Allylated Monosaccharides as Precursors in Triple Reductive Amination Strategies: Synthesis of Castanospermine and Swainsonine

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The feasibility of the triple-reductive amination reaction for the synthesis of complex indolizidine frameworks is illustrated by application to the potent glycosidase inhibitors castanospermine and swainsonine. The target compounds were obtained from known carbohydrate precursors in yields of 23 and 14%, over nine and 13 steps, respectively. The iodoetherification reaction of allylated monosaccharides was shown to be a practical reaction for the synthesis of the tricarbonyl precursors for the key triple reductive amination reactions.

The polyhydroxindolizidine alkaloids, of which castanospermine **1**[1] and swainsonine **2**[2] are two of the more prominent derivatives, are noted for their potent glycosidase inhibitory activity[3] (Figure 1). Analogues have been used as biochemical tools and have been examined as chemotherapeutic agents against diabetes,[4] cancer,[5] and HIV.[6] Their activity is believed to a result of their ability to mimic the transition state involved in substrate hydrolysis.[3] For example, the activity of castanospermine against glucosidases has been tied to the similarity of the six-membered ring to the glucosyl cation.[7] In a less obvious way, the anti-mannosidase activity of swainsonine has been related to the resemblance of the five-membered ring to the mannosyl cation.[8] It has been suggested that their rigid, bicyclic structures are responsible for their potent activity.[9] In connection with the design of more fine-tuned analogues, numerous syntheses of **1** and **2** and their diastereomers have been reported.[10−13]

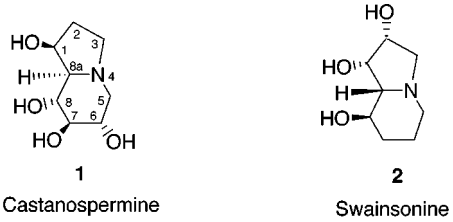

Figure 1.

The majority of syntheses are sugar-based, although, with the advancement in technologies for enantioselective synthesis, non-carbohydrate syntheses are becoming increasingly popular. Carbohydrate approaches capitalize on the easy availability of diastereomeric starting materials and generally involve introduction of one or more new carbinol centers in a sugar precursor, thence conver-

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(10) For a recent review on the synthesis of polyhydroxindolizidines, see: Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045−4066, and ref 3d,g.

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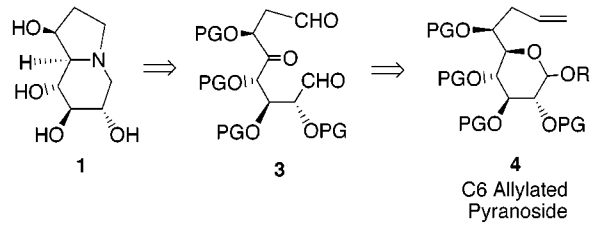
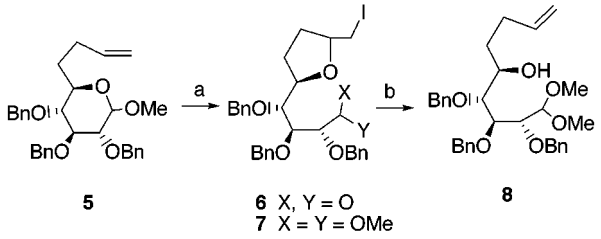
Scheme 1



Scheme 2[a]



[a] Key: (a) IDCP, H_2O or MeOH, CH_2Cl_2; (b) Zn.

sion to the bicyclic indolizidine framework. Many of the published procedures suffer from poor stereoselectivity, and inefficient protecting group chemistry, especially with respect to handling of the amino residue. We have recently described the synthesis of castanospermine via a novel triple-reductive amination strategy on a carbohydrate-derived tricarbonyl precursor **3** (Scheme 1).[14−16] The C6-allylated pyranoside **4** afforded easy access to **3**, and the overall strategy benefits from the fact that the amino residue is introduced at a late stage in the synthesis, with concomitant formation of the indolizidine framework. Herein, we illustrate the application of this methodology to castanospermine and swainsonine.

Studies from this laboratory have shown that C6-allylated monosaccharides (e.g., **5**) on treatment with halonium ion undergo a facile, high-yielding reaction to the halo-THF aldehyde **6** (Scheme 2).[17] When the reaction is performed under anhydrous conditions, in the presence of an alcohol, the acetal **7** is obtained. This suggested a route to the requisite tricarbonyl precursors because the hydroxy alkene **8** obtainable by reductive opening of **7** can be regarded as a masked keto-dialdehyde. Since the halocyclization reaction is general for monosaccharides, this approach may be used to access diastereomeric tricarbonyl derivatives.

The tricarbonyl compound for castanospermine was obtained from the readily available aldehyde **9**,[18] as decribed in our preliminary report (Scheme 3).[14] The allylated glucoside **10** was prepared through the Whitesides allylation procedure on **9**[19,20] and benzylation of the major product (9:1 ratio of epimers). Compound **10** was converted to the alkenyl-acetal-alcohol **11** in 74% overall yield, via the two-step iodoetherification−reductive elimination reaction sequence. Swern oxidation of **11** to the ketone **12**, ozonolysis of **12**, and acid hydrolysis of the resulting keto aldehyde led to **13′**, the structure of which was assigned on the basis of the ^1H and ^{13}C NMR and mass data. There was no evidence for the tautomeric bis-aldehyde structure **13**.

Treatment of **13** (**13′**) in anhydrous methanol in the presence of freshly activated, powdered molecular sieves, with 1.5 equiv of ammonium formate and 1.5 equiv of sodium cyanoborohydride, over 24 h, led to the formation of a major compound **14** in 78% yield. There was no evidence for formation of the C8a epimeric product. Reactions performed under conditions that were not strictly anhydrous required large excesses of sodium cyanoborohydride and resulted in much lower yields. Hydrogenolysis of **14** provided a semisolid product (80%) that yielded castanospermine **1** on recrystallization from ethanol. The product was essentially identical to natural castanospermine[1] (mp, ^1H and ^{13}C NMR, α_D). The overall yield from **9** was 23% over nine steps.

The efficiency of the TRA suggests that initial amination on **13** occurs at one of the carbonyl groups (more likely one or other of the two aldehydes), and the resulting carbinolamine **I** or **II** undergoes sequential intramolecular reactions with the remaining carbonyl groups, at an appreciably faster rate than competing intermolecular processes (Scheme 4). Attempts to isolate the intermediate products were not successful. Reduction in the amount of sodium cyanoborohydride or shorter reaction times led to varying amounts of the final product and a complex mixture of more polar components which were not separable. Following this mechanism, the C8 stereogenic center in the indolizidine product could arise via the hydride reduction of any one or more of the mono- and bicyclic iminium ions **IV**, **V**, and **VI**. These species are all expected to undergo preferred, α-face, nucleophilic attack. Stereoselective hydride delivery anti to the benzyloxy substituent of five-membered iminium ions such as **IV** is documented.[21] Nucleophilic addition to cyclic six-membered iminium ions such as **V** is expected to occur via a half chair **15** in which the benzyloxy substituents are in pseudoequatorial positions (Scheme 5). Addition of hydride in an axial trajectory to give **16** is favored because this results in a chairlike transition-state geometry, as opposed to equatorial attack which leads to a boatlike geometry.[22,23] Application of this model to the bicyclic species **VI** would give the same facial bias. The congruence of these individual stereoselectivities means that the relative contributions of **IV**, **V**, and **VI** in the reaction manifold is likely to be of little effect on the overall stereoselectivity of the TRA.

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(15) To the best of our knowledge, the triple reductive amination has not been previously reported. Double-reductive amination strategies are well documented: (a) Abe, K.; Okumura, T.; Tsugoshi, T.; Nakamura, N. *Synthesis* **1984**, 597−598. (b) Zou, W.; Szarek, W. A. *Carbohydr. Res.* **1993**, *242*, 311−314. (c) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175−3185. (d) Martin, O. R.; Saavedra, O. M. *J. Org. Chem.* **1996**, *61*, 6987−6993.

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(17) Khan, N.; Xiao, H.; Cheng, X.; Mootoo, D. R. *Tetrahedron* **1999**, *55*, 8303−8312.

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(20) The configuration of the new carbinol center was tentatively assigned by comparison of ^1H NMR of both epimers with those of related chain extended gluco derivatives: ref 17b.

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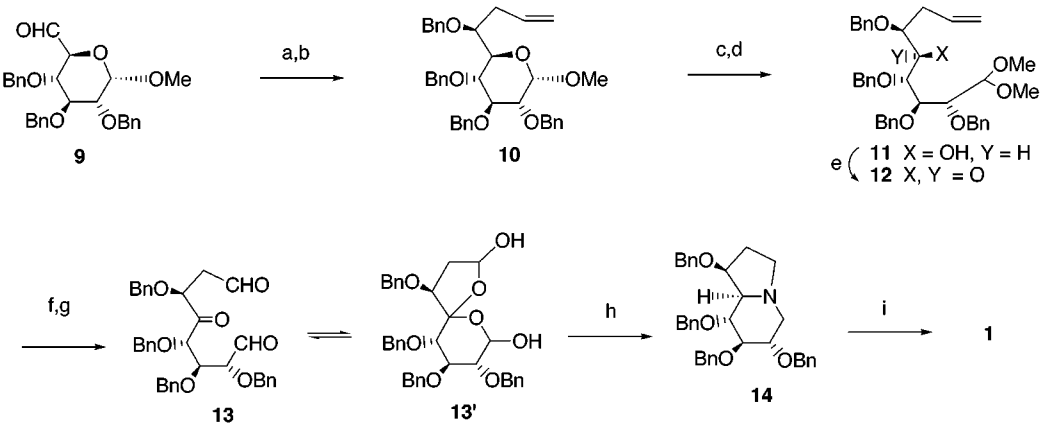
(22) The double reductive amination on 5-ketoglucose and benzyhydrylamine proceeds with high stereoselectivity for the 2,5-imino-D-glucitol: ref 15c.

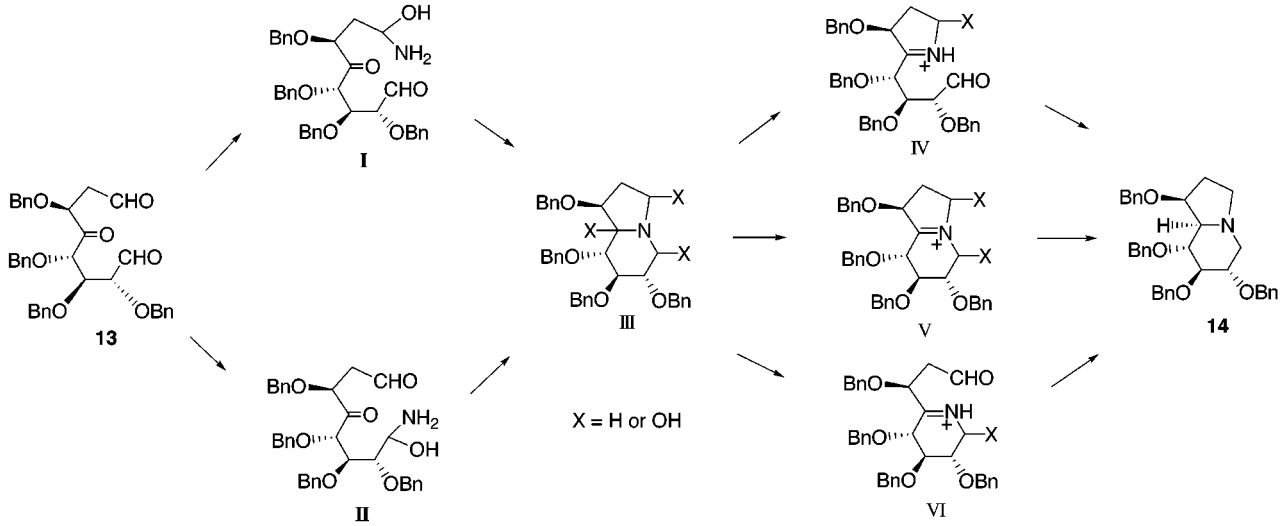
(23) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289−296.

Scheme 3[a]

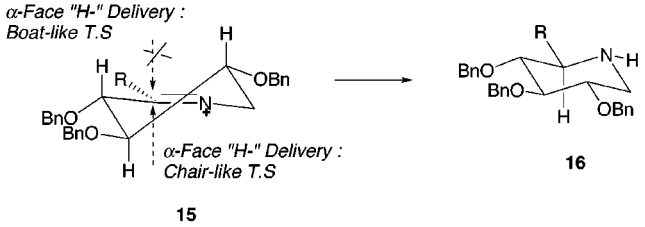


[a] Key: (a) allyl bromide, Sn, CH_3CN-H_2O (10:1), ultrasound; (b) BnBr, NaH, *n*-Bu_4NI, DMF; (c) IDCP, CH_2Cl_2–MeOH; (d) Zn, 95% EtOH, △; (e) Swern oxidation; (f) O_3, CH_2Cl_2, −78 °C then Ph_3P; (g) THF–9 M HCl; (h) NH_4HCO_2, $NaCNBH_3$, MeOH; (i) 10% Pd–C, MeOH–HCOOH.

Scheme 4



Scheme 5



It follows from the foregoing discussion that systems in which the individual iminium ions are expected to have the same stereochemical bias are good candidates for highly stereoselective TRAs. Accordingly, stereoselective synthesis of swainsonine should be possible from a tricarbonyl derivative such as **17**, since hydride attack on the associated iminium ions **VII**, **VIII**, and **IX** is expected to occur preferentially from the *β*-direction. We envisaged the synthesis of an appropriate tricarbonyl precursor from the C5-allylated 2,3-*O*-isopropylidene-furanose **18** (Scheme 6).

The aldehyde **20** was prepared from 2,3:5,6-di-*O*-mannofuranose **19** in 80% overall yield, via modification of the procedure which was developed for the methyl furanoside derivative of **20** (Scheme 7).[24] Reaction of **20** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ gave the (*R*) alcohol **21** (79%) and the (*S*)-epimer (3%). The stereochemistry was tentatively assigned on the basis of the reported stereoselectivity of these allylation conditions on related aldehydes.[25] The desired alcohol **21** was converted to the benzyl ether **18**, which was treated according to the standard iodocyclization–THF opening sequence to give the hydroxyalkene **22**. Hydroboration of **22** followed by oxidation of the diol product led to the ketoaldehyde **23**. DDQ-mediated removal of the *p*-methoxybenzyl, in the presence of triethylamine,[26] provided a mixture of two compounds, for which the physical data supported isomeric structures **24a**,**b**. For example, the major, more polar component **24a** showed an IR absorption at 3454 cm^{-1} but no peaks for free carbonyl groups. ^{1}HNMR signals were observed at δ 3.57 (s, 3H), 5.04 (d, 1H) and 5.17 (m, 1H) corresponding to the OMe and acetal hydrogens, respectively. No signals for carbonyl

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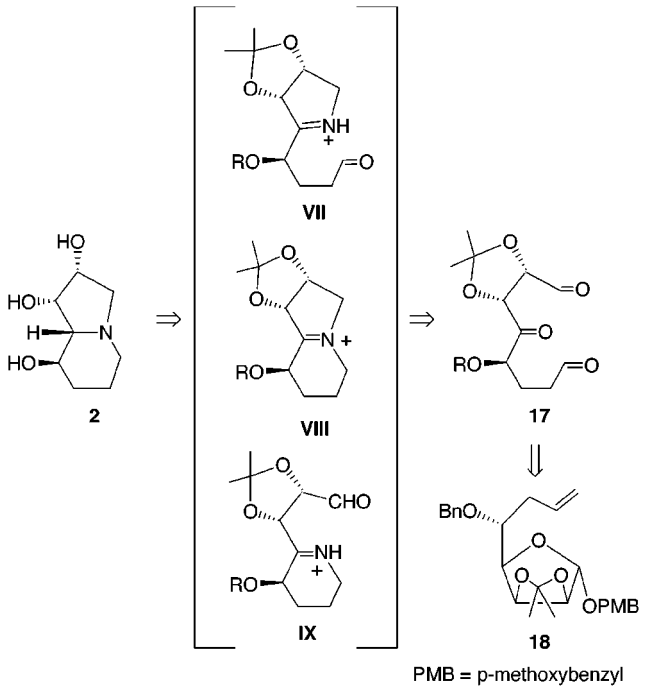
(25) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809–2819.

(26) Li, P.; Hung-Jang, G.; Sun, L.; Zhao, K. *J. Org. Chem.* **1998**, *63*, 366–369. *J. Org. Chem.* **1992**, *57*, 3977–3987.

Scheme 6



carbons were observed in the ^{13}C NMR, but resonances at δ 92.3, 104.3, 106.0, and 113.1, corresponding to acetal carbons were present. The mass spectrometry data were also in agreement with **24a**. Careful 2D COSY analysis of the acetal protons and the respective vicinal protons favored **24a** over the methyl pyranoside regioisomer (in which the OH and MeO substituents in **24a** are juxtaposed). The minor compound **24b** showed very similar physical characteristics to **24a**.

Compounds **24a**,**b** were individually subjected to the TRA since the reaction conditions are expected to lead to insitu formation of the tricarbonyl derivative. Indeed, the identical indolizidine product **25**[12f,g] was obtained as a single stereoisomer in 69 and 66% yields from **24a** and **24b**, respectively. Since **25** has previously been converted to swainsonine, this constitutes a formal synthesis.[12g] Hydrolysis of acetonide in **25** followed by hydrogenolysis of the benzyl ether provided a product which was essentially identical with natural swainsonine.[2c,12g] (mp, ^1H and ^{13}C NMR, α_D). The overall yield of swainsonine from **19** was approximately 14% over 13 steps.

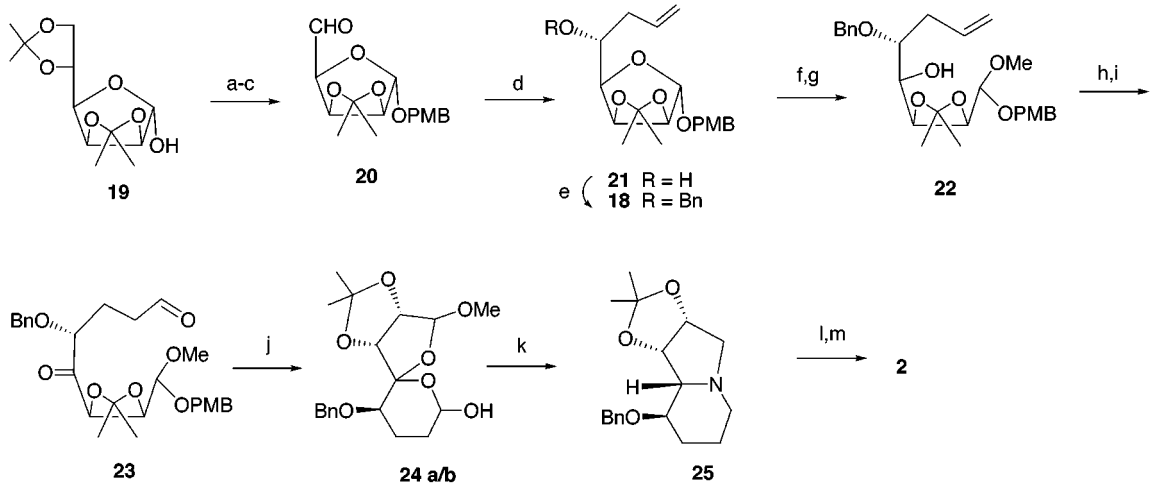
In summary, the TRA strategy appears to be well suited to stereochemically defined indolizidine motifs. The synthesis of castanospermine and swainsonine illustrates that allylated monosaccharides are practical precursors for the key tricarbonyl intermediates required for this methodology. A wide range of analogue structures will be possible in view of the number of easily accessible monosaccharide precursors of different configurations and constitution. It should be also possible to extend these principles to bicyclo [*m*.*n*.0] frameworks which are embedded in other classes of alkaloids. These directions are being pursued and will be reported in due course.

Experimental Section

General Procedures. TLC was performed on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Flash column chromatography (FCC) was performed using Kieselgel 60 (230−400 mesh, E. Merck) and employed a stepwise solvent polarity gradient, correlated with TLC mobility. The spots were visualized by UV, charring with a solution of ammonium molybdate (VI) tetrahydrate (12.5 g) and cerium (IV) sulfate tetrahydrate (5.0 g) in 10% aqueous H_2SO_4 (500 mL), or in the case of amine derivatives, with a solution of 0.3% ninhydrin and 0.3% acetic acid in butanol. Unless otherwise stated, ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Elemental analysis were performed by Schwarzkopf Microanalysis Laboratory. High-resolution mass spectroscopy was carried out at the Mass Spectral Facility at the University of Illinois at Urbana-Champaign. Melting points are reported uncorrected.

Methyl 7,8,9-Trideoxy-2,3,4,6-tetra-*O*-benzyl-L-glycero-α-D-gluco-non-8-eno-pyranoside (10). Tin powder (121 mg, 1.02 mmol, 100 mesh) and allyl bromide (0.136 mL, 1.53 mmol) were added to a solution of aldehyde **9** (236 mg, 0.51 mmol) in a mixture of 10:1 CH_3CN-H_2O (11 mL). The reaction was placed in an ultrasonic bath for 16 h. NaOH (6 M) was then added to the reaction mixture to pH 8, and the resulting slurry was filtered through a Celite pad. The filtrate was extracted with ether (3 × 30 mL), and the organic phase was washed with brine (30 mL), dried (Na_2SO_4), filtered, and evaporated

Scheme 7[a]



[a] Key: (a) PMBCL, NaH, *n*-Bu_4NI, DMF; (b) HOAc; (c) $NaIO_4$; (d) allyltrimethylsilane, $BF_3{\cdot}OEt_2$; (e) BnBr, NaH, *n*-Bu_4NI, DMF; (f) IDCP, CH_2Cl_2-MeOH; (g) Zn, 95% EtOH, △; (h) BH_3, THF, then Na_2O_2; (i) Swern oxidation; (j) DDQ, Et_3N, $CH_2Cl_2-H_2O$; (k) NH_4HCO_2, $NaCNBH_3$, MeOH; (l) 10% Pd−C, MeOH−HCOOH; (m) HCl, $THF-H_2O$.

in vacuo. ^{1}H NMR analysis of the crude product indicated a 9:1 ratio of products. FCC afforded a major (193 mg, 75%) and a minor product (20 mg, 8%).

For major product: R_f = 0.70 (40% EtOAc−petroleum ether); IR ($CHCl_3$) 3528, 1640, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.23 (m, 1H), 2.36 (m, 1H), 3.32 (s, 3H), 3.46 (dd, 1H, J = 3.6, 9.6 Hz), 3.50 (d, 1H, J = 9.3 Hz), 3.65 (t, 1H, J = 9.3 Hz), 3.86 (m, 1H), 3.95 (t, 1H, J = 9.3 Hz), 4.55 (d, 1H, J = 3.6 Hz), 4.69 (ABq, $\Delta\delta$ = 0.15 ppm, 2H, J = 12.0 Hz), 4.76 (ABq, $\Delta\delta$ = 0.22 ppm, 2H, J = 10.8 Hz), 4.87 (ABq, $\Delta\delta$ = 0.15 ppm, 2H, J = 10.8 Hz), 5.07 (m, 2H), 5.78 (m, 1H), 7.25−7.32 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 38.8, 55.5, 68.1, 71.8, 73.6, 75.3, 75.9, 77.8, 80.0, 82.3, 98.6, 118.0, 127.7, 127.9, 128.1, 128.3, 128.6, 135.0, 138.3, 138.5, 139.0.

For minor product: R_f = 0.65 (40% EtOAc−petroleum ether); ^{1}H NMR ($CDCl_3$) δ 2.20 (m, 2H), 2.28 (br, 1H), 2,70 (br d, 1H, J = 5.0 Hz, D_2O ex), 3.31 (s, 3H), 3.43 (m, 2H), 3.62 (dd, 1H, J = 4.5, 9.9 Hz), 3.77 (m, 1H), 3.96 (t, 1H, J = 9.3 Hz), 4.50 (d, 1H, J = 3.6 Hz), 4.65 (ABq, $\Delta\delta$ = 0.13 ppm, 2H, J = 11.7 Hz), 4.74 (ABq, $\Delta\delta$ = 0.32 ppm, 2H, J = 11.1 Hz), 4.84 (ABq, $\Delta\delta$ = 0.22 ppm, 2H, J = 10.8 Hz), 5.00 (m, 2H), 5.79 (m, 1H), 7.15−7.36 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 36.8, 55.4, 71.7, 71.8, 73.4, 74.8, 75.8, 79.8, 80.4, 82.5, 98.0, 117.4, 127.7−128.5 (several lines), 135.3, 137.9, 138.2, 138.7.

NaH (0.50 g, 60% suspension in oil, 12.5 mmol) and ^{n}Bu$_4$NI (0.22 g, 0.38 mmol) was added to a solution of the major product from the previous step (4.8 g, 9.5 mmol) in dry THF (40 mL), at 0 °C. The slurry was stirred at this temperature for 20 min, at which time benzyl bromide (2.70 mL, 22.7 mmol) was added. The reaction was warmed to room temperature and stirred for 16 h. The temperature was then lowered to 0 °C, and MeOH (1 mL) was added. After an additional 15 min, the mixture was diluted with water (100 mL) and extracted with ether (3 × 50 mL). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4), and filtered. Concentration of the filtrate in vacuo gave a brown oil, which when subjected to FCC provided pyranoside alkene **10** (5.50 g, 97%): R_f = 0.80 (20% EtOAc−petroleum ether); $[\alpha]^{23}_D$ −20° (c = 5.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.58 (m, 2H), 3.41 (s, 3H), 3.59 (dd, 1H, J = 3.6, 9.9 Hz), 3.72 (m, 2H), 3.89 (dd, 1H, J = 5.4, 8.4 Hz), 4.02 (t, 1H, J = 9.6 Hz), 4.34 (d, 1H, J = 11.1 Hz), 4.38 (d, 1H, J = 11.7 Hz), 4.69 (m, 2H), 4.81 (ABq, $\Delta\delta$ = 0.02 ppm, 2H, J = 10.5 Hz), 4.96 (d, 1H, 10.5 Hz), 5.01 (d, 1H, J = 10.5 Hz), 5.14 (m, 2H), 5.86 (m, 1H), 7.34 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 34.5, 55.8, 71.1, 72.0, 73.6, 74.7, 75.7, 76.0, 80.1, 82.6, 98.6, 117.8, 127.6−128.6 (several lines), 134.8, 138.2, 138.4, 138.8; HRMS (FAB) calcd for $C_{38}H_{42}O_6Na$ (M + Na) 617.2879, found 617.2876.

7,8,9-Trideoxy-2,3,4,6-tetra-*O*-benzyl-L-glycero-D-*gluco*-non-8-enose Dimethyl Acetal (11). IDCP (3.2 g, 6.9 mmol) was added to a solution of pyranoside alkene **10** (2.7 g, 4.6 mmol) in a mixture of CH_2Cl_2 (50 mL) and MeOH (0.75 mL, 23 mmol) under argon. The reaction mixture was stirred at room temperature for 1 h, poured into 10% aqueous $Na_2S_2O_3$, and extracted with ether (3 × 50 mL). The organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give a brown oil. This material was used directly in the next step. For characterization purposes, a sample was purified by FCC: R_f = 0.50 (20% EtOAc−petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.65, 2.19, 2.43 (all m, 2H), 3.21 (m, 2H), 3.27, 3.31, 3.46, 3.51 (s, 6H), 3.95 (m, 3H), 4.21−4.38 (m, 5H), 4.50 − 4.92 (m, 7H), 7.34 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 10.1, 12.5, 35.6, 37.9, 54.5, 54.7, 56.1, 56.3, 71.0, 71.1, 74.1, 74.4, 74.9, 75.0, 75.4, 76.3, 76.7, 78.6, 79.1, 80.1, 81.7, 82.5, 83.6, 85.7, 106.1, 106.3, 127.3−128.5 (several lines), 138.0, 138.2, 138.9, 139.1, 139.4, 139.5.

The crude material from the previous step was dissolved in 95% ethanol (50 mL) and stirred with freshly activated zinc powder (11 g) at reflux for 1 h. The suspension was then diluted with ether and filtered through a short column of florisil. Concentration of the filtrate under reduced pressure followed by FCC of the residual, dark brown oil afforded hydroxyalkene **11** (2.1 g, 74% from **10**): R_f = 0.5 (20% EtOAc−petroleum ether); $[\alpha]^{23}_D$ +27° (c = 4.1, $CHCl_3$); IR (film) 3476, 1641, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.55 (m, 2H), 3.37 (s, 3H), 3.48 (s, 3H), 3.55 (m, 1H), 3.72 (m, 2H), 3.87 (m, 1H), 4.02 (t, 1H, J = 9.3 Hz), 4.32 (d, 1H, J = 11.1 Hz), 4.37 (d, 1H, J = 11.7 Hz), 4.67 (m, 3H), 4.79 (ABq, $\Delta\delta$ = 0.02 ppm, J = 10.5 Hz, 2H), 4.89 (d, 1H, J = 11.4 Hz), 4.99 (d, 1H, J = 10.5 Hz), 5.13 (m, 2H), 5.81 (m, 1H), 7.32 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 34.5, 55.8, 71.1, 72.0, 73.6, 74.8, 75.8, 76.0, 80.1, 82.7, 98.6, 117.8, 127.7−128.6 (several lines), 134.8, 138.2, 138.3, 138.8. Anal. Calcd for $C_{39}H_{46}O_7$: C, 74.74; H, 7.40; O, 17.86. Found: C, 74.35; H, 7.43; O, 18.22.

Ketone−Alkene (12). DMSO (0.88 mL, 13 mmol) was slowly added at −78 °C to a mixture of oxalyl chloride (0.90 mL, 11 mmol) and anhydrous CH_2Cl_2 (10 mL). The reaction mixture was stirred at this temperature for 20 min, at which time a solution of **11** (2.1 g, 3.4 mmol) in CH_2Cl_2 (15 mL) was slowly introduced. After an additional 20 min, Et_3N (2.9 mL, 21 mmol) was slowly added. The reaction mixture was then warmed to room temperature and diluted with ether (50 mL). The resulting suspension was washed with saturated $NaHCO_3$ (25 mL) and the aqueous layer extracted with ether (3 × 25 mL). The combined organic phase was washed with brine (25 mL), dried (Na_2SO_4), filtered and evaporated in vacuo. FCC of the residual syrup afforded ketone **12** (2.0 g, 95%): R_f = 0.6 (20% EtOAc−petroleum ether); $[\alpha]^{23}_D$ −17° (c = 4.1, $CHCl_3$); IR (film) 1725, 1641, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (m, 1H), 2.45 (m, 1H), 3.38 (s, 3H), 3.45 (s, 3H), 3.85 (dd, 1H, J = 3.9, 6.3 Hz), 4.15 (m, 2H), 4.32 (d, 1H, J = 5.7 Hz), 4.40 (m, 2H), 4.55 (m, 2H), 4.71 (m, 4H), 4.79 (d, 1H, J = 11.1 Hz), 4.98 (m, 2H), 5.72 (m, 1H), 7.25 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 36.5, 54.4, 55.8, 71.9, 73.4, 74.3, 74.8, 77.8, 79.7, 80.8, 81.7, 105.5, 117.6, 127.5−128.8 (several lines), 133.9, 137.9, 138.2, 138.4, 138.9, 207.9; HRMS (FAB) calcd for $C_{39}H_{44}O_7Na$ (M + Na) 647.2985, found 647.2985.

Tricarbonyl Precursor 13 (13′). O_3 was bubbled at −78 °C through a solution of **12 (**1.83 g, 2.94 mmol) in a mixture of CH_2Cl_2 (15 mL) and MeOH (3 mL). The progress of the reaction was monitored by TLC until complete disappearance of the starting material. The reaction mixture was then purged with argon and warmed to room temperature. Methanol (15 mL) and Ph_3P (1.2 g, 4.6 mmol) were added, and stirring was continued under an argon atmosphere for 1 h. Concentration of the reaction mixture followed by FCC of the residual slurry afforded the ketoaldehyde derivative (1.73 g, 95%): R_f = 0.35 (20% EtOAc−petroleum ether); IR (film) 1709 (broad), 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (ddd, 1H, J = 2.1, 8.4, 14 Hz), 2.61 (dd, 1H, J = 3.6, 14 Hz), 3.38 (s, 3H), 3.43 (s, 3H), 3.82 (dd, 1H, J = 4.5, 5.7 Hz), 4.15 (m, 2H), 4.31 (d, 1H, J = 5.7 Hz), 4.35 (d, 1H, J = 11.4 Hz), 4.51−4.82 (m, 8H), 7.26 (m, 20H), 9.41 (d, 1H, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 45.2, 54.9, 56.0, 72.6, 73.8, 74.4, 75.3, 77.8, 78.0, 80.0, 81.0, 105.8, 127.7−128.7 (several lines), 137.5, 137.7, 138.1, 138.8, 199.4, 208.1.

HCl (9 M, 15 mL) was added to a solution of the material obtained from the previous step (1.73 g, 2.78 mmol), in THF (45 mL). The reaction mixture was stirred at room temperature for 1 h and then carefully neutralized by addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with ether (3 × 50 mL), and the combined organic phase was washed with brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated in vacuo. FCC of the semisolid residue afforded **13′** as an amorphous, white solid (1.66 g). Recrystalliztion from EtOAc−petroleum ether afforded white needles (0.70 g, 40%), mp 147−148 °C. FCC of the mother liquor afforded a second crop of crystals (0.72 g, 41%): R_f = 0.3 (30% EtOAc−petroleum ether); $[\alpha]^{23}_D$ +16.5° (c 1.80, $CHCl_3$); IR ($CHCl_3$) 3387 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.99, 2.13, 2.39 (all m, 2H), 3.56 (m, 2H), 3.90 (m, 2H), 4.18−4.50 (m, 4H), 4.70−5.03 (m, 4H), 5.17−5.53 (m, 2H), 7.25 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 37.4, 37.8, 72.4, 74.9, 75.3, 75.4, 75.9, 76.0, 76.7, 78.1, 78.2, 82.0, 82.2, 83.7, 93.7, 93.9, 97.3, 98.1, 103.5, 103.7, 127.7−128.7 (several lines), 137.5, 137.6, 138.0, 138.6, 138.7; MS (CI-NH_3) 598 (M − H_2O + NH_4^+). Anal. Calcd for **13′** $C_{36}H_{38}O_8$: C, 72.22; H, 6.40; O, 21.38. Found: C, 71.96; H, 6.58; O, 21.46.

(1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetrabenzyloxyoctahydroindolizidine (14). To a mixture of **13** (80 mg, 0.14 mmol), ammonium formate (16 mg, 0.23 mmol), and freshly activated,

powdered 3A molecular sieves in anhydrous MeOH (2 mL) was added $NaCNBH_3$ (63 mg, 0.30 mmol). The reaction mixture was stirred for 24 h at room temperature and then filtered through a bed of Celite. The filtrate was diluted with CH_2Cl_2 (10 mL), washed succesively with saturated aqueous $NaHCO_3$ (4 mL) and brine (2 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. FCC of the crude residue provided **14** (63 mg, 78%): R_f = 0.5 (15% EtOAc−toluene); $[\alpha]^{23}_D$ +32° (*c* 1.0, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 1.73 (m, 3H), 1.91 (t, 1H, *J* = 10.2 Hz), 2.00 (dd, 1H, *J* = 5.1, 9.6 Hz), 2.89 (m, 1H), 3.15 (dd, 1H, *J* = 4.8, 10.2 Hz), 3.68 (t, 1H, *J* = 8.7 Hz), 3.80 (m, 1H), 3.93 (m, 1H), 4.18 (t, 1H, *J* = 8.7 Hz), 4.20 (ABq, $\Delta\delta$ = 0.22 ppm, 2H, *J* = 11.7 Hz), 4.50 (ABq, $\Delta\delta$ = 0.05 ppm, 2H, *J* = 11.7 Hz), 4.94 (ABq, $\Delta\delta$ = 0.25 ppm, 2H, *J* = 11.7 Hz), 5.00 (ABq, $\Delta\delta$ = 0.16 ppm, 2H, *J* = 11.4 Hz), 7.23 (m, 20H); ^{13}C NMR (C_6D_6) δ 31.2, 53.2, 55.3, 70.9, 72.4, 73.1, 74.9, 76.0, 78.5, 78.6, 80.2, 88.7, 127.6−128.9 (several lines), 139.5, 139.9, 140.4, 140.9. Anal. Calcd for $C_{36}H_{39}O_4N$: C, 78.66; H, 7.15; O, 11.64; N, 2.55. Found: C, 78.45; H, 7.37; O, 11.69; N, 2.49.

Castanospermine (1). HCOOH (1 mL) was added to a mixture of **14** (120 mg, 0.22 mmol), 10% Pd−C (500 mg), and MeOH (4 mL) under an argon atmosphere. The suspension was was stirred for 2 h and then filtered through a pad of Celite. The filter cake was washed several times with MeOH and then concentrated in vacuo. The residual syrup was dissolved in ethanol and stirred with Amberlite IRA-(OH) ion-exchange resin (500 mg) for 30 min. The mixture was filtered through Celite and the filtrate concentrated in vacuo to give a semisolid residue (33 mg, 80%). Recrystallization from ethanol afforded white prisms (29 mg, 70%): mp 202−208 °C dec (lit.[1a] mp 212−215 °C dec); $[\alpha]^{23}_D$ +70° (*c* 0.33, H_2O) [lit.[1a] $[\alpha]_D$ +79.7° (*c* = 0.93, H_2O)]; R_f = 0.25 (30% MeOH−$CHCl_3$); ^{1}H NMR and TLC data were identical with those of a commercial sample of castanospermine;[27] ^{1}H NMR (D_2O) δ 1.0.69 (m, 1H), 2.03 (m, 1H), 2.20 (m, 1H), 2.32 (m, 1H), 3.07 (dt, 1H, *J* = 2.1, 9.6 Hz), 3.16 (dd, 1H, *J* = 5.1, 11.1 Hz), 3.59 (m, 1H), 4.40 (m, 1H); ^{13}C NMR (D_2O) δ 31.7, 50.6, 54.4, 68.0, 68.6, 69.1, 70.4, 78.0; MS (ES) *m*/*z* 190 (M + H).

***p*-Methoxybenzyl 6,7,8-Trideoxy-5-*O*-benzyl-2,3-O-(1-methylethylidene)-α-D-*manno*-oct-7-enofuranoside (18).** Boron trifluoride etherate (4.9 mL, 39.4 mmol) was added to a solution of aldehyde **20** (8.1 g, 26 mmol) in dry CH_2Cl_2 (300 mL), at −78 °C. The solution was stirred at this temperature for 20 min, at which time allyltrimethylsilane (5.0 mL, 31 mmol) was added. The reaction mixture was maintained at −78 °C for 2 h and then poured into saturated aqueous $NaHCO_3$ (300 mL). The mixture was extracted with ether (3 × 200 mL), and the organic phase was washed with brine (200 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. FCC of the residue provided **21** (7.2 g, 77%) and a minor product (0.3 g, 3%).

For **21**: R_f = 0.50 (20% EtOAc−petroleum ether); $[\alpha]^{23}_D$ +66.9° (*c* = 0.75, $CHCl_3$); IR ($CHCl_3$) 3492, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.47 (s, 3H), 2.34 (m, 1H), 2.55 (m, 1H), 2.80 (br d, 1H, *J* = 5.1 Hz, D_2O ex), 3.78 (s, 3H), 3.88 (dd, 1H, *J* = 3.6, 8.1 Hz), 4.01 (m, 1H), 4.53 (ABq, $\Delta\delta$ = 0.18 ppm, *J* = 11.4 Hz, 2H), 4.62 (d, 1H, *J* = 6.0 Hz), 4.83 (dd, 1H, *J* = 5.7, 3.6 Hz), 5.14 (s, 1H), 5.18 (m, 2H), 5.95 (m, 1H), 6.91 (d, 2H, *J* = 8.4 Hz), 7.27 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.9, 38.9, 55.1, 68.5, 69.0, 80.0, 81.4, 84.9, 104.9, 112.4, 113.8, 117.6, 129.3, 129.7, 134.5, 159.3. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.06; H, 7.48.

For minor product: R_f = 0.55 (20% EtOAc−petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.46 (s, 3H), 2.43 (m, 2H), 3.13 (br s, 1H, D_2O ex), 3.78 (s, 3H), 3.89 (dd, 1H, *J* = 5.1, 3.6 Hz), 4.10 (q, 1H, *J* = 5.1 Hz), 4.51 (ABq, $\Delta\delta$ = 0.15 ppm, *J* = 11.4 Hz, 2H), 4.63 (d, 1H, *J* = 5.7 Hz), 4.73 (dd, 1H, *J* = 5.7, 3.6 Hz), 5.14 (m, 3H), 5.91 (m, 1H), 6.87 (d, 2H, *J* = 8.7 Hz), 7.27 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 24.5, 25.9, 37.9, 55.2, 68.7, 69.5, 80.5, 81.1, 85.5, 104.7, 112.6, 113.9, 117.5, 129.3, 129.8, 134.5, 159.4.

A portion of the product from the previous step (1.4 g, 4.3 mmol) was benzylated following the procedure used for compound **10**. Benzyl ether **18** (1.7 g, 97%) was obtained: R_f = 0.60 (10% EtOAc−petroleum ether); $[\alpha]^{23}_D$ +34.3° (*c* 1.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.45 (s, 3H), 2.39 (m, 1H), 2.61 (m, 1H), 3.79 (s, 3H), 3.90 (m, 2H), 4.47 (ABq, $\Delta\delta$ = 0.17 ppm, *J* = 11.1 Hz, 2H), 4.59 (d, 1H, *J* = 6.0 Hz), 4.65 (m, 2H), 4.82 (dd, 1H, *J* = 3.3, 6.0 Hz), 5.05 (s, 1H), 5.18 (m, 2H), 6.02 (m, 1H), 6.86 (d, 2H, *J* = 8.4 Hz), 7.23 (d, 2H, *J* = 8.4 Hz), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.2, 26.4, 36.4, 55.5, 68.6, 72.7, 76.0, 80.0, 80.6, 85.2, 105.2, 112.4, 114.1, 117.6, 127.7, 128.2, 128.4, 129.7, 130.0, 134.8, 139.0, 159.5; HRMS (FAB) calcd for $C_{26}H_{31}O_6$ (M − H) 439.2121, found 439.2119.

6,7,8-Trideoxy-5-*O*-benzyl-2,3-*O*-(1-methylethylidene)-D-*manno*-oct-7-enose *p*-methoxybenzyl Methyl Acetal (22). Treatment of compound **18** (9.3 g, 21.1 mmol) following the two-step iodoetherification−reductive elimination sequence that was used for the synthesis of **11** (see the Supporting Information), provided **22** (7.8 g, 78%): R_f = 0.50 (20% EtOAc−petroleum ether); $[\alpha]^{23}_D$ −41.3° (*c* = 2.7, $CHCl_3$); IR (film) 3510, 1640, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.49 (s, 3H), 2.33 (d, 1H, *J* = 11.7 Hz, D_2O ex), 2.34 (m, 1H), 2.56 (m, 1H), 3.42 (s, 3H), 3.42 (m, 1H, partially buried under s at δ 3.70), 3.70 (s, 3H), 3.77 (t, 1H, *J* = 9.0 Hz), 4.25 (t, 1H, *J* = 7.2 Hz), 4.46 (m, 3H), 4.60 (m, 2H), 4.94 (d, 1H, *J* = 7.2 Hz), 5.08 (m, 2H), 5.88 (m, 1H), 6.79 (d, 2H, *J* = 8.7 Hz), 7.22 (d, 2H, *J* = 8.7 Hz), 7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.5, 26.8, 34.9, 53.4, 55.2, 69.3, 72.0, 74.8, 76.0, 79.2, 101.1, 108.3, 113.9, 117.3, 127.5, 127.7, 128.3, 129.5, 129.8 (several lines), 134.7, 138.6, 159.4. Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.24; H, 8.01.

Ketoaldehyde 23. 9-BBN in THF (74 mL of a 0.5 M solution, 37 mmol) was added at 0 °C to a solution of **22** (5.8 g, 12 mmol) in dry THF (250 mL). After 1 h, the reaction was warmed to room temperature and maintained at this temperature for 18 h. The reaction was then cooled to 0 °C, and a mixture of 30% H_2O_2 (55 mL) and 30% NaOH (55 mL) was slowly added. The solution was extracted with ether (3 × 200 mL). The organic phase was washed with brine (200 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo. FCC of the residue gave the diol derivative (5.2 g, 86%): R_f = 0.30 (50% EtOAc−petroleum ether); IR ($CHCl_3$) 3450, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.50 (s, 3H), 1.60 (m, 3H), 1.80 (m, 1H), 2.69 (d, 1H, *J* = 8.7 Hz), 2.90 (br s, 1H, D_2O ex), 3.42 (s, 3H), 3.42 (m, buried under s at δ 3.42), 3.55 (m, 2H), 3.68 (s, 3H), 3.78 (t, 1H, *J* = 8.1 Hz), 4.27 (t, 1H, *J* = 7.5 Hz), 4.45 (m, 3H), 4.62 (d, 1H, *J* = 10.8 Hz), 4.97 (d, 1H, *J* = 7.2 Hz), 6.80 (d, 2H, *J* = 8.7 Hz), 7.26 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 24.3, 26.4, 26.5, 27.3, 53.2, 55.0, 62.5, 69.1, 71.7, 74.9, 75.8, 79.2, 100.9, 108.1, 113.8, 127.4, 127.5, 128.1, 129.4, 129.6, 138.4.

The Swern oxidation procedure which was used for the preparation of **12** was applied to a sample of the diol from the previous step (2.3 g, 4.7 mmol), using DMSO (2.0 mL, 28 mmol), oxalyl chloride (2.1 mL, 24 mmol) and Et_3N (6.8 mL, 47 mmol). Ketoaldehyde **23** (1.9 g, 84%) was obtained as a yellow oil: R_f = 0.75 (50% EtOAc−petroleum ether); $[\alpha]^{23}_D$ −17.2° (*c* 7.10, $CHCl_3$); IR ($CHCl_3$) 1709 (broad), 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.54 (s, 3H), 1.76 (m, 1H), 1.96 (m, 1H), 2.32 (m, 2H), 3.37 (s, 3H), 3.71 (s, 3H), 3.92 (dd, 1H, *J* = 8.1, 3.9 Hz), 4.28 (m, 2H), 4.42 (t, 1H, *J* = 6.6 Hz), 4.52 (m, 2H), 4.63 (d, 1H, *J* = 6.0 Hz), 4.79 (d, 1H, *J* = 6.6 Hz), 6.78 (d, 2H, *J* = 8.4 Hz), 7.17 (d, 2H, *J* = 8.4 Hz), 7.24−7.26 (m, 7H), 9.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.1, 25.4, 27.0, 39.7, 54.2, 55.2, 68.7, 72.5, 76.7, 78.2, 81.9, 100.5, 110.6, 113.8, 127.9, 128.2, 128.4, 129.4, 129.7, 137.4, 159.3, 201.4, 205.1; HRMS (FAB) calcd for $C_{27}H_{33}O_8$ (M − H) 485.2175, found 485.2176.

Tricarbonyl Precursor 24a,b. DDQ (135 mg, 0.595 mmol) was added at 0 °C, to a mixture of **23** (102 mg, 0.209 mmol), in Et_3N (0.03 mL, 0.22 mmol), CH_2Cl_2 (10 mL), and H_2O (1 mL). After 20 min, the reaction mixture warmed to room temperature and stirred at this temperature for an additional 3 h. The reaction mixture was then poured into saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phase was washed with brine (25 mL), dried (Na_2SO_4), filtered and evaporated in vacuo. FCC of the residue

(27) Purchased from Tocris Cookson, Inc.

afforded unreacted **23** (10 mg), **24a** (41 mg, 59% based on recovered **23**) and **24b** (14 mg, 20% based on recovered **23**).

For **24a**: R_f = 0.25 (15% EtOAc−petroleum ether); $[\alpha]^{23}_D$ −68.8° (*c* 3.50, $CHCl_3$); IR ($CHCl_3$) 3454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35, 1.48 (both s, 3H ea), 1.65−1.95 (m, 4H), 2.75 (d, *J* = 10.8 Hz, 1H, D_2O ex), 3.56 (s, 3H), 3.60 (m, 1H), 4.60 (m, 3H), 4.75 (m, 1H), 5.04 (d, *J* = 3.0 Hz, 1H), 5.17 (m, 1H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.7, 25.4, 26.1, 28.1, 58.5, 70.8, 71.9, 78.4, 83.0, 92.2, 104.2, 106.0, 113.1, 127.3, 128.2, 128.4, 138.5; HRMS (FAB) calcd for $C_{19}H_{26}O_7Na$ (M + Na), 389.1576, found 389.1581.

For **24b**: R_f = 0.40 (15% EtOAc−petroleum ether); IR ($CHCl_3$) 3454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32, 1.42 (both s, 3H ea), 1.70−1.95 (m, 4H), 2.88 (br d, *J* = 10 Hz, 1H, D_2O ex), 3.45 (s, 3H), 3.58 (m, 1H), 4.65 (s, 2H), 4.73 (m, 2H), 4.95 (s, 1H), 5.10 (m, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 22.9, 25.6, 26.9, 27.7, 56.8, 71.2, 72.1, 84.4, 85.2, 92.4, 111.6, 112.5, 112.6, 127.7, 128.3, 128.5, 138.5; HRMS (FAB): calcd for $C_{19}H_{24}O_6$ (M − OH), 349.1651, found 349.1651.

(1*S*,2*R*,8*R*,8a*R*)-8-(Benzyloxy)-1,2-(isopropylidenedioxy)-octahydroindolizidine (25). A mixture of **24a** (110 mg, 0.30 mmol), ammonium formate (40 mg, 0.60 mmol), $NaCNBH_3$ (280 mg, 2.6 mmol), freshly activated, powdered 4A molecular sieves, and anhydrous MeOH (3 mL) was stirred at room temperature for 24 h. The reaction mixture was then processed as described for the preparation of **14**. FCC of the crude residue provided **25** (67 mg, 69%). R_f = 0.30 (50% EtOAc−petroleum ether); $[\alpha]^{23}_D$ −67° (*c* 3.1, $CHCl_3$) [lit.[12f] $[\alpha]^{20}_D$ −64.2° (*c* 0.50, $CHCl_3$), lit.[12g] $[\alpha]^{26}_D$ −58.9° (*c* 0.27, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 1.14−1.26 (m, 1H), 1.35 (s, 3H), 1.51 (s, 3H), 1.51−1.65 (m, 2H), 1.69 (dd, 1H, *J* = 4.0, 8.8 Hz), 1.83 (dt, *J* = 3.0, 11.0 Hz, 1H), 2.09 (dd, *J* = 4.4, 10.6 Hz, 1H), 2.10 (m, 1H), 2.97 (bd, *J* = 10.6 Hz, 1H), 3.12 (d, *J* = 10.6 Hz, 1H), 3.64 (ddd, 1H, *J* = 4.4, 8.8, 11.0 Hz, 1H), 4.59 (dd, 4.4, 6.2 Hz, 1H), 4.68 (s, 2H), 4.73 (dd, 1H, *J* = 4.3, 6.2 Hz, 1H), 7.20−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.3, 25.3, 26.3, 30.9, 51.9, 60.5, 71.6, 72.6, 74.5, 78.2, 79.6, 111.0, 127.4, 127.9, 128.3, 139.4; HRMS (FAB) calcd for $C_{18}H_{26}NO_3$ (M + H) 304.1912, found 304.1916.

Treatment of **24b** (30 mg, 0.085 mmol) according to the procedure described for **24a** provided **25** (17 mg, 66%).

Swainsonine (2). HCOOH (1 mL) was added to a mixture of **25** (86 mg, 0.22 mmol), 10% Pd−C (500 mg), and MeOH (4 mL) under an argon atmosphere. The suspension was stirred for 2 h, then filtered through a pad of Celite. The filter cake was washed several times with methanol and then concentrated in vacuo. The residue was dissolved in a mixture of 6 N HCl (1 mL) and THF (3 mL) and stirred at room temperature for 2 h. The volatiles were then removed under reduced pressure. The residual syrup was dissolved in ethanol and stirred with Amberlite IRA-(OH) ion-exchange resin (500 mg) for 30 min. The mixture was filtered through Celite and the filtrate concentrated in vacuo to give a semisolid residue **2** (39 mg, 80%). Recrystallization from $CHCl_3$−MeOH−Et_2O afforded needles: mp 138−142 °C (lit.[2c] mp 144−145 °C, lit.[12g] mp 141−143 °C); ^1H NMR and TLC data were identical with those for a commercial sample of swainsonine;[28] R_f = 0.30 (30% CH_3OH−EtOAc); $[\alpha]^{23}_D$ −86° (c 0.30, CH_3OH) [lit.[2c] $[\alpha]^{25}_D$ −87.2° (*c* = 1.03, CH_3OH), lit.[12g] $[\alpha]^{26}_D$ −82.6° (*c* = 1.03, CH_3OH)]; ^1H NMR (D_2O) δ 1.21 (m, 1H), 1.49 (m, 1H), 1.66 (broad, 1H), 1.86 (dd, 1H, *J* = 3.6, 9.0 Hz), 1.93 (dd, 1H, *J* = 2.7, 14.3 Hz), 2.02 (m, 1H), 2.49 (dd, 1H, *J* = 13.2, 9.8 Hz), 2.83 (dd, 1H, *J* = 13.2, 2.1 Hz), 2.87 (broad, 1H), 3.76 (dt, 1H, *J* = 3.9, 10.2 Hz), 4.19 (dd, 1H, *J* = 3.9, 5.7 Hz), 4.30 (m, 1H); ^{13}C NMR (D_2O) δ 23.6, 32.9, 52.0, 61.3, 66.8, 69.4, 70.0, 73.3; MS (ES) *m*/*z* 174 (M + H).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **1**, **2**, **10**, **12**−**14**, **18**, and **20**−**25** and detailed procedures for **20** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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