A Practical Synthesis of (−)-Swainsonine

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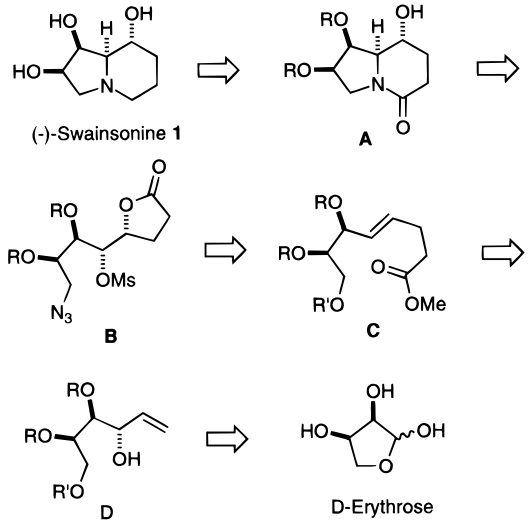
The indolizidine alkaloid (−)-swainsonine (**1**) is of long-standing interest due to its diverse biological activity.[1,2] It may be considered an azasugar analog of mannose and is indeed a potent inhibitor of many mannosidases including the glycoprotein-processing enzyme mannosidase II.[3−7] Swainsonine is the first glycoprotein-processing inhibitor to be selected for clinical testing as an anticancer drug,[8,9] but its high cost has hindered clinical trials.[10] Apparently, there is still no cost-effective way to either isolate swainsonine from natural sources or to prepare it synthetically. While a great deal of effort has been expended on developing synthetic routes to swainsonine,[11] there is still a need for a practical synthesis of this important alkaloid. Perhaps the most practical routes developed to date are those reported by the research groups of Fleet[11m,r] and Cha.[11n] The shortest synthetic route, developed in our group, has not proven amenable to scale-up.[11o] Recent efforts in our laboratories directed toward preparing analogs of swainsonine have led to the development of a practical route to this important alkaloid. We report herein a synthesis of (−)-swainsonine that is relatively short and efficient and uses simple reactions that allow good reproducibility and material throughput. Multigram quantities of the pure alkaloid were easily prepared using small-scale laboratory equipment.

Our strategy for the synthesis of swainsonine is shown in Scheme 1. The lactam **A** may arise from a reductive double-cyclization of the azido lactone **B**, which should be available by dihydroxylation of **C**. The γ,δ-unsaturated carboxylic acid derivative **C** was proposed to be available by a Claisen rearrangement of the allylic alcohol **D** derived by addition of a vinyl organometallic to a derivative of D-erythrose. We have previously used the reductive double-cyclization of an azide bearing two remote electrophilic centers for the synthesis of other bioactive alkaloids and their analogs.[12,13]

Scheme 1. Retrosynthetic Analysis of (−)-Swainsonine: Reductive Cyclization of an Azide Bearing Two Remote Electrophilic Sites



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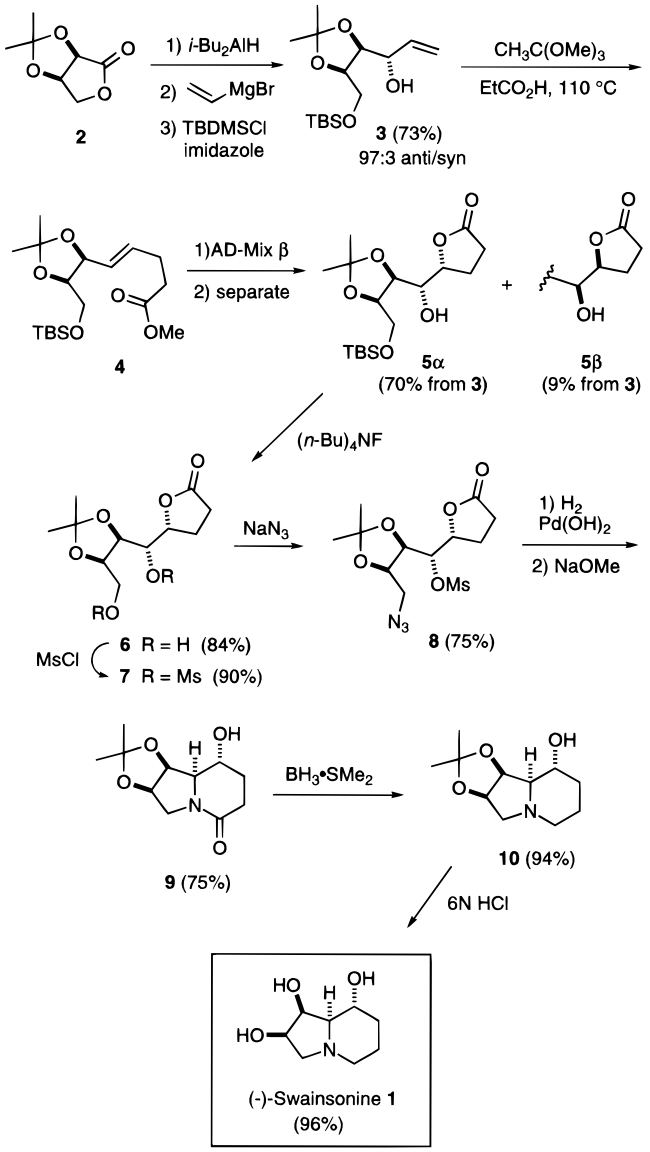
Scheme 2. Synthesis of (−)-Swainsonine



The synthesis of swainsonine (Scheme 2) began with 2,3-*O*-isopropylidene-D-erythronolactone (**2**), which is commercially available (Aldrich) or may be prepared in large quantities from inexpensive D-isoascorbic acid.[14,15] Reduction of **2** with diisobutylaluminum hydride[16] provided 2,3,-*O*-isopropylidene-D-erythrose. Addition of vinylmagnesium bromide[17] followed by selective monoprotection of the resulting diol afforded the allylic alcohol **3** (97:3 *anti/syn*) in 73% yield from **2**. Separation of the diastereomeric mixture was possible; however, it was unnecessary, since both allylic alcohols **3** produce the same γ,δ-unsaturated ester **4** when subjected to Johnson orthoester Claisen rearrangement conditions.[18] The rearrangement produced only the *E*-isomer within the limits of detection by high-field ^{1}H-NMR. Without purification, **4** was submitted to the Sharpless dihydroxylation procedure,[19,20] affording the lactones **5**α and **5**β in 70% and 9% yields, respectively, after separation.[21]

Removal of the silyl protecting group from **5**α gave the diol **6**, which was smoothly converted to the crystalline dimesylate **7**. Selective displacement of the less hindered mesylate of **7** with sodium azide afforded **8**. Palladium-catalyzed hydrogenolysis of **8** to the amine followed by filtration of the catalyst and treatment of the filtrate with sodium methoxide caused cyclization to the known crystalline bicyclic lactam **9** in 75% yield. Reduction[22] of **9** with borane−methyl sulfide complex gave a 94% yield of crystalline **10**, also a known compound,[11h,k,n,s] which was hydrolyzed to swainsonine (**1**) in 96% yield. While not the shortest synthesis,[11o] this route involves simple, reproducible steps that work well on a substantial scale. Using this method, 4.5 g of swainsonine was prepared in 20% overall yield from the lactone **2**, requiring 11 steps involving three chromatographic separations and five crystallizations.

To summarize, a simple route to the clinically useful anticancer agent (−)-swainsonine (**1**) has been developed. Given the current scarcity and high cost of this material, this preparation may be useful to researchers in this area. Finally, the possibility of preparing analogs of swainsonine substituted at C(6) and C(7) arises by simple modifications in the Claisen rearrangement step. This strategy has recently been reduced to practice in our laboratories. The preparation of these analogs and their biological activity will be reported separately.

Experimental Section

General Methods. 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, 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. All reactions were conducted under an atmosphere of dry nitrogen. 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 either stained with iodine vapor or phosphomolybdic acid solution. Flash column chromatography was performed according to the general procedure described by Still[23] using flash grade Merck Silica Gel 60 (230−400 mesh). Gas chromatographic (GC) analyses were performed using a 530 μm methylpolysiloxane column (3 μm film thickness, 5 m 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. High resolution mass spectrometric (HRMS)

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(21) Alternatively, Cha's method might be used to transform **4** into swainsonine. Cha and co-workers made a compound similar to **4** (ethyl ester, *Z*-alkene, free hydroxy instead of (*tert*-butyldimethylsilyl)oxy) by a Wittig route.

(22) While the reduction of **9** to **10** has been reported by Fleet using BH_3·Me_2S,[11m] their procedure involves isolation of the borane complex of **10**. Our procedure is adapted from a similar one by Keck which was used to make an epimer of swainsonine: Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083−6089.

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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.

(3*S*,4*S*,5*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)-1-hexen-3-ol (3). The reduction of 2,3-*O*-isopropylidene-D-erythronolactone (**2**) was performed using a modified version of Cohen's procedure.[16] Diisobutylaluminum hydride (101 mL of a 1.5 M solution in toluene, 152 mmol) was added in a dropwise fashion via an addition funnel to a cold (−78 °C) solution of 2,3-*O*-isopropylidene-D-erythronolactone (**2**)[14] (20.0 g, 126 mmol) in CH_2Cl_2 (360 mL). After 2 h, methanol (20 mL) was added, followed by brine (10 mL). After warming to room temperature, the mixture was diluted with ether (500 mL), and $MgSO_4$ (150 g) was added. After stirring vigorously for 4 h, the mixture was filtered with suction through a sintered glass funnel, and the filter cake was washed with ether (100 mL). The filtrate was concentrated to give 17.0 g (84%) of crude 2,3-*O*-isopropylidene-D-erythrose as a pale yellow oil that was used without further purification.

The addition of vinylmagnesium bromide to 2,3-*O*-isopropylidene-D-erythrose was carried out according to Mekki *et al.*[17,24] The crude lactol was dissolved in THF (380 mL) and cooled to −78 °C, and vinylmagnesium bromide (315 mL of a 1 M solution in THF, 315 mmol) was added in a dropwise fashion *via* an addition funnel. The mixture was then warmed to 0 °C. After 6 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The resulting mixture was diluted with water (200 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give 19.5 g of a yellow oil that was used without further purification. Purification of a small sample by chromatography (3:1 to 2:1 hexane/EtOAc gradient) provided an analytically pure sample of the pure *anti*-diol, (2*R*,3*S*,4*S*)-2,3-*O*-isopropylidene-1,2,3,4-tetrahydroxy-5-hexene:[24] R_f = 0.14 (3:1 hexane/EtOAc); bp 94−100 °C at 0.25 mmHg; $[\alpha]^{23}_D$ −42.5° (*c* 1.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (ddd, J = 5.6, 10.6, 17.3 Hz, 1H), 5.38 (dt, J = 1.4, 17.3 Hz, 1H), 5.27 (dt, J = 1.4, 10.5 Hz, 1H), 4.3 (m, 2H), 4.05 (dd, J = 5.8, 8.4 Hz, 1H), 4.02 (m, 1H), 3.8 (m, 3H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 116.5, 108.4, 79.6, 77.3, 70.6, 60.7, 27.7, 25.3: IR (neat) 3383 (s), 2987 (s), 2937 (m), 1456 (w), 1382 (m), 1220 (s), 1048 (s); MS (CI, CH_4) *m*/*z* (rel intensity) 189 [$(M + H)^+$, 40], 173 (22), 131 (80), 113 (100); HRMS (CI, CH_4) calcd for $C_9H_{16}O_4H$ [$(M + H)^+$] 189.1127, found 189.1122. Anal Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.44; H, 8.60.

The crude diol mixture was dissolved in THF/DMF (3:1, 400 mL). The solution was cooled to 0 °C, and *tert*-butyldimethylsilyl chloride (18.8 g, 125 mmol) and imidazole (17.6 g, 259 mmol) were added. After 45 min, the mixture was poured into ether (400 mL), and the organic layer was washed with 1 M HCl (2 × 200 mL). The combined aqueous layers were back-extracted with ether (2 × 100 mL). The combined organic layers were washed with water, 5% $NaHCO_3$, and brine and then dried ($MgSO_4$), filtered, and concentrated. Chromatography (100:1 to 20:1 hex/EtOAc gradient) provided 27.1 g (71% from **2**) of the *anti*-allylic alcohol **3** followed by 0.88 g (2% from **2**) of the *syn*-allylic alcohol diastereomer. Data for **3**-*anti* R_f = 0.48 (6:1 hexane/EtOAc); $[\alpha]^{23}_D$ −36.3° (*c* 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.02 (ddd, J = 5.2, 10.6, 17.2 Hz, 1H), 5.44 (dt, J = 1.6, 17.2 Hz, 1H), 5.25 (dt, J = 1.6, 10.6 Hz, 1H), 4.3−4.2 (m, 2H), 4.19 (d, J = 3.2 Hz, 1H), 4.06 (dd, J = 5.5, 9.2 Hz, 1H), 3.86 (dd, J = 9.9, 10.5 Hz, 1H), 3.65 (dd, J = 3.5, 10.5 Hz, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 0.92 (s, 9H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.4, 115.7, 108.5, 80.6, 77.2, 69.8, 62.0, 28.0, 25.8, 25.3, 18.3, −5.47, −5.52; IR (neat) 3470 (br m), 2933 (s), 2885 (s), 2859 (s), 1472 (m), 1380 (m), 1077 (s) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 303 [$(M + H)^+$, 18], 285 (9), 262 (19), 245 (100), 227 (42), 173 (46); HRMS (CI, NH_3) calcd for $C_{15}H_{30}O_4SiH$ [$(M + H)^+$] 303.1992, found 303.1984. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.29; H, 10.00.

Data for minor isomer (**3**-*syn*): R_f = 0.41 (6:1 hex/EtOAc); $[\alpha]^{23}_D$ −3.9° (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.01 (ddd, J = 5.2, 10.6, 17.2 Hz, 1H), 5.40 (dt, J = 1.7, 17.2 Hz, 1H), 5.22 (dt, J = 1.6, 10.6 Hz, 1H), 4.37 (m, 1H), 4.21 (td, J = 4.4, 6.7 Hz, 1H), 4.13 (dd, J = 4.0, 6.5 Hz, 1H), 3.96 (dd, J = 7.0, 10.7 Hz, 1H), 3.76 (dd, J = 4.4, 10.7 Hz, 1H), 3.01 (d, J = 5.8 Hz, 1H), 1.49 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 137.7, 115.8, 108.2, 79.6, 77.3, 67.0, 61.7, 27.2, 25.8, 24.9, 18.3, −5.6; IR (neat) 3475 (br, m) 2931 (s), 1858 (s), 1472 (m), 1381 (m) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 303 [$(M + H)^+$, 1.5], 287 (6), 245 (100), 227 (26), 117 (41); HRMS (CI, NH_3) calcd for $C_{15}H_{30}O_4SiH$ [$(M + H)^+$] 303.1992, found 303.1983. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.61; H, 10.01.

Methyl (*E*)-(6*S*,7*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-4-octenoate (4). Trimethyl orthoacetate (77 mL, 640 mmol) and propionic acid (1.9 mL, 26 mmol) were added to a solution of the allylic alcohol **3** (27.9 g, 92.3 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 = 4.0 min) and the appearance of product (t_R = 5.2 min, see General Methods above for GC conditions). After 24 h, the mixture was cooled to room temperature and concentrated to give 32.7 g (99%) of the title compound **4** as a pale yellow oil that was used without further purification. Purification of a small sample by chromatography (10:1 hex/EtOAc) provided an analytically pure sample. R_f = 0.40 (6:1 hex/EtOAc); $[\alpha]^{23}_D$ −0.9° (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.77 (m, 1H), 5.57 (dd, J = 7.7, 15.4 Hz, 1H), 4.58 (t, J = 7.1 Hz, 1H), 4.15 (dd, J = 6.1, 12.2 Hz, 1H), 3.68 (s, 3H), 3.59 (m, 2H), 2.41 (m, 4H), 1.46 (s, 3H), 1.36 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.3, 132.8, 126.5, 108.3, 78.6, 78.3, 62.3, 51.6, 33.4, 27.9, 27.6, 25.8, 25.4, 18.2, −5.4; IR (neat) 2930 (s), 2857 (m), 1743 (s), 1438 (m), 1375 (m) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 376 [$(M + NH_4)^+$, 12], 318 (87), 301 (100), 271 (29), 186 (32), 169 (29), 151 (28); HRMS (CI, NH_3) calcd for $C_{18}H_{34}O_5SiNH_4$ [$(M + NH_4)^+$] 376.2519, found 376.2519. Anal. Calcd for $C_{18}H_{34}O_5Si$: C, 60.30; H, 9.56. Found:: C, 60.12; H 9.61.

(5*R*)-5-[(1′*S*,2′*R*,3′*R*)-(4′-[(*tert*-Butyldimethylsilyl)oxy]-1′-hydroxy-2′,3′-(isopropylidenedioxy)butyl]tetrahydrofuran-2-one (5α) and (5*S*)-5-[(1′*R*,2′*R*,3′*R*)-4′-[(*tert*-Butyldimethylsilyl)oxy]-1′-hydroxy-2′,3′-(isopropylidenedioxy)-butyl]tetrahydrofuran-2-one (5*β*). The dihydroxylation was performed using the general procedure reported by Sharpless.[19] A solution of the crude alkene **4** (32.0 g, 89.2 mmol) in *t*-BuOH (150 mL) was added to a cold (0 °C), mechanically stirred, biphasic mixture of water (475 mL) and *tert*-butyl alcohol (300 mL) containing potassium ferricyanide (93 g, 280 mmol), potassium carbonate (39 g, 280 mmol), potassium osmate dihydrate (0.35 g, 0.95 mmol), $(DHQD)_2$−PHAL (0.75 g, 0.96 mmol),[19] and methanesulfonamide (9.0 g, 94.5 mmol). The solution was allowed to warm slowly to room temperature. GC was used to monitor the disappearance of the alkene **4** (t_R = 5.2 min) and the appearance of the product (t_R = 6.8 min, see General Methods above for GC conditions). After 18 h, sodium sulfite (150 g) was added, and the mixture was stirred an additional 1 h. EtOAc (400 mL) was then added, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 400 mL). The combined organic layers were washed with 2 N KOH (400 mL) and then dried ($MgSO_4$) and concentrated. Chromatography (10:1 to 3:1 hex/EtOAc gradient) provided 22.6 g (70% from **3**) of **5**α as a colorless oil followed by 2.98 g (9% from **3**) of **5**β as a colorless oil. Data for **5**α: R_f = 0.28 (3:1 hex/EtOAc); $[\alpha]^{23}_D$ −36.3° (*c* 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.84 (ddt, J = 1.4, 5.7, 7.2 Hz, 1H), 4.42 (dd, J = 5.6, 9.7 Hz, 1H), 4.26 (ddd, J = 3.6, 5.6, 9.9 Hz, 1H), 4.14 (br d, J = 3.3 Hz, 1H), 3.77 (m, 2H), 3.65 (dd, J = 3.5, 10.5 Hz, 1H), 2.72 (m, 1H), 2.44 (m, 1H), 2.32 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 0.91 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.0, 108.7, 79.1, 76.6, 76.4, 71.0, 61.8, 28.4, 27.9, 25.7, 25.3, 23.8, 18.2, −5.6, −5.7; IR (neat) 3430 (br w), 2934 (m), 2858 (m), 1778 (s), 1472 (w), 1370 (m) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 378 [$(M + NH_4)^+$, 52], 361 [$(M + H)^+$, 100], 170 (27), 153 (27); HRMS (CI, CH_4) calcd for $C_{17}H_{32}O_6SiH$ [$(M + H)^+$] 361.2046, found 361.2035. Anal. Calcd for $C_{17}H_{32}O_6Si$: C, 56.64; H, 8.95. Found: C, 56.58; H, 9.04.

Data for **5**β: R_f = 0.18 (3:1 hex/EtOAc); $[\alpha]^{23}_D$ +4.5° (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.77 (td, J = 2.9, 6.6 Hz,

(24) Since the communication by Mekki *et al.* does not provide experimental procedures or spectroscopic data,[17] we have chosen to include these details herein.

1H), 4.31 (t, J = 6.0 Hz, 1H), 4.18 (ddd, J = 3.6, 5.8, 8.5 Hz, 1H), 3.94 (ddd, J = 3.0, 4.1, 6.0 Hz, 1H), 3.83 (dd, J = 8.5, 10.7 Hz, 1H), 3.66 (dd, J = 3.6, 10.7 Hz, 1H), 2.85 (d, J = 4.2 Hz, 1H), 2.69 (m, 1H), 2.46 (m, 1H), 2.28 (m, 2H), 1.45 (s, 3H), 1.36 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 177.3, 108.4, 79.8, 77.2, 76.8, 70.6, 61.6, 28.2, 27.6, 25.8, 25.3, 24.1, 18.3, −5.4; IR (neat) 3470 (br, m), 2954 (m), 2858 (m), 1778 (s), 1463 (m), 1381 (m) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 378 [$(M + NH_4)^+$, 100], 361 [$(M + H)^+$, 31], 320 (20), 303, (20), 170 (18), 153 (23); HRMS (CI, NH_3 and CH_4) calcd for $C_{17}H_{32}O_6$-SiH [$(M + H)^+$] 361.2046, found 361.2033. Anal. Calcd for $C_{17}H_{32}O_6Si$: C, 56.64; H, 8.95. Found: C, 56.27; H, 8.91.

(5*R*)-5-[(1′*S*,2′*R*,3′*R*)-1′,4′-Dihydroxy-2′,3′-(isopropylidenedioxy)butyl]tetrahydrofuran-2-one (6). A solution of tetra-*n*-butylammonium fluoride (19.8 g of a 75% w/w solution in water, 56.7 mmol) in THF (50 mL) was added to a cold (0 °C) solution of **5**α (18.6 g, 51.6 mmol) in THF (250 mL). After 1.5 h, silica gel (25 g) and water (10 mL) were added, and the mixture was stirred another 10 min. The mixture was then filtered through Celite, rinsing with ether (300 mL). The filtrate was dried ($MgSO_4$) and concentrated. Chromatography (30:60:1 to 30:60:10 hex/EtOAc/EtOH gradient) provided 11.7 g (84%) of the diol **6** as a pale yellow oil. R_f = 0.25 (20:1 $CHCl_3$/MeOH); $[\alpha]^{23}_D$ −66.9° (c 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.87 (m, 1H), 4.33 (m, 2H), 4.22 (d, J = 6.3 Hz, 1H), 3.8 (m, 3 H), 3.38 (t, J = 5.7 Hz, 1H), 2.68 (ddd, J = 7.2, 9.3, 17.5 Hz, 1H), 2.50 (ddd, J = 7.3, 10.0, 17.5 Hz, 1H), 2.33 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.5, 108.6, 80.0, 76.8, 76.2, 70.8, 60.7, 28.6, 27.8, 25.2, 23.6; IR (neat) 3390 (br, s), 2987 (s), 2939 (s), 1770 (s), 1372 (s) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 264 [$(M + NH_4)^+$, 100], 247 [$(M + H)^+$, 55], 229 (15), 206 (15), 160 (11); HRMS (CI, NH_3) calcd for $C_{11}H_{18}O_6H$ [$(M + H)^+$] 247.1182, found 247.1187. Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.44; H, 7.33.

(5*R*)-5-[(1′*S*,2′*R*,3′*R*)-1′,4′-Bis(methanesulfonyloxy)-2′,3′-(isopropylidenedioxy)butyl]tetrahydrofuran-2-one (7). Methanesulfonyl chloride (10.1 mL, 130 mmol) was added to a cold (0 °C) solution of the diol **6** (10.7 g, 43.3 mmol) and DMAP (0.265 g, 2.16 mmol) in pyridine (130 mL). The mixture was stirred for 30 min and then placed in a refrigerator (2 °C). After 16 h, ethyl acetate (400 mL) was added, and the solution was washed with 10% HCl (3 × 100 mL). The aqueous layers were back-extracted with ethyl acetate (100 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give a foamy yellow solid. Recrystallization from EtOAc/hex (∼1:1) provided 15.7 g (90%) of the dimesylate **7** as a pale yellow crystalline solid in three crops. R_f = 0.11 (1:1 hex/EtOAc); mp 120−123 °C; $[\alpha]^{23}_D$ +39.8° (c 1.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.81 (ddd, J = 2.9, 5.9, 7.7 Hz, 1H), 4.52 (td, J = 3.1, 6.4 Hz, 1H), 4.46 (dd, J = 3.1, 10.8 Hz, 1H), 4.40 (dd, J = 4.8, 5.8, 1H), 4.32 (dd, J = 6.6, 10.8 Hz, 1H), 3.25 (s, 3H), 3.08 (s, 3H), 2.74 (m, 1H), 2.58 (m, 1H), 2.44 (m, 2H), 1.54 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 175.9, 109.4, 78.8, 77.9, 76.1, 75.1, 69.3, 39.2, 37.3, 27.4, 27.3, 25.6, 23.9; IR (neat) 3027 (w), 2989 (m), 2942 (m), 1784 (s), 1462 (w), 1359 (s) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 420 [$(M + NH_4)^+$, 100], 403 [$(M + H)^+$, 2], 246 (56); HRMS (CI, NH_3) calcd for $C_{13}H_{22}O_{10}S_2NH_4$ [$(M + NH_4)^+$] 420.0998, found 420.0998. Anal. Calcd for $C_{13}H_{22}O_{10}S_2$: C, 38.80, H, 5.51. Found: C, 38.93; H, 5.63.

(5*R*)-5-[(1′*S*,2′*R*,3′*R*)-4′-Azido-2′,3′-(isopropylidenedioxy)-1′-(methanesulfonyloxy)butyl]tetrahydrofuran-2-one (8). Sodium azide (12.1 g, 187 mmol) was added to a solution of the dimesylate **7** (15.0 g, 37.4 mmol) in DMSO (110 mL), and the flask was heated at 80 °C (oil bath). After 36 h, the solution was cooled and poured into water (300 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Crystallization from $CHCl_3$/Et_2O provided 8.50 g (65%) of the azidomesylate **8** as a white crystalline solid in two crops. The mother liquor was concentrated and chromatography (2:1 hex/EtOAc to 50:50:1 hex/EtOAc/EtOH gradient) provided 0.99 g (9%) of the diazide [R_f = 0.62 (1:1 hex/EtOAc)], followed by an additional 1.33 g of **8** [total yield 9.83 g (75%)], and 0.75 g (5%) of recovered starting dimesylate **7**. Data for **8**: R_f = 0.33 (1:1 hex/EtOAc); $[\alpha]^{23}_D$ +75.0° (c 0.52, $CHCl_3$); mp 136 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.01 (dd, J = 3.8, 6.0 Hz, 1H), 4.81 (ddd, J = 3.7, 6.1, 7.8 Hz, 1H), 4.43 (ddd, J = 3.5, 5.9, 7.2 Hz, 1H), 4.35 (t, J = 5.7 Hz, 1H), 3.53 (dd, J = 3.5, 13.1 Hz, 1H), 3.47 (dd, J = 7.2, 13.1 Hz, 1H), 3.22 (s, 3H), 2.69 (m, 1H), 2.56 (dd, J = 7.1, 9.8 Hz, 1H), 2.3−2.5 (m, 2H), 1.54 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 175.8, 109.2, 78.8, 78.1, 76.6, 75.8, 51.6, 39.2, 27.6, 27.5, 25.4, 24.2; IR (neat) 2990 (m), 2940 (m), 2105 (s), 1784 (s), 1360 (s) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 367 [$(M + NH_4)^+$, 100], 322 (16), 228 (24); HRMS (CI, NH_3) calcd for $C_{12}H_{19}N_3O_7$-SNH_4 [$(M + NH_4)^+$] 367.1287, found 367.1288. Anal. Calcd for $C_{12}H_{19}N_3O_7S$: C, 41.26; H, 5.48; N, 12.03. Found: C, 40.97; H, 5.36; N, 11.98.

(1*S*,2*R*,8*R*,8a*R*)-8-Hydroxy-1,2-(isopropylidenedioxy)indolizidin-5-one (9). Palladium hydroxide on carbon (1.50 g) was added to a solution of the azido mesylate 8 (9.75 g, 27.9 mmol) in MeOH (500 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 6 h, the hydrogen was evacuated and the mixture was filtered through Celite, rinsing with MeOH (100 mL). Sodium methoxide (3.20 g, 59.3 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 1625 cm^{-1}. After 60 h, the solution was cooled to room temperature and concentrated to a volume of ca. 50 mL, causing precipitation of a white solid. The mixture was diluted with CH_2Cl_2 (500 mL), florisil (50 g) 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 to give an yellow oil that crystallized upon standing. Recrystallization from EtOAc/ether (1:2) provided 3.85 g (61%) of lactam **9** as a white crystalline solid. The mother liquor was concentrated to give a yellow oil that was purified by chromatography (10% EtOH/EtOAc) to give another 0.91 g of crystalline **9** [total yield: 4.76 g (75%)]. R_f = 0.38 (10:1 CHC_3/MeOH); mp 129 °C (lit. 126−128 °C,[11m] 125−127 °C[11h]); $[\alpha]^{23}_D$ +12.6° (c 1.06, MeOH), [lit. $[\alpha]^{25}_D$ +4.3° (c 0.16, MeOH)[11h]]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (dd, J = 4.5, 6.0 Hz, 1H), 4.75 (t, J = 5.5 Hz, 1H), 4.19 (d, J = 13.5 Hz, 1H), 4.15 (ddd, J = 4.2, 8.4, 15.5 Hz, 1H), 3.33 (dd, J = 4.5, 13.6 Hz, 1H), 2.69 (d, J = 4.5 Hz, 1H), 2.53 (ddd, J = 2.9, 6.6, 18.0 Hz, 1H), 2.41 (ddd, J = 6.4, 11.7, 18.0 Hz, 1H), 2.13 (m, 1H), 1.87 (m, 1H), 1.43 (s, 3H), 1.34 (s, 3H); ^{13} C NMR ($CDCl_3$, 75 MHz) δ 168.2, 112.1, 79.8, 77.6, 77.2, 66.3, 65.4, 50.6, 29.8, 26.4, 24.7; IR (neat) 3361 (br m), 2987 (m), 2938 (m), 2870 (m), 1625 (s), 1471 (m), 1454 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel intensity) 227 (M^+, 58), 212 (53), 152 (51), 85 (100), 68 (53), 43 (76); HRMS calcd for $C_{11}H_{17}NO_4$ (M^+) 227.1157, found 227.1159. These data are consistent with literature values.[11h]

(1*S*,2*R*,8*R*,8a*R*)-8-Hydroxy-1,2-(isopropylidenedioxy)indolizine (10).[22] Borane−methyl sulfide complex (59 mL of a 2 M solution in THF, 118 mmol) was added over a period of 30 min via an addition funnel to a cooled (0 °C) solution of the lactam **9** (6.65 g, 29.3 mmol) in THF (725 mL). After 30 min, the solution was warmed to room temperature. After another 2 h, the reaction was quenched by the slow addition of ethanol (440 mL, caution: hydrogen evolution) and concentrated to give a viscous oil which was redissolved in EtOH (700 mL) and heated at reflux for 2 h. After cooling to room temperature, the solution was concentrated to give 6.6 g of a colorless, crystalline solid which was recrystallized from 200 mL of hot hexanes to provide 5.87 g (94%) of the title compound, R_f = 0.41 (10:1 $CHCl_3$/MeOH); mp 101−103 °C (lit. mp 104−106° C,[11h] 106−108 °C,[11k] 100−103 °C,[11n] 101−104 °C[11s]); $[\alpha]^{23}_D$ −81.7° (c 1.10, MeOH), [lit. $[\alpha]^{25}_D$ −73.3° (c 0.35, MeOH),[11h] $[\alpha]^{20}_D$ −65.8° (c 0.5, MeOH),[11k] $[\alpha]^{25}_D$ −67.3° (c 0.46, MeOH),[11s] $[\alpha]^{25}_D$ −72.76 (c 0.43, MeOH)[11n]] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (dd, J = 4.6, 6.2 Hz, 1H), 4.61 (dd, J = 4.2, 6.3 Hz, 1H), 3.83 (m, 1H), 3.15 (d, J = 10.7 Hz, 1H), 2.99 (dt, J = 3.0, 10.4 Hz, 1H), 2.33 (br s, 1H), 2.12 (dd, J = 4.2, 10.7 Hz, 1H), 2.05 (m, 1H), 1.85 (m, 1H), 1.6−1.7 (m, 3H), 1.51 (s, 3H), 1.34 (s, 3H), 1.2−1.3 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 111.3, 79.1, 78.2, 73.6, 67.3, 59.8, 51.6, 32.9, 25.9, 24.7, 24.0; IR (neat) 3198 (br m), 2980 (m), 2941 (s), 2857 (w), 2792 (m), 1466 (w), 1446 (w), 1371 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel intensity) 213 (M^+, 53), 198 (24), 138 (100), 113 (82), 96 (712), 43 (41); HRMS calcd for $C_{11}H_{19}NO_3$ (M^+) 213.1365, found 213.1367. These data are consistent with those reported in the literature.[11n]

(1*S*,2*R*,8*R*,8a*R*)-1,2,8-Trihydroxyindolizidine [(−)-Swainsonine] (1). Prepared according to the published procedure.[11n]

A solution of **10** (5.75 g, 27 mmol) in THF (27 mL) was treated with 6 N HCl (27 mL) at room temperature for 12 h. The solution was then concentrated the residue was applied to an ion exchange column (Dowex 1 × 8 200 OH^-, 30 g), which was eluted with water. The fractions containing **1** were identified by TLC (iodine stain). These fractions were concentrated to give a white crystalline solid which was recrystallized from $CHCl_3$/MeOH/ether to give 4.50 g (96%) of swainsonine (**1**) in three crops. R_f = 0.35 (3:1 $CHCl_3$/MeOH w/1% NH_4OH); mp 139−142 °C (lit. mp 141−143 °C,[11k,s] 144−145 °C,[1b] 140−142 °C[11n]); $[\alpha]^{23}_D$ −74.0° (*c* 0.98, MeOH) [lit. $[\alpha]^{25}_D$ −82.6° (*c* 1.03, MeOH),[11s] $[\alpha]^{25}_D$ −73.8° (*c* 0.21, EtOH),[11e] $[\alpha]^{25}_D$ −75.7° (*c* 2.33, MeOH)[11n]]; ^{1}H NMR (300 MHz, D_2O) δ 4.39 (ddd, J = 2.8, 5.9, 8.0 Hz, 1H), 4.29 (dd, J = 3.5, 5.8 Hz, 1H), 3.84 (app td, J = 4.6, 10.3 Hz, 1H), 3.0 (m, 1H), 2.97 (dd, J = 2.8, 11.3 Hz, 1H), 2.70 (dd, J = 8.1, 11.3 Hz, 1H), 2.04−2.15 (m, 3H), 1.76 (m, 1H), 1.55 (qt, J = 4.1, 13.2 Hz, 1H), 1.28 (qd, J = 4.5, 12.3 Hz, 1H); ^{13}C NMR (90 MHz, D_2O, MeOH internal standard) δ 72.6, 69.4, 68.9, 66.0, 60.3, 51.6, 32.2, 22.9; IR (neat) 3366 (br s), 2944 (s), 2884 (m), 2804 (m), 2727 (m), 1660 (w), 1378 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (rel intensity) 173 (M^+, 16), 155 (30), 113 (73), 96 (73), 83 (100); HRMS calcd for $C_8H_{15}NO_3$ (M^+) 173.1052, found 173.1052. These data are consistent with those reported in the literature.[11n]

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