An Acylnitroso Cycloaddition Approach to the Synthesis of Highly Oxygenated Indolizidine Alkaloids

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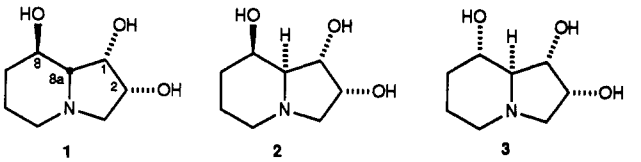
A synthetic approach to the synthesis of highly oxygenated indolizidine alkaloids is described. A key feature of the approach is intramolecular [4 + 2] cycloaddition between an acylnitroso dienophile and a tethered diene moiety, followed by ring contraction of the 1,2-oxazine so formed to a pyrrolidine. The requisite intermediates were prepared in optically pure form from L-glutamic acid.

Swainsonine (1) is a trihydroxylated indolizidine alkaloid originally isolated from fungal cultures[1] and later found in several plants.[2] Since its initial isolation, 1 has aroused considerable interest, primarily due to its potent and highly specific α-D-mannosidase inhibitory activity.[2b,3] *In vivo*, 1 inhibits the processing of mannose-containing oligosaccharides and glycoproteins[2c,4] and produces a reversible phenocopy of mannosidosis, an inherited lysomal storage disease.[5] More recently, 1 has been shown to exhibit pronounced immunoregulatory activity, stimulating the production of lymphocytes and enhancing the expression of conclavine A receptors on spleen cells.[6] The alkaloid also inhibits the metastasis and growth of cancer cells *in vivo*.[7] In light of these diverse biological activities, it is hardly surprising that 1 has received considerable attention as a synthetic target. No less than nine total syntheses of the molecule have been reported to date.[8] In addition to studies on the natural product, the synthesis and biological testing of optically active stereoisomers of 1 has been the focus of several investigations. Thus far, eight optically active diastereomers of the natural product have been reported.[9] Several of these isomers show α-D-mannosidase inhibitory activity comparable to the natural product.[9g,10] In particular, 8a-epi- (2) and 8,8a-di-*epi*-swainsonine (3) are 93 and 100% effective (relative to swainsonine) in the inhibition of lysomal α-D-mannosidase activity.



In light of the intense interest in this class of alkaloids, we undertook a study designed to provide a general means for the synthesis of polyhydroxylated indolizidine alkaloids. Specifically, we envisioned the use of an intramolecular acylnitroso Diels–Alder reaction for the construction of the bicyclic [4.3.0] framework of the alkaloid. The intramolecular acylnitroso Diels–Alder reaction has been applied previously for the total synthesis of pyrrolidizine alkaloids in our laboratories.[11] More recently, similar methodology was utilized by Iida and co-workers in their syntheses of gephrotoxin and monomorine.[12] Fuchs has also used the intramolecular acylnitroso Diels–Alder reaction as a key step in his synthesis of cephalotaxin.[13] Numerous bimolecular reactions have also been employed for the synthesis of nitrogen-containing materials.

Our general retrosynthetic analysis of trihydroxylated indolizidine alkaloids is outlined in Scheme I. The *cis* 1,2-diol moiety present in 1 could be obtained by hydroxylation of an appropriately substituted bicyclic [4.4.0] 1,2-oxazine 4 (or a ring-opened derivative). This could in turn be obtained *via* intramolecular acylnitroso Diels–Alder reaction of a γ-alkoxy acylnitroso species 5 which would be generated *in situ* by oxidation of the corresponding hydroxamic acid. In addition to providing a vehicle for

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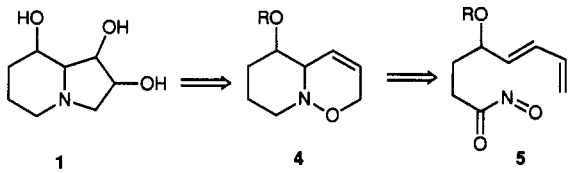
Scheme I

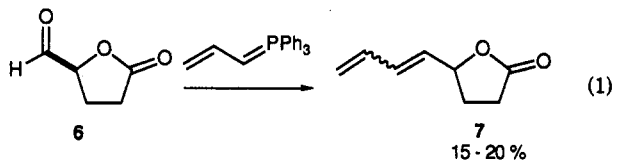


1 4 5

further investigation of the intramolecular acylnitroso Diels–Alder reaction, we felt that this strategy for the synthesis of trihydroxylated indolizidine alkaloids was fundamentally different from previous syntheses. The execution of this approach is described below.

Results and Discussion

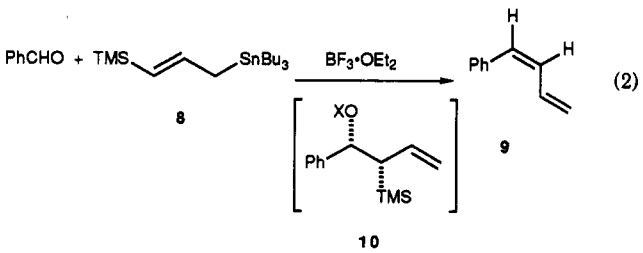
Our synthetic approach began with the known, optically pure, carboxaldehyde γ-lactone **6**, available in three steps from L-glutamic acid.[14] This aldehyde has previously been described as a viscous oil which polymerized upon distillation. However, we found that by using base-washed glassware for the isolation and distillation of **6**, we could obtain this material as a clear, well-behaved oil which was stable for several hours at room temperature. Wittig reaction of **6** with allylidenetriphenylphosphorane gave the desired 1,3-diene **7**, but in a disappointing 15–20% yield as a 1:1 mixture of *E* and *Z* isomers (eq 1). Several



6 7 15 - 20 % (1)

other phosphorus-based reagents, previously used for the synthesis of 1,3-dienes, also failed to provide **7** in acceptable yield.

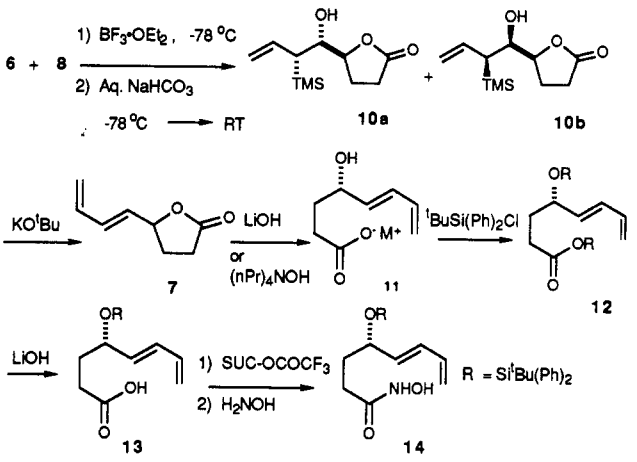
After considerable effort, we turned to an apparently little-known reaction previously reported by Yamamoto. He and co-workers had found the reaction of vinyl silane **8** with benzaldehyde at low temperature in the presence of BF_3·OEt_2, followed by warming to 0 °C, gave 1-phenyl-1,3-butadiene (**9**), exclusively as the *Z* isomer.[15] Although he was not able to isolate and fully characterize an intermediate, he proposed **10** was initially formed, which, under the reaction conditions, underwent a Lewis acid promoted *anti* Peterson elimination to form the *Z* diene, (eq 2).



8 9 10 (2)

Upon reaction of **6** with **8**, using the conditions reported by Yamamoto (addition of BF_3·OEt_2 to a solution of the aldehyde and **8** in THF at −78 °C, followed by warming

Scheme II



to 0 °C), we were disappointed to find that once again we could isolate **7** in only low yield. However, additional experiments revealed that when the reaction mixture was quenched at −78 °C with saturated aqueous $NaHCO_3$ and the resulting mixture was allowed to warm to room temperature, subsequent workup and chromatography resulted in the isolation of the α-hydroxysilanes, **10a,b**, as a 1:1 mixture of diastereomers in 85% yield. Exposure of either of these silanes, either separately or as a mixture, to catalytic potassium *tert*-butoxide in THF resulted in the formation of the desired diene **7**, exclusively as the *E* isomer (>250:1 *E*/*Z* as determined by capillary GC analysis), in 98% yield. Thus, this simple modification of Yamamoto's procedure results in the stereoselective synthesis of **7** in an overall yield of 83% from the aldehyde **6**. This methodology should prove to be of general utility for the synthesis of 1,3-dienes, particularly with labile substrates such as **6**.

With the diene **7** in hand, we next addressed the conversion of the lactone functionality to a suitable hydroxamic acid derivative. Direct reaction of the lactone with hydroxylamine under basic conditions resulted only in recovery of starting material. Similarly, the lactone failed to react with sodium methoxide, even under forcing conditions. After considerable investigation it was found that hydrolysis of the lactone with lithium hydroxide in aqueous THF followed by evaporation of the solvent and drying afforded the lithium carboxylate salt **11**. This salt was reacted with *tert*-butyldiphenylchlorosilane and imidazole (2.5 equiv each) in DMF at room temperature for 24 h, giving the bis-silylated product **12** in 70% isolated yield. In addition, a 25% yield of recovered starting material was also isolated from the reaction mixture. In subsequent experiments, we discovered that by using tetrapropylammonium hydroxide as the hydroxide source in the reaction mixture and increasing the reaction time to 3 days, **12** could be obtained in 95% isolated yield. The simplicity and effectiveness of this transformation is noteworthy; however, use of *tert*-butyldiphenylchlorosilane is essential for the success of this reaction. If *tert*-butyl*dimethyl*chlorosilane is used, only small amounts (15–20%) of the corresponding bis-*tert*-butyldimethylsilane adduct are obtained, while recovered starting material accounts for the remainder of the material isolated. The bis-silane **12** could then be hydrolyzed by reaction with 1 equiv of lithium hydroxide, giving the carboxylic acid **13** in quantitative yield. Conversion of **13** to the hydroxamic acid was accomplished by a slight modification of the

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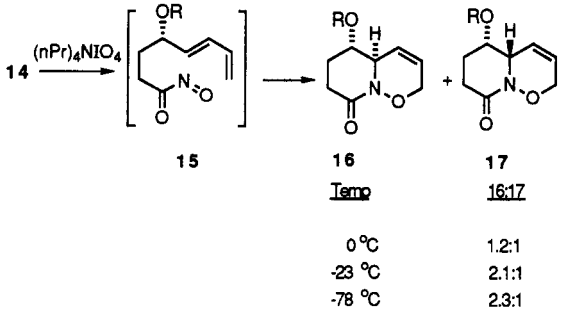
Scheme III

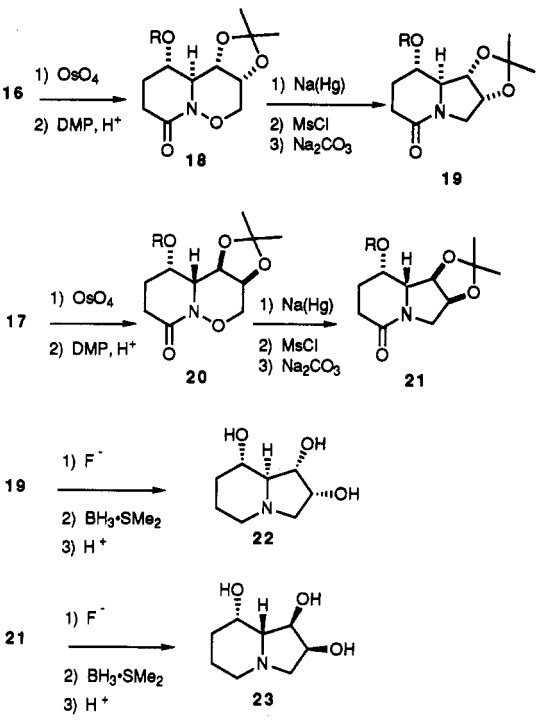


method of Miller.[16] Thus, reaction of **13** with *O*-(trifluoroacetyl)-*N*-hydroxysuccinimide in pyridine gave the corresponding *N*-hydroxysuccinimide ester.[17] This was then added to a solution of hydroxylamine hydrochloride and Hünig's base in chloroform, giving **14** in 83% yield, with 10–15% recovery of **13**.

With the successful synthesis of **14** completed, the stage was set for the penultimate intramolecular acylnitroso Diels–Alder reaction. Addition of **14** to a cooled solution of tetrapropylammonium periodate in CH_2Cl_2 resulted in the formation of the bicyclic [4.4.0] 1,2-oxazines **16** and **17** as a mixture of diastereomers, *via* [4 + 2] cycloaddition of the acylnitroso intermediate **15** (Scheme III). Due to broad signals in the NMR spectra of **16** and **17**, we were unable to assign the relative stereochemistry of these two diastereomers at this point. The assignment of configuration of the bridgehead proton in each of these products was determined at a later point in the synthesis and will be discussed in due course. The ratio of the two diastereomers was only slightly dependent upon the reaction temperature. From the data obtained in these experiments it is apparent that the limit of the kinetic ratio of these two isomers is quickly approached: the ratio of the two isomers increases by only 0.2 by decreasing the reaction temperature from −23 °C to −78 °C. Although we had hoped for a better ratio of the two diastereomeric Diels–Alder products, the results obtained in this case are not altogether surprising in light of previous work with the intramolecular acylnitroso Diels–Alder reaction.[11,13] The low level of stereoselectivity in this and previous examples is most probably due to the extremely high reactivity of the acylnitroso species as a dienophile. Undoubtedly, this high reactivity attenuates the influence of steric and electronic control elements which lead to the high levels of diastereoselectivity commonly found for intramolecular Diels–Alder reactions.

With the bicyclic 1,2-oxazines **16** and **17** in hand, we made very rapid progress in completing the synthesis of several diastereomers of (−)-swainsonine. Hydroxylation of **16** with OsO_4 followed by protection gave the triol derivative **18** as a single diastereomer in 82% overall yield. In like fashion, **17** was converted to **20** in 77% yield. The stereochemistry of the newly formed diol unit of the acetonides **18** and **20** were unambiguously assigned, relative to the H_{8a} proton (swainsonine numbering), by means of high-field homonuclear decoupling experiments. The coupling constant between H_{8a} and H_1 of **18** and **20** is 9.7 and 8.4 Hz, respectively, clearly indicative that these two isomers are of the stereochemistry indicated. Once again, however, the coupling constants between the H_8 and H_{8a}

Scheme IV



protons could not be determined, and we were thus not able to determine the relative stereochemistry between these two centers.

Reductive cleavage of the N–O bond of **18** was readily accomplished by exposure to 6% sodium amalgam in buffered ethanol, giving the hydroxy lactam in quantitative yield.[18] Direct mesylation of the primary hydroxyl with methanesulfonyl chloride and triethylamine in CH_2Cl_2 at 0 °C, followed by heating the resulting mesylate at reflux in aqueous dioxane in the presence of K_2CO_3,[9a] gave the indolizidinone **19** in 83% overall yield from the 1,2-oxazine. Likewise, **20** was treated in an analogous fashion to give the indolizidinone **21** in 70% overall yield from **20** (Scheme IV). It was at this point in the synthesis that we were finally able to discern the relative stereochemistry between the H_8 and H_{8a} protons in **19** and **21** and therefore the stereochemistry of **16** and **17** originally obtained in the Diels–Alder reaction. Homonuclear decoupling experiments clearly reveal a 7.9-Hz coupling between H_8 and H_{8a} of **19**, and therefore these two protons must be *anti* to one another. Similar experiments show **21** has a coupling of 2.4 Hz between these two protons and therefore **21** possesses the *syn* relationship between H_8 and H_{8a}. From these data it follows that **16** and **17** are the *anti* and *syn* cycloadducts, respectively.

The synthesis of the trihydroxyindolizidine alkaloids was then completed using a series of straight forward reactions. Thus, removal of the silyl group in **19** with fluoride ion, followed by reduction of the lactam and hydrolysis gave (−)-8,8a-di-*epi*-swainsonine (**22**). This compound was identical in all respects (^1H and ^{13}C NMR, IR, TLC R_f, $[\alpha]_D$) to the compound previously reported by Tadano and co-workers.[9a] In a similar manner, **21** was carried through the same series of reactions to give (+)-1,2,8-tri-*epi*-swainsonine (**23**). This optically active diastereomer of swainsonine has not been previously de-

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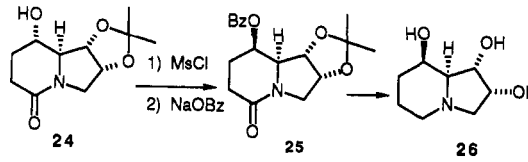
scribed in the literature. Thus, this work represents the first total synthesis of **23**. As an additional structure proof of **23**, the hydroxy lactam **24** was mesylated, followed by displacement with benzoate.[9a] Presumably, this results in the C_8-inverted benzoate **25**. Reduction and hydrolysis of **25** as previously described gave (−)-8a-*epi*-swainsonine (**26**) (eq 3). All spectral properties of **26** were in good



24 25 26 (3)

agreement with those previously reported. In addition, all spectral data of **26** and **23**, its enantiomer, were superimposible, while the optical rotations were +45.6° and −43.7°, respectively.

This serves to confirm the structure of **23**, as well as providing yet another optically active stereoisomer of (−)-swainsonine from this route. Work is in progress within our laboratories to utilize other intermediates available in this route for further syntheses of polyhydroxylated indolizidine alkaloids and will be reported in due course.

Experimental Section

All reactions were carried out under an atmosphere of nitrogen. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Eds.; Pergamon: Oxford, 1966). Reagent grade AcOH, MeOH, and acetone were purchased and used without further purification. Yields were calculated for material judged homogeneous by TLC and NMR. Melting points are uncorrected. NMR spectra were obtained at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Mass spectra were recorded in the electron impact (EI) or chemical ionization (CI) mode. Exact masses were calculated by peak matching with an internal standard whose mass was within ±10% of the unknown compound. Optical rotations were obtained using a microcell with a 1-dm path length, concentrations are in g/100 mL. Elemental analyses were performed by Desert Analytics of Tucson, Arizona. In cases where exact masses were obtained in lieu of combustion analyses, TLC and ^{1}H and ^{13}C NMR spectroscopy were used as criteria for purity; these spectra are available as supplementary material.

Preparation of (*E*)-Trimethyl-[3-(tributylstannyl)-1-propenyl]silane (8). To a solution of allyltrimethylsilane (34.8 mL, 0.219 mol) and tetramethylethylenediamine (39.6 mL, 0.219 mol) in THF (350 mL) at −78 °C was added, dropwise, *sec*-butyllithium (182 mL of a 1.2 M solution, 0.219 mol), over a 30-min period. The resulting solution was warmed to −30 °C and stirred for 30 min. Tri-*n*-butylstannyl chloride (67.6 mL, 0.249 mol) was added dropwise to the reaction mixture, and after 15 min the reaction was quenched by adding saturated aqueous $NaHCO_3$ (50 mL). The reaction mixture was diluted with ether (500 mL), the layers were separated, and the organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine and dried (Na_2SO_4), followed by concentration. Vacuum distillation of the residue (bp 115–125 °C, 0.05 mm) gave 91.4 g (91%) of the desired silane as a clear oil: R_f 0.86 (5% EtOAc/hexanes); IR (neat) cm^{-1} 2980, 2960, 1600, 1245, 860, 830; 300-MHz ^{1}H NMR ($CDCl_3$) δ 6.16 (ddd, J = 18.3, 16.6, 8.3 Hz, 1 H), 5.32 (dd, J = 18.2, 1.1 Hz, 1 H), 1.88 (dd, J = 8.3, 1.1 Hz, 2 H), 1.51–0.75 (m, 27 H), 0.41 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 146.8, 123.4, 29.2, 27.4, 20.1, 13.8, 9.4, −0.8. Anal. Calcd for $C_{18}H_{40}SiSn$: C, 53.60; H, 10.00. Found: C, 53.56; H, 10.01.

Preparation of (*S*)-Tetrahydro-5-[3(*S*)-(trimethylsilyl)-4(*R*)-hydroxyl-1-buten-4-yl]-2-furanone and (*S*)-Tetrahydro-5-[3(*R*)-(trimethylsilyl)-4(*S*)-hydroxyl-1-buten-4-yl]-2-furanone (10a,b). To a solution of (*S*)-(−)-tetrahydro-5-oxo-2-furancarboxaldehyde (**6**) (4.27 g, 0.037 mol) and trimethylvinylsilane **8** (14.3 g, 0.0360 mol) in CH_2Cl_2 (100 mL) at −78 °C was added boron trifluoride–etherate (4.83 mL, 0.0393 mol) dropwise. After stirring at −78 °C for 30 min, the reaction mixture was carefully quenched by adding saturated aqueous $NaHCO_3$ (50 mL), followed by removal of the cold bath and warming of the reaction mixture to rt. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were then washed successively with saturated aqueous KF and brine followed by drying (Na_2SO_4). Concentration followed by flash chromatography of the residue, eluting with 35% EtOAc/hexanes, gave the desired α-hydroxysilanes **10a** and **10b** (6.97 g, 86%) as a 1:1 mixture of diastereomers. Analysis of the faster running diastereomer **10a**: mp 60–62 °C; R_f 0.40 (35% EtOAc/hexanes); $[\alpha]_D$ + 1.7° (*c* 5.0, $CHCl_3$); IR ($CDCl_3$), cm^{-1} 3450, 2980, 1765, 1630, 840; 300-MHz ^{1}H NMR ($CDCl_3$) δ 5.55 (dt, J = 16.9, 10.5 Hz, 1H), 4.90 (dd, J = 10.3, 1.8 Hz, 1 H), 4.85 (ddd, J = 16.9, 1.8, 1.0 Hz, 1 H), 4.56 (dt, J = 7.5, 2.4 Hz, 1 H), 4.18 (dd, J = 11.2, 1.0 Hz, 1 H), 2.56–2.41 (m, 2 H), 2.32–2.19 (m, 1 H), 2.08–1.96 (m, 1 H), 1.69 (dd, J = 10.8, 1.0 Hz, 1 H), 0.04 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 177.9, 135.5, 114.4, 82.7, 71.1, 38.0, 28.9, 19.4, −1.7. Anal. Calcd for $C_{11}H_{20}O_3Si$: C, 57.86; H, 8.83. Found: C, 57.83; H, 8.78. Analysis of slower running diastereomer **10b**: R_f 0.24 (35% EtOAc/hexanes); $[\alpha]_D$ +35.1° (*c* 3.0, $CHCl_3$); IR (neat) cm^{-1} 3440, 2950, 2900, 1765, 1650, 1245, 1190, 845; 300-MHz ^{1}H NMR ($CDCl_3$) δ 5.59 (dt, J = 17.0, 10.4 Hz, 1 H), 4.97–4.86 (m, 2 H), 4.62 (dt, J = 7.4, 2.2 Hz, 1 H), 3.63 (bt, J = 8.1 Hz, 1 H), 2.50 (m, 2 H), 2.16 (m, 2 H), 0.025 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 177.8, 136.0, 115.3, 81.6, 74.2, 40.4, 28.9, 24.2, −1.7. Anal. Calcd for $C_{11}H_{20}O_3Si$: C, 57.86; H, 8.83. Found: C, 57.67; H, 9.14.

Preparation of (*S*)-(+)-Dihydro-5-[(*E*)-1,3-butadienyl]-2(3H)-furanone (7). To a stirred solution of the allylsilanes **10a** and **10b** (1.37 g, 6.00 mmol) in THF (15 mL) was added potassium *tert*-butoxide (67.3 mg, 0.600 mmol) in one portion. After stirring at rt for 15 min, the reaction mixture was diluted with 50 mL of EtOAc and washed successively with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. Drying (Na_2SO_4), followed by concentration and flash chromatography, eluting with 35% EtOAc/hexanes gave **7** (779 mg, 94%) as a colorless oil: R_f 0.32 (35% EtOAc/hexanes); $[\alpha]_D$ +54.3° (*c* 8.6, $CHCl_3$); IR ($CDCl_3$) cm^{-1} 3160, 3095, 2980, 2950, 1770, 1605, 1400, 1170, 1000; 300-MHz ^{1}H NMR ($CDCl_3$) δ 6.27 (m, 2 H), 5.66 (ddd, J = 14.6, 6.7, 1.0 Hz, 1 H), 5.24 (m, 1 H), 5.15 (m, 1 H), 4.93 (dd, J = 13.9, 7.0 Hz, 1 H), 2.52–2.31 (m, 2 H), 2.01–1.89 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 176.8, 135.3, 133.3, 130.1, 119.5, 80.1, 28.6, 28.4; mass spectrum (EI) *m/z* (rel inten) (M+) 138 (86.6), 110 (14.0), 109 (4.4), 95 (100), 83 (34.4), 56 (91); exact mass calcd for $C_8H_{10}O_2$ 138.0681, found 138.0679.

Preparation of *tert*-Butyldiphenylsilyl 4(*S*)-(−)-[(*tert*-Butyldiphenylsilyl)oxy]-5(*E*),7-octadienoate (12). To a solution of **7** (264 mg, 1.91 mmol) in THF/MeOH (4:1, 10 mL) was added tetrapropylammonium hydroxide (4.1 mL of a 0.1 g/mL solution in H_2O, 410 mg, 1.91 mmol). After stirring at rt for 30 min, the reaction mixture was concentrated without heating to dryness. The resulting residue was dried by adding and evaporating (without heating) 5 × 10-mL portions of absolute ethanol. The residue was dissolved in DMF (10 mL) and treated with imidazole (221 mg, 3.25 mmol), *tert*-butyldiphenylsilyl chloride (832 mg, 3.06 mmol) and catalytic 4-DMAP. After stirring at rt for 3 days, the reaction mixture was taken up in ether (100 mL), washed successively with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4) and concentrated, followed by flash chromatography of the residue, eluting with 5% EtOAc/hexanes, giving **12** as a clear oil (1.12 g, 96%): R_f 0.54 (10% EtOAc/hexanes); $[\alpha]_D$ −9.8° (*c* 2.2, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3050, 2935, 2860, 1720, 1430, 1105; 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.67–7.33 (m, 10 H), 6.20 (ddd, J = 17.0, 16.9, 10.2 Hz, 1 H), 5.89 (dd, J = 14.7, 10.5 Hz, 1 H), 5.58 (dd, J = 15.4, 6.7 Hz, 1 H), 5.05 (d, J = 15.2 Hz, 1 H), 5.00 (dd, J = 8.8, 1.5 Hz, 1 H), 4.28 (dd, J = 11.6, 5.8 Hz, 1 H), 2.49–2.42 (m, 2 H), 1.90–1.82 (m, 2 H), 1.07 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 136.0, 135.9, 135.4, 130.0, 127.7, 127.6, 127.5, 117.2, 72.9, 32.8, 31.3, 27.1, 27.0, 19.4, 19.2. Anal. Calcd for $C_{40}H_{48}O_3Si_2$: C, 75.90; H, 7.64. Found: C, 76.11; H, 7.73.

Preparation of (*S*)-(−)-4-[(*tert*-Butyldiphenylsilyl)oxy]-5(*E*),7-Octadienoic Acid (13). To a solution of **12** (8.83 g, 0.0140

mol) in THF/MeOH/H_2O (4:1:1, 50 mL) was added LiOH·H_2O (0.644 g, 0.0153 mol) and the resulting solution was stirred at rt. After 15 min, 25 mL of saturated aqueous NH_4Cl was added, and the layers were separated. The aqueous layer was extracted with of EtOAc (3 × 25 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and then concentrated. Flash chromatography of the residue, eluting with 25% EtOAc/hexanes, gave **13** as an amorphous solid (5.17 g, 0.0131 mol, 94%): R_f 0.34 (35% EtOAc/hexanes); $[\alpha]_D$ −16.4° (*c* 6.2, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3300, 3080, 2940, 2860, 1710, 1605, 1590, 1425, 1100, 1000, 820, 700; 300-MHz ^1H NMR ($CDCl_3$) δ 7.67–7.34 (m, 10 H), 6.19 (ddd, *J* = 17.0, 17.0, 10.2 Hz, 1 H), 5.91 (dd, *J* = 15.2, 10.5 Hz, 1 H), 5.56 (dd, *J* = 15.2, 6.7 Hz, 1 H), 5.05 (d, *J* = 17.5 Hz, 1 H), 5.00 (d, *J* = 10.5 Hz, 1 H), 4.28 (dd, *J* = 12.0, 5.6 Hz, 1 H), 2.35 (ddd, *J* = 13.7, 7.9, 7.9 Hz, 2 H), 1.81 (ddd, *J* = 13.2, 7.7, 7.7 Hz, 2 H), 1.07 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 180.2, 136.2, 136.0, 135.9, 135.1, 134.0, 131.6, 129.8, 129.6, 127.8, 127.6, 127.5, 117.3, 72.7, 32.3, 29.2, 27.1, 19.4. Anal. Calcd for $C_{24}H_{30}O_3Si$: C, 73.06; H, 7.92. Found: C, 73.21; H, 7.88.

Preparation of *N*-Succinimidyl 4(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-5(*E*),7-octadienoate. To a solution of the carboxylic acid **13** (418 mg, 1.06 mmol) in THF (5 mL) was added *N*-(trifluoroacetyl)succinimide (280 mg, 1.32 mmol) and pyridine (168 mg, 2.12 mmol) and the resulting solution was stirred overnight at rt. The reaction mixture was taken up in EtOAc (25 mL), washed successively with 1% HCl, saturated aqueous $NaHCO_3$, and brine, followed by drying (Na_2SO_4). Concentration of the resulting solution gave the desired succinimide ester (528 mg, 100%) of sufficient purity for use in the next reaction. An analytical sample was prepared by flash chromatography, eluting with 35% EtOAc/hexanes: R_f 0.19 (25% EtOAc/hexanes); $[\alpha]_D$ −8.15° (*c* 1.3, $CHCl_3$); IR (neat) cm^{-1} 3080, 2915, 2880, 1810, 1780, 1740, 1430, 1360, 1200, 1100, 920; 300-MHz ^1H NMR ($CDCl_3$) δ 7.67–7.26 (m, 10 H), 6.19 (ddd, *J* = 16.9, 10.0, 10.0 Hz, 1 H), 5.91 (dd, *J* = 15.3, 10.5 Hz, 1 H), 5.55 (dd, *J* = 15.3, 6.7 Hz, 1 H), 5.50 (m, 2 H), 4.32 (dd, *J* = 11.5, 5.7 Hz, 1 H), 2.82 (s, 4 H), 2.63 (m, 2 H), 1.91 (m, 2 H), 1.07 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 169.1, 168.8, 136.1, 136.0, 135.9, 134.5, 133.8, 132.0, 129.8, 129.7, 127.71, 127.67, 127.5, 117.7, 72.3, 32.1, 27.1, 26.2, 25.6, 19.4. Anal. Calcd for $C_{28}H_{33}NO_5Si$: C, 68.40; H, 6.77. Found: C, 68.25; H, 6.59.

Preparation of (*S*)-(−)-4-[(*tert*-Butyldiphenylsilyl)oxy]-5(*E*),7-octadienohydroxamic Acid (14). Diisopropylethylamine (1.64 g, 13.1 mmol) in $CHCl_3$ (5 mL) was added dropwise to a slurry of H_2NOH·HCl (454 mg, 6.53 mmol) in $CHCl_3$ (15 mL) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. The succinimide ester (642 mg, 1.30 mmol) in $CHCl_3$ (10 mL) was added dropwise to this solution, and the resulting mixture was stirred at 0 °C for 2 h and then allowed to warm to rt. The reaction mixture was washed with saturated aqueous NH_4Cl, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography, eluting with 50% EtOAc/hexanes, gave the hydroxamic acid **14** (530 mg, 80%): R_f 0.14 (5% MeOH/$CHCl_3$); $[\alpha]_D$ −20.9° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3410, 3050, 2940, 2860, 1660, 1105, 1000; 300-MHz ^1H NMR ($CDCl_3$) δ 7.95 (bs, 1H), 7.62 (m, 4 H), 7.37 (m, 6 H), 6.20 (ddd, *J* = 16.9, 10.2, 1.0 Hz, 1 H), 5.92 (dd, *J* = 15.2, 10.4 Hz, 1 H), 5.56 (dd, *J* = 15.2, 6.4 Hz, 1 H), 5.07 (dd, *J* = 15.6, 1.0 Hz, 1 H), 5.02 (dd, *J* = 8.7, 1.0 Hz, 1 H), 4.26 (dd, *J* = 10.7, 5.0 Hz, 1 H), 2.08 (m, 2 H), 1.79 (m, 2 H), 1.06 (s, 9 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 171.1, 136.2, 136.0, 135.9, 135.0, 134.1, 133.6, 131.6, 129.9, 129.8, 127.8, 127.6, 117.5, 72.8, 32.8, 28.1, 27.1, 19.4. Anal. Calcd for $C_{24}H_{31}NO_3Si$: C, 70.38; H, 7.63. Found: C, 70.25; H, 7.63.

Preparation of (5*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]pyrido[1,2-*b*][1,2]oxazin-8-ones 16 and 17. To a solution of tetrapropylammonium periodate (188 mg, 0.499 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added, dropwise, a solution of the hydroxamic acid **14** (186 mg, 0.454 mmol) in CH_2Cl_2 (5 mL). After stirring at −78 °C for 4 h, the reaction mixture was allowed to warm to 0 °C over a 30-min period. The solution was taken up in EtOAc (50 mL) and washed with 2 × 10-mL portions of saturated aqueous Na_2SO_3 and then dried over Na_2SO_4. Concentration followed by flash chromatography of the residue eluting with 75% EtOAc/hexanes gave 180 mg (96%) of **16** and **17** as a mixture of diastereomers. The isomers were separated by preparative HPLC (10-μm silica, 25 cm × 21.4 mm column) eluting with 30% THF/hexanes, to give a 2.4:1 ratio of the two diastereomeric cycloadducts. Analysis of the major 8*S*,8a*R* (swainsonine numbering) isomer **16**: R_f 0.20 (50% EtOAc/hexanes); $[\alpha]_D$ −75.9° (*c* 3.9, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3085, 3075, 2980, 2970, 2880, 1680, 1110; 300-MHz ^1H NMR ($CDCl_3$) δ 7.69–7.26 (m, 10 H), 5.81 (m, 2 H), 4.62 (bd, *J* = 15.8 Hz, 1 H), 4.38 (bs, 1 H), 4.25 (bd, *J* = 15.8 Hz, 1 H), 3.77 (ddd, *J* = 9.0, 6.0, 3.2 Hz, 1 H), 2.64 (ddt, *J* = 17.1, 5.4, 1.0 Hz, 1 H), 2.18 (m, 1 H), 1.77–1.60 (m, 2 H), 1.08 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 165.6, 135.8, 130.2, 130.1, 128.0, 127.9, 124.5, 71.3, 68.8, 63.3, 28.9, 27.7, 26.9, 19.3. Anal. Calcd for $C_{24}H_{29}O_3NSi$: C, 70.73; H, 7.17. Found: C, 70.51; H, 7.11. Analysis of the minor 8*S*,8a*S* (swainsonine numbering) isomer **17**: R_f 0.20 (50% EtOAc/hexanes); $[\alpha]_D$ −37.3° (*c* 2.7, $CHCl_3$); IR (neat) cm^{-1} 3080, 2980, 2975, 1675, 1110; 300-MHz ^1H NMR ($CDCl_3$) δ 7.68–7.26 (m, 10 H), 5.90 (m, 1 H), 5.58 (m, 1 H), 4.72 (m, 1 H), 4.37 (bs, 1 H), 4.34–4.22 (m, 2 H), 2.73 (ddd, *J* = 16.2, 10.1, 5.5 Hz, 1 H), 2.36 (dt, *J* = 17.3, 5.5 Hz, 1 H), 1.77 (m, 2 H), 1.06 (s, 9 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 165.9, 136.0, 127.9, 127.8, 126.0, 125.5, 124.1, 69.1, 68.6, 61.6, 28.6, 27.0, 26.9, 19.5. Anal. Calcd for $C_{24}H_{29}O_3NSi$: C, 70.73; H, 7.17. Found: C, 70.73; H, 7.11.

Preparation of 1(*S*),2(*S*),8(*S*),8a(*S*)-Acetonide 18. To a solution of the 1,2-oxazine **16** (51.6 mg, 0.126 mmol) in acetone/water (8:1, 2 mL) was added NMO (25.9 mg, 0.252 mmol) and catalytic OsO_4 (2 drops of a solution of 1 g of OsO_4 in 100 mL of THF), and the resulting solution was stirred at rt for 24 h. The reaction mixture was concentrated to dryness by blowing air over the solution and the residue was dissolved in EtOAc and filtered through a plug of silica gel. The solution was concentrated to dryness and the residue was dissolved in 2,2-dimethoxypropane (5 mL). A small spatula of Dowex (H^+) resin beads were added and the solution was stirred at rt for 4 h. The reaction mixture was filtered through a small plug of Celite, and concentrated. The residue was purified by flash chromatography, eluting with 20% EtOH/EtOAc to give 49.7 mg (82%) of the desired acetonide **18** as a clear oil: R_f 0.20 (EtOAc); $[\alpha]_D$ −64.3° (*c* 3.6, $CHCl_3$); IR ($CDCl_3$) cm^{-1} 2940, 1665, 1360, 1090; 300-MHz ^1H NMR ($CDCl_3$) δ 7.65–7.30 (m, 10 H), 4.40 (d, *J* = 13.2 Hz, 1 H), 4.30 (bs, 1 H), 4.22 (dd, *J* = 13.2, 2.3 Hz, 1 H), 4.20 (dd, *J* = 5.5, 2.3 Hz, 1 H), 3.92 (d, *J* = 9.7 Hz, 1 H), 3.77 (dd, *J* = 9.7, 5.2 Hz, 1 H), 2.88 (ddd, *J* = 19.0, 12.8, 6.2 Hz, 1 H), 2.25 (m, 1 H), 1.66–1.56 (m, 2 H), 1.34 (s, 3 H), 1.30 (s, 3 H), 1.08 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 164.9, 135.74, 135.69, 133.1, 130.1, 130.0, 127.9, 127.8, 127.8, 110.2, 72.0, 71.7, 70.6, 67.1, 66.8, 27.8, 27.3, 27.0, 26.0, 24.1, 19.2; mass spectrum (EI), *m*/*z* (rel inten), (M−57) 424 (93.7), 350 (75.0), 272 (64.4), 199 (100); exact mass calcd for $C_{23}H_{26}O_5NSi$ 424.1579, found 424.1571.

Preparation of 1(*R*),2(*R*),8(*S*),8a(*R*)-Acetonide 20. This compound was prepared from **18** in the same manner as the isomeric material in 77% yield. Analysis of **20**: R_f 0.36 (75% EtOAc/hexanes); $[\alpha]_D$ +59.6° (*c* 3.1, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 2920, 1660, 1360, 1100, 1070; 300-MHz ^1H NMR ($CDCl_3$) δ 7.75–7.33 (m, 10 H), 4.73 (dd, *J* = 8.4, 5.6 Hz, 1 H), 4.48 (bs, 1 H), 4.44 (d, *J* = 13.2 Hz, 1 H), 4.27 (dd, *J* = 5.6, 1.7 Hz, 1 H), 4.19 (dd, *J* = 13.2, 2.2 Hz, 1 H), 3.68 (dd, *J* = 8.6, 4.0 Hz, 1 H), 2.69–2.59 (m, 1 H), 2.13 (m, 1 H), 1.56 (m, 2 H), 1.49 (s, 3 H), 1.35 (s, 3 H), 1.11 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 166.6, 136.0, 135.8, 133.5, 132.7, 130.1, 130.0, 127.9, 127.7, 109.8, 71.9, 70.2, 69.0, 66.5, 65.6, 28.0, 27.9, 27.1, 27.0, 26.0, 19.5; mass spectrum (EI) *m*/*z* (rel inten) (M−57) 424 (90.3), 408 (16.2), 366 (63.7), 272 (60.9), 199 (100); exact mass calcd for $C_{23}H_{26}O_5NSi$ 424.1579, found 424.1574.

Preparation of (1(*S*),2(*R*),8(*S*),8a(*S*))-8-(*tert*-Butyldiphenylsiloxy)-1,2-(isopropylidenedioxy)-octahydro-5-indolizidinone 19. To a solution of **18** (339 mg, 0.729 mmol) in ethanol (25 mL) at 0 °C was added Na_2HPO_4 (497 mg, 3.52 mmol) followed by freshly powdered 6% Na(Hg) (3.38 g, 10× by weight), and the resulting slurry was stirred at 0 °C for 1 h. The reaction mixture was then filtered through a pad of silica gel overlaid with Celite, eluted with 20% EtOH/EtOAc, and then concentrated. The residue was dissolved in EtOAc (50 mL), washed with saturated aqueous NH_4Cl, and dried (Na_2SO_4). Concentration gave the free lactam (344 mg, 100%) as a colorless solid (R_f 0.14, EtOAc). To a stirring solution of the lactam (344 mg, 0.700 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (144 mg, 1.42 mmol) followed by methanesulfonyl chloride (89.5 mg, 0.781 mmol), and the resulting solution was stirred at 0 °C for 30 min. The reaction mixture was washed with water (10 mL), the aqueous

layer was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried (Na_2SO_4) and then concentrated to give the corresponding mesylate (R_f 0.24, EtOAc) (387 mg, 98%) as an amorphous solid. To a solution of the mesylate (387 mg, 0.685 mmol) in dioxane/H_2O (4:1, 10 mL) was added K_2CO_3 (392 mg, 2.84 mmol) and the resulting solution was heated at 90 °C for 5 h and then concentrated. The residue was dissolved in EtOAc (50 mL), washed with saturated aqueous NH_4Cl, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue, eluting with 90% EtOAc/hexanes, gave the desired bicyclic lactam **19** (272 mg, 83% overall) as a colorless oil: R_f 0.42 (EtOAc); $[\alpha]_D$ −19.4° (*c* 3.3, $CHCl_3$); IR (neat) cm^{-1} 3030, 2930, 1450, 1375, 1110, 1085; 300-MHz ^1H NMR ($CDCl_3$) δ 7.76–7.26 (m, 10 H), 4.52 (ddd, *J* = 6.6, 6.1, 3.4 Hz, 1 H), 4.16 (dd, *J* = 6.1, 6.0 Hz, 2 H), 3.66 (ddd, *J* = 7.9, 7.9, 7.9 Hz, 1 H), 3.53 (dd, *J* = 7.9, 5.9 Hz, 1 H), 3.25 (dd, *J* = 13.6, 3.4 Hz, 1 H), 2.40 (ddd, *J* = 9.6, 4.7, 4.7 Hz, 1 H), 2.04 (ddd, *J* = 17.8, 8.8, 8.8 Hz, 1 H), 1.79 (m, 2 H), 1.56 (s, 3 H), 1.32 (s, 3 H), 1.09 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 167.9, 136.0, 135.8, 133.8, 133.1, 129.9, 129.8, 127.62, 127.58, 113.5, 83.4, 76.4, 70.6, 68.1, 49.3, 29.7, 29.3, 27.6, 26.8, 25.4, 19.1; mass spectrum (EI) *m/z* (rel inten) (M−57) 408 (13.4), 350 (82.8), 272 (80.2), 244 (11.5), 199 (23.6); exact mass calcd for $C_{23}H_{28}NO_4Si$ (M−57.070425, tBu^+) 408.1631, found 408.1638.

Preparation of (1(*R*),2(*S*),8(*S*),8a(*R*))-8-(*tert*-Butyldiphenylsiloxy)-1,2-(isopropylidenedioxy)octahydro-5-indolizidinone 21. This material was prepared from **20** in an analogous manner to that for the isomeric material in 70% overall yield. R_f of lactam alcohol: 0.20 (EtOAc). R_f of mesylate: 0.51 (EtOAc). Analysis of final product **21**: R_f 0.43 (75% EtOAc/hexanes); $[\alpha]_D$ +2.47° (*c* 1.04, $CHCl_3$); IR (neat) cm^{-1} 2930, 1630, 1450, 1380, 1375, 1110, 1085; 300-MHz ^1H NMR ($CDCl_3$) δ 7.66–7.28 (m, 10 H), 4.76 (dd, *J* = 6.2, 6.2 Hz, 1 H), 4.65 (ddd, *J* = 6.2, 6.2, 2.4 Hz, 1 H), 4.45 (ddd, *J* = 6.2, 2.4, 2.0 Hz, 1 H), 3.46 (dd, *J* = 6.3, 2.4 Hz, 1 H), 3.46 (dd, *J* = 13.2, 4.1 Hz, 1 H), 2.45 (m, 1 H), 2.20 (ddd, *J* = 17.9, 6.8, 2.1 Hz, 1 H), 1.65 (m, 2 H), 1.48 (s, 3 H), 1.29 (s, 3 H), 1.07 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 168.7, 135.7, 133.4, 130.1, 127.9, 113.0, 79.9, 76.4, 67.8, 65.0, 49.6, 27.7, 26.2, 25.5; mass spectrum (EI) *m/z* (rel inten) (M−57) 408 (38.2), 350 (100), 272 (91.1), 244 (12.7), 199 (40.1); exact mass calcd for $C_{23}H_{28}NO_4Si$ (M−57.070425, tBu^+) 408.1631, found 408.1634.

Preparation of (1(*S*),2(*R*),8(*S*),8a(*S*))-8-Hydroxy-1,2-(isopropylidenedioxy)octahydro-5-indolizidinone. To a solution of the silyl ether **19** (272 mg, 0.584 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (0.87 mL of a 1.0 M solution in THF, 0.876 mmol) and the resulting solution was stirred for 12 h at rt. The reaction mixture was concentrated, and the residue was dissolved in EtOAc (25 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography, eluting with EtOAc to give the desired alcohol (127 mg, 96%) as a clear oil: R_f 0.19 (EtOAc); $[\alpha]_D$ −26.2° (*c* 1.7, $CDCl_3$); IR ($CDCl_3$) cm^{-1} 3600, 2990, 2970, 1640, 1450, 1410, 1375, 1210, 1080; 300-MHz ^1H NMR ($CDCl_3$) δ 4.74 (ddd, *J* = 6.4, 6.4, 2.7 Hz, 1 H), 4.53 (dd, *J* = 6.2, 6.2 Hz, 1 H), 4.18 (dd, *J* = 13.7, 6.4 Hz, 1 H), 3.71 (ddd, *J* = 11.3, 9.0, 4.0 Hz, 1 H), 3.41 (dd, *J* = 13.2, 2.3 Hz, 1 H), 3.37 (dd, *J* = 8.6, 6.0 Hz, 1 H), 2.98 (bs, 1 H), 2.55 (ddd, *J* = 18.1, 6.7, 1.9 Hz, 1 H), 2.36 (ddd, *J* = 18.5, 11.7, 7.0 Hz, 1 H), 2.11 (m, 1 H), 1.84 (ddd, *J* = 24.4, 11.5, 6.8 Hz, 1 H), 1.56 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.0, 114.0, 84.0, 76.6, 69.7, 67.9, 49.3, 29.7, 29.6, 27.6, 25.4; mass spectrum (EI), *m/z* (rel inten) 227 (77), 212 (55), 169 (42), 152 (67); exact mass calcd for $C_{11}H_{17}NO_4$ 227.1157, found 227.1157.

Preparation of (1(*R*),2(*S*),8(*S*),8a(*R*))-8-Hydroxy-1,2-(isopropylidenedioxy)octahydro-5-indolizidinone. This material was prepared from silyl ether **21** in an analogous manner in 95% yield: R_f 0.36 (EtOH/toluene 1:4); $[\alpha]_D$ + 33.0° (*c* 1.2, $CDCl_3$); IR ($CHCl_3$) cm^{-1} 3600, 2940, 1640, 1450, 1375, 1210, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (dd, *J* = 6.2, 6.2 Hz, 1 H), 4.50 (ddd, *J* = 6.2, 6.2, 2.2 Hz, 1 H), 4.33 (ddd, *J* = 4.4, 4.4, 2.3 Hz, 1 H), 4.15 (dd, *J* = 13.9, 6.2 Hz, 1 H), 3.51 (dd, *J* = 6.5, 2.3 Hz, 1 H), 3.47 (dd, *J* = 14.3, 1.6 Hz, 1 H), 2.91 (bm, 1 H), 2.56–2.29 (m, 2 H), 2.12–1.89 (m, 2 H), 1.53 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 113.1, 79.5, 76.5, 66.9, 62.4, 49.6, 28.2, 27.8, 26.0, 25.6; mass spectrum (EI), *m/z* (rel inten) (M+) 227 (79), 212 (50), 169 (42), 152 (67); exact mass calcd for $C_{11}H_{17}NO_4$ 227.1157, found 227.1160.

Preparation of (1(*S*),2(*R*),8(*S*),8a(*S*))-1,2-*O*-Isopropylideneoctahydro-1,2,8-indolizidinetriol. To a solution of (1(*S*),2(*R*),8(*S*),8a(*S*))-8-hydroxy-1,2-(isopropylidenedioxy)octahydro-5-indolizidinone (38.2 mg, 0.168 mmol) in THF (5 mL) was added BH_3·SMe_2 (0.841 mmol, 84 uL of a 10.0 M solution), and the resulting solution was stirred at rt for 4 h. The reaction mixture was carefully quenched by adding EtOH (3 mL) and the solution was concentrated. The residue was dissolved in EtOH (5 mL) and refluxed for 2 h, cooled to rt, and concentrated. The residue was purified by flash chromatography, eluting with 10% EtOH/EtOAc to give the free amine (31.5 mg, 88%) as a clear oil: R_f 0.31 (10% EtOH/EtOAc); $[\alpha]_D$ −15.8° (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3950, 2930, 1340, 1050; 300-MHz ^1H NMR ($CDCl_3$) δ 4.69 (dd, *J* = 11.8, 6.3 Hz, 1 H), 4.44 (dd, *J* = 6.6, 6.6 Hz, 1 H), 3.44 (bs, 1 H), 3.37 (dd, *J* = 9.1, 6.7 Hz, 1 H), 2.84 (db, *J* = 8.4 Hz, 1 H), 2.37 (dd, *J* = 9.4, 5.3 Hz, 1 H), 2.12–1.93 (m, 3 H), 1.69–1.54 (m, 3 H), 1.50 (s, 3 H), 1.31 (s, 3 H), 1.29–1.19 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 83.6, 77.6, 77.3, 74.5, 59.8, 51.3, 33.7, 29.1, 27.2, 25.1, 23.9; mass spectrum (EI), *m/z* (rel inten) (M+) 213 (52), 198 (7), 156 (11), 155 (6), 138 (100), 113 (90); exact mass calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1363.

Preparation of (1(*R*),2(*S*),8(*S*),8a(*R*))-1,2-*O*-Isopropylideneoctahydro-1,2,8-indolizidinetriol. This material was prepared from (1(*R*),2(*S*),8(*S*),8a(*R*))-8-hydroxy-1,2-(isopropylidenedioxy)octahydro-5-indolizidinone in an analogous manner in 87% yield. R_f 0.20 (10% EtOH/hexanes); $[\alpha]_D$ +54.2° (*c* 0.50, $CHCl_3$); IR ($CDCl_3$) cm^{-1} 3510, 2940, 1380, 1370, 1205, 1155, 1070, 1005; 300-MHz ^1H NMR ($CDCl_3$) δ 4.63 (m, 2 H), 4.05 (bs, 1 H), 3.38 (dd, *J* = 9.6, 6.2 Hz, 1 H), 2.94 (dd, *J* = 11.3, 4.4 Hz, 1 H), 2.38 (bs, 1 H), 2.36 (dd, *J* = 9.4, 5.34 Hz, 1 H), 2.24–2.15 (m, 2 H), 1.93–1.73 (m, 2 H), 1.51 (s, 3 H), 1.50–1.37 (m, 2 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 113.9, 79.8, 77.1, 72.4, 64.8, 60.4, 52.4, 30.8, 27.1, 25.0, 19.2; mass spectrum (EI) *m/z* (rel inten) (M+) 213 (22.3), 198 (5.7), 156 (10.2), 155 (8.3), 138 (100), 126 (12.7), 113 (78.3); exact mass calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1367.

Preparation of (1(*S*),2(*R*),8(*S*),8a(*S*))-Octahydro-1,2,8-indolizidinetriol (8,8a-di-*epi*-swainsonine) 22. A solution of the acetonide (28.6 mg, 0.134 mmol) in 1 M HCl (2 mL) was refluxed for 30 min, cooled to rt, and concentrated. The residue was chromatographed on an Amberlyst-IRA 400 (OH^-) ion-exchanged column, and the ninhydrin-positive fractions were combined and concentrated. The residue was then chromatographed by flash chromatography, eluting with NH_4OH/*n*-BuOH/EtOH/CH_2Cl_2 (1:3:3:3) to give 8,8a-di-*epi*-swainsonine (**22**) (19.5 mg, 84%) as a white, crystalline solid: mp 129–130 °C; R_f 0.33 (NH_4OH/*n*-BuOH/EtOH/CH_2Cl_2 (1:3:3:3)); $[\alpha]_D$ −18.7° (*c* 0.55, MeOH); IR ($CHCl_3$) cm^{-1} 3350, 2930, 2820, 1360, 1260; 300-MHz ^1H NMR (D_2O) δ 4.00 (dd, *J* = 13.4, 6.8 Hz, 1 H), 3.76 (dd, *J* = 7.6, 7.6 Hz, 1 H), 3.36 (ddd, *J* = 10.5, 10.5, 4.4 Hz, 1 H), 3.24 (dd, *J* = 10.7, 6.7 Hz, 1 H), 2.76 (bd, *J* = 11.4 Hz, 1 H), 2.21 (dd, *J* = 10.7, 5.9 Hz, 1 H), 2.07 (ddd, *J* = 11.4, 11.4, 2.9 Hz, 1 H), 1.98 (dd, *J* = 8.5, 8.5 Hz, 1 H), 1.82 (m, 1 H), 1.57 (m, 1 H), 1.31 (m, 1 H), 1.15 (m, 1 H); ^{13}C NMR (D_2O) δ 75.9, 74.0, 72.6, 69.8, 61.7, 53.6, 34.5, 24.8; mass spectrum (EI) *m/z* (rel inten) (M+) 173 (10), 156 (6), 155 (10), 138 (5), 113 (100), 96 (76); exact mass calcd for $C_8H_{15}NO_3$ 173.1052, found 173.1052.

Preparation of (1(*R*),2(*S*),8(*S*),8a(*R*))-Octahydro-1,2,8-indolizidinetriol (1,2,8-tri-*epi*-swainsonine) 23. This material was prepared from (1(*R*),2(*S*),8(*S*),8a(*R*))-1,2-*O*-isopropylideneoctahydro-1,2,8-indolizidinetriol in an analogous manner in 83% yield: mp 120–123 °C; R_f 0.37 (NH_4OH/*n*-BuOH/EtOH/CH_2Cl_2 (1:3:3:3)); $[\alpha]_D$ +45.6° (*c* 0.40, MeOH); IR ($CHCl_3$) cm^{-1}; 300-MHz ^1H NMR (D_2O) δ 4.08 (bs, 2 H), 3.84 (dd, *J* = 10.0, 6.5 Hz, 1 H), 3.57 (dd, *J* = 11.8, 6.3 Hz, 1 H), 3.16 (bd, *J* = 10.3 Hz, 1 H), 2.70 (bd, *J* = 9.7 Hz, 1 H), 2.55 (db, *J* = 11.5 Hz, 2 H), 1.80–1.67 (bm, 2 H), 1.52 (bd, *J* = 14.3 Hz, 2 H); 300-MHz ^1H NMR (CD_3OD) δ 3.94 (m, 2 H), 3.85 (dd, *J* = 8.5, 7.0 Hz, 1 H), 3.34 (dd, *J* = 10.3, 6.4 Hz, 1 H), 2.93 (bd, *J* = 10.7 Hz, 1 H), 2.14 (m, 3 H), 1.82–1.74 (bm, 2 H), 1.44–1.37 (bm, 2 H); ^{13}C NMR (D_2O) δ 71.4, 68.9, 64.7, 62.0, 55.5, 31.5, 20.9; ^{13}C NMR (CD_3OD) δ 72.0, 70.7, 68.0, 64.1, 62.3, 54.0, 31.8, 20.4; mass spectrum (EI) *m/z* (rel inten) (M+) 173 (22.6), 172 (3.5), 156 (13.4), 155 (22.9), 116 (32.5), 113 (100), 96 (75.2); exact mass calcd for $C_8H_{15}NO_3$ 173.1052, found 173.1064.

Preparation of (1(*S*),2(*R*),8(*R*),8a(*S*))-8-(Benzoyloxy)-1,2-(isopropylidenedioxy)octahydro-5-indolizidinone 25. To a

solution of (1(*S*),2(*R*),8(*S*),8a(*S*))-8-hydroxy-1,2-(isopropylidenedioxy)octahydro-5-indolizidinone (42.3 mg, 0.186 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added methanesulfonyl chloride (42.6 mg, 0.372 mmol) and triethylamine (75.3 mg, 0.744 mmol), and the resulting solution was stirred at 0 °C for 30 min. The solution was concentrated to dryness, dissolved in EtOAc (10 mL), washed with water and brine, dried (Na_2SO_4), and concentrated to give the desired mesylate (100%): R_f 0.42 (10% EtOH/EtOAc). A solution of the mesylate (56.7 mg, 0.186 mmol) and sodium benzoate (53.6 mg, 0.372 mmol) in DMF (2 mL) was refluxed for 4 h and then concentrated. The residue was taken up in EtOAc (10 mL), washed with 1% HCl and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue, eluting with 5% EtOH/EtOAc, gave **25** (53.0 mg, 86%) as a clear oil: R_f 0.58 (10% EtOH/EtOAc); $[\alpha]_D$ −43.7° (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3020, 2995, 2940, 1720, 1640, 1450, 1375, 1265, 1085, 845; 300-MHz ^1H NMR ($CDCl_3$) δ 5.73 (ddd, *J* = 4.0, 2.4, 2.4 Hz, 1 H), 4.74 (ddd, *J* = 6.0, 6.0 Hz, 2.1 Hz, 1 H), 4.57 (dd, *J* = 6.2, 6.2 Hz, 1 H), 4.29 (dd, *J* = 13.9, 6.2 Hz, 1 H), 3.79 (dd, *J* = 6.6, 2.6 Hz, 1 H), 3.56 (dd, *J* = 13.9, 1.8 Hz, 1 H), 2.50 (m, 2 H), 2.35 (m, 1 H), 2.05 (m, 1 H), 1.56 (s, 3 H), 1.34 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.2, 165.4, 133.6, 129.7, 129.4, 128.7, 113.6, 79.6, 76.4, 65.8, 65.7, 49.3, 27.8, 26.4, 25.6, 25.6; mass spectrum (EI) *m/z* (rel inten) (M+) 331 (1.9), 316 (2.2), 209 (72.2), 152 (52.9), 105 (100); exact mass calcd for $C_{18}H_{21}NO_5$ 331.1412, found 331.1419.

Preparation of (1(*S*),2(*R*),8(*R*),8a(*S*))-8-Hydroxy-1,2-(isopropylidenedioxy)octahydro-5-indolizidinone. To a solution of the amide **25** (47.0 mg, 0.142 mmol) in THF (3 mL) was added $BH_3 \cdot SMe_2$ (70 μL of a 10.0 M neat solution, 0.710 mmol) and the resulting solution was stirred at rt for 2 h. The reaction mixture was quenched by carefully adding EtOH (5 mL) and then concentrated. The residue was dissolved in MeOH (5 mL), K_2CO_3 (39.1 mg, 0.284 mmol) was added, and the resulting solution was refluxed for 4 h. The reaction mixture was cooled to rt, neutralized to pH 7.0 with 1% HCl, and concentrated. The residue was purified by flash chromatography, eluting with 10% EtOH/EtOAc to give the amine (28.6 mg, 94%) as a clear oil: R_f 0.28 (10% EtOH/EtOAc); $[\alpha]_D$ −43.7° (*c* 1.13, $CHCl_3$), IR ($CDCl_3$) cm^{-1} 3510, 2940, 1380, 1370, 1205, 1155, 1070, 1005; 300-MHz ^1H NMR ($CDCl_3$) δ 4.63 (m, 2 H), 4.05 (bs, 1 H), 3.38 (dd, *J* = 9.6, 6.2 Hz, 1 H), 2.94 (dd, *J* = 11.3, 4.4 Hz, 1 H), 2.38 (bs, 1 H), 2.36 (dd, *J* = 9.4, 5.34 Hz, 1 H), 2.24–2.15 (m, 2 H), 1.93–1.73 (m, 2 H), 1.51 (s, 3 H), 1.50–1.37 (m, 2 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 113.9, 79.8, 77.1, 72.3, 64.7, 60.3, 52.3, 30.8, 27.1, 25.0, 19.1; mass spectrum (EI) *m/z* (rel inten) (M+) 213 (54.8), 212 (4.1), 198 (9.9), 156 (23.6), 155 (12.7), 138 (100), 126 (27.4), 122 (5.1), 113 (89.2); exact mass calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1361.

Preparation of (1(*S*),2(*R*),8(*R*),8a(*S*))-Octahydro-1,2,8-indolizidinetriol (8,8a-di-*epi*-swainsonine) 26. This material was prepared from (1(*S*),2(*R*),8(*S*),8a(*S*))-1,2-*O*-isopropylideneoctahydro-1,2,8-indolizidinetriol as previously described in 86% yield: mp 121–123 °C; R_f 0.37 (NH_4OH/nBuOH/EtOH/CH_2Cl_2 (1:3:3:3)); $[\alpha]_D$ −49.8° (*c* 0.71, MeOH); IR ($CHCl_3$) cm^{-1}; 300-MHz ^1H NMR (D_2O) δ 4.08 (bs, 2 H), 3.84 (dd, *J* = 10.0, 6.5 Hz, 1 H), 3.57 (dd, *J* = 11.8, 6.3 Hz, 1 H), 3.16 (bd, *J* = 10.3 Hz, 1 H), 2.70 (bd, *J* = 9.7 Hz, 1 H), 2.55 (db, *J* = 11.5 Hz, 2 H), 1.80–1.67 (bm, 2 H), 1.52 (bd, *J* = 14.3 Hz, 2 H); 300-MHz ^1H NMR (CD_3OD) δ 3.94 (m, 2 H), 3.85 (dd, *J* = 8.5, 7.0 Hz, 1 H), 3.34 (dd, *J* = 10.3, 6.4 Hz, 1 H), 2.93 (bd, *J* = 10.7 Hz, 1 H), 2.14 (m, 3 H), 1.82–1.74 (bm, 2 H), 1.44–1.37 (bm, 2 H); ^{13}C NMR (D_2O) δ 71.4, 68.9, 64.7, 62.0, 55.5, 31.5, 20.9; ^{13}C NMR (CD_3OD) δ 72.1, 70.7, 68.0, 64.2, 62.5, 54.0, 31.9, 20.6; mass spectrum (EI) *m/z* (rel inten) (M+) 173 (27.6), 172 (6.7), 156 (11.9), 155 (28.1), 116 (26.0); exact mass calcd for $C_8H_{15}NO_3$ 173.1052, found 173.1051.

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Supplementary Material Available: Photocopies (8.5 × 11) of ^1H and ^{13}C NMR spectra for all compounds for which exact masses rather than C,H analyses were obtained: **7**, **18–26**, and unnumbered intermediates in the conversion of **19–22** and **21–23** (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.