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Synthesis of the Novel Mannosidase Inhibitors (3*R*)- and (3*S*)-3-(Hydroxymethyl)swainsonine‡

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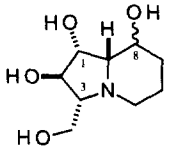
Abstract: Swainsonine (**9**) is an important mannosidase inhibitor that has been examined clinically as an anticancer drug. The preparation of analogs of swainsonine bearing a hydroxymethyl group at C(3), i.e., (3*R*)-3-(hydroxymethyl)swainsonine [(**10**), (3*R*)-HMS] and (3*S*)-3-(hydroxymethyl)swainsonine [(**11**), (3*S*)-HMS] is described. The synthesis of each analog begins with D-ribose, and involves a Claisen rearrangement, a Sharpless osmylation, and a reductive double-cyclization of either an azido mesylate bearing a lactone (i.e. **24** ⇒ **11**) or an azido epoxide bearing a lactone (i.e. **27** ⇒ **10**). Both (3*R*)-HMS and (3*S*)-HMS were found to be effective inhibitors of α-mannosidase from jack bean.

INTRODUCTION

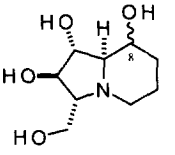
One of the major challenges in using azasugars inhibitors of glycosidase enzymes as biochemical tools or drugs is that they generally suffer from a lack of specificity.[1-3] We recently completed the synthesis of the four hydroxymethyl-substituted polyhydroxylated indolizidines **1-4** shown in Figure 1,[4] which may be considered ring-expanded analogs (homologs) of the known pyrrolizidine alkaloids alexine (**5**), 7-epialexine (**6**), australine (**7**), and 7-epiaustraline (**8**). The pyrrolizidines **5-8** generally exhibit glucosidase inhibitory activity. For example, **5**,[5,6] **7**,[5,7,8] and **8**[5,7,8] are good inhibitors of amyloglucosidase and glucosidase I.[8,9] These and other polyhydroxylated alkaloids show promising biological activity, e.g. **8** shows anti-HIV activity.[9] We had reason to believe that the ring-expanded analogs **1-4** would have increased glucosidase inhibitory activity.[4] Indeed, all four hydroxymethyl-substituted indolizidines were found to be good inhibitors of amyloglucosidase, although they were weaker inhibitors than the natural pyrrolizidine parent compounds.[4] Surprisingly, **1-4** were also found to inhibit *α-mannosidase* (jack bean), albeit weakly. This is in contrast to the pyrrolizidine inhibitors **5-8**, which have not been reported to exhibit mannosidase inhibitory activity.[7,8] The fact that **1-4** are mannosidase inhibitors at all is significant, since most good mannosidase inhibitors are epimeric to **1-4** at the carbon corresponding to C(1),[10,11] for example swainsonine **9**, the first glycoprotein-processing inhibitor to be selected for clinical testing as an anticancer drug.[3,12-14] This suggests that 3-hydroxymethyl-substituted swainsonine analogs, e.g. (3*R*)-(hydroxymethyl)swainsonine [**10**, (3*R*)-HMS] and (3*S*)-(hydroxymethyl)swainsonine [**11**, (3*S*)-HMS], might be potent mannosidase inhibitors and perhaps be useful as anticancer agents. Further, the hydroxymethyl substituents of **11**, and especially **10**, are expected to occupy the same region of space in the enzyme binding pocket that the anomeric substituent on a D-mannose residue does in the natural substrate. The hydroxymethyl oxygen of **10** or **11** could thus serve as a site of attachment for another sugar residue, or other sugar-like substituents, to afford disaccharide mimics that would more closely resemble the Man(α-1,3)Man or Man(α-1,6)Man linkage recognized and cleaved by the

‡Dedicated with gratitude and admiration to Professor Samuel J. Danishefsky, an inspiring mentor and scientist.

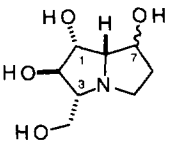
human glycoprotein processing enzyme mannosidase II,[15,16] hopefully resulting in more potent and selective inhibitors of this important enzyme. A number of disaccharide mimics involving other azasugar inhibitors are known and have been reported to be selective glycosidase inhibitors.[17,18] We report herein the synthesis and preliminary biological screening of both C(3) diastereomers of 3-HMS.



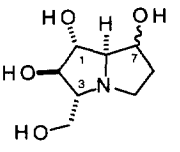
1: Homoalexine (β-OH)
2: 8-Epi-homoalexine (α-OH)



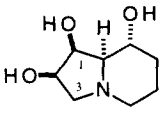
3: Homoaustraline (β-OH)
4: 8-Epi-homoaustraline (α-OH)



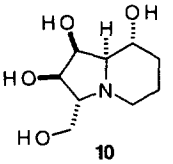
5: Alexine (β-OH)
6: 7-Epialexine (α-OH)



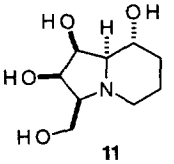
7: Australine (β-OH)
8: 7-Epiaustraline (α-OH)



9
Swainsonine



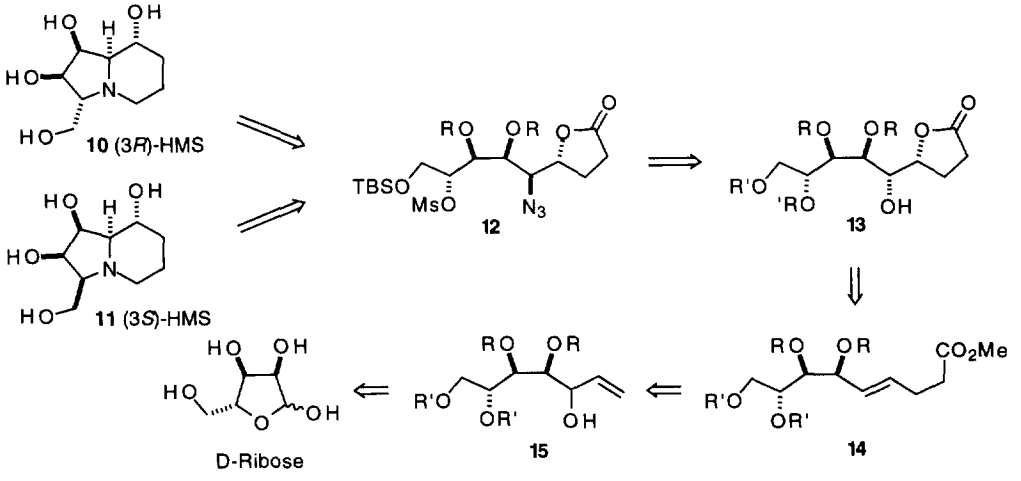
10
(3*R*)-3-(Hydroxymethyl)swainsonine
(3*R*)-HMS



11
(3*S*)-3-(Hydroxymethyl)swainsonine
(3*S*)-HMS

Figure 1. *(Hydroxymethyl)pyrrolizidines and -indolizidines..*

A retrosynthetic analysis of **10** and **11** is presented in Scheme 1. We have previously shown that azides bearing two tethered electrophilic sites may be used to synthesize pyrrolizidines, indolizidines, and quinolizidines via a reductive double-cyclization.[19] We chose to implement this method using a route that would allow us to prepare either **10** or **11** from a common precursor. Thus, catalytic reduction of the azide **12** to the primary amine should result in subsequent *N*-alkylation and *N*-acylation by the mesylate and ester,

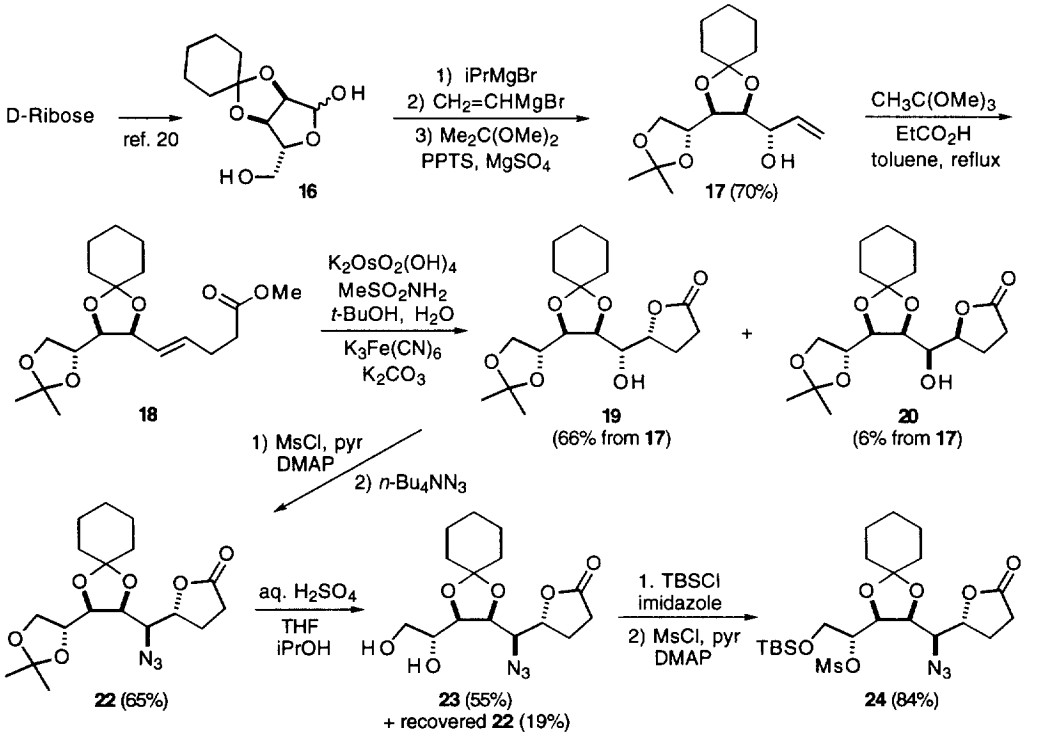


Scheme 1. *Retrosynthetic analysis of 3-(hydroxymethyl)swainsonine (3-HMS).*

respectively, affording **11** after lactam reduction and deprotection. Alternatively, removal of the silyl group of **12** with fluoride ion should produce an epoxide, which upon azide reduction will result in double-cyclization to give **10** after lactam reduction and deprotection. The azide **12** should be available by S_N2 displacement of an activated derivative of the alcohol **13**, which we planned to make by *syn*-dihydroxylation of the alkene **14**. The *E*-alkene **14** would be prepared by Claisen rearrangement of the allylic alcohol **15**, which in turn may be synthesized by the addition of a vinylic organometallic to a derivative of D-ribose.

RESULTS AND DISCUSSION

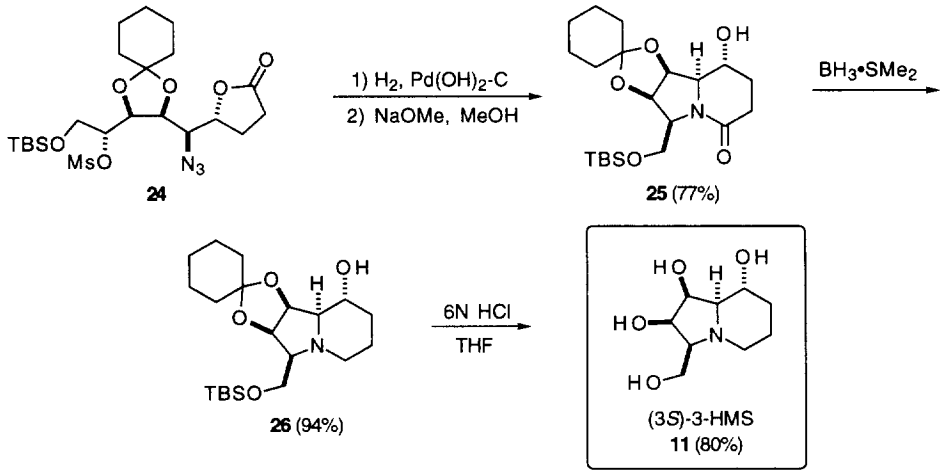
The synthesis of the two diastereomers of 3-HMS began with 2,3-*O*-cyclohexylidene-D-ribose (**16**), prepared from D-ribose by the method of Mori and Kikuchi[20] (Scheme 2). Deprotonation of **16** followed by addition of vinylmagnesium bromide gave a triol, which was subjected to acetonide formation without purification, resulting in the formation of the allylic alcohol **17** as a single diastereomer, as judged by 300 MHz ^{1}H NMR spectroscopy. This outcome was expected, since the addition of vinylmagnesium bromide to 2,3-*O*-isopropylidene-D-ribose[21] and the addition of other Grignard reagents to **16**[20] have been reported to occur with high stereoselectivity. Johnson orthoester Claisen rearrangement[22] of **17** proceeded smoothly to afford the γ,δ-unsaturated ester **18**, which was subjected without purification to Sharpless asymmetric dihydroxylation conditions.[23,24] The desired hydroxy lactone **19** was obtained in 66% overall yield from **17** by crystallization and chromatography, which also provided the minor isomer **20** in 6% yield. The double diastereodifferentiation afforded by the Sharpless dihydroxylation was necessary for this level of stereo-



Scheme 2. *Synthesis of the key azido mesylate 24.*

selectivity. Mesylation of **19**, followed by azide displacement, gave the azido lactone **22**. Selective hydrolysis of the acetonide group of **22** in the presence of the cyclohexylidene group was possible with aqueous sulfuric acid. The best results were obtained by running the reaction to partial conversion; a substantial amount of tetraol was formed at full conversion. Selective silylation of the primary hydroxyl group of the diol **23**, followed by mesylation of the secondary hydroxyl group, afforded the key azido mesylate **24**. We were now in a position to explore the double reductive cyclization reactions.

Completion of the synthesis of (3*S*)-3-HMS (**11**) is shown in Scheme 3. Catalytic hydrogenation of the azido mesylate **24** generated a primary amine, which was alkylated *in situ* by the mesylate. The resultant pyrrolidino lactone was heated with methanolic sodium methoxide to promote *N*-acylation, affording the indolizidinone **25** in good yield. Borane reduction of **25** gave the indolizidine **26**, which was deprotected to produce (3*S*)-3-(hydroxymethyl)swainsonine (**11**). The synthesis of **11** from 2,3-*O*-cyclohexylidene-D-ribose (**16**) proceeded in 8% overall yield, requiring 12 steps.

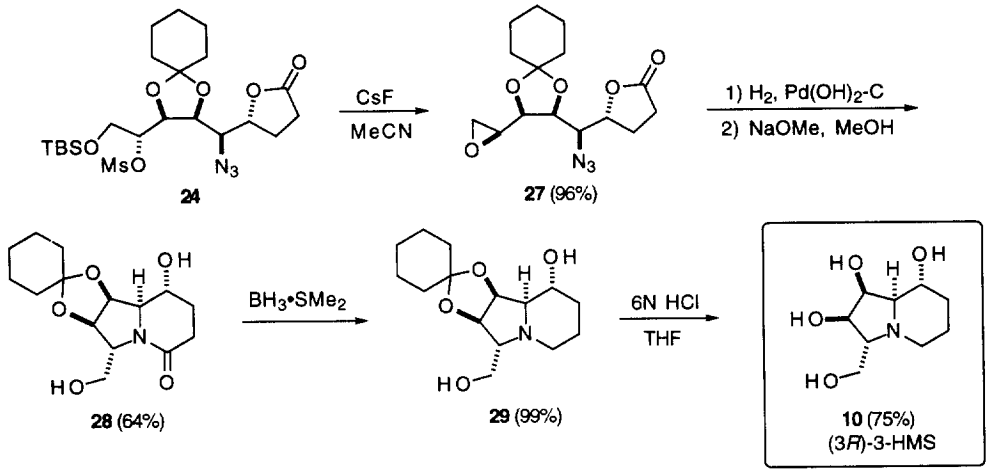


Scheme 3. *Synthesis of (3S)-3-(hydroxymethyl)swainsonine by reductive double cyclization.*

The steps required to complete the synthesis of (3*R*)-3-HMS (**10**) are shown in Scheme 4. Initial attempts to convert the azido mesylate **24** to the epoxide **27** using tetra-*n*-butylammonium fluoride led to poor results, affording mostly the hydroxy mesylate. However, the use of anhydrous cesium fluoride in warm acetonitrile provided the epoxide directly in high yield.[25] Reductive double-cyclization of the azido epoxide **27** as described above provided the indolizidinone **28**. Reduction of **28** with borane-methyl sulfide complex produced the indolizidine **29**, which was deprotected to afford (3*R*)-3-(hydroxymethyl)swainsonine (**10**). The synthesis of **10** from 2,3-*O*-cyclohexylidene-D-ribose (**16**) proceeded in 6% overall yield, requiring 13 steps.

BIOLOGICAL EVALUATION

Initial screening in our laboratories using standard techniques[8] showed that the hydroxymethyl-substituted swainsonine analogs **10** and **11** were indeed inhibitors of α-mannosidase (jack bean). As predicted, (3*R*)-HMS (**10**), bearing an α-oriented hydroxymethyl group, was a better inhibitor, with an IC_{50} of 1.2 μM versus 45 μM for (3*R*)-HMS (**11**), which bears a β-oriented hydroxymethyl group. These values



Scheme 4 *Synthesis of (3R)-3-(hydroxymethyl)swainsonine by reductive double cyclization.*

compare with an IC_{50} of 0.1 μM for swainsonine (**9**). Although (3*R*)- and (3*S*)-HMS are not as potent as swainsonine, the tolerance of a hydroxymethyl group at C(3) is encouraging for the incorporation of other substituents (e.g., another sugar) at this position. We are currently subjecting both diastereomers of 3-HMS to more extensive screening, including anticancer activity, and we are exploring the synthesis and biological activity of C(3) derivatives of 3-HMS.

EXPERIMENTAL SECTION

General. All commercial reagents (if liquid) were distilled prior to use. All other solid reagents were used as obtained. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Toluene, benzene, dichloromethane, dimethyl sulfoxide, and triethylamine were distilled from calcium hydride. Dimethylformamide was distilled from barium oxide at reduced pressure. Methanol and ethanol were distilled from calcium oxide. Analytical thin layer chromatography (tlc) was conducted on precoated silica gel plates (Kieselgel 60 F_{254}, 0.25 mm thickness, manufactured by E. Merck & Co., Germany). For visualization, tlc plates were stained with iodine vapor or phosphomolybdic acid solution. Gas chromatographic (GC) analyses were performed using a 530μ methylpolysiloxane column (3μ film thickness, 5m length) using flame ionization detection. A standard temperature program of 100 °C for 2 min followed by a 40 °C/min ramp to 200 °C was used. Elemental analyses were performed by the University of Michigan Department of Chemistry CHN / AA Services Branch. ^{1}H NMR spectral assignments were made on the basis of two dimensional correlated off resonance spectroscopy (COSY) experiments. High resolution mass spectrometric (HRMS) measurements are accurate to within 2.2 ppm (electron impact, EI), 3.9 ppm (chemical ionization, CI), or 3.3 ppm (fast-atom bombardment, FAB), based on measurement of the performance of the mass spectrometer on a standard organic sample. Flash column chromatography was performed according to the general procedure described by Still[26] using flash grade Merck Silica Gel 60 (230-400 mesh). The enzyme α-mannosidase (from jack bean) and the corresponding *p*-nitrophenyl α-D-mannopyranoside substrate was obtained from Sigma Chemical Co. Enzyme inhibition was assayed colorimetrically by monitoring the

release of *p*-nitrophenol from *p*-nitrophenyl α-D-mannopyranoside according to the procedure described by Tropea, *et. al.*[8]

(2*R*,3*R*,4*S*,5*S*)-3,4-Cyclohexylidenedioxy-1,2-isopropylidenedioxy-6-hepten-5-ol (17). Isopropylmagnesium bromide (131 mL of a 2 M solution in THF, 262 mmol) was added in a dropwise fashion via an addition funnel to a cooled (0 °C) solution of 2,3-*O*-cyclohexylidene-D-ribose[20] (40.3 g, 175 mmol) in THF (600 ml). After the addition was complete, the solution was allowed to stir for 15 min, then vinylmagnesium bromide (440 mL of a 1 M solution in THF, 440 mmol) was added via an addition funnel over a period of 1 h. After the addition was complete, the solution was allowed to warm to room temperature. After 12 h, the solution was cooled back to 0 °C, and was quenched by the addition of saturated aqueous NH_4Cl (200 mL). The resulting mixture was diluted with water (500 mL) and extracted with EtOAc (3 x 500 mL). The organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give 49.7 g of crude (2*R*,3*R*,4*S*,5*S*)-3,4-cyclohexylidenedioxy-1,2,5-trihydroxy-6-heptene as a yellow oil that was used without further purification. [R_f = 0.09 (2:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (ddd, J = 5.6, 10.6, 17.3 Hz, 1H), 5.38 (dt, J = 1, 17.3 Hz, 1H), 5.27 (dt, J = 1, 10.5 Hz, 1H), 4.69 (br s, 1H), 4.35 (m, 2H), 4.11 (dd, J = 5.0, 8.8 Hz, 1H), 4.03 (dd, J = 5.8, 8.8, 1H), 3.90 (m, 2H), 3.71 (m, 1H), 3.33 (br s, 1H), 1.5-1.7 (m, 8H), 1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 116.3, 109.5, 79.8, 77.5, 70.7, 69.7, 64.6, 37.9, 35.0, 25.1, 24.1, 23.8.] The crude triol was dissolved in THF (500 mL) and 2,2-dimethoxypropane (55 g, 525 mmol), pyridinium *p*-toluenesulfonate (2.2 g, 8.8 mmol), and magnesium sulfate (10 g) were added. After 18 h, the mixture was poured into ether (500 mL) and washed with saturated aqueous $NaHCO_3$ (300 mL) and brine (200 mL), then dried ($MgSO_4$), filtered, and concentrated. Only one stereoisomer of **17** was observed in the 300 MHz ^{1}H NMR spectrum of the crude product. Chromatography (20:1 to 10:1 hex/EtOAc gradient) provided 36.5 g (70%) of the title compound, R_f = 0.39 (6:1 hexane/EtOAc); $[\alpha]^{23}_D$ +1.9 (*c* 1.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (ddd, J = 4.6, 10.7, 17.3 Hz, 1H), 5.46 (dt, J = 1.8, 17.3 Hz, 1H), 5.24 (dt, J = 1.8, 10.7 Hz, 1H), 4.36 (m, 1H), 4.20 (m, 2H), 4.04 (m, 3H), 3.91 (2, J = 3.4 Hz, 1H), 1.5-1.65 (m, 8H), 1.45 (s, 3H), 1.39 (s, 3H), 1.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 115.1, 110.4, 109.4, 80.3, 78.2, 73.3, 69.3, 68.2, 38.1, 34.9, 25.6, 25.5, 25.1, 24.0, 23.7; IR (neat) 3500 (m), 2936 (s), 2864 (m), 1450 (m), 1373 (m); MS (CI, NH_3) *m/z* (rel intensity) 316 [(M + NH_4)$^+$, 4], 299 [(M + H)$^+$, 24], 241 (29), 201 (100), 183 (59), 143 (41); HRMS (CI, NH_3) calcd for $C_{16}H_{26}O_5H$ [(M + H)$^+$] 299.1858, found 299.185; Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found C, 64.29; H, 8.68.

Methyl *E*-(6*S*,7*S*,8*R*)-6,7-Cyclohexylidenedioxy-8,9-isopropylidenedioxy-4-nonenoate (18). Trimethyl orthoacetate (75 mL, 625 mmol) and propionic acid (1.8 mL, 25 mmol) were added to a solution of the allylic alcohol **17** (36.5 g, 122 mmol) in toluene (500 mL). The flask was fitted with a distillation head and the mixture was heated at reflux, distilling off methanol as it formed. GC was used to monitor the disappearance of starting material (t_R=4.8 min) and the appearance of product (t_R=6.8 min, see General methods above for GC conditions). After 18 h, the mixture was cooled to room temperature and concentrated to give 43 g (99%) of the title compound as a pale yellow oil that was used without further purification. Only one stereoisomer of **18** was observed in the 300 MHz ^{1}H NMR spectrum of the crude product. Purification of a small sample by chromatography (15:1 to 10:1 hex/EtOAc) provided an analytically pure sample, R_f = 0.17 (8:1 hex/EtOAc); $[\alpha]^{23}_D$ -1.0 (*c* 1.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.83 (m, 1H), 5.57 (dd, J = 7.1, 15.3 Hz, 1H), 4.63 (t, J = 6.0 Hz, 1H), 4.04 (m, 3H), 3.93 (m, 1H), 3.68 (s, 3H), 2.41 (m, 4H), 1.5-1.7 (m, 8H), 1.40 (m, 2H), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.3, 132.3, 126.7, 109.3, 109.2, 78.5, 77.6, 74.0, 67.3, 51.5, 37.6, 34.8, 33.4, 27.5, 26.7, 25.5, 25.1, 24.0, 23.7; IR (neat) 2986 (m), 2936 (s), 2862 (m), 1741 (s), 1440 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 354 (M$^+$, 22), 155 (13), 101 (100); HRMS (EI, 70

eV) calcd for $C_{19}H_{30}O_6$ (M^+) 354.2042, found 354.2028. Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.39; H, 8.53. Found: C, 64.03; H 8.50.

(5*R*)-5-[(1*R*,2*S*,3*R*,4*R*)-2,3-Cyclohexylidenedioxy-4,5-isopropylidenedioxy-1-hydroxypentyl]tetrahydrofuran-2-one (19) and (5*S*)-5-[(1*S*,2*S*,3*R*,4*R*)-2,3-Cyclohexylidenedioxy-4,5-isopropylidenedioxy-1-hydroxypentyl]tetrahydrofuran-2-one (20). The dihydroxylation was performed using the general procedure reported by Sharpless.[23] A solution of the crude alkene **18** (43.0 g, 121 mmol) in *tert*-butanol (200 mL) was added to a cold (0 °C), mechanically stirred, biphasic mixture of water (500 mL) and *tert*-butanol (300 mL) containing potassium ferricyanide (120 g, 366 mmol), potassium carbonate (50 g, 366 mmol), potassium osmate dihydrate (0.225 g, 0.61 mmol), $(DHQD)_2$-PHAL[23] (0.95 g, 1.2 mmol), and methanesulfonamide (12.8 g, 134 mmol). GC was used to monitor the disappearance of the alkene **18** (t_R=6.8 min) and the appearance of the product (t_R=11.3 min, see General methods above for GC conditions). After 36 h, sodium sulfite (185 g) was added and the mixture was stirred an additional 2 h. EtOAc (500 mL) was then added, the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with 2 M KOH (400 mL), then dried ($MgSO_4$) and concentrated. Crystallization from hex/EtOAc (10:1) provided 26.8 g of lactone **19** in two crops. The mother liquor was concentrated to give a yellow oil that was purified by chromatography (4:1 to 2:1 hex/EtOAc gradient) to provide an additional 1.78 g of lactone **19** (combined yield 66% from **17**) followed by 2.61 g (6%) of minor lactone diastereomer **20**. Data for **19**: R_f = 0.15 (3:1 hex/EtOAc); $[\alpha]^{23}_D$ -8.3 (*c* 1.38, $CHCl_3$); mp 139-141 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.88 (m, 1H), 4.39 (dd, *J* = 5.0, 9.6 Hz, 1H), 4.0-4.2 (m, 4H), 3.85 (dd, *J* = 1.4, 3.7 Hz, 1H), 3.80 (ddd, *J* = 1.6, 3.7, 9.6 Hz, 1H), 2.74 (m, 1H), 2.46 (m, 1H), 2.35 (m, 2H), 1.5-1.7 (m, 8H), 1.43 (s, 3H), 1.39 (s, 3H), 1.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 177.9, 110.6, 109.7, 79.2, 77.7, 75.9, 73.2, 71.0, 68.0, 37.9, 34.6, 28.3, 26.5, 25.4, 24.9, 23.9, 23.8, 23.6; IR (neat) 3470 (br m), 2936 (s), 1776 (s), 1450 (w), 1372 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 356 (M^+, 24), 313 (17), 255 (18), 101 (61), 85 (77), 55 (90), 43 (100); HRMS (EI, 70 eV) calcd for $C_{18}H_{28}O_7$ (M^+) 356.1835, found 356.1836. Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found C, 60.74; H, 8.14. Data for **20**: R_f = 0.10 (3:1 hex/EtOAc); $[\alpha]^{23}_D$ +16.6 (*c* 1.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.78 (td, *J* = 2.9, 6.9 Hz, 1H), 4.32 (t, *J* = 5.8 Hz, 1H), 4.25 (dt, *J* = 5.8, 9.6 Hz, 1H), 4.14 (dd, *J* = 6.2, 8.8 Hz, 1H), 4.03 (m, 2H), 3.96 (dd, *J* = 5.6, 8.7 Hz, 1H), 2.69 (dt, *J* = 8.2, 17.5 Hz, 1H), 2.50 (m, 2H), 2.30 (m, 2H), 1.5-1.7 (m, 8H), 1.39 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) 177.6, 110.0, 109.6, 79.9, 77.6, 76.3, 73.3, 70.7, 68.2, 37.4, 34.5, 28.3, 26.8, 25.4, 25.0, 24.0, 23.6; IR (neat) 3465 (br, m), 2935 (s), 1776 (s), 1450 (w), 1370 (m) cm^{-1}; MS (EI, 70eV) *m/z* (rel intensity) 356 (M^+, 66), 313 (58), 255 (48), 183 (65), 101 (96), 85 (100), 55 (86), 43 (92); HRMS (EI, 70 eV) calcd for $C_{18}H_{28}O_7$ (M^+) 356.1835, found 356.1831.

(5*R*)-5-[(1*S*,2*S*,3*S*,4*R*)-1-Azido-2,3-cyclohexylidenedioxy-4,5-isopropylidenedioxypentyl]tetrahydrofuran-2-one (22). Methanesulfonyl chloride (1.86 mL, 2.75 g, 24 mmol) was added to a cold (0 °C) solution of the alcohol **19** (7.13 g, 20.0 mmol) and 4-dimethylaminopyridine (0.120 g, 1.0 mmol) in pyridine (60 mL). The mixture was stirred for 10 min and then placed in a refrigerator (2 °C). After 24 h, ether (300 mL) was added and the solution was washed with 10% HCl (3 x 100 mL). The aqueous layers were back-extracted with ether (100 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, then dried ($MgSO_4$), and concentrated to give 8.2 g of the crude mesylate as a foamy yellow solid that was used without further purification, R_f = 0.22 (2:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.08 (m, 2H), 4.36 (dd, *J* = 5.1, 6.7 Hz, 1H), 4.25 (dt, *J* = 6.3, 9.4 Hz, 1H), 4.13 (dd, *J* = 6.0, 8.6, 1H), 4.07 (dd, *J* = 5.1, 9.4 Hz, 1H), 3.91 (dd, *J* = 6.5, 8.6 Hz, 1H), 3.20 (s, 3H), 2.75 (m, 1H), 2.53 (q, *J* = 8.7 Hz, 1H), 2.41 (m, 2H), 1.58 (m, 8H), 1.41 (s, 3H), 1.40 (m, 2H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.1, 110.3, 109.4, 78.8, 78.0, 77.8,

75.4, 72.8, 68.3, 39.2, 37.6, 34.6, 27.8, 26.8, 25.5, 24.9, 23.9, 23.7. The crude mesylate was dissolved in THF (20 mL), tetra-*n*-butylammonium azide[27] (60 mL of a 1 M solution in THF, 60 mmol) was added, and the mixture was warmed to reflux. After 48 h, the solution was cooled, poured into water (100 mL), and extracted with ether (3 x 200 mL). The combined organic extracts were washed with brine, then dried ($MgSO_4$), and concentrated. Chromatography (6:1 hex/EtOAc) provided 4.95 g (65%) of the title compound as a colorless oil, R_f = 0.46 (2:1 hex/EtOAc); $[\alpha]^{23}_D$ -31.4 (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.80 (td, *J* = 6.0, 7.2 Hz, 1H), 4.34 (m, 2H), 4.17 (dd, *J* = 6.2, 8.7 Hz, 1H), 4.02 (dd, *J* = 6.2, 9.6 Hz, 1H), 3.93 (m, 2H), 2.61 (m, 2H), 2.35 (m, 2H), 1.5-1.7 (m, 8H), 1.40 (s, 3H), 1.39 (m, 2H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.9, 110.1, 110.0, 78.9, 77.9, 75.9, 73.4, 68.5, 62.1, 36.9, 34.3, 28.3, 26.9, 25.4, 25.1, 24.2, 24.1, 23.8; IR (neat) 2936 (m), 2112 (s), 1784 (s), 1451 (w), 1372 (m) cm^{-1}; MS (EI, 70eV) *m/z* (rel intensity) 381 (M^+, 60), 338 (79), 183 (80), 101 (100), 85 (80); HRMS (EI, 70 eV) calcd for $C_{18}H_{27}N_3O_6$ (M^+) 381.1900, found 381.1903. Anal. Calcd for $C_{18}H_{27}N_3O_6$: C, 56.68; H, 7.13; N, 11.02. Found C, 56.58; H, 7.14; N, 10.89.

(5*R*)-5-[(1*S*,2*S*,3*R*,4*R*)-1-Azido-2,3-cyclohexylidenedioxy-4,5-dihydroxypentyl]tetrahydrofuran-2-one (23). A solution of the azide **22** (3.45 g, 9.05 mmol) in THF/isopropanol (1:1, 20 mL) was treated with 1 M sulfuric acid (10 mL). After 18 h, the mixture was diluted with EtOAc (150 mL), washed with 20% Na_2CO_3 (50 mL) and brine (50 mL), then dried ($MgSO_4$), and concentrated. Chromatography (2:1 hex/EtOAc to 25:25:1 hex/EtOAc/EtOH gradient) provided 0.64 g (19%) of recovered **22** followed by 1.70 g (55%) of the title compound as a colorless oil, R_f = 0.15 (50:50:1 hex/EtOAc/EtOH); $[\alpha]^{23}_D$ -21.8 (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.84 (q, *J* = 6.8 Hz, 1H), 4.36 (dd, *J* = 4.6, 6.0 Hz, 1H), 4.08 (dd, *J* = 6.1, 9.6 Hz, 1H), 3.85-4.02 (m, 3H), 3.73 (m, 1H), 3.01 (m, 1H), 2.60 (m, 2H), 2.35 (m, 3H), 1.5-1.7 (m, 8H), 1.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 176.7, 109.9, 79.0, 76.0, 69.6, 64.7, 61.7, 36.7, 34.2, 28.2, 25.0, 24.1, 24.0, 23.7; IR (neat) 3390 (br s), 2938 (s), 2862 (m), 2112 (s), 1775 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 359 [$(M + NH_4)^+$, 64), 342 [$(M + H)^+$, 18], 314 (100), 296 (47), 243 (69); HRMS (CI, NH_4) calcd for $C_{15}H_{23}N_3O_6H$ [$(M + H)^+$] 342.1665, found 342.1673. Anal. Calcd for $C_{15}H_{23}N_3O_6$: C, 52.78; H, 6.79; N, 12.31. Found C, 52.79; H, 6.80; N, 12.14.

(5*R*)-5-[(1*S*,2*S*,3*S*,4*R*)-1-Azido-5-(*tert*-butyldimethylsilyloxy)-2,3-cyclohexylidenedioxy-4-methanesulfonyloxypentyl]tetrahydrofuran-2-one (24). *tert*-Butyldimethylsilyl chloride (0.77 g, 5.1 mmol) and imidazole (0.83 g, 12.2 mmol) were added to a cooled (0 °C) solution of the diol **23** (1.66 g, 4.86 mmol) in THF/DMF (2:1, 20 mL). After 1 h, the mixture was poured into ether (100 mL) and washed with 1 M HCl (2 x 50 mL). The combined aqueous layers were back-extracted with ether (2 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, then dried ($MgSO_4$), filtered, and concentrated to give 2.25 g of a pale yellow oil that was used without further purification, R_f = 0.20 (4:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.83 (q, *J* = 6.8 Hz, 1H), 4.34 (dd, *J* = 4.0, 6.3 Hz, 1H), 4.06 (dd, *J* = 6.4, 9.7 Hz, 1H), 3.98 (dd, *J* = 4.0, 6.2 Hz, 1H), 3.91 (m, 1H), 3.86 (dd *J* = 3.2, 9.8 Hz, 1H), 3.71 (dd, *J* = 5.0, 9.9 Hz, 1H), 2.45-2.72 (m, 3H), 2.33 (m, 2H), 1.50-1.75 (m, 8H), 1.44 (m, 2H), 0.93 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 176.2, 109.8, 78.8, 75.9, 75.5, 69.2, 64.2, 61.8, 36.6, 34.2, 28.2, 25.8, 25.1, 24.2, 24.0, 23.7, 18.3, -5.4, -5.5. The crude alcohol was dissolved in pyridine (20 mL), 4-dimethylaminopyridine (30 mg, 0.24 mmol) was added, and the resulting mixture was cooled to 0 °C. Methanesulfonyl chloride (0.49 mL, 0.72 g, 6.3 mmol) was added in a dropwise fashion and the mixture was stirred at 0 °C for 10 min, then placed in a refrigerator (2 °C). After 24 h, ether (100 mL) was added and the solution was washed with 10% HCl (3 x 30 mL). The aqueous layers were back-extracted with ether (100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL) and brine (30 mL), then dried ($MgSO_4$), and concentrated.

Crystallization from ether/hexanes provided 1.96 g of the mesylate **24**. Concentration of the mother liquior followed by purification by chromatography (4:1 hex/EtOAc) provided another 0.23 g of **24** (combined yield 84%), R_f = 0.39 (2:1 hex/EtOAc); $[\alpha]^{23}_D$ -47.7 (*c* 1.20, $CHCl_3$); mp 109 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.02 (ddd, *J* = 2.2, 3.6, 8.9 Hz, 1H), 4.76 (q, *J* = 7.3 Hz, 1H), 4.52 (dd, *J* = 2.3, 6.8 Hz, 1H), 4.42 (dd, *J* = 6.9, 8.9 Hz, 1H), 4.18 (dd, *J* = 2.2, 12.2 Hz, 1H), 3.94 (dd, *J* = 3.7, 12.2 Hz, 1H), 3.69 (dd, *J* = 2.2, 8.1 Hz, 1H), 3.12 (s, 3H), 2.4-2.7 (m, 3H), 2.30 (m, 1H), 1.75 (m, 2H), 1.3-1.7 (m, 6H), 1.41 (m, 2H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 176.9, 110.0, 80.3, 78.1, 75.1, 72.8, 62.1, 60.5, 39.6, 35.9, 33.6, 27.9, 25.8, 25.3, 25.0, 24.0, 23.6, 18.3, -5.5, -5.6; IR (neat) 2935 (s), 2858 (m), 2110 (s), 1788 (s) 1359 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 551 [$(M + NH_4)^+$, 64), 410 (100), 352 (26), 243 (32); HRMS (CI, NH_4) calcd for $C_{22}H_{39}N_3O_8SSiNH_4$ [$(M + NH_4)^+$] 551.2571, found 551.2554. Anal. Calcd for $C_{22}H_{39}N_3O_8SSi$ C, 49.51; H, 7.37; N, 7.87. Found C, 49.72; H, 7.25; N, 7.87.

(1*S*,2*R*,3*S*,8*R*,8a*R*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-1,2-cyclohexylidenedioxy-8-hydroxyindolizidin-5-one (25). Palladium hydroxide on carbon (80 mg) was added to a solution of the azide **24** (0.534 g, 1.0 mmol) in MeOH/EtOAc (1:1, 15 mL). The flask was evacuated by aspirator and purged with hydrogen three times, and the resulting heterogeneous mixture was stirred under a balloon of hydrogen. After 2 h, the hydrogen was evacuated and the mixture was filtered through Celite and concentrated. The residue was redissolved in MeOH (20 mL) and the solution was warmed to reflux. After 30 min, sodium methoxide (81 mg, 1.5 mmol) was added. The reaction was monitored by IR for the disappearance of the lactone carbonyl stretch at 1784 cm^{-1} and appearance of the lactam carbonyl stretch at 1630 cm^{-1}. After 60 h, the solution was cooled to room temperature and concentrated. The residue was dissolved in CH_2Cl_2/MeOH (10:1, 5 mL), florisil (200 mg) was added, and the mixture was stirred at room temperature for 30 min. The suspension was then filtered through Celite, and the filtrate was concentrated. Chromatography (50:1 to 10:1 CH_2Cl_2/MeOH gradient) provided 315 mg (77%) of the title compound as a colorless crystalline solid, R_f = 0.20 (20:1 CH_2Cl_2/MeOH); mp 110 °C; $[\alpha]^{23}_D$ +38.7 (*c* 1.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (dd, *J* = 4.9, 9.2 Hz, 1H), 4.71 (m, 2H), 4.13 (ddd, *J* = 4.4, 8.8, 11.1 Hz, 1H), 3.95 (t, *J* = 10.2 Hz, 1H), 3.52 (dt, *J* = 4.3, 10.4 Hz, 1H), 3.21 (dd, *J* = 4.9, 8.5 Hz, 1H), 2.65 (br s, 1H), 2.39 (m, 2H), 2.08 (m, 1H), 1.81 (m, 1H), 1.3-1.7 (m, 10H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 170.6, 112.1, 78.5, 76.7, 67.5, 65.7, 64.7, 59.2, 35.9, 34.4, 31.0, 29.2, 25.8, 25.1, 23.9, 23.6, 18.3, -5.4, -5.5; IR (neat) 3380 (br m), 2935 (s), 2856 (m), 1633 (s) 1101 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 412 [$(M + H)^+$, 100), 354 (8); HRMS calcd for $C_{21}H_{37}NO_5SiH$ [$(M + H)^+$] 412.2519, found 412.2519. Anal. Calcd for $C_{21}H_{37}NO_5Si$: C, 61.28; H, 9.06; N, 3.40. Found C, 60.98; H, 9.16; N, 3.43.

(1*S*,2*R*,3*S*,8*R*,8a*R*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-1,2-cyclohexylidene-8-hydroxyindolizidine (26) Borane-methyl sulfide complex (1.0 mL of a 2 M solution in THF, 2.0 mmol) was added to a cooled (0 °C) solution of the lactam **25** (206 mg, 0.50 mmol) in THF (10 mL). After 15 min, the solution was allowed to warm to room temperature. After 4 h, the reaction was quenched by the slow addition of ethanol (8 mL) and then concentrated. The residue was redissolved in EtOH (10 mL), and the solution was warmed to reflux. After 2 h, the mixture was cooled to room temperature and concentrated. Chromatography (4:1 hex/EtOAc) provided 188 mg (94%) of the title compound as a colorless crystalline solid, R_f = 0.19 (4:1 hex/EtOAc); mp 108 °C; $[\alpha]^{23}_D$ +22.0 (*c* 1.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (dd, *J* = 4.6, 6.4 Hz, 1H), 4.60 (dd, *J* = 4.3, 6.3 Hz, 1H), 3.92 (dd, *J* = 6.9, 9.9 Hz, 1H), 3.81 (m, 1H), 3.74 (dd, *J* = 5.2, 9.9 Hz, 1H), 3.11 (m, 1H), 2.23 (m, 2H), 2.05 (m, 1H), 1.4-1.9 (m, 13H), 1.25 (m, 2H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 112.2, 79.2, 77.7, 74.7, 70.5, 67.6, 61.3, 51.2, 35.8, 35.5, 33.2, 26.0, 25.4, 24.3, 24.2, 24.0, 18.4, -5.2; IR (neat) 3305 (br m), 2929 (s), 2856 (m), 2800 (w) cm^{-1}; MS (CI, NH_3) *m/z* (rel

intensity) 398 [(M + H)$^+$, 47], 382 (20), 340 (14), 252 (100); HRMS calcd for $C_{21}H_{39}NO_4SiH$ [(M + H)$^+$] 398.2727, found 398.2730. Anal. Calcd for $C_{21}H_{39}NO_4Si$: C, 63.43; H, 9.89; N, 3.52. Found C, 63.51; H, 9.86; N, 3.64.

(1*S*,2*R*,3*S*,8*R*,8a*R*)-3-(Hydroxymethyl)-1,2,8-trihydroxyindolizidine [(3*S*)-3-(Hydroxymethyl)swainsonine] (11). A solution of the indolizidine **26** (140 mg, 0.35 mmol) in THF (3.5 mL) was treated with 6N HCl (3.5 mL) at room temperature. After 24 h, the solution was concentrated and the residue was redissolved in MeOH (5 mL). Dowex 1x8 200 mesh OH^- ion exchange resin (2 g) was added and the mixture was stirred for 15 min. The mixture was then filtered and the filtrate concentrated. Chromatography (100:25:1 CH_2Cl_2/MeOH/Aq. NH_4OH gradient) provided 57 mg (80%) of the title compound as a colorless oil, R_f = 0.57 (50:25:1 CH_2Cl_2/MeOH/Aq. NH_4OH); $[\alpha]^{23}_D$ -27.0 (*c* 0.50, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 4.25 (dd, *J* = 5.5, 8.3 Hz, 1H, H_2), 4.11 (dd, *J* = 3.3, 5.5 Hz, 1H, H_1), 3.74 (m, 2H, H_8 and H_9), 3.61 (dd, *J* = 3.4, 11.3 Hz, 1H, H_9), 3.05 (m, 1H, H_{5eq}), 2.52 (m, 1H, H_3), 2.25 (m, 1H, H_{7eq}), 1.95 (td, *J*= 3.2, 11.2 Hz, 1H, H_{5ax}) 1.88 (dd, *J* = 3.2, 9.1 Hz, 1H, H_{8a}), 1.5-1.7 (m, 2H, H_{6eq} and H_{6ax}), 1.21 (qd,*J* = 5.0, 12.5 Hz, 1H, H_{7ax}); ^{13}C NMR (CD_3OD, 90 MHz) δ 73.5, 72.4, 70.5, 69.0, 67.2, 60.3, 52.1, 34.7, 25.0; IR (neat) 3350 (br s), 2938 (m), 2800 (w), 1142 (m), 1083 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 204 [(M + H)$^+$, 100], 150 (28), 136 (34); HRMS calcd for $C_9H_{17}NO_4H$ [(M + H)$^+$] 204.1236, found 204.1226.

(5*R*)-5-[(1*S*,2*S*,3*R*,4*S*)-1-Azido-2,3-cyclohexylidenedioxy-4,5-epoxypentyl]tetrahydrofuran-2-one (27). In a glove bag under an atmosphere of dry N_2, anhydrous cesium fluoride (0.305 g, 2.0 mmol) was transferred to a flask containing a magnetic stir bar. A rubber septum was placed on the flask before removing from the glove bag. The cesium fluoride was then suspended in CH_3CN (15 mL) and the mesylate **24** (534 mg, 1.0 mmol) was added as a solution in CH_3CN (5 mL). The flask was then fitted with a condensor and the mixture was warmed to reflux. After 2 h, the mixture was cooled to room temperature, then poured into EtOAc (100 mL) and washed with water (30 mL) and brine (30 mL). The aqueous layers were back-extracted with EtOAc (50 mL). The combined organic layers were dried (Na_2SO_4), then filtered and concentrated. Chromatography (2:1 hex/EtOAc) provided 0.310 g (96%) of the title compound as a colorless oil, R_f = 0.13 (2:1 hex/EtOAc); $[\alpha]^{23}_D$ -22.0 (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.66 (q, *J* = 7.4 Hz, 1H), 4.44 (dd, *J* = 4.1, 7.0 Hz, 1H), 3.95 (dd, *J* = 6.1, 6.9 Hz, 1H), 3.45 (dd, *J* = 4.1, 7.7 Hz, 1H), 3.26 (ddd, *J* = 2.7, 4.1, 6.0 Hz, 1H), 2.84 (dd, *J* = 4.2, 4.9 Hz, 1H), 2.64 (m, 3H), 2.50 (m, 1H), 2.26 (m, 1H), 1.3-1.9 (m, 10H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 175.7, 110.7, 78.2, 78.0, 76.3, 62.6, 50.5, 43.4, 35.9, 34.0, 28.0, 25.2, 25.0, 24.0, 23.7; IR (neat) 2936 (s), 2860 (m), 2113 (s), 1784 (s) cm^{-1}; MS (EI, 70eV) *m/z* (rel intensity) 323 (M$^+$, 40), 294 (25), 280 (100), 183 (28), 85 (53), 55 (70); HRMS (EI, 70eV) calcd for $C_{15}H_{21}N_3O_5$ (M$^+$) 323.1481, found 323.1483.

(1*S*,2*R*,3*R*,8*R*,8a*R*)-1,2-Cyclohexylidenedioxy-3-(hydroxymethyl)-8-hydroxyindolizidin-5-one (28). Palladium hydroxide on carbon (70 mg) was added to a solution of the azide **27** (0.460 g, 1.42 mmol) in MeOH/EtOAc (1:1, 22 mL). The flask was evacuated by aspirator and purged with hydrogen three times, and the resulting heterogeneous mixture was stirred under a balloon of hydrogen. After 2 h, the hydrogen was evacuated and the mixture was filtered through Celite and concentrated. The residue was redissolved in MeOH (25 mL), sodium methoxide (80 mg, 1.48 mmol) was added, and the solution was warmed to reflux. The reaction was monitored by IR for the disappearance of the lactone carbonyl stretch at 1784 cm^{-1} and appearance of the lactam carbonyl stretch at 1615 cm^{-1}. After 60 h, the solution was cooled to room temperature and concentrated. The mixture was diluted with CH_2Cl_2/MeOH (10:1, 5 mL), florisil (200 mg) was added, and the mixture was stirred at room temperature for 30 min. The suspension was then filtered

through Celite, and the filtrate was concentrated. Chromatography (20:1 CH_2Cl_2/MeOH) provided 270 mg (64%) of the title compound as a colorless crystalline solid, R_f = 0.34 (10:1 CH_2Cl_2/MeOH); mp 190 °C; $[\alpha]^{23}_D$ -32.7 (*c* 0.55, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (t, *J* = 5.3 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.43 (br t, *J* = 5.0 Hz, 1H), 4.10 (ddd, *J* = 4.0, 8.6, 11.4 Hz, 1H), 3.85 (dd, *J* = 4.1, 10.9 Hz, 1H), 3.69 (dd, *J* = 6.4, 11.0 Hz, 1H), 3.65 (dd, *J* = 4.8, 8.6 Hz, 1H), 2.35-2.60 (m, 3H), 2.11 (m, 1H), 1.89 (qd, *J* = 6.8, 11.6 Hz, 1H), 1.3-1.7 (m, 11H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 169.8, 113.1, 80.0, 79.4, 66.3, 65.9, 65.3, 63.3, 36.3, 34.4, 29.7, 29.1, 25.0, 24.0, 23.7; IR (neat) 3360 (br m), 2930 (m), 2860 (m), 1614 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel intensity) 297 (M^+, 73), 266 (71), 254 (100), 152 (46), 134 (70), 85 (44); HRMS calcd for $C_{15}H_{23}NO_5$ (M^+) 297.1576, found 297.1589. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found C, 60.44; H, 7.75; N, 4.48.

(1*S*,2*R*,3*R*,8*R*,8a*R*)-1,2-Cyclohexylidenedioxy-3-(hydroxymethyl)-8-hydroxyindolizidine (29). Borane-methyl sulfide complex (1.25 mL of a 2 M solution in THF, 2.5 mmol) was added to a cooled (0 °C) solution of the lactam **28** (140 mg, 0.47 mmol) in CH_2Cl_2 (10 mL). The solution was allowed to warm to room temperature. After 4 h, the reaction was quenched by the slow addition of ethanol (8 mL) and then concentrated. The residue was redissolved in EtOH (10 mL) and the solution was warmed to reflux. After 2 h, the mixture was cooled to room temperature and concentrated. Chromatography (50:1 to 10:1 CH_2Cl_2/MeOH gradient) provided 132 mg (99%) of the title compound as a colorless crystalline solid, R_f = 0.21 (20:1 $CHCl_3$/MeOH); mp 172 °C; $[\alpha]^{23}_D$ -75.1 (*c* 1.40, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (t, *J* = 6.5 Hz, 1H, H_1), 4.70 (dd, *J* = 2.2, 7.0 Hz, 1H, H_2), 3.75 (m, 1H, H_8), 3.68 (m, 2H, H_9), 3.25 (dd, *J* = 2.7, 5.3 Hz, 1H, H_3), 2.87 (m, 3H, H_{8a}, H_5 and H_{OH}), 2.57 (td, *J* = 3.3, 12.6 Hz, 1H, H_5), 2.25 (br s, 1H, H_{OH}), 2.07 (m, 1H, H_7), 1.78 (m, 2H), 1.5-1.7 (m, 8H), 1.41 (m, 2H), 1.34 (m, 1H, H_7); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 113.7, 81.7, 79.2, 68.7, 66.6, 65.2, 59.5, 44.8, 35.4, 33.8, 32.0, 25.1, 24.1, 23.5, 21.0; IR (neat) 3375 (br m), 2930 (s), 2860 (m), 1441 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 284 [$(M + H)^+$, 100], 252 (69); HRMS calcd for $C_{15}H_{25}NO_4H$ [$(M + H)^+$] 284.1861, found 284.1864. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found C, 63.76; H, 8.93; N, 4.88.

(1*S*,2*R*,3*R*,8*R*,8a*R*)-3-(Hydroxymethyl)-1,2,8-trihydroxyindolizidine [(3*R*)-3-(Hydroxymethyl)swainsonine] (10). A solution of the indolizidine **29** (110 mg, 0.39 mmol) in THF (4 mL) was treated with 6N HCl (4 mL) at room temperature. After 24 h, the solution was concentrated and the residue was redissolved in MeOH (5 mL). Dowex 1x8 200 mesh OH^- ion exchange resin (2 g) was added and the mixture was stirred for 15 min. The mixture was then filtered and the filtrate concentrated. Chromatography (75:25:1 to 50:25:1 CH_2Cl_2/MeOH/Aq. NH_4OH gradient) provided 59 mg (75%) of the title compound as a colorless oil, R_f = 0.26 (50:25:1 CH_2Cl_2/MeOH/Aq. NH_4OH); $[\alpha]^{23}_D$ -47.9 (*c* 0.78, MeOH); ^{1}H NMR (360 MHz, CD_3OD) δ 4.14 (dd, *J* = 3.8, 5.6 Hz, 1H, H_1), 4.08 (dd, *J* = 4.4, 5.6 Hz, 1H, H_2), 3.78 (ddd, *J* = 4.6, 9.2, 11.3 Hz, 1H, H_8), 3.71 (dd, *J* = 4.1, 11.6 Hz, 1H, H_9), 3.68 (dd, *J* = 4.2, 11.6 Hz, 1H, H_9), 2.98 (dd, *J* = 4.2, 8.4 Hz, 1H, H_3), 2.94 (m, 1H, H_{5eq}), 2.57 (dd, *J* = 4.0, 9.4 Hz, 1H, H_{8a}) 2.54 (dd, *J* = 4.5, 11.8 Hz, 1H, H_{5ax}), 1.99 (m, 1H, H_{7eq}), 1.50-1.65 (m, 2H, H_6), 1.20 (qd, *J* = 5.4, 12.0 Hz, 1H, H_{7ax}); ^{13}C NMR (CD_3OD, 90 MHz) δ 74.3, 71.8, 71.3, 69.5, 67.6, 61.9, 46.8, 34.1, 23.9; IR (neat) 3355 (br s), 2935 (m), 2860 (w), 1444 (w), 1071 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 204 [$(M + H)^+$, 100], 168 (48), 150 (75), 136 (56); HRMS calcd for $C_9H_{17}NO_4H$ [$(M + H)^+$] 204.1236, found 204.1236.

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