 H, CHOAc); ^{13}C NMR ($CDCl_3$) δ 20.03, 72.06, 163.26, 169.63; exact mass calcd for $C_6H_5O_5$ ($M^+ - C_2H_3O_2$) *m/e* 157.0136, found 157.0143.

Ammonia was passed through a solution of 111 g (0.51 mol) of the above anhydride in 1500 mL of dichloromethane contained in a flask equipped with a mechanical stirrer, condenser, and a gas inlet for 5 h. The solvent was removed under reduced pressure and the residue dried in vacuo. To the residue was added 400 mL of acetyl chloride, and the resulting slurry was warmed under reflux for 12 h. Most of the excess acetyl chloride was removed by distillation at 1 atm, and the residual volatile materials were removed under vacuum. To the residue was added 400 mL of ethyl acetate, and the resulting slurry was filtered through Celite. The filter cake was washed with 1000 mL of ethyl acetate and filtered. The combined filtrates were concentrated in vacuo, and the residue was crystallized from dichloromethane–hexane to give 53.0 g (48%) of imide **4**: mp 146–147 °C; $[\alpha]^{20}_D$ = −126.5° (*c* 0.965, $CHCl_3$); IR (CH_2Cl_2) 3370, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.22 (s, 6 H, $COCH_3$), 5.56 (s, 2 H, CHOAc), 8.92 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 20.26 (q), 73.26 (d), 169.05 (s), 169.95 (s); mass spectrum, *m/e* (relative intensity) 173 (14), 155 (11), 144 (4), 131 (20), 43 (100); exact mass calcd for $C_6H_7NO_5$ ($M^+ - C_2H_2O$) *m/e* 173.0324, found 173.0348.

Anal. Calcd for $C_8H_9NO_6$: C, 44.64; H, 4.22. Found: C, 44.81; H, 4.34.

5-(Trimethylsilyl)-4-pentyn-1-ol (7).[16] To a solution of 12.9 g (0.33 mol) of 4-pentyn-1-ol (**6**) in 250 mL of tetrahydrofuran at −78 °C was added 235 mL (0.33 mol) of 1.40 M *n*-butyllithium in hexane over a period of 45 min. The mixture was stirred at −78 °C for an additional 30 min followed by the addition of 36.5 g (0.34 mol) of trimethylsilyl chloride dropwise over a period of 30 min. The mixture was allowed to warm to room temperature and was stirred overnight. The solution was cooled to 0–5 °C, and 100 mL of 5% aqueous hydrochloric acid was added. The organic phase was separated, and the aqueous phase was extracted with two 150-mL portions of diethyl ether. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled to provide 22.1 g (92%) of alcohol **7**: bp 74–77 °C/1.3 mmHg; IR (neat) 3340, 2170 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.14 (s, 9 H, $SiCH_3$), 1.77 (quintet, *J* = 6 Hz, 2 H, CH_2), 1.83 (br s, 1 H, OH), 2.37 (t, *J* = 6 Hz, 2 H, $\equiv CCH_2$), 3.73 (t, *J* = 6 Hz, 2 H, OCH_2).

(3*S*,4*S*)-3,4-Diacetoxy-1-[5-(trimethylsilyl)-4-pentynyl]-2,5-pyrrolidinedione (8). To a solution of 13.8 g (64.1 mmol) of imide **4**, 10.0 g (64.1 mmol) of alcohol **7**, and 17.6 g (67.2 mmol) of triphenylphosphine in 175 mL of tetrahydrofuran at 0–5 °C under an atmosphere of argon was added a solution of 12.3 g (67.2 mmol) of diethyl azodicarboxylate in 25 mL of tetrahydrofuran dropwise over a period of 30 min. The solution was stirred for at 0–5 °C for 1 h and at room temperature for 8 h. The mixture was concentrated in vacuo, and the residue was triturated with 250 mL of ethyl acetate–hexane (3:7). The precipitate was collected and rinsed with 500 mL of ethyl acetate–hexane (2:8). The combined filtrates were concentrated in vacuo. The residue was chromatographed over 250 g of silica gel (ethyl acetate–hexane, 1:4) in two batches to give 19.4 g (86%) of imide **8**: $[\alpha]^{25}_D$ = −68.2° (*c* 3.398, $CHCl_3$); IR (neat) 2180, 1755, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.15 (s, 9 H, $SiCH_3$), 1.87 (quintet, *J* = 7.2 Hz, 2 H, CH_2), 2.19 (s, 6 H, $COCH_3$), 2.28 (t, *J* = 7.1 Hz, 2 H, $\equiv CCH_2$), 3.69 (m, 2 H, NCH_2), 5.49 (s, 2 H, CHOAc); ^{13}C NMR ($CDCl_3$) δ 0.04 (q), 17.4 (t), 20.2 (q), 26.3 (t), 38.7 (t), 72.8 (d), 85.7 (s), 105.3 (s), 169.2 (s), 169.8 (s); exact mass calcd for $C_{15}H_{20}NO_6Si$ ($M^+ - CH_3$) *m/e* 338.1060, found 338.1031.

(3*S*,4*S*,5*RS*)-3,4,5-Triacetoxy-1-[5-(trimethylsilyl)-4-pentynyl]-2-pyrrolidinone (10). To a well-stirred solution of 14.2 g (40.2 mmol) of imide **8** in 300 mL of methanol at −30 °C was added 12.2 g (321 mmol) of sodium borohydride in six portions over a period of 45 min. The mixture was stirred at −30 °C for an additional hour, and then 200 mL of saturated aqueous sodium bicarbonate and 150 mL of water were added in sequence. The organic layer was separated, and the aqueous layer was extracted with four 125-mL portions of dichloromethane. The combined organic layers were washed with 150 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in 100 mL of dichloromethane, and 6 mL of acetic anhydride, 10 mL of triethylamine, and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine were added. The mixture was stirred at room temperature for 4 h, diluted with 200 mL of dichloromethane, and washed with 150 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with three 75-mL portions of dichloromethane, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 230 g of silica gel (ethyl acetate–hexane, 1:3) to afford 9.90 g (62%) of triacetate **10**: IR (neat) 2180, 1760–1725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, major diastereomer) δ 0.15 (s, 9 H, $SiCH_3$), 1.75 (m, 1 H, CH_2), 1.85 (m, 1 H, CH_2), 2.13 (s, 3 H, $COCH_3$), 2.15 (s, 3 H, $COCH_3$), 2.16 (s, 3 H, $COCH_3$), 2.26 (t, *J* = 6.7 Hz, 1 H, $\equiv CCH_2$), 2.27 (t, *J* = 6.9 Hz, 1 H, $\equiv CCH_2$), 3.18 (ddd, *J* = 14.1, 8.5, 5.6 Hz, 1 H, NCH_2), 3.60 (ddd, *J* = 14.2, 8.5, 6.8 Hz, 1 H, NCH_2), 5.11 (dd, *J* = 4.1, 2.1 Hz, 1 H, CHOAc), 5.23 (d, *J* = 4.1 Hz, 1 H, CHOAc), 6.07 (d, *J* = 2.1 Hz, 1 H, NCHOAc); exact mass calcd for $C_{17}H_{24}NO_7Si$ ($M^+ - CH_3$) *m/e* 382.1322, found 382.1322.

(3*S*,4*S*,5*RS*)-3,4-Diacetoxy-1-[5-(trimethylsilyl)-4-pentynyl]-5-(phenylthio)-2-pyrrolidinone (11). A mixture of 6.40 g (16.1 mmol) of triacetate **10**, 2.13 g (19.4 mmol) of thiophenol, and a catalytic amount of *p*-toluenesulfonic acid in 75 mL of dichloromethane was stirred at room temperature under argon for 12 h. The reaction mixture was diluted with 200 mL of dichloromethane and washed sequentially with 100 mL of saturated aqueous sodium bicarbonate and 100 mL of saturated aqueous sodium chloride. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 90 g of silica gel (ethyl acetate–hexane, 1:1) to provide 5.91 g (92%) of sulfide **11**: IR (neat) 2180, 1760, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.15–0.16 (2 s, 9 H, $SiCH_3$), 1.69–1.88 (m, 2 H, CH_2), 1.99–2.22 (4 s, 6 H, $COCH_3$), 2.26 (t, *J* = 7 Hz, 1 H, $\equiv CCH_2$), 2.27 (t, *J* = 7 Hz, 1 H, $\equiv CCH_2$), 3.38 (ddd, *J* = 13.9, 7.9, 6.1 Hz, 1 H, NCH_2), 3.56 (ddd, *J* = 13.7, 8.0, 5.6 Hz, 1 H, NCH_2), 4.76–4.79 (m, 1 H, CHOAc), 5.24–5.36 (m, with d at 5.25, *J* = 7.1 Hz, 2 H, NCHS and CHOAc), 7.35–7.48 (m, 5 H, ArH); exact mass calcd for $C_{16}H_{24}NO_5Si$ ($M^+ - C_6H_5S$) *m/e* 338.1424, found 338.1409.

(1*R*)-(1β,2α,8*E*,8aβ)-1,2-Diacetoxy-8-[(trimethylsilyl)methylene]hexahydro-3(2*H*)-indolizinone (13), (1*R*)-(1β,2α,8*Z*,8aβ)-1,2-Diacetoxy-8-[(trimethylsilyl)methylene]hexahydro-3(2*H*)-indolizinone (14), and (3*S*,4*S*)-3,4-Diacetoxy-1-[5-(trimethylsilyl)-4-pentynyl]-2-pyrrolidinone (12). To a solution of 8.01 g (17.9 mmol) of sulfide **11** in 420 mL of dry benzene under reflux was added a solution of 7.74 g (26.6 mmol) of tri-*n*-butyltin hydride and 170 mg of azobis(isobutyronitrile) in 40 mL of dry benzene via syringe pump at a rate of 1.7 mL h^{-1}. The mixture was warmed under reflux for an additional hour, cooled to room temperature, and concentrated in vacuo. The residue was chromatographed over 250 g of silica gel (ethyl acetate–hexane, 1:1), which removed most of the tin byproducts and afforded 995 mg of pure vinylsilane **14** and 2.81 g of a mixture of vinylsilanes **14** and **13** and reduction product **12**, along with 1.45 g of pure vinylsilane **13**. The mixture of vinylsilanes and reduction product was chromatographed over a Lobar size C column (ethyl acetate–hexane, 1:1; then ethyl acetate–hexane, 2:1) to give a total of 2.33 g (39%) of vinylsilane **14**, 676 mg (11%) of reduction product **12**, and 1.91 g (31%) of vinylsilane **13**. Vinylsilane **14**: mp 120–123 °C; $[\alpha]^{25}_D$ = −110.1° (*c* 1.73, $CHCl_3$); IR (CH_2Cl_2) 1750, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 9 H, $SiCH_3$), 1.62 (m, 2 H, CH_2), 1.98 (s, 3 H, $COCH_3$), 2.05 (s, 3 H, $COCH_3$), 2.06 (m, 1 H, $=CCH_2$), 2.31 (ddd, *J* = 13.0, 11.7, 2.4 Hz, 1 H, $=CCH_2$), 2.64 (dddd, *J* = 14.1, 13.6, 9.8, 1.2 Hz, 1 H, NCH_2), 4.00 (ddd, *J* = 13.6, 9.9, 2.2 Hz, 1 H, NCH_2), 4.36 (d, 7.4 Hz, 1 H, NCH), 5.29 (dd, *J* = 7.8, 7.5 Hz, 1 H, CHOAc), 5.43 (dd, *J* = 8.0, 1.3 Hz, 1 H, CHOAc), 5.52 (br s, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 0.26 (q), 20.7 (q), 20.8 (q), 23.9 (t), 30.8 (t), 34.9 (t), 59.9 (d), 75.2 (d), 75.8 (d), 130.8 (d), 149.9

(37) Shriner, R. L.; Furrow, C. L. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 242.

(s), 165.8 (s), 169.9 (s), 170.3 (s); exact mass calcd for $C_{16}H_{25}NO_5Si$ m/e 339.1499, found 339.1499.

Anal. Calcd for $C_{16}H_{25}NO_5Si$: C, 56.61; H, 7.43. Found: C, 56.14; H, 6.91.

Reduction product **12**: IR (neat) 2170, 1750, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 9 H, $SiCH_3$), 1.68 (quintet, J = 7.1 Hz, 2 H, CH_2), 2.01 (s, 3 H, $COCH_3$), 2.06 (s, 3 H, $COCH_3$), 2.17 (t, J = 7.0 Hz, 1 H, $\equiv CCH_2$), 2.18 (t, J = 7.1 Hz, 1 H, $\equiv CCH_2$), 3.21 (dd, J = 10.4, 5.7 Hz, 1 H, NCH_2), 3.24 (dt, J = 13.8, 7.0 Hz, 1 H, NCH_2), 3.39 (dt, J = 13.8, 6.9 Hz, 1 H, NCH_2), 3.75 (dd, J = 10.4, 8.0 Hz, 1 H, NCH_2), 5.21 (dt, J = 8.0, 5.9 Hz, 1 H, CHOAc), 5.34 (d, J = 6.1 Hz, 1 H, CHOAc); ^{13}C NMR ($CDCl_3$) δ 0.06 (q), 17.4 (t), 20.6 (q), 25.9 (t), 42.3 (t), 49.6 (t), 71.5 (d), 74.5 (d), 85.7 (s), 105.5 (s), 167.2 (s), 169.8 (s), 170.3 (s); exact mass calcd for $C_{16}H_{25}NO_5Si$ m/e 339.1499, found 399.1483.

Vinylsilane **13**: mp 74–76.5 °C; $[\alpha]^{25}_D$ = +23.1° (c 1.80, $CHCl_3$); IR (CH_2Cl_2) 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 9 H, $SiCH_3$), 1.45 (m, 1 H, CH_2), 1.78 (m, 1 H, CH_2), 2.01 (s, 3 H, $COCH_3$), 2.05 (m, 1 H, $=CCH_2$), 2.06 (s, 3 H, $COCH_3$), 2.61 (dt, J = 14.1, 3.7 Hz, 1 H, $=CCH_2$), 2.78 (tdd, J = 13.3, 3.9, 1.3 Hz, 1 H, NCH_2), 3.90 (d, J = 6.8 Hz, 1 H, NCH), 4.12 (ddd, J = 13.2, 2.7, 1.5 Hz, 1 H, NCH_2), 5.27 (br s, 1 H, $=CH$), 5.36 (dd, J = 6.6, 1.5 Hz, 1 H, CHOAc), 5.49 (t, J = 6.6 Hz, 1 H, CHOAc); ^{13}C NMR ($CDCl_3$) δ 0.04 (q), 20.7 (q), 20.8 (t), 24.7 (t), 39.7 (t), 61.4 (d), 74.5 (d), 75.0 (d), 149.4 (d), 165.4 (d), 169.4 (s), 169.8 (s), 170.3 (s); exact mass calcd for $C_{14}H_{22}NO_3Si$ ($M^+ - C_2H_3O_2$) m/e 280.1369, found 280.1347.

(1*R*)-(1β,2α,8aβ)-1,2-Diacetoxy-8-methylenehexahydro-3-(2*H*)-indolizinone (15). To a stirred solution of 989 mg (2.92 mmol) of vinylsilane **14** in 12 mL of a 2% aqueous acetonitrile solution was added 1.10 g (3.49 mmol) of *p*-toluenesulfinic acid in one portion. The mixture was stirred at room temperature for 48 h, and the solution was concentrated in vacuo. The residue was dissolved in 30 mL of dichloromethane, and 1.08 g (10.6 mmol) of acetic anhydride, 1.09 g (10.8 mmol) of triethylamine, and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine were added in sequence. The reaction mixture was stirred for 3 h and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (ethyl acetate–hexane, 1:1) to give 498 mg (64%) of olefin **15**: mp 90–95 °C; $[\alpha]^{25}_D$ = +0.43° (c 0.935, $CHCl_3$); IR (CH_2Cl_2) 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55 (m, 1 H, CH_2), 1.85 (m, 1 H, CH_2), 2.03 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, $COCH_3$), 2.10–2.25 (m, 1 H, $=CCH_2$), 2.44 (ddd, J = 14.2, 5.7, 3.2 Hz, 1 H, $=CCH_2$), 2.76 (tdd, J = 13.3, 4.8, 1.9 Hz, 1 H, NCH_2), 3.92 (d, J = 6.7 Hz, 1 H, NCH), 4.16 (dd, J = 13, 5 Hz, 1 H, NCH_2), 4.81 (t, J = 1.6 Hz, 1 H, $=CH_2$), 4.88 (t, J = 1.6 Hz, 1 H, $=CH_2$), 5.45 (dd, J = 6.6, 1.5 Hz, 1 H, CHOAc), 5.54 (t, J = 6.6 Hz, 1 H, CHOAc); ^{13}C NMR ($CDCl_3$) δ 20.5 (q), 24.8 (t), 32.8 (t), 39.6 (t), 59.4 (d), 74.4 (d), 74.9 (d), 109.5 (t), 141.7 (s), 165.1 (s), 169.8 (s), 170.1 (s); exact mass calcd for $C_{11}H_{13}NO_3$ ($M^+ - C_2H_4O_2$) m/e 207.0895, found 207.0890.

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.40; H, 6.41. Found: C, 58.28; H, 6.63.

(1*R*)-(1β,2α,8β,8aβ)-1,2-Diacetoxy-8-hydroxyhexahydro-3(2*H*)-indolizinone (5). An ozone–oxygen stream (Welsbach ozone generator) was bubbled through a solution of 460 mg (1.72 mmol) of olefin **15** in 30 mL of dichloromethane, previously cooled in a dry ice–acetone bath, until a blue color persisted. The solution was purged with nitrogen, and 1 mL of dimethyl sulfide was added. The cooling bath was removed, and the mixture was stirred for 10 h. The solvent was removed in vacuo, and the residue was dissolved in 5 mL of methanol. The solution was cooled to −40 °C, and 131 mg (3.44 mmol) of sodium borohydride was added over a 15-min period. The resulting solution was stirred at −40 °C for 1 h and partitioned between 10 mL of saturated aqueous sodium bicarbonate and 100 mL of ethyl acetate, and the layers were separated. The aqueous phase was extracted with five 100-mL portions of ethyl acetate, and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (dichloromethane–ethyl acetate, 1:1) to give 317 mg (68%) of alcohol **5**: mp 172.5–175.0 °C; $[\alpha]^{20}_D$ = −171.9° (c 0.580, $CHCl_3$); IR (CH_2Cl_2) 3495, 1750, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39–1.57 (m, 2 H, CH_2), 1.79 (ddd, J = 13.4, 3.2, 1.5 Hz, 1 H, CH_2), 2.14–2.18 (m, with s at 2.16, 7 H, $COCH_3$ and CH_2), 2.62 (td, J = 13.1, 2.7 Hz, 1 H, NCH_2), 3.15 (dd, J = 9.3, 4.2 Hz, 1 H, NCH), 3.43 (br s, 1 H, OH), 3.54 (ddd, J = 13.5, 9.4, 4.2 Hz, 1 H, CHO), 4.16 (dd, J = 13.3, 4.7 Hz, 1 H, NCH_2), 5.23 (t, J = 4.6 Hz, 1 H, CHOAc), 5.20 (dd, J = 5.2, 1.4 Hz, 1 H, CHOAc); ^{13}C NMR ($CDCl_3$) δ 20.48 (q), 20.81 (q), 22.48 (t), 32.00 (t), 39.27 (t), 65.36 (d), 70.63 (d), 75.13 (d), 75.63 (d), 165.44 (s), 169.80 (s), 171.50 (s); mass spectrum, m/e (relative intensity) 211 ($M^+ - C_2H_4O_2$, 12), 170 (6), 169 (63), 152 (18), 141 (31), 43 (100); exact mass calcd for $C_{10}H_{13}NO_4$ ($M^+ - C_2H_4O_2$) m/e 211.0845, found 211.0845.

Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.12; H, 6.32; N, 5.17. Found: C, 53.09; H, 6.66; N, 5.43.

5-Phenyl-4-pentyn-1-ol (17).[38] To a stirred solution of 2.50 g (12.3 mmol) of iodobenzene, 1.00 g (11.9 mmol) of 4-pentyn-1-ol, and 100 mg (0.142 mmol) of bis(triphenylphosphine)palladium(II) chloride in 65 mL of diethylamine was added 50 mg (0.263 mmol) of copper(I) iodide, and the resulting solution was stirred for 2.5 h. The solvent was removed in vacuo, and the resulting brownish-orange semisolid (4.00 g) was chromatographed over 80 g of silica gel (ethyl acetate–hexane, 1:3) to give 1.44 g (76%) of alcohol **17** as a colorless oil after bulb-to-bulb distillation (bp 135 °C at 0.45 mm): IR (neat) 3340, 2230 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 1.77 (quintet, J = 6 Hz, 2 H, CH_2), 2.20 (s, 1 H, OH), 2.53 (t, J = 6 Hz, 2 H, $\equiv CCH_2$), 3.77 (t, J = 6 Hz, 2 H, CH_2O), 7.17–7.50 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 15.92 (t) 31.36 (t), 61.69 (t), 81.09 (s), 89.31 (s), 123.71 (s), 127.61 (d), 128.16 (d), 131.49 (d); exact mass calcd for $C_{11}H_{12}O$ m/e 160.0887, found 160.0883.

(3*S*,4*S*)-3,4-Diacetoxy-1-(5-phenyl-4-pentynyl)-2,5-pyrrolidinedione (18). To a stirred solution of 1.76 g (8.19 mmol) of imide **4**, 1.21 g (7.56 mmol) of alcohol **17**, and 2.21 g (8.43 mmol) of triphenylphosphine in 30 mL of dry tetrahydrofuran cooled in an ice bath, was added a solution of 1.60 g (9.18 mmol) of diethyl azodicarboxylate over a 35-min period. The resulting solution was stirred for 15 min in the cooling bath and for 3.5 h at room temperature. The solvent was removed in vacuo, and the semisolid residue was triturated with 50 mL of ethyl acetate–hexane (3:7) and filtered. The filtrate was concentrated in vacuo to afford a brownish-yellow oil (4.9 g), which was chromatographed over a column of 75 g of silica gel (lower layer) and 40 g of activity III alumina (upper layer) (ethyl acetate–hexane, 1:3; then ethyl acetate–hexane, 1:2) to give 2.60 g (96%) of imide **18** as a pale yellow oil: $[\alpha]^{20}_D$ = −62.63° (c 0.99, $CHCl_3$); IR (CCl_4) 1755, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.97 (quintet, J = 7 Hz, 2 H, CH_2), 2.16 (s, 6 H, $COCH_3$), 2.48 (t, J = 7 Hz, 2 H, $\equiv CCH_2$), 3.77 (dquintet, J = 7.0, 5.3 Hz, 2 H, NCH_2), 5.49 (s, 2 H, CHOAc), 7.24–7.43 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 17.04 (t), 20.25 (q), 26.18 (t), 38.82 (t), 72.71 (d), 81.49 (s), 88.20 (s), 123.51 (s), 127.70 (d), 128.15 (d), 131.57 (d), 169.34 (s), 169.77 (s); exact mass calcd for $C_{19}H_{19}NO_6$ m/e 357.1213, found 357.1232.

(3*S*,4*S*,5*RS*)-3,4-Diacetoxy-5-hydroxy-1-(5-phenyl-4-pentynyl)-2-pyrrolidinone (19). To a stirred solution of 1.63 g (4.57 mmol) of imide **18** in 125 mL of methanol, cooled to −7 °C in an ice–salt bath, was added 875 mg (23.1 mmol) of sodium borohydride in one portion, and the resulting solution was stirred for 12 min. The reaction mixture was partitioned between 200 mL of dichloromethane, 100 mL of saturated aqueous sodium bicarbonate, and 50 mL of water. The layers were separated, and the aqueous phase was extracted with three 150-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow oil (1.67 g), which was chromatographed over 50 g of silica gel (ethyl acetate–hexane, 2:3; then ethyl acetate–hexane, 1:1) to afford 1.49 g (91%) of the carbinol lactam **19** as a white solid: mp 99.5–103.5 °C; IR (CH_2Cl_2) 3510, 1755, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz; major diastereomer) δ 1.85–2.01 (m, 2 H, CH_2), 2.09 (s, 3 H, $COCH_3$), 2.10 (ddd, J = 9.7, 6.9, 2.7 Hz, 2 H, $\equiv CCH_2$), 2.16 (s, 3 H, $COCH_3$), 3.46 (ddd, J = 13.9, 7.7, 6.1 Hz, 1 H, NCH_2), 3.63–3.74 (m, 1 H, NCH_2), 3.92 (br d, J = 5.3 Hz, 1 H, OH), 5.00 (d, J = 3.9 Hz, 1 H, CHOAc), 5.02–5.07 (m, 2 H, CHOAc and NCHO), 7.25–7.43 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$, peaks due to major diastereomer) δ 17.03 (t), 20.40 (q), 20.46 (q), 26.14 (t), 39.41 (t), 73.98 (d), 79.09 (d), 81.27 (s), 83.99 (d), 88.60 (s), 123.4 (s), 127.62 (d), 128.09 (d), 131.42 (d), 167.08 (s), 170.31 (s), 170.41

(38) For earlier methods for the preparation of this compound, see: (a) Yamaguchi, M.; Nobayashi, Y., Hirao, I. *Tetrahedron* **1984**, *40*, 4261. (b) Surzur, J. M.; Dupuy, C.; Bertrand, M. P.; Nouguier, R. *J. Org. Chem.* **1972**, *37*, 2782.

(s); exact mass calcd for $C_{19}H_{21}NO_6$ m/e 359.1369, found 359.1366.

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.50; H, 5.87; N, 3.71.

(3*S*,4*S*,5*RS*)-3,4,5-Triacetoxy-1-(5-phenyl-4-pentynyl)-2-pyrrolidinone (20). To a stirred solution of 4.25 g (11.9 mmol) of imide **18** in 360 mL of methanol, cooled to −6 °C in an ice–salt bath, was added 2.58 g (68.2 mmol) of sodium borohydride in one portion. The resulting solution was stirred for 12 min and partitioned between 475 mL of dichloromethane, 250 mL of saturated aqueous sodium bicarbonate, and 125 mL of water. The layers were separated, and the aqueous phase was washed with three 250-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residual pale yellow oil (4.73 g) was dissolved in 90 mL of dry dichloromethane, and 1.81 g (17.9 mmol) of triethylamine, 1.82 g (17.9 mmol) of acetic anhydride, and 100 mg of 4-(*N*,*N*-dimethylamino)pyridine were added in sequence. The mixture was stirred for 30 min and partitioned between 130 mL of dichloromethane and 100 mL of saturated aqueous bicarbonate. The organic phase was washed with 100 mL of water and 125-mL portions of saturated aqueous sodium chloride. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residual oil (5.40 g) was chromatographed over 100 g of silica gel (ethyl acetate–hexane, 2:5) to give 4.58 g (96%) of the triacetate **20** as a pale yellow oil: IR (CH_2Cl_2) 1755, 1735, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz; major diastereomer) δ 1.81–2.00 (m, 2 H, CH_2), 2.07 (s, 3 H, $COCH_3$), 2.12 (s, 3 H, $COCH_3$), 2.16 (s, 3 H, $COCH_3$), 2.46 (ddd, J = 9.6, 6.7, 2.6 Hz, 2 H, $\equiv CCH_2$), 3.24 (ddd, J = 13.9, 8.0, 5.6 Hz, 1 H, NCH_2), 3.72 (dt, J = 14.0, 7.8 Hz, 1 H, NCH_2), 5.21 (dd, J = 4.3, 2.2 Hz, 1 H, CHOAc), 5.33 (d, J = 4.2 Hz, 1 H, CHOAc), 6.21 (d, J = 2.2 Hz, 1 H, NCHOAc), 7.21–7.43 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$, peaks due to major diastereomer) δ 16.90 (t), 20.41 (q, 2 C), 20.67 (q), 26.18 (t), 40.23 (t), 73.00 (d), 76.12 (d), 81.51 (s), 83.66 (d), 88.26 (s), 123.47 (s), 127.70 (d), 128.14 (d), 131.52 (d), 167.66 (s), 169.45 (s, 2 C), 169.76 (s); exact mass calcd for $C_{21}H_{23}NO_7$ m/e 401.1475, found 401.1492.

(3*S*,4*S*,5*RS*)-3,4-Diacetoxy-1-(5-phenyl-4-pentynyl)-5-(phenylthio)-2-pyrrolidinone (21). From Triacetate 20. To a stirred mixture of 3.03 g (7.56 mmol) of triacetate **20** and 833 mg (7.56 mmol) of thiophenol was added 90 mg of *p*-toluenesulfonic acid monohydrate in one portion. The resulting viscous mixture was stirred for 45 min and partitioned between 350 mL of diethyl ether and 150 mL of 1 N aqueous sodium hydroxide. The layers were separated, and the organic phase was washed with 150 mL of 1 N aqueous sodium hydroxide, 100 mL of water, and 150 mL of saturated aqueous sodium chloride. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residual pale yellow oil (3.32 g) was chromatographed over 65 g of silica gel (ethyl acetate–hexane, 1:3) to afford 2.80 g (82%) of a mixture of diastereomeric phenylthio lactams **21** as a colorless oil: IR (neat) 1750, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.76–1.97 (m, 2 H, CH_2), 2.00–2.20 (4 s, 6 H, $COCH_3$), 2.39–2.51 (m, 2 H, $\equiv CCH_2$), 3.40–4.04 (m, 2 H, NCH_2), 4.81–4.89 (m, with d at 4.88, 1 H, CHOAc), 5.28–5.49 (m, 2 H, NCHS and CHOAc), 7.24–7.49 (m, 10 H, Ar H); mass spectrum, m/e (relative intensity) 451 (M^+, 1), 300 (30), 258 (12), 253 (10), 240 (16), 200 (13), 199 (86), 180 (15), 105 (40), 43 (100); exact mass calcd for $C_{25}H_{25}NO_5S$ m/e 451.1455, found 451.1409.

From Carbinol Lactam 19. To a stirred solution of 374 mg (1.85 mmol) of tri-*n*-butylphosphine in 3.8 mL of dry benzene, in a flask protected from light, was added 400 mg (1.83 mmol) of diphenyl disulfide in one portion. The resulting solution was stirred for 11 min, and 504 mg (1.40 mmol) of carbinol lactam **19** was added in one portion. The solution was stirred for 17 h and partitioned between 50 mL of diethyl ether and 35 mL of 1 N aqueous sodium hydroxide. The layers were separated, and the organic phase was washed with 35 mL of 1 N aqueous sodium hydroxide and 40 mL of saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The semisolid residue (1.05 g) was chromatographed over 50 g of silica gel (ethyl acetate–hexane, 1:2) to give 487 mg (77%) of phenylthio lactam **21** as an oil, identical in all respects with material isolated above.

(3*S*,4*S*,5*RS*)-3,4-Diacetoxy-1-(5-phenyl-4-pentynyl)-5-(phenylseleno)-2-pyrrolidinone (22). To a stirred mixture of 871 mg (2.17 mmol) of triacetate **20** and 10 mg of *p*-toluenesulfonic acid monohydrate was added 341 mg (2.17 mmol) of selenophenol in one portion. The resulting viscous mixture was stirred for 75 min and then chromatographed directly over 30 g of silica gel (ethyl acetate–hexane, 2:5) to afford 1.08 g (90%) of a mixture of diastereomeric phenylseleno lactams **22** as a pale yellow oil: IR (neat) 1750, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.76–1.95 (m, 2 H, CH_2), 2.02–2.12 (4 s, 6 H, $COCH_3$), 2.41–2.47 (m, 2 H, $\equiv CCH_2$), 3.33–3.58 (m, 1 H, NCH_2), 3.88–4.04 (m, 1 H, NCH_2), 4.83–4.90 (2 d, 1 H, CHOAc), 5.27–5.32 (2 d, 1 H, CHOAc), 5.43–5.48 (2 d, 1 H, NCHSe), 7.26–7.59 (m, 10 H, Ar H); mass spectrum, m/e (relative intensity) 300 (100), 258 (52), 240 (15), 143 (6), 141 (11), 105 (35), 43 (31).

(1*R*)-(1β,2α,8*E*,8aβ)-1,2-Diacetoxy-8-(phenylmethylene)-hexahydro-3(2*H*)-indolizinone (23) and (1*R*)-(1β,2α,8*Z*,8aβ)-1,2-Diacetoxy-8-(phenylmethylene)hexahydro-3(2*H*)-indolizinone (24). From Phenylthio Lactam 21. To a solution of 452 mg (1.00 mmol) of phenylthio lactam **21** in 19 mL of dry degassed benzene under reflux was added a solution of 383 mg (1.32 mmol) of freshly distilled tri-*n*-butyltin hydride and 13 mg of AIBN in 3.5 mL of dry degassed benzene over a 17.5 h period. The mixture was warmed under reflux for 2 h and concentrated in vacuo, and the residue was partitioned between 25 mL of acetonitrile and 20 mL of hexane. The layers were separated, and the acetonitrile phase was washed with two 20-mL portions of hexane. The acetonitrile phase was concentrated in vacuo, and the residue (452 mg) was chromatographed over a column of 20 g of silica gel (lower layer) and 5 g of activity III alumina (upper layer) (ethyl acetate–hexane, 2:3, then ethyl acetate–hexane, 1:1) to give 314 mg (91%) of a 1.2:1 mixture of (*E*)- and (*Z*)-indolizinones **23** and **24**, respectively, containing about 12% other products by GC. This material was used in subsequent reactions. On one occasion, treatment of 1.44 g (3.18 mmol) of phenylthio lactam **21** with 1.76 g (6.06 mmol) of tri-*n*-butyltin hydride and 60 mg of AIBN afforded 889 mg (82%) of a 1.4:1 mixture of lactams **23** and **24**, containing about 16% of other products by GC. Further purification of this mixture by MPLC over a Lobar size C column (ethyl acetate–hexane, 1:1) afforded 403 mg (37%) of impure *Z*-olefin **24** (77% pure by GC). Continued elution gave 400 mg (37%) of pure lactam **23** as a pale yellow oil: IR (neat) 1745, 1715 cm^{-1}; $[\alpha]^{20}_D$ = +42.1° (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.53–1.60 (m, 1 H, CH_2), 1.77–1.84 (m, 1 H, CH_2), 2.10–2.19 (m, with 2 s at δ 2.13 and 2.17, 7 H, $COCH_3$, $COCH_3$, and CH_2), 2.92–3.01 (m, 2 H, CH_2 and NCH_2), 4.19–4.25 (m, with d at 4.20, 2 H, NCH_2 and NCH), 5.58 (dd, J = 6.6, 1.4 Hz, 1 H, CHOAc), 5.76 (t, J = 6.7 Hz, 1 H, CHOAc), 6.43 (s, 1 H, =CH), 7.17–7.36 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$) 20.57 (q), 20.72 (q), 23.98 (t), 26.59 (t), 39.66 (t), 59.90 (d), 74.42 (d), 74.89 (d), 124.73 (d), 127.05 (d), 128.20 (d), 128.80 (d), 134.73 (s), 135.87 (s), 165.27 (s), 169.90 (s), 170.16 (s); mass spectrum, m/e (relative intensity) 283 (31), 255 (8), 241 (62), 224 (19), 172 (28), 105 (25), 91 (17), 77 (19), 43 (100); exact mass calcd for $C_{19}H_{21}NO_5$ m/e 343.1420, found 343.1371.

From Phenylseleno Lactam 22. To a solution of 615 mg (1.23 mmol) of phenylseleno lactam **22** in 23 mL of dry degassed benzene under reflux was added a solution of 474 mg (1.63 mmol) of freshly distilled tri-*n*-butyltin hydride and 17 mg of AIBN in 4 mL of dry degassed benzene over a 19.5-h period. The mixture was warmed under reflux for 2 h and concentrated in vacuo and the residue partitioned between 30 mL of hexane and 40 mL of acetonitrile. The layers were separated, and the acetonitrile phase was washed with 30 mL of hexane. The acetonitrile phase was concentrated in vacuo, and the residue (480 mg) was chromatographed over 15 g of silica gel and 5 g of activity III alumina (upper layer) (ethyl acetate–hexane, 2:3; then ethyl acetate–hexane, 1:1) to give 387 mg (92%) of a 6.1:1 mixture of *Z* and *E* olefins **24** and **23**, respectively, containing about 14% of two other products by GC. On one occasion, cyclization of 926 mg (1.86 mmol) of phenylseleno lactam **22** with 713 mg (2.45 mmol) of tri-*n*-butyltin hydride and 25 mg of AIBN afforded 543 mg (85%) of a 7.7:1 mixture of *Z* and *E* olefins **24** and **23**, also containing about 14% of two other products. Medium-pressure liquid chromatography of this mixture over a Lobar size B column afforded initially 211 mg (33%) of impure *Z*-lactam **24** (71% pure by GC). Continued elution gave 245 mg (38%) of *Z*-olefin **24**. Olefin **24**: mp 88–92 °C; $[\alpha]^{20}_D$ = −206.6° (*c* 0.605, $CHCl_3$); IR ($CHCl_3$) 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.75–1.89 (m, with s at 1.76, 4 H,

$COCH_3$ and CH_2), 2.08–2.19 (m, with s at 2.13, 4 H, $COCH_3$ and CH_2), 2.31 (ddd, J = 13.8, 7.0, 2.1 Hz, 1 H, CH_2), 2.43–2.48 (m, 1 H, CH_2), 2.85 (dt, J = 13.7, 8.4 Hz, 1 H, NCH_2), 4.16 (dddd, J = 13.6, 10.0, 8.4, 3.5 Hz, 1 H, NCH_2), 4.91 (d, J = 5.9 Hz, 1 H, NCH), 5.40–5.44 (m, 2 H, CHOAc), 6.59 (s, 1 H, =CH), 7.24–7.35 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$, 16 of 17 expected signals observed) δ 20.40 (q), 20.60 (q), 23.32 (t), 28.31 (t), 35.35 (t), 57.15 (d), 74.98 (d), 75.67 (d), 127.18 (d), 128.39 (d), 129.32 (d), 135.68 (s), 136.02 (s), 166.05 (s), 169.67 (s), 170.06 (s); mass spectrum, m/e (relative intensity) 301 ($M^+ - C_2H_2O$, 2), 283 (15), 242 (20), 241 (85), 240 (12), 224 (43), 223 (100), 195 (19), 172 (100), 129 (18), 115 (13), 43 (85); exact mass calcd for $C_{19}H_{21}NO_5$ m/e 343.1420, found 343.1384. A satisfactory elemental analysis was not obtained for this compound. Later fractions afforded 52 mg (8%) of pure indolizidinone **23**, identical to material described above.

(1*R*)-(1β,2α,8β,8aβ)-1,2-Diacetoxy-8-hydroxyhexahydro-3(2*H*)-indolizinone (5). An ozone–oxygen stream (Welsbach ozone generator) was bubbled through a stirred solution of 817 mg (2.38 mmol) of a mixture of olefins **23** and **24** (4.3:1; 82% pure by GC) in 75 mL of dry methanol, previously cooled in a dry ice–acetone bath. The gas flow was continued for 4 min, after which time TLC analysis showed the reaction to be complete. The solution was purged with nitrogen for 5 min, and 500 μL of dimethyl sulfide was added. The cooling bath was removed, and the mixture was stirred for 2.5 h. The mixture was cooled to −50 to −60 °C, and 320 mg (8.46 mmol) of sodium borohydride was added in one portion. The mixture was stirred for 10 min, an additional 310 mg (8.19 mmol) of sodium borohydride was added, and the solution was stirred for an additional 10 min. The reaction mixture was partitioned between 150 mL of dichloromethane, 60 mL of saturated aqueous sodium bicarbonate, and 30 mL of water. The layers were separated, and the aqueous phase was extracted with three 100-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The oily solid residue (909 mg) was chromatographed over 35 g of silica gel (dichloromethane–ethyl acetate, 3:2) to afford 379 mg (74%) of alcohol **5** as a white solid: mp 161–169 °C. This material was used in subsequent reactions. Recrystallization of a sample from ethyl acetate gave an analytical sample (mp 172.5–175.0 °C), identical in all respects with the material prepared from **15** (vide supra).

(1*R*)-(1β,2α,8β,8aβ)-1,2-Diacetoxy-8-[(2,2-dimethylpropanoyl)oxy]hexahydro-3(2*H*)-indolizinone (25). To a stirred solution of 723 mg (2.68 mmol) of alcohol **5** and 70 mg of 4-(*N*,*N*-dimethylamino)pyridine in 13 mL of pyridine was added 1.16 g (9.62 mmol, 1.20 mL) of trimethylacetyl chloride, and the resulting solution was stirred for 27 h. The reaction mixture was filtered through 50 g of silica gel (ethyl acetate–hexane, 3:2), and the filtrate was concentrated in vacuo. The residual pale yellow oil (1.32 g) was chromatographed over 35 g of silica gel (ethyl acetate–hexane, 1:1; then ethyl acetate–hexane, 3:2) to afford 880 mg (93%) of the indolizidone **25** as a colorless oil: IR (neat) 1735 cm^{-1} (br); $[\alpha]^{20}_D$ = −49.9° (*c* 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (s, 9 H, CCH_3), 1.46 (qd, J = 13.3, 3.7 Hz, 1 H, CH_2), 1.60 (dq, J = 11.9, 3.5, 1.6 Hz, 1 H, CH_2), 1.82 (ddd, J = 11.9, 3.5, 1.6 Hz, 1 H, CH_2), 2.06 (s, 3 H, $COCH_3$), 2.15 (s, 3 H, $COCH_3$), 2.18–2.22 (m, 1 H, CH_2), 2.67 (ddd, J = 12.9, 2.7 Hz, 1 H, NCH_2), 3.47 (dd, J = 9.8, 4.3 Hz, 1 H, NCH), 4.20 (dd, J = 13.3, 4.9 Hz, 1 H, NCH_2), 4.65 (ddd, J = 14.2, 11.0, 4.3 Hz, 1 H, CHOPiv), 5.28 (t, J = 4.9 Hz, 1 H, CHOAc), 5.32 (dd, J = 5.0, 1.4 Hz, 1 H, CHOAc); ^{13}C NMR ($CDCl_3$) δ 20.59 (q), 20.73 (q), 22.51 (t), 26.93 (q), 29.51 (t), 38.73 (s), 39.40 (t), 61.78 (d), 71.96 (d), 74.63 (d), 75.25 (d), 166.12 (s), 169.23 (s), 170.01 (s), 177.33 (s); mass spectrum, m/e (relative intensity) 298 ($M^+ - C_4H_9$, 2), 295 ($M^+ - C_2H_2O_2$, 3), 253 (10), 211 (14), 194 (25), 168 (16), 151 (100), 57 (67), 43 (35); exact mass calcd for $C_{15}H_{21}NO_5$ ($M^+ - C_2H_2O_2$) m/e 295.1420, found 295.1422.

(1*R*)-(1β,2α,8β,8aβ)-2,8-Bis[(2,2-dimethylpropanoyl)oxy]-1-hydroxyhexahydro-3(2*H*)-indolizinone (27) and (1*R*)-(1β,2α,8β,8aβ)-1,2,8-Tris[(2,2-dimethylpropanoyl)oxy]hexahydro-3(2*H*)-indolizinone (28). A mixture of 410 mg (1.15 mmol) of pivaloate **25** and 11 mL of a 50% methanolic ammonia solution was stirred for 4 h. The volatile components were removed in vacuo. The residue was dissolved in 5 mL of dry pyridine, and 166 mg (1.38 mmol, 170 μL) of trimethylacetyl chloride was added. The solution was stirred for 27 h and filtered through 25 g of silica gel (ethyl acetate–hexane, 3:2). The filtrate was concentrated in vacuo, and the residue (530 mg) was chromatographed over 40 g of silica gel (ethyl acetate–hexane, 2:3) to afford 100 mg (20%) of the triacylated indolizidinone **28** as a white solid: mp 118–123 °C; $[\alpha]^{20}_D$ = −69.2° (*c* 0.640, $CHCl_3$); IR (CH_2Cl_2) 1725 cm^{-1} (br); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.16 (s, 9 H, CCH_3), 1.20 (s, 9 H, CCH_3), 1.24 (s, 9 H, CCH_3), 1.45 (dddd, J = 13.0, 9.9, 3.3 Hz, 1 H, CH_2), 1.60–1.69 (m, 1 H, CH_2), 1.80 (dq, J = 14.9, 3.6, 1.6 Hz, 1 H, CH_2), 2.24 (m, 1 H, CH_2), 2.68 (ddd, J = 13.0, 9.9, 3.3 Hz, 1 H, NCH_2), 3.47 (dd, J = 9.9, 3.0 Hz, 1 H, NCH), 4.21 (dd, J = 13.3, 4.9 Hz, 1 H, NCH_2), 4.66 (dd d, J = 14.4, 10.8, 4.2 Hz, 1 H, CHOPiv), 5.21–5.23 (m, 2 H, CHOPiv); ^{13}C NMR ($CDCl_3$) δ 22.60 (t), 26.90 (q, 3 C), 29.58 (t), 38.44 (s), 38.56 (s), 38.68 (s), 39.37 (t), 62.43 (d), 71.92 (d), 73.88 (d), 75.51 (d), 166.32 (s), 176.50 (s), 177.11 (s), 177.35 (s); mass spectrum, m/e (relative intensity) 337 ($M^+ - C_5H_{10}O_2$, 1), 291 (3), 235 (7), 57 (100); exact mass calcd for $C_{18}H_{27}NO_5$ ($M^+ - C_5H_{10}O_2$) m/e 337.1890, found 337.1891.

Anal. Calcd for $C_{23}H_{37}NO_7$: C, 62.83; H, 8.49; N, 3.19. Found: C, 62.59; H, 8.24; N, 3.02.

Continued elution afforded 299 mg of impure hydroxyindolizidinone **27**, which was further purified by chromatography over 30 g of silica gel (ethyl acetate–hexane, 1:2) to give 274 mg (67%) of alcohol **27** as a white solid: mp 123–126 °C; $[\alpha]^{20}_D$ = −5.20° (*c* 0.500, $CHCl_3$); IR (CH_2Cl_2) 3515, 1715 cm^{-1} (br); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.21 (s, 9 H, CCH_3), 1.27 (s, 9 H, CCH_3), 1.53–1.59 (m, 2 H, CH_2), 1.82–1.85 (m, 1 H, CH_2), 2.05–2.15 (m, 1 H, CH_2), 2.62–2.69 (m, 1 H, NCH_2), 3.26 (dd, J = 9.5, 5.5 Hz, 1 H, NCH), 3.39 (br s, 1 H, OH), 4.08–4.18 (m, with t at 4.12, J = 5.8 Hz, 2 H, NCH_2 and CHO), 4.68 (ddd, J = 15.9, 10.7, 5.0 Hz, 1 H, CHOPiv), 4.99 (dd, J = 6.0, 1.5 Hz, 1 H, CHOPiv); ^{13}C NMR ($CDCl_3$) δ 22.33 (t), 27.01 (q), 27.05 (q), 29.48 (t), 38.73 (s), 38.83 (s), 39.08 (t), 62.91 (d), 72.27 (d), 76.72 (d), 79.39 (d), 166.19 (s), 178.07 (s), 179.97 (s); mass spectrum, m/e (relative intensity) 253 ($M^+ - C_5H_{10}O_2$, 4), 168 (5), 151 (100), 57 (68); exact mass calcd for $C_{13}H_{19}NO_4$ ($M^+ - C_5H_{10}O_2$) m/e 253.1315, found 253.1323.

Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.81; H, 8.23; N, 3.94. Found: C, 60.70; H, 8.18; N, 4.03.

(1*S*)-(1α,2α,8β,8aβ)-1-Acetoxy-2,8-bis[(2,2-dimethylpropanoyl)oxy]hexahydro-3(2*H*)-indolizinone (29). To a stirred solution of 123 mg (0.347 mmol) of hydroxy lactam **27** in 4 mL of dry dichloromethane, cooled in an ice bath, were added 83.1 mg (1.05 mmol, 85 μL) of dry pyridine and 200 mg (0.709 mmol, 120 μL) of trifluoromethanesulfonic anhydride[39] in sequence. The resulting solution was stirred for 1 h, followed by the sequential addition of 140 mg (1.43 mmol) of anhydrous potassium acetate, 370 mg (1.40 mmol) of 18-crown-6, and 2.0 mL of dry *N*,*N*-dimethylformamide. The pale orange solution was stirred for 29.5 h, allowing the cooling bath to slowly warm up to room temperature. The reaction mixture was filtered through 20 g of silica gel (ethyl acetate–hexane, 3:2) and the filtrate concentrated in vacuo to give an amber-brown oil (167 mg). This material was dissolved in 2.0 mL of dry dichloromethane, and 50 mg (0.494 mmol) of triethylamine, 50 mg (0.490 mmol) of acetic anhydride, and 2 crystals of 4-(*N*,*N*-dimethylamino)pyridine were added in sequence. The solution was stirred for 45 min and concentrated in vacuo. The resulting semisolid residue was chromatographed over 30 g of silica gel (ethyl acetate–hexane, 2:3). Preliminary fractions gave 10.4 mg of compounds believed to contain elimination products, along with several other compounds (GC–MS analysis showed 3 major components).

Continued elution afforded 117 mg (85%) of acetoxy lactam **29** as an off-white solid: mp 147–155 °C; $[\alpha]^{25}_D$ = −41.2° (*c* 0.680, $CHCl_3$); IR (CH_2Cl_2) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (s, 9 H, CCH_3), 1.21 (s, 9 H, CCH_3), 1.43 (dq, J = 13.4, 3.3 Hz, 1 H, CH_2), 1.59 (qdd, J = 12.9, 4.8, 3.1 Hz, 1 H, CH_2), 1.86 (br dd, J = 13.8, 1.8 Hz, 1 H, CH_2), 2.09 (s, 3 H, $COCH_3$), 2.27–2.30 (m, 1 H, CH_2), 2.66 (ddd, J = 12.9, 2.6 Hz, 1 H, NCH_2), 3.61 (dd, J = 9.7, 3.9 Hz, 1 H, NCH), 4.13 (dd, J = 13.3, 4.7 Hz, 1 H, NCH_2), 4.81 (ddd, J = 14.1, 10.9, 4.4 Hz, 1 H, CHOPiv), 5.46 (d, J = 5.1 Hz, 1 H, CHOPiv), 5.69 (t, J = 4.1 Hz, 1 H, CHOAc); ^{13}C NMR ($CDCl_3$) δ 20.25 (q), 21.78 (t), 26.88 (q), 26.99 (q), 28.88 (t), 38.60

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(s), 39.11 (s), 39.30 (t), 58.77 (d), 65.30 (d), 66.27 (d), 69.56 (d), 167.44 (s), 169.36 (s), 176.71 (s), 176.83 (s); mass spectrum, *m/e* (relative intensity) 340 ($M^+ - C_4H_9$, 4), 295 (6), 253 (10), 194 (66), 152 (71), 151 (72), 57 (100), 43 (44); exact mass calcd for $C_{17}H_{26}NO_6$ ($M^+ - C_4H_9$) *m/e* 340.1761, found 340.1772.

Anal. Calcd for $C_{20}H_{31}NO_7$: C, 60.42; H, 7.87; N, 3.53. Found: C, 60.65; H, 7.76; N, 3.76.

(1*R*)-(1β,2α,8β,8aβ)-1-Acetoxy-2,8-bis[(2,2-dimethylpropanoyl)oxy]hexahydro-3(2*H*)-indolizinone (30). A solution of 10 mg (0.028 mmol) of alcohol **27**, 10 μL (0.106 mmol) of acetic anhydride, and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine in 1 mL of pyridine was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, and the resiude was filtered through a column of silica gel (ethyl acetate–hexane, 1:1) to give 10 mg (89%) of acetate **30**: IR (CH_2Cl_2) 1725 cm^{-1} (br); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (s, 9 H, CCH_3), 1.25 (s, 9 H, CCH_3), 1.37–1.49 (m, 2 H, CH_2), 1.79 (m, 1 H, CH_2), 2.06 (s, 3 H, $COCH_3$), 2.21 (m, 1 H, CH_2), 2.67 (dt, *J* = 13.1, 2.3 Hz, 1 H, NCH_2), 3.48 (dd, *J* = 9.9, 4.0 Hz, 1 H, NCH), 4.19 (dd, *J* = 13.4, 4.4 Hz, 1 H, NCH_2), 4.65 (ddd, *J* = 14.3, 10.5, 4.0 Hz, 1 H, CHOPiv), 5.26–5.29 (m, 2 H, CHOAc and CHOPiv); mass spectrum, *m/e* (relative intensity) 337 ($M^+ - C_2H_4O_2$, 2), 295 ($M^+ - C_5H_{10}O_2$, 5), 236 (9), 235 (7), 193 (22), 152 (26), 151 (100), 85 (14), 57 (82), 43 (11); exact mass calcd for $C_{15}H_{21}NO_5$ ($M^+ - C_5H_{10}O_2$) *m/e* 295.1420, found 295.1402.

(1*S*)-(1α,2α,8β,8aβ)-1-Acetoxy-2,8-bis[(2,2-dimethylpropanoyl)oxy]hexahydro-3(2*H*)-indolizinethione (31). To a stirred solution of 106 mg (0.266 mmol) of indolizidinone **29** in 9 mL of dry toluene was added 59 mg (0.146 mmol) of Lawesson's reagent[33] in one portion, and the mixture was heated at reflux for 1 h. The solution was concentrated in vacuo, and the resulting pale yellow solid was chromatographed over 20 g of silica gel (dichloromethane) to give 106 mg (97%) of thiolactam **31** as a white solid: mp 189–191 °C; $[\alpha]^{20}_D$ = −136.6° (*c* 0.535, $CHCl_3$); IR (CH_2Cl_2) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.16 (s, 9 H, CCH_3), 1.20 (s, 9 H, CCH_3), 1.48–1.56 (m, 1 H, CH_2), 1.70 (qdd, *J* = 13.3, 5.0, 3.2 Hz, 1 H, CH_2), 1.97 (ddd, *J* = 14.2, 3.7, 1.7 Hz, 1 H, CH_2), 2.14 (s, 3 H, $COCH_3$), 2.31–2.36 (m, 1 H, CH_2), 2.82 (br t, *J* = 13.4 Hz, 1 H, NCH_2), 3.83 (dd, *J* = 10.0, 4.1 Hz, 1 H, NCH), 4.80 (dd, *J* = 14.0, 4.9 Hz, 1 H, NCH_2), 4.87 (ddd, *J* = 14.4, 11.2, 4.4 Hz, 1 H, CHOPiv), 5.64 (dd, *J* = 5.2, 2.2 Hz, 1 H, CHOPiv), 5.77 (dd, *J* = 5.1, 4.1 Hz, 1 H, CHOAc); ^{13}C NMR ($CDCl_3$) δ 20.37 (q), 21.18 (t), 26.85 (q), 26.97 (q), 28.55 (t), 38.58 (s), 39.10 (s), 44.28 (t), 65.28 (d), 65.99 (d), 66.25 (d), 77.13 (d), 169.18 (s), 176.63 (s), 176.72 (s), 195.49 (s); exact mass calcd for $C_{20}H_{31}NO_6S$ *m/e* 413.1873, found 413.1847.

Anal. Calcd for $C_{20}H_{31}NO_6S$: C, 58.09; H, 7.56; N, 3.39. Found: C, 57.93; H, 7.64; N, 3.40.

(1*S*)-(1α,2α,8β,8aβ)-1-Acetoxy-2,8-bis[(2,2-dimethylpropanoyl)oxy]octahydroindolizine (32). To a stirred suspension of 88.7 mg (0.215 mmol) of thiolactam **31** in 4.0 mL of absolute ethanol was added a 9.0-mL suspension of W-2 Raney nickel in ethanol.[34] The reaction mixture was warmed under reflux for 1 h and filtered through Celite. The filter cake was washed with 100 mL of ethanol, and the filtrate and washings were concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (ethyl acetate–hexane, 2:3) to give 78.6 mg (96%) of amine **32** as a waxy solid: mp 55.5–59.5 °C; $[\alpha]^{20}_D$ = −72.4° (*c* 0.605, $CHCl_3$); IR (CCl_4) 1735 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.85–0.93 (m, 2 H, CH_2), 1.22 (s, 9 H, CCH_3), 1.29 (s, 9 H, CCH_3), 1.41–1.48 (m, 2 H, CH_2), 1.66 (s, 3 H, $COCH_3$), 1.77 (dd, *J* = 9.4, 4.0 Hz, 1 H, NCH), 2.06–2.10 (m, 1 H, NCH_2), 2.20 (dd, *J* = 10.6, 8.1 Hz, 1 H, NCH_2), 2.55 (br d, *J* = 7.0 Hz, 1 H, NCH_2), 2.93 (dd, *J* = 10.7, 2.3 Hz, 1 H, NCH_2), 5.04 (ddd, *J* = 14.3, 10.8, 4.7 Hz, 1 H, CHOPiv), 5.12 (ddd, *J* = 8.4, 2.5 Hz, 1 H, CHOPiv), 5.47 (dd, *J* = 6.3, 4.1 Hz, 1 H, CHOAc); ^{13}C NMR (C_6D_6) δ 20.32 (q), 23.67 (t), 27.25 (q), 27.49 (q), 29.90 (t), 38.72 (s), 39.19 (s), 51.50 (t), 59.13 (t), 68.42 (d), 68.87 (d), 70.03 (d), 70.53 (d), 169.38 (s), 176.62 (s), 176.88 (s); mass spectrum, *m/e* (relative intensity) 281 ($M^+ - C_5H_{10}O_2$, 27), 222 (34), 138 (11), 137 (18), 136 (10), 120 (100), 57 (72); exact mass calcd for $C_{15}H_{23}NO_4$ ($M^+ - C_5H_{10}O_2$) *m/e* 281.1628, found 281.1651.

Anal. Calcd for $C_{20}H_{33}NO_6$: C, 62.63; H, 8.68; N, 3.65. Found: C, 62.44; H, 8.78; N, 3.61.

(1*S*)-(1α,2α,8β,8aβ)-Octahydro-1,2,8-indolizinetriol [(−)-Swainsonine] (1). To a stirred solution of 67.4 mg (0.176 mmol) of indolizine **32** in 8.0 mL of methanol was added 8.0 mL of a 40% aqueous methylamine solution, and the resulting solution was stirred for 46 h. The solvent was removed in vacuo, and the residue was chromatographed over 10 g of silica gel (acetone–chloroform–water–ammonium hydroxide, 75:12.5:10:2.5) to afford a semisolid residue, which was recrystallized from chloroform to give 19.0 mg (63%) of (−)-swainsonine (**1**) as an off-white solid: mp 134–136 °C dec (lit.[1b] mp 144–145 °C dec); $[\alpha]^{20}_D$ = −81.2° (*c* 0.515, MeOH) [lit.[1b] $[\alpha]^{20}_D$ = −87.2° (*c* 2.1, MeOH)]; IR (KBr) 3390 cm^{-1}; mass spectrum, *m/e* (relative intensity) 173 (M^+, 26), 155 (51), 113 (100), 96 (89), 69 (91); exact mass calcd for $C_8H_{15}NO_3$ *m/e* 173.1053, found 173.1094. ^1H NMR and ^{13}C NMR spectra were in accord with those reported elsewhere at different magnetic field strength.[1b,2b] A carbon–hydrogen shift correlation spectrum appears in the supplementary material.

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Registry No. **1**, 72741-87-8; **3**, 147-71-7; **4**, 117269-82-6; **4** (anhydride), 70728-23-3; **5**, 117269-83-7; **6**, 5390-04-5; **7**, 13224-84-5; **8**, 117269-84-8; **9**, 117269-85-9; (5*R*)-**10**, 117270-05-0; (5*S*)-**10**, 117269-86-0; (5*R*)-**11**, 117270-06-1; (5*S*)-**11**, 117269-87-1; **12**, 117269-88-2; **13**, 117269-89-3; **14**, 117404-76-9; **15**, 117269-90-6; **16**, 117269-91-7; **17**, 24595-58-2; **18**, 117269-92-8; (5*R*)-**19**, 117269-93-9; (5*S*)-**19**, 117308-35-7; (5*R*)-**20**, 117269-94-0; (5*S*)-**20**, 117339-84-1; (5*R*)-**21**, 117269-95-1; (5*S*)-**21**, 117308-36-8; (5*R*)-**22**, 117269-96-2; (5*S*)-**22**, 117270-07-2; **23**, 117269-97-3; **24**, 117404-77-0; **25**, 117269-98-4; **26**, 117269-99-5; **27**, 117270-00-5; **28**, 117270-01-6; **29**, 117270-02-7; **30**, 117404-78-1; **31**, 117270-03-8; **32**, 117270-04-9.

Supplementary Material Available: Carbon–hydrogen shift correlation spectrum of **1** (1 page). Ordering information is given on any current masthead page.