Total Syntheses of (+)-2,8,8a-Tri-*epi*-swainsonine and (−)-1-*epi*-Swainsonine

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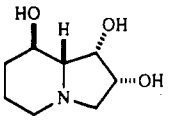
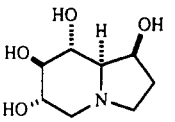
Parallel syntheses of the title swainsonine-related enantiomers **9** and **15** were achieved in five steps and in 55% overall yield via enantiomeric threose *N*-benzylimines **4** and **10**, derived from L- and D-tartaric acid, respectively. A stereospecific 4 + 4 homologative procedure using 2-(trimethylsiloxy)-furan (TMSOF), obtained from 2-furaldehyde, was employed to form the eight-carbon skeleton of the indolizidine triols and to install the proper chirality. Remarkably, the syntheses were completed by cyclizations of tetrahydroxypiperidine intermediates **8** and **14** to **9** and **15**, respectively (ca. 90%; PPh_3, CCl_4, Et_3N in DMF at room temperature), without recourse to protecting groups.

The chemistry of indolizidine alkaloids has recently become a very active area of study.[1] In particular, polyhydroxylated representatives such as swainsonine,[2] castanospermine,[3] and certain natural and synthetic analogues[4] have attracted special interest by virtue of their varied and clinically useful biological actions.[5]

Earlier, we described the preparation of a variety of homochiral γ-substituted butenolides of type **2** via four-carbon homologation of simple aldehydo or imino precursors **1** with 2-(trimethylsiloxy)furan (TMSOF) or 2-*N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-pyrrole (TBSOP) (Scheme I).[6] These butenolides can be conveniently employed as chiral templates for the total syntheses of natural and synthetic products of type **3** and **3′** endowed with varied chirality and patterns of oxygen and nitrogen substitution. This approach has been exploited in the total syntheses of higher-carbon sugars,[7] *C*-glycosyl α-amino acids,[8] and azasugars.[9]



(-)-Swainsonine



(+)-Castanospermine

In this paper, we show that butenolide templates can indeed be employed to prepare certain swainsonine stereoisomers. In particular, we present herein a concise and extremely efficient route to (1*S*,2*S*,8*S*,8a*S*)-1,2,8-indolizidinetriol (2,8,8a-tri-*epi*-swainsonine) (**9**) and its enantiomer, 1-*epi*-swainsonine (**15**), from chiral starting materials L- and D-threose *N*-benzylimines **4** and **10**.

The parallel routes to **9** (left side) and **15** (right side) are outlined in Scheme II. L- and D-threose *N*-benzylimines **4** and **10** were prepared from the D and L forms of diethyl tartrate.[10] The reaction of **4** with TMSOF in CH_2Cl_2 at

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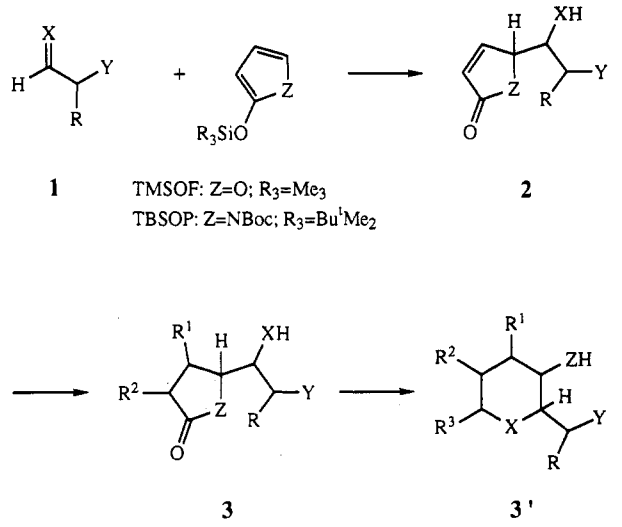
Scheme I[a]



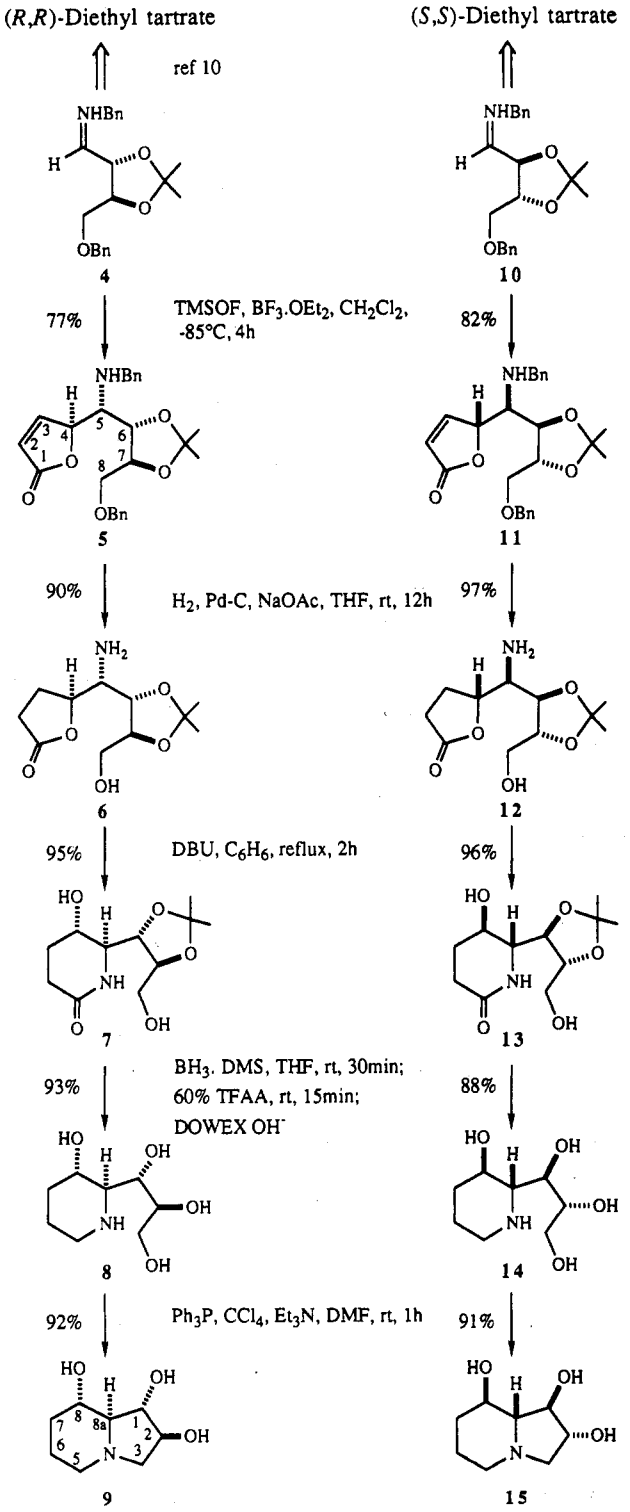
[a] X, Y, Z = O, N functionalities; R–R³ = H, C, O, N substituents.

–85 °C in the presence of BF_3 etherate gave, after being quenched with aqueous $NaHCO_3$ at the same temperature, the expected butenolide **5** in 77% isolated yield with no detectable (^{1}H NMR) stereoisomeric contamination (>98% de). That **5** possessed the L-talo absolute configuration as shown was not rigorously established at this stage but was confirmed by the subsequent conversion of **5** to target system **9** of proven configuration. Double-bond saturation with concomitant reductive cleavage of both the C–O and the C–N benzylic bonds to provide aminobutanolide **6** was effected under controlled hydrogenation conditions in 90% yield with 10% Pd on carbon in buffered (NaOAc) THF at room temperature. Next, upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at reflux, amino γ-lactone **6** underwent clean ring expansion to provide δ-lactam **7** in 95% isolated yield. The stereochemistry shown for **7** was not unequivocally established; however, the ^{1}H NMR was informative, showing the C-5 hydrogen as a triplet at δ 3.58 with $J_{3ax,4} = J_{4,5} = 9.0$ Hz and corroborating the trans diaxial relationship between the C-4 and C-5 protons (4,5-*erythro* stereochemistry).

Treatment of **7** with 3 equiv of BH_3–dimethyl sulfide complex in THF at room temperature effected the reduction of the lactam carbonyl to the corresponding amine–borane adduct. Deprotection of the crude adduct was smoothly accomplished with 60% aqueous trifluoroacetic acid at room temperature. Ion-exchange resin chromatographic purification (Dowex 1×8, OH– form) afforded free base **8** in 93% isolated yield.

Once the fully deprotected tetrahydroxypiperidine **8** with the three-carbon segment in appropriate position was prepared, all that remained was the construction of the final bicyclic skeleton of **9**. Two options were considered for attempting direct cyclization: (1) dehydrative annulation with a PPh_3/DEAD system[11] and (2) intramolecular displacement of the activated primary OH function by the piperidine nitrogen mediated by $PPh_3/CCl_4/Et_3N$.[4a,c,k,12] In our hands, attempts to exploit Mitsunobu-like protocols

Scheme II



were unsuccessful, but cyclization induced by 2 mol equiv of the three-component system $PPh_3/CCl_4/Et_3N$ (1:1:1 ratio) in rigorously anhydrous DMF at room temperature in the dark resulted in complete conversion of monocyclic matrix **8** into the expected bicyclic (+)-2,8,8a-tri-*epi*-swainsonine **9** in 92% isolated yield (56% overall yield from **4**).

The synthesis of known compound (–)-1-*epi*-swainsonine (**15**)[4b] presented the opportunity to test the feasibility of this butenolide strategy for the synthesis of indolizidine triols and to optimize the protocol. Preparation of the requisite butenolide **11** began with imine **10** derived from

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unnatural (*S,S*)-diethyl tartrate. By means of exactly the same chemistry as that used for **9**, **15** was synthesized via **11**, **12**, **13**, and **14** in a nice 61% yield for the entire sequence (Scheme II, right side). As expected, the two enantiomers, **9** and **15**, exhibited superimposable ^1H and ^{13}C NMR spectra and equal but opposite rotations in methanol, $[\alpha]_D$ = +31.62° and −32.14°, respectively. The $[\alpha]_D$ literature value for **15** (−33.2°), its reported ^{13}C NMR spectrum, and its mp value[4b] coincided with those obtained by us.

The ^1H NMR spectrum of **9** in D_2O was richly detailed and allowed complete stereochemical assignment. The indolizidine was shown to exist predominantly in a trans-fused conformation with the piperidine ring in a $^8C_5$ chair conformation (Figure 1). This conformation was deduced from the large vicinal coupling constants (J = 9–10 Hz) displayed by the five consecutive axial hydrogens (C-5 to C-8a) in alternating α,β positions. In addition, NOED experiments performed by short irradiation of the H-8 and H-8a proton resonances at 3.48 and 1.75 ppm, respectively, indicated the expected cisoid relationship between the H-8, H-1, and H-6β protons (ca 8% enhancement) and between the H-8a, H-3α, and H-5α protons (ca 11%). Further diagnostic enhancements obtained from the NOESY map of **9** include H-3α vs H-5α and H-5α vs H-7α correlations.

In conclusion, we have been able to establish a new, highly efficient route to certain polyhydroxylated members of the swainsonine family of alkaloids. It is of particular significance, in a preparative context, that gram quantities of enantiomers **9** and **15** have been synthesized in >55% overall yields in a concise five-step route by means of such inexpensive materials as imines **4** and **10**, obtained from diethyl tartrate, and 2-(trimethylsiloxy)furan, obtained from 2-furaldehyde. One of the highlights of this route is the extremely facile (1 h at room temperature) and nearly quantitative cyclization of fully deprotected tetrahydroxypiperidines **8** and **14** to **9** and **15**, respectively, mediated by the $PPh_3/CCl_4/Et_3N$/DMF multicomponent system. We are confident that our methodology, given its conceptual simplicity and flexibility, will provide efficient access to other swainsonine stereoisomers as well as to indolizidines and quinolizidines containing polyhydroxylated domains.[13]

Experimental Section[14]

2-(Trimethylsiloxy)furan (TMSOF). TMSOF was prepared on a multigram scale from commercial 2-furaldehyde (Aldrich), via 2(5*H*)-furanone, according to literature protocols.[15] TMSOF is also commercially available (Fluka).

2,3-*O*-Isopropylidene-4-*O*-benzyl-L- and -D-threose. These materials were prepared from commercial diethyl L- and D-tartrate (Aldrich) via the corresponding 2,3-*O*-isopropylidenethreitols.[10] The threitol intermediates are also commercially available (Fluka, Aldrich).

2,3-*O*-Isopropylidene-4-*O*-benzyl-L- and -D-threose *N*-Benzylimine (4 and 10). These imines were prepared by the reaction of the corresponding aldehydes (1.0 equiv) with benzylamine (1.0 equiv) in anhydrous diethyl ether in the presence of anhydrous $MgSO_4$ for 2 h at room temperature. After filtration and removal of the solvent, imines **4** and **10** were quantitatively

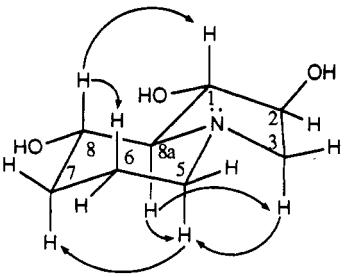

Figure 1. NOE correlations in **9**.

obtained as viscous oils, which were used as such in the subsequent reactions. For **4**: ^1H NMR ($CDCl_3$) δ 7.80 (d, 1H, H-1), 7.25 (m, 10H, Ph), 4.60 (m, 4H), 4.35 (dd, 1H, J = 8.4, 4.8 Hz, H-2), 4.24 (ddd, 1 H, J = 9.0, 5.7, 3.3 Hz, H-3), 3.70 (dd, 1H, J = 10.5, 3.3 Hz), 3.63 (dd, 1H, J = 10.5, 6.0 Hz), 1.46 (s, 3H), 1.45 (s, 3H).

5-(*N*-Benzylamino)-6,7-*O*-isopropylidene-8-*O*-benzyl-2,3,5-trideoxy-L-*talo*-oct-2-enono-1,4-lactone (5). To a solution of **4** (4.5 g, 13.2 mmol) in dry CH_2Cl_2 (100 mL) at −85 °C was added 2-(trimethylsiloxy)furan (2.18 mL, 13.2 mmol) dropwise under argon. With stirring, BF_3 etherate (1.88 mL, 13.2 mmol), cooled to the same temperature, was added via cannula over 5 min, and the reaction was allowed to stir for 4 h. The reaction was then quenched at −85 °C with an aqueous saturated $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL); the organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (60:40 hexane/ethyl acetate; spray reagent, ethanolic 7% phosphomolybdic acid; R_f = 0.37) to afford 4.32 g of **5** (77%) as an oil: $[\alpha]^{20}_D$ = −62.44° (c 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, 1H, J = 6.0, 1.8 Hz, H-3), 7.30 (m, 10H, Ph), 6.17 (dd, 1H, J = 5.7, 2.1 Hz, H-2), 5.40 (td, 1H, J = 4.2, 2.1 Hz, H-4), 4.55 (m, 2H), 4.06 (m, 1H), 3.5–3.9 (m, 6H), 3.15 (dd, 1H, J = 7.8, 4.5 Hz, H-5), 1.37 (s, 6H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.85, 154.53, 139.42, 137.73, 128.37, 128.31, 127.75, 127.70, 127.20, 122.32, 109.61, 83.91, 79.30, 77.42, 73.44, 70.87, 61.08, 53.08, 26.97, 26.91.

Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.70; H, 7.10; N, 3.27.

5-Amino-6,7-*O*-isopropylidene-2,3,5-trideoxy-L-*talo*-octono-1,4-lactone (6). A solution of **5** (3.90 g, 9.21 mmol) in THF (100 mL) was hydrogenated in the presence of 10% Pd on carbon (303 mg) and NaOAc (400 mg) at room temperature for 12 h. After the catalyst was filtered, the solution was evaporated, and the residue was purified by flash chromatography on silica gel (90:10 ethyl acetate/methanol; spray reagent, ethanolic 7% phosphomolybdic acid; R_f = 0.30) to afford 2.03 g of **6** (90%) as an oil: $[\alpha]^{20}_D$ = +5.71° (c 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (ddd, 1H, J = 9.0, 6.9, 3.6 Hz, H-4), 3.95 (td, 1H, J = 7.8, 3.3 Hz, H-7), 3.85 (dd, 1H, J = 10.8, 3.3 Hz, H-8a), 3.60 (dd, 1H, J = 11.1, 8.1 Hz, H-8b), 3.47 (dd, 1H, J = 9.6, 7.8 Hz, H-6), 3.27 (dd, 1H, J = 9.3, 3.6 Hz, H-5), 2.80 (bs, 2H, OH, NH), 2.60 (m, 2H, H-2a, H-2b), 2.0–2.3 (m, 2H, H-3a, H-3b), 1.40 (s, 3H, Me), 1.36 (s, 3H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.01, 108.78, 81.23, 81.07, 80.05, 62.35, 53.98, 28.58, 26.61, 26.52, 20.83.

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.90; H, 7.85; N, 5.78.

6,7-*O*-Isopropylidene-2,3-dideoxy-L-*talo*-octono-δ-lactam (7). To a solution of **6** (1.95 g, 7.95 mmol) in benzene (40 mL) was added 1.19 mL (7.95 mmol) of DBU. The reaction was heated at reflux for 2 h. The solvent was removed in vacuo, and the residue was chromatographed on silica gel (80:20 ethyl acetate/methanol; spray reagent, ethanolic 7% phosphomolibdic acid; R_f = 0.35) to afford 1.85 g (95%) of **7** as a glass: $[\alpha]^{20}_D$ = +36.47° (c 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H, NH), 5.63 (s, 1H, OH), 4.06 (s, 1H, OH), 3.90 (m, 4H, H-4, H_2-8, H-6), 3.58 (t, 1H, J = 9.0 Hz, H-5), 3.31 (t, 1H, J = 8.0 Hz, H-7), 2.49 (ddd, 1H, J = 18.3, 6.3, 3.6 Hz, H-2α), 2.36 (ddd, 1H, J = 18.0, 10.8, 6.3 Hz, H-2β), 2.09 (dddd, 1H, J = 13.5, 6.3, 2.7, 2.6 Hz, H-3β), 1.86 (dddd, 1H, J = 13.5, 11.1, 11.0, 6.3 Hz, H-3α), 1.42 (s, 3H, Me), 1.40 (s, 3H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.52, 109.63, 83.80, 80.28, 68.28, 62.35, 59.66, 28.70, 27.66, 26.63, 26.57; IR (neat) 1651 cm^{-1}.

(13) It is reasonable to expect that swainsonine stereoisomers with 1*R*,2*S*,8*R*,8a*R* and 1*S*,2*R*,8*S*,8a*S* stereochemistries could be prepared by means of an erythrose-based variant of the route described above. Similar syntheses from pentose derivatives leading to hydroxylated quinolizidines should also be possible.

(14) For general procedures see ref 9.

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Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.77; H, 7.75; N, 5.80.

1,2,3,5-Tetradeoxy-1,5-imino-L-*talo*-octitol (8). To a solution of **7** (1.75 g, 7.13 mmol) in THF (30 mL) was added, drop-by-drop at room temperature, BH_3·DMS (2.03 mL, 21.39 mmol). The reaction was stirred for 30 min, quenched by careful addition of methanol (15 mL), and evaporated to dryness under reduced pressure. The crude amine–borane adduct was dissolved in 60% aqueous trifluoroacetic acid (10 mL) at room temperature and allowed to stir for 15 min. The mixture was then evaporated to dryness under reduced pressure. The oily residue was dissolved in distilled water (10 mL) and passed through a column charged with DOWEX 1×8 (OH– form) resin (spray reagent, 0.2% ninhydrin in ethanol). Evaporation of water and lyophilization afforded pure free base **8**: yield 1.26 g (93%); a glassy solid; $[\alpha]^{20}_D$ = +16.66° (*c* 1.2, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 3.87 (m, 2H, H-6, H-7), 3.66 (m, 2H, H_2-8), 3.01 (dm, 1H, J = 12.3 Hz, H-1β), 2.60 (dd, 1H, J = 9.3, 4.8, Hz, H-5), 2.50 (td, 1H, J = 12.0, 2.7 Hz, H-1α), 2.09 (dm, 1H, J = 10.5 Hz, H-3β), 1.74 (dt, 1H, J = 13.2, 2.4 Hz, H-2α), 1.52 (qt, 1H, J = 12.3, 4.2 Hz, H-2β), 1.40 (qm, 1H, J = 10.8 Hz, H-3α); ^{13}C NMR (75.4 MHz, CD_3OD) δ 73.48, 73.26, 70.16, 65.71, 64.42, 46.51, 34.68, 26.11. Trifluoroacetate salt: ^{1}H NMR (300 MHz, D_2O) δ 4.13 (dd, 1H, J = 3.9, 2.1 Hz, H-6), 3.98 (ddd, 1H, J = 7.8, 5.4, 2.4 Hz, H-7), 3.87 (td, 1H, J = 10.2, 4.5 Hz, H-4), 3.64 (m, 2H, H_2-8), 3.33 (dm, 1H, J = 12.9 Hz, H-1β), 3.15 (dd, 1H, J = 10.5, 4.2 Hz, H-5), 2.83 (td, 1H, J = 12.9, 3.0 Hz, H-1α), 2.14 (dt, 1H, J = 12.9, 3.3 Hz, H-3β), 1.93 (dt, 1H, J = 13.2, 3.0 Hz, H-2α), 1.70 (qt, 1H, J = 13.2, 3.0 Hz, H-2β), 1.51 (qd, 1H, J = 12.9, 3.0 Hz, H-3α); ^{13}C NMR (75.4 MHz, D_2O) δ 70.78, 66.57, 65.32, 64.09, 62.51, 44.61, 31.29, 20.48.

Anal. Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: 50.32; H, 8.93; N, 7.27.

(1*S*,2*S*,8*S*,8a*S*)-1,2,8-Trihydroxyindolizidine (2,8,8a-Tri-*epi*-swainsonine) (9). To piperidine **8** (1.20 g, 6.27 mmol) in dry DMF (20 mL) were added triphenylphosphine (3.29 g, 12.54 mmol), dry carbon tetrachloride (1.21 mL, 12.54 mmol), and freshly distilled triethylamine (1.73 mL, 12.41 mmol). The solution was allowed to react at room temperature for 1 h and then quenched with methanol (30 mL). After 30 min, the mixture was concentrated in vacuo and flash chromatographed on silica gel (50:20 CH_2Cl_2/MeOH; spray reagent 0.2% ninhydrin in ethanol; R_f = 0.33) to afford **9**: yield 999 mg (92%); a glass; $[\alpha]^{20}_D$ = +31.62° (*c* 1.07, MeOH); $[\alpha]^{20}_{546}$ = +37.21°; $[\alpha]^{20}_{436}$ = +58.60°; $[\alpha]^{20}_{365}$ = +82.79; ^{1}H NMR (300 MHz, D_2O) δ 3.96 (ddd, 1H, J = 6.6, 2.7, 1.2 Hz, H-2), 3.82 (dd, 1H, J = 7.8, 2.7 Hz, H-1), 3.48 (ddd, 1H, J = 10.8, 9.3, 4.5 Hz, H-8), 1.92 (m, 2H, H-7β, H-5α), 1.75 (dd, 1H, J = 9.0, 7.8 Hz, H-8α), 1.63 (dddd, 1H, J = 14.1, 4.8, 4.8, 2.4 Hz, H-6α), 1.43 (qt, 1H, J = 13.2, 4.2 Hz, H-6β), 1.15 (qd, 1H, J = 12.9, 10.8, 4.5 Hz, H-7α); ^{13}C NMR (75.4 MHz, D_2O) δ 84.19, 78.01, 75.14, 72.71, 61.32, 52.75, 34.15, 24.49.

Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.42; H, 8.69; N, 8.12.

5-(*N*-Benzylamino)-6,7-*O*-isopropylidene-8-*O*-benzyl-2,3,5-trideoxy-D-*talo*-oct-2-enono-1,4-lactone (11). Compound **11** was obtained from **10** (3.5 g, 10.3 mmol) as described previously for its enantiomer **5**: yield 3.5 g (82%); an oil; $[\alpha]^{20}_D$ = +61.98° (*c* 1.5, $CHCl_3$).

Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.75; H, 6.75; N, 3.45.

5-Amino-6,7-*O*-isopropylidene-2,3,5-trideoxy-D-*talo*-octono-1,4-lactone (12). Compound **12** was prepared from **11** (3.0 g, 7.08 mmol) as described for its enantiomer **6**: yield 1.68 g (97%); an oil; $[\alpha]^{20}_D$ = –5.45° (*c* 2.0, $CHCl_3$).

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.76; H, 7.55; N, 5.92.

6,7-*O*-Isopropylidene-2,3-dideoxy-D-*talo*-octono-δ-lactam (13). Compound **13** was prepared from **12** (1.6 g, 6.52 mmol) as previously described for its enantiomer **7**: yield 1.53 g (96%); a glass; $[\alpha]^{20}_D$ = –35.78° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.55; H, 7.76; N, 5.83.

1,2,3,5-Tetradeoxy-1,5-imino-D-*talo*-octitol (14). Compound **14** was prepared from **13** (1.4 g, 5.70 mmol) as previously described for its enantiomer **8**: yield 959 mg (88%); a glassy solid; $[\alpha]^{20}_D$ = –16.95° (*c* 2.0, MeOH).

Anal. Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: 50.45; H, 8.83; N, 7.47.

(1*R*,2*R*,8*R*,8a*R*)-1,2,8-Trihydroxyindolizidine (1-*epi*-Swainsonine) (15). Compound **15** was prepared from **14** (930 mg, 4.86 mmol) as previously described for its enantiomer **9**: yield 766 mg (91%); colorless crystals (MeCN/MeOH (3:1)); mp 111–113 °C; $[\alpha]^{20}_D$ = –32.14° (*c* 1.5, MeOH); $[\alpha]^{20}_{546}$ = –37.41°; $[\alpha]^{20}_{436}$ = –58.23°; $[\alpha]^{20}_{365}$ = –82.54° (lit.[4b] mp 109–110 °C; $[\alpha]^{20}_D$ = –33.2° (*c* 0.85, MeOH)).

Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.38; H, 8.79; N, 8.16.

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