hydrous Na_2SO_4 and the solvent evaporated to obtain a white residue that was passed through a small silica gel column in hexane/EtOAc (1:1) to obtain the amine **14** (5.6 mg): ^1H NMR (360 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 2.23 (m), 2.03 (br dq, J = 6.5, 6.5 Hz), 1.77 (dq, J = 12.2, 3.6 Hz), 1.66 (m, 2 H), 1.56 (m), 1.40 (m), 1.26 (m), 1.24 (m), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.02 (m), 1.00 (d, 3 H, J = 6.5 Hz), 0.83 (d, 3 H, J = 6.8 Hz), 0.81 (m), 0.77 (m, 2 H); EIMS m/z 235 (M^+, 7).

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Supplementary Material Available: IR and NMR spectra of **6-8**, **12**, and **14** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Stereocontrolled Total Synthesis of the Unnatural Enantiomers of Castanospermine and 1-*epi*-Castanospermine

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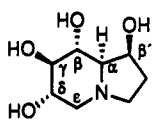
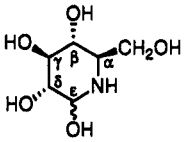
A concise practical synthesis (13 steps, ca. 10-12% overall yield) of the unnatural enantiomer of castanospermine ((-)-1) and its 1-epimer **2** from 2,3,4-tri-*O*-benzyl-D-xylose (**3**) is described. Key steps in the synthesis are two organometal aldehyde additions, vinylation of **3** to **4** and allylation of **6a** to **11**, both of which proceed with a considerably high degree of stereocontrol. The fused ring system is generated from the acyclic amino polyol derivative **16a** by two successive S_N2-type cyclizations. Notably, the annulation of the six-membered ring makes use of tetravalent phosphonium reagents (Appel or Mitsunobu type) which cyclize the amino alcohol **22a/b** directly to **23a/b** without need for N-deprotection and O-activation manipulations.

Introduction

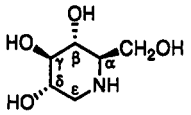
Castanospermine (+)-1, a tetrahydroxylated indolizidine alkaloid, can be isolated in appreciable amounts from the tropical trees Castanospermum australe[1] and Alexa Leiopetale,[2] respectively. The compound has attracted considerable interest due to its high anticancer,[3] antiviral,[4] and antiretroviral[5] activities. (+)-1 is a potent inhibitor for various α- and β-glucosidases[6] (including those involved in the processing of glycoproteins) similar to nojirimycin and 1-deoxynojirimycin,[7] whereas it is ineffective toward α- and β-galactosidases and α-mannosidases. Possibly this specifity is connected with the substitution pattern of the α-δ-region, which is quite similar to that in nojirimycin, 1-deoxynojirymicin, and D-glucose itself and may serve as a recognition pattern in the substrate-enzyme interaction. In this connection a change of these crucial configurations



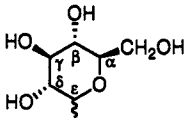
Castanospermine (+)-1



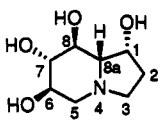
Nojirimycin



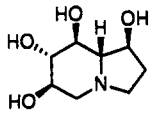
1-Deoxynojirimycin



D-Glucose



(-)-1



2

† Preparative work.

‡ Crystal structure analysis of compound **23b**.

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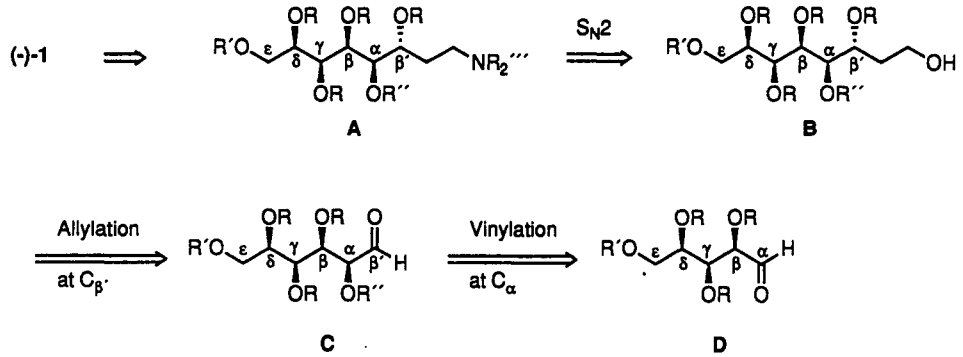
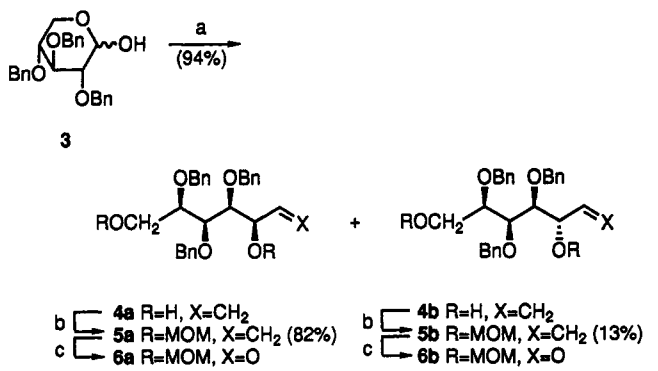
Scheme I. Retrosynthetic Considerations



to the opposite appeared of interest.[8] We thus decided to prepare the unnatural enantiomer of castanospermine ((−)-1) and, as the influence of the β′-position has never been studied so far, also of its 1-epimer **2**. Despite the great number of synthetic approaches toward (+)-1 and some of its epimers,[9] no total synthesis has been reported for (−)-1 and its 1-epimer **2**.

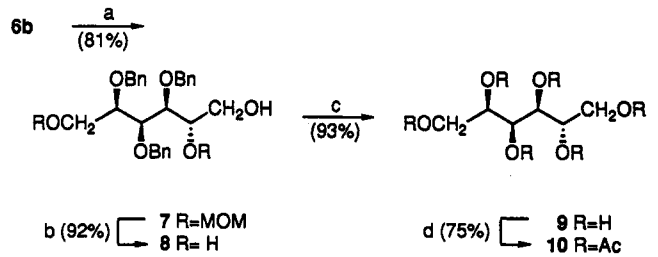
Our retrosynthetic plan is shown in Scheme I. Following Corey's concept of strategic bonds[10] we disconnected the molecule to form the amino polyol **A** as a precursor. In the synthetic direction this implies a 2-fold S_N2-type cyclization between the nitrogen and the α- and ε-positions. R′ and R″ must be so chosen that they provide good leaving-group qualities to the corresponding hydroxyl functions. It remained a matter of practicability whether these cyclizations could be performed in one operation or in succession. **A** may be generated from polyol **B** by a Mitsunobu-type substitution.[11] **B** should be derived from **D** by two successive organometal–aldehyde additions, namely a vinylation of **D** to **C**, and an allylation of **C** to **B**. **D** is a close derivative of D-xylose with pseudomeso character, so that by appropriate manipulation of the terminal functions one may easily get access to the opposite enantiomeric series. Considering the stereochemical course of the vinylation and the allylation steps, one notices that the vinylation must be performed under chelate Cram control,[12] whereas the allylation should follow the Felkin–Anh model,[13] as long as (−)-1 is the target. If, however, **2** is the desired product, the allylation requires chelate Cram stereochemistry. Quite obviously, our synthetic plan hinged on the possibility of exerting a reasonable degree of stereocontrol on both chain-extending addition steps.

Scheme II[a]



[a] Key: (a) CH_2=CHMgBr, THF; (b) MOMCl, CH_2Cl_2, EtN(*i*-Pr)$_2$; HPLC-separation; (c) O_3, CH_2Cl_2, PPh_3.

Scheme III[a]



[a] Key: (a) $LiAlH_4$, ether; (b) HCl, MeOH; (c) H_2, Pd/C; (d) Ac_2O, pyridine.

Results and Discussion

We started our synthesis from the known[14] D-xylose derivative **3**, which furnished the adducts **4a/b** on treatment with vinylmagnesium bromide (Scheme II). The diastereomeric ratio of **4a**:**4b** significantly varied with the solvent. In THF a 87:13 mixture was obtained, whereas in ether the selectivity increased to 96:4. The mixture was converted to the di-MOM derivatives **5a/b**, which were separated in large quantities by HPLC. Ozonolysis provided the aldehydes **6a** and **6b**, both configurationally stable under the conditions. For configurational assignment (Scheme III) **6b** was reduced to **7** and converted into L-glucitol **9** and its peracetate **10** by routine operations. **9** and **10** were identical in all respects with the authentic

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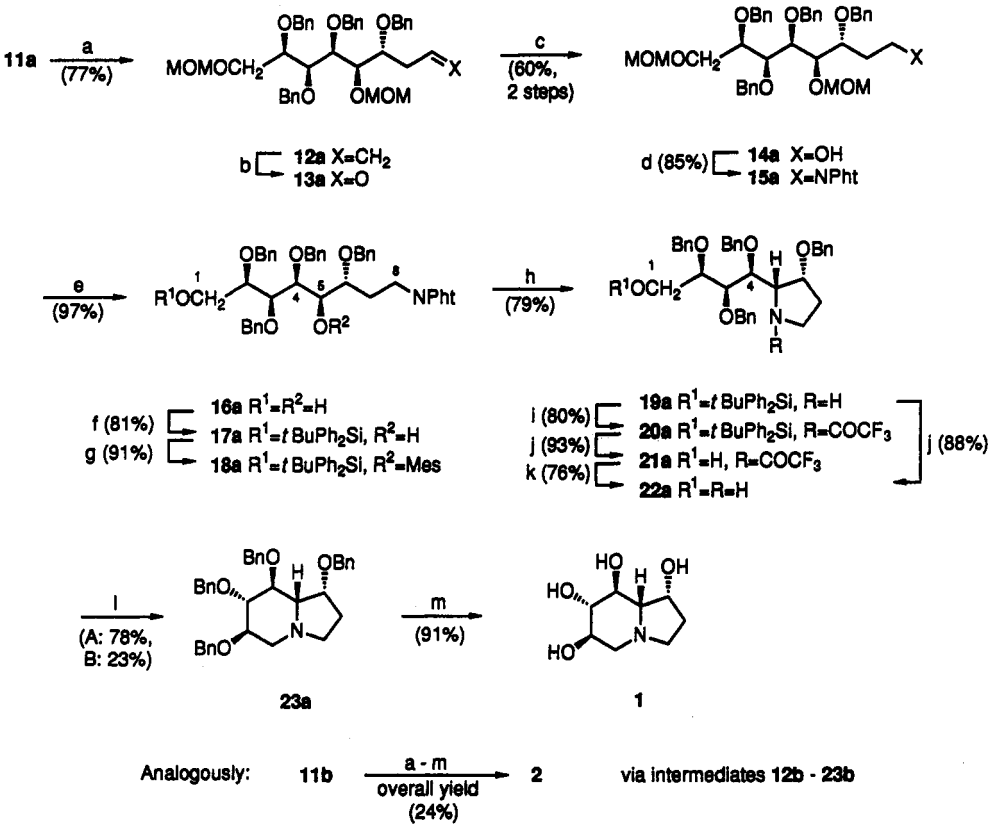
Scheme IV[a]

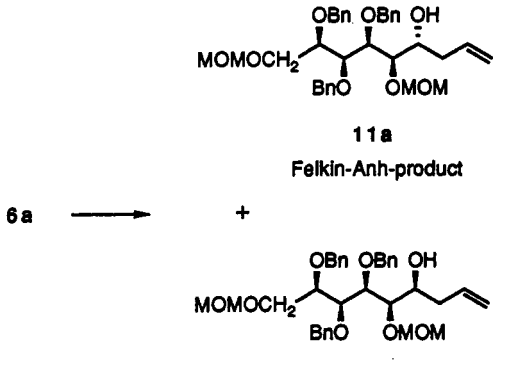


[a] Key: (a) NaH, DMF; BnBr; (b) O_3, CH_2Cl_2; Ph_3P; (c) LAH, ether, 0 °C → rt; (d) phthalimide, PPh_3, DEAD, THF; (e) HCl, MeOH, 50–60 °C; (f) MsCl, pyridine, 0 °C → rt; (g) *t*-$BuPh_2Cl$, DMF, imidazole; (h) $N_2H_4 \cdot H_2O$, EtOH; (i) $(CF_3CO)_2O$, DMAP, pyridine; (j) *n*-Bu_4NF, THF, rt; (k) $Ba(OH)_2$, 40 °C; H_2SO_4; (l) method A: PPh_3, CCl_4, NEt_3, acetonitrile; method B: PPh_3, DEAD, THF; (m) 10% Pd/C, H_2, MeOH, HCl.

substances.[15] This means that the vinyl addition to **3**, which in all likeliness proceeds via a small equilibrium concentration of the free aldehyde,[16] shows a strong re-preference, formally in keeping with the chelate Cram model.

The synthesis was continued with the allylation of aldehyde **6a**. As can be seen from Table I the stereochemical course may be directed over a wide range from the Felkin–Anh product **11a** to the chelate Cram adduct **11b** depending on the reagent employed. A reasonable control in favor of **11a** may be obtained from Hiyama–Nozaki addition[17] (run 1), whereas diallylzinc (run 2) exhibits only a modest selection in the same direction.[18] All other reagents follow the chelate Cram pathway,[19,20] allyltributyltin in the presence of Lewis acids affording the highest selectivity (run 6/7). These stereoselections may be the result of the 2-*O*-MOM-protective group which in general shows a high tendency toward chelate formation. Such chelates are in full agreement with the mechanism formulated for the allylstannane additions to α-alkoxy aldehydes,[20] so that the high preference for **11b** in runs 6/7 is not surprising. On the other hand, the pronounced tendency of the Hiyama–Nozaki reagent (run 1) to follow a nonchelated mechanism is noteworthy, though well precedented.[17] **11a** and **b** were separated by column

Table I. Allylation of 6



run	reagent	11a:11b	yield (%)
1	allyl bromide, $CrCl_3$, $LiAlH_4$[17]	85:15[a]	55
2	$(allyl)_2Zn$[18]	66:34[a]	64
3	allylMgBr	36:64[a]	62
4	allylMgBr + CuI (20%)	26:74[a]	71
5	allylTi(O-*i*-Pr)$_4$ MgCl[19]	24:76[b]	73
6	allylSnBu$_3$, $ZnBr_2$[20]	10:90[b]	68
7	allylSnBu$_3$, $MgBr_2$[20]	5:95[b]	76

[a] Diastereomer ratio determined by HPLC separation. [b] ^1H-NMR and analytical HPLC interpretation.

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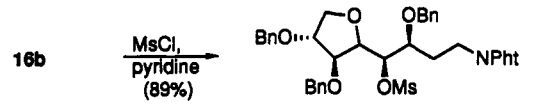
chromatography or HPLC and used for the preparation of (−)-1 (Scheme IV) and 2, respectively, along analogous routes (Scheme IV). Specifically, **11a** was converted into **14a** via benzylation followed by ozonolysis and reduction of the resulting aldehyde. Mitsunobu reaction with phthalimide as the nucleophile[11] provided **15a**. With respect to C–N ring closure a 2-fold tandem cyclization was first envisaged by removing MOM protective groups from **15a** and treating diol **16a** with mesyl chloride. On testing this cyclization in the **b**-series none of the expected dimesylate was isolated; instead tetrahydrofuran **24** had been

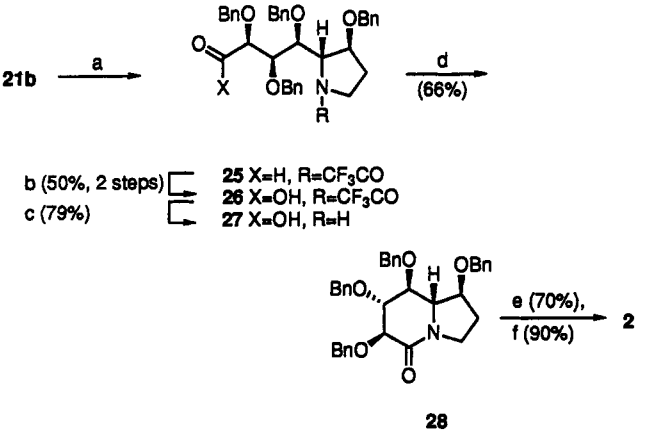


24

formed in 89% yield. Quite obviously, the 1-OMs leaving group had invoked a neighboring-group participation of the 4-OBn moiety, resulting in a S_N2-type cyclization and debenzylation.[21] After this failure, we resorted to successive cyclization. Thus, after converting **16a** into **17a** and **18a**, respectively, hydrazinolysis of **18a** removed the phthalimide protective group from the 8-amino function and induced cyclization to pyrrolidine **19a** in one operation.

To annulate the six-membered ring we first tried a conventional sequence including *N*-protection of **19a** to **20a** and O-desilylation of **20a** to **21a** followed by 1-O-mesylation and N-deprotection. As in the formation of **24**, the mesylation of the 1-OH function was immediately followed by tetrahydrofuran formation with the 4-OBn moiety! After some experimentation we realized that O-activation was possible without N-protection by means of a tetravalent phosphonium species, in the form of either the Appel[22] or the Mitsunobu[23] reagent. Thus, amino alcohol **22a** obtained from **21a** by N-deprotection was cyclized to **23a** in 78% and 23% yield, respectively. This success made the intermediates **20a**/**21a** superfluous, and the sequence could be shortened by desilylating amine **19a** directly to amino alcohol **22a**. The conversion of **23a** to **1** was uneventfully effected by debenzylation to give material whose spectral data and mp were consistent with those reported for (+)-1 previously.[1,9] The optical rotation showed the opposite sign $[\alpha]^{20}_D$ −81.1 (*c* 2.0, H_2O) (lit.[1] $[\alpha]^{25}_D$ +79.9 (*c* 0.93, H_2O), lit.[9b] $[\alpha]^{20}_D$ +81.9 (*c* 0.72, H_2O)). In a totally analogous fashion, the 1-epimer **2** was prepared from **11b**. The optical rotation of **2** was highly dependent on the pH of the solvent. So the following values were obtained: $[\alpha]^{20}_D$ −21 (*c* 0.5, H_2O, pH 7.1), $[\alpha]^{20}_D$ − 10 (*c* 0.4, H_2O, pH 6), and $[\alpha]^{20}_D$ +4 (*c* 0.3, H_2O, pH 5). This may explain discrepancies with the optical rotations of **2** (opposite enantiomeric series) reported in literature: $[\alpha]^{20}_D$ +6 (*c* 0.45, H_2O),[9a] $[\alpha]^{20}_D$ −39.1 (*c* 0.4, H_2O).[9b] Additional evidence for the stereochemistry at C-1 in **23a** and **23b** was provided by NOE experiments. In particular, irridiation of H-1 induced a significant enhancement of the H-8a signal in **23a**, and of the H-8 signal in **23b**, indicating that H-1 is cis to H-8a in **23a** and cis to H-8 in **23b**. Finally the structure of **23b** was established by single crystal X-ray analysis. The six-membered ring adopts a chair conformation with three equatorial benzyl ether groups. The pyrrolidine ring is annulated in trans stereochemistry and shows an envelope conformation. Further details concerning the NOE and X-ray experiments are given in the supplementary material.

Scheme V[a]



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[a] Key: (a) $(CO)_2Cl_2$, DMSO; CH_2Cl_2; NEt_3; (b) $KMnO_4$, *t*-BuOH, buffer; (c) $Ba(OH)_2$, 40 °C; H_2SO_4; (d) PCl_5, 0 °C, 2 h; (e) BH_3, THF; (f) 10% Pd/C, H_2, MeOH, HCl.

In the **b** series, an alternative way was tested for the annulation of the six-membered ring (Scheme V). **21b** was oxidized to the carboxylic acid **26** via aldehyde **25**. Deprotection of the pyrrolidine nitrogen furnished the amino acid **27**, which underwent cyclization on treatment with PCl_5 or TFA. The resulting bicyclic lactam **28** was reduced to amine **23b** with diborane[24] and debenzylated with hydrogen to give **2**, identical in all respects with the material described earlier in this paper.

Conclusion

In conclusion, we have described efficient syntheses of *ent*-castanospermine ((−)-1) and its 1-epimer **2** from an inexpensive monosaccharide (D-xylose). Our approach is rather concise (13 steps from **13** to (−)-1 and **2**, overall yields ca. 10–12%) and furnishes appreciable amounts (200 mg and more) of the desired compounds. Due to the pseudomeso structure of **D** (≙ **3**) the opposite enantiomeric series should also be accessible by appropriate manipulation of the terminal functional groups. Moreover, the overall sequence should analogously be applicable to tribenzylated pentoses other than **3** (arabinose, ribose, etc.),[14] thus providing a wide variety of castanospermine epimers.

Experimental Section

General Methods. NMR spectra were measured either on a Bruker WH 270 or AC 250 spectrometer in $CDCl_3$ with TMS as an internal standard unless noted otherwise. IR spectra were recorded on a Perkin-Elmer IR 580 B infrared spectrometer or a Nicolet FTIR-interferometer system 5 SXC using KBr pellets; given in cm^{-1}. Mass spectra were measured on a Varian MAT 112 S (CI) and a Varian MAT 711 (EI). The elemental analyses were determined on a Perkin-Elmer 2400 CHN-elemental analyser. Optical rotations were obtained in $CHCl_3$, unless stated otherwise, with a Perkin-Elmer 241 polarimeter. Melting points are uncorrected HPLC separations were performed on Nucleosil 50 with particle sizes 5 μm (analytical) and 7 μm (preparative), with RI and UV detection. Preparative column chromatography was performed on silica gel Merck 60 (0.063–0.04 mm). All reactions were carried out under an argon atmosphere in purified solvents

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with magnetic stirring and were controlled with TLC plates (Merck 5554).

Starting Materials. D-Xylose was purchased from Janssen. 2,3,4-Tri-*O*-benzyl-D-xylose (**3**) was prepared from D-xylose according to a procedure by Tejima et al.[14] MOMCl was prepared as described by Marvel and Porter.[25]

(2*R*,3*S*,4*S*,5*R*/*S*)-2,3,4-Tri-*O*-benzyl-6-heptene-1,2,3,4,5-pentol (4a/4b). To a stirred solution of **3** (78 g, 186 mmol) in THF (1.2 L) vinylmagnesium bromide (previously prepared from magnesium (14.6 g, 0.6 mol) and vinyl bromide (45.2 mL, 0.61 mol) in THF (350 mL) was added dropwise over a period of 45 min at 0 °C. After the solution was stirred at rt for 2 d a saturated solution of NH_4Cl and 2 M HCl was added. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. After chromatography of the residue on silica gel (hexane/ethyl acetate (2/1)) **4a/4b** (78.1 g, 94%, ratio **4a/4b** (7.2/1)) was obtained as a colorless oil: $[\alpha]^{20}_D$ +0.9 (*c* 1.9, $CHCl_3$); ^{1}H-NMR δ 7.35 (mc, 15 H), 5.88 (ddd, 1 H, J = 5, 10, 17.5 Hz), 5.26 (dt, 1 H, J = 4, 17 Hz), 5.16 (dt, 1 H, J = 4, 10.5 Hz), 4.78–4.54 (m, 6 H), 4.22 (m, 1 H), 3.92–3.64 (m, 5 H), 2.49 (s, 2 H); ^{13}C-NMR δ 138.50, 137.98, 137.87, 128.41, 128.36, 128.30, 128.21, 128.04, 127.85, 127.79, 127.75, 115.44, 81.39, 79.37, 78.58, 74.69, 72.36, 71.88, 61.49; IR 3439, 1091, 1070, 1050. Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.98; H, 7.19. Found: C, 75.06; H, 7.15.

(2*R*,3*S*,4*R*,5*R*/*S*)-2,3,4-Tri-*O*-benzyl-1,5-bis-*O*-(methoxymethyl)-6-heptene-1,2,3,4,5-pentol (5a/5b). To a solution of **4a/4b** (66.1 g, 147.5 mmol) in CH_2Cl_2 (180 mL) and *N*-ethyldiisopropylamine (78 mL, 458 mmol) was added MOMCl (33.6 mL, 442.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C and stirred for 24 h. A saturated aqueous solution of $NaHCO_3$ was added, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Chromatography (hexane/ethyl acetate (2/1)) and subsequent preparative HPLC (15% ethyl acetate in hexane) gave **5a** (64.5 g, 82%) and **5b** (8.6 g, 11%) as oils.

5a: $[\alpha]^{20}_D$ −55.5 (*c* 1.9, $CHCl_3$); ^{1}H-NMR δ 7.3 (mc, 15 H), 5.74 (ddd, 1 H, J = 7.5, 11, 18.5 Hz), 5.2 (dd, 1 H, J = 2.5, 11 Hz), 5.12 (dd, 1 H, J = 2.5, 18.5 Hz), 4.84–4.44 (m, 10 H), 4.12 (dd, 1 H, J = 5, 7 Hz), 3.93 (dd, 1 H, J = 4, 7 Hz), 3.88 (dd, 1 H, J = 5, 9 Hz), 3.8 (dd, 1 H, J = 4, 7 Hz), 3.68 (m, 2 H), 3.34 (s, 3 H), 3.32 (s, 3 H); ^{13}C-NMR δ 138.55, 138.33, 135.16, 128.16, 128.05, 127.98, 127.46, 127.35, 127.31, 118.30, 96.52, 94.02, 81.05, 78.55, 77.53, 77.27, 74.70, 74.60, 72.46, 67.49, 55.70, 55.08; IR 1150, 1110, 1030, 915. Anal. Calcd for $C_{32}H_{40}O_7$: C, 71.62; H, 7.51. Found: C, 71.64; H, 7.53.

5b: $[\alpha]^{20}_D$ +23.3 (*c* 2.9, $CHCl_3$); ^{1}H-NMR δ 7.33 (mc, 15 H), 5.98 (ddd, 1 H, J = 7.5, 10, 17.5 Hz), 5.32 (dd, 1 H, J = 2.5, 10 Hz), 5.12 (dd, 1 H, J = 2.5, 17.5 Hz), 4.88–4.48 (m, 10 H), 4.29 (dd, 1 H, J = 4, 7.5 Hz), 3.94 (dd, 1 H, J = 5, 7 Hz), 3.72 (m, 4 H), 3.3 (d, 6 H); ^{13}C-NMR δ 138.74, 138.57, 138.29, 134.88, 128.08, 128.01, 127.98, 127.84, 127.79, 127.38, 127.28, 127.17, 118.94, 96.52, 93.76, 81.22, 78.78, 78.08, 77.91, 74.62, 74.03, 72.52, 67.40, 55.36, 55.07; IR 1150, 1110, 1030, 920. Anal. Calcd for $C_{32}H_{40}O_7$: C, 71.62; H, 7.51. Found: C, 71.64; H, 7.46.

(2*S*,3*R*,4*S*,5*R*)-3,4,5-Tris(benzyloxy)-2,6-bis(methoxymethoxy)hexanal (6a). **5a** (64.4 g, 120 mmol) in CH_2Cl_2 (500 mL) was treated with ozone at −78 °C until the solution was faintly blue. PPh_3 (35.2 g, 134 mmol) was added and stirred for 1 h at −78 °C and 2 h at rt. The mixture was concentrated at reduced pressure, diluted with ether, and left for crystallization. The filtrate was concentrated and subjected to the following reaction without further purification.

(2*S*,3*S*,4*R*,5*S*)-2,3,4-Tri-*O*-benzyl-1,5-bis-*O*-(methoxymethyl)hexane-1,2,3,4,5,6-hexol (7). To a suspension of $LiAlH_4$ (320 mg, 8.65 mmol) in ether (30 mL) was added at 0 °C a solution of aldehyde (**6b**), which was previously prepared by ozonisating **5b** (3.47 g, 6.47 mmol) in CH_2Cl_2 as described for **5a**, stirred at rt for 7 h, quenched by aqueous NH_4Cl, extracted with ether, washed with water and brine, dried ($MgSO_4$), and evaporated. Chromatography (hexane/ethyl acetate (1/1)) gave **7** (2.84 g, 81%) as a colorless oil: $[\alpha]^{20}_D$ −23.3 (*c* 2.6, $CHCl_3$); ^{1}H-NMR δ 7.34 (m, 15 H), 4.8–4.46 (m, 10 H), 3.87 (dd, 2 H, J = 5.5, 11 Hz), 3.84–3.74 (m, 4 H), 3.72 (d, 1 H, J = 4 Hz), 3.64 (dd, 1 H, J = 5.5, 11 Hz), 3.38 (s, 3 H), 3.32 (s, 3 H), 3.04 (m, 1 H); ^{13}C-NMR δ 138.26, 129.60, 128.16, 128.00, 127.80, 127.54, 127.49, 127.43, 96.60, 80.81, 79.83, 78.82, 78.45, 74.44, 74.07, 72.77, 67.29, 62.40, 55.48, 55.13; IR 3470, 1212, 1150, 1110, 1040. Anal. Calcd for $C_{31}H_{40}O_8$: C, 68.87; H, 7.46. Found: C, 68.63; H, 7.37.

(2*R*,3*S*,4*S*,5*S*)-2,3,4-Tri-*O*-benzylhexane-1,2,3,4,5,6-hexol (8). **7** (2.5 g, 4.6 mmol) was treated in methanol (15 mL) with HCl (1 mL, 25%) at 60 °C for 2 h. Saturated aqueous $NaHCO_3$ was added at rt, and the mixture was concentrated in vacuo and diluted with a mixture of ether/water. The ether layer was washed with water and brine, dried ($MgSO_4$), and evaporated. Column chromatography (ethyl acetate/methanol (6/1)) gave **8** (1.92 g, 92%) as a colorless oil: $[\alpha]^{20}_D$ −13.5 (*c* 1.75, $CHCl_3$); ^{1}H-NMR δ 7.26 (m, 15 H), 4.68 (d, 2 H), 4.66 (d, 2 H), 4.58 (d, 2 H), 3.88–3.6 (m, 8 H), 3.46 (m, 1 H, J = 5 Hz), 2.41 (t, 1 H, J = 6 Hz), 2.3 (t, 1 H, J = 6.5 Hz); ^{13}C-NMR δ 137.88, 137.64, 133.07, 129.60, 128.44, 128.28, 128.07, 127.98, 127.95, 127.85, 127.70, 79.34, 79.21, 77.23, 74.28, 73.55, 73.08, 71.74, 63.52, 61.63; IR 3420. Anal. Calcd for $C_{27}H_{32}O_6$: C, 71.66; H, 7.13. Found: C, 71.39; H, 7.03.

L-Glucitol (9). A solution of **8** (1.8 g, 3.98 mmol) in methanol (20 mL) including 10% Pd/C (500 mg) and a catalytic amount of acetic acid was hydrogenated at 2.7 bar for 17 h. Filtration over Celite and evaporation gave a light yellow oil (680 mg, 93%), which crystallized on standing: mp 88 °C (lit.[15] mp 89–91 °C); $[\alpha]^{20}_D$ +3.2 (*c* 0.9, H_2O) (lit.[15] $[\alpha]^{20}_D$ +1.7). Anal. Calcd for $C_6H_{14}O_6$: C, 39.56; H, 7.75. Found: C, 39.73; H, 7.80.

L-Glucitol Hexa-*O*-acetate. (2*R*,3*S*,4*S*,5*S*)-1,2,3,4,5,6-Hexa-*O*-acetylhexane-1,2,3,4,5,6-hexol (10). **9** (680 mg, 3.7 mmol) in pyridine (5 mL) was treated with DMAP (200 mg, 1.63 mmol) and acetic anhydride (3.8 mL, 40 mmol) at 0 °C, stirred for 1.5 h at rt, quenched with water, extracted with ether, washed with water and brine, dried ($MgSO_4$), and chromatographed (ethyl acetate/methanol (6/1)) to give crystalline **10** (1.21 g, 75%): mp 97.5 °C (lit.[15] mp 98–99 °C); $[\alpha]^{20}_D$ −9.6 (*c* 3.7, $CHCl_3$) (lit.[15] $[\alpha]^{20}_D$ −10 ($CHCl_3$)); ^{1}H-NMR δ 5.43 (m, 2 H), 5.26 (m, 1 H), 5.05 (m, 1 H), 4.36 (dd, 1 H, J = 4.5, 11 Hz), 4.26 (dd, 1 H, J = 4, 12.5 Hz), 4.12 (dd, 1 H, J = 5, 12.5 Hz), 4.04 (dd, 1 H, J = 5.5, 11.5 Hz), 2.16 (s, 3 H), 2.07 (m, 15 H). Anal. Calcd for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03. Found: C, 49.59; H, 6.01.

(2*R*,3*S*,4*R*,5*R*,6*R*/*S*)-2,3,4-Tri-*O*-benzyl-1,5-bis-*O*-(methoxymethyl)-8-nonene-1,2,3,4,5,6-hexol (11a/11b). A. A solution of allylmagnesium chloride (prepared from magnesium (7 g, 290 mmol) and allyl chloride (28 mL, 343 mmol) in THF (260 mL)) was added to a solution of aldehyde **6a** (ca. 120 mmol) in THF (100 mL) at −20 °C. The reaction mixture was allowed to warm to rt overnight. The reaction was quenched by a saturated solution of NH_4Cl and 2 M HCl, extracted with ether, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate (2/1)), and the two diastereomers were separated by preparative HPLC (20% ethyl acetate in hexane). **11a** (24.5 g, 35%) and **11b** (35.8 g, 51.4%) were isolated as colorless oils. **11a**: $[\alpha]^{20}_D$ +1.62 (*c* 3.5, $CHCl_3$); ^{1}H-NMR δ 7.3 (mc, 15 H), 5.84 (m, 1 H), 5.08 (dd, 1 H), 5.06 (dd, 1 H), 4.78–4.48 (m, 10 H), 3.94 (m, 1 H), 3.86 (m, 2 H), 3.72 (m, 2 H), 3.6 (m, 2 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 3.04 (s, 1 H), 2.3 (m, 1 H), 2.12 (m, 1 H); ^{13}C-NMR δ 138.28, 137.92, 137.80, 135.28, 128.40, 128.26, 128.04, 127.71, 127.65, 127.60, 116.86, 97.62, 96.64, 79.87, 77.90, 77.79, 77.69, 74.25, 73.76, 72.71, 70.98, 67.82, 56.06, 55.18, 37.61; IR 3394, 1274, 1098, 1070, 1027. Anal. Calcd for $C_{34}H_{44}O_8$: C, 70.32; H, 7.64. Found: C, 70.09; H, 7.62.

11b: $[\alpha]^{20}_D$ +12.8 (*c* 2.1, $CHCl_3$); ^{1}H-NMR δ 7.28 (mc, 15 H), 5.7 (m, 1 H), 5.03 (dd, 1 H), 5.02 (dd, 1 H), 4.78–4.48 (m, 10 H), 3.92 (m, 1 H), 3.84 (m, 2 H), 3.72–3.56 (m, 3 H), 3.52 (m, 1 H), 3.4 (s, 3 H), 3.3 (s, 3 H), 2.86 (s, 1 H), 2.06 (m, 2 H); ^{13}C-NMR δ 138.26, 138.14, 138.06, 135.01, 128.26, 128.14, 127.97, 127.66, 127.60, 117.15, 98.41, 96.66, 81.03, 78.28, 78.03, 77.82, 74.25, 72.69, 70.34, 67.46, 56.15, 55.20, 38.16; IR 3466, 1151, 1098, 1037, 1028. Anal. Calcd for $C_{34}H_{44}O_8$: C, 70.32; H, 7.64. Found: C, 70.11; H, 7.64.

B. To a solution of aldehyde **6a** (ca. 74.5 mmol), prepared from alkene **5a** (39.9 g, 74.5 mmol) by ozonation, dissolved in THF (400 mL) was added diallylzinc (280 mL, 1 M in THF) at −12 °C. The mixture was allowed to reach rt overnight, quenched by aqueous

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NH_4Cl and 2 M HCl, extracted with ether, washed with water and brine, dried ($MgSO_4$), and chromatographed (hexane/ethyl acetate (2/1)). Preparative HPLC gave **11a** (19.76 g, 45.6%) and **11b** (11.02 g, 25.5%).

C. To a suspension of $CrCl_3$ (820 mg, 5.2 mmol) in THF (30 mL) was added $LiAlH_4$ (102 mg, 2.6 mmol) in small portions at 0 °C and stirred for 1.5 h at rt. The aldehyde **6a** (1.95 mmol) in THF (15 mL) and the allyl bromide (0.3 mL, 3.55 mmol) in THF (2 mL) were added at −6.5 °C and stirred for 2.5 d at that temperature. Anhydrous Na_2SO_4 and aqueous NaOH were added (pH 9–10), stirred for 20 min at rt, filtered over a pad of silica gel/Na_2SO_4 (3/1), and washed with ether. The filtrate was concentrated and purified by column chromatography (hexane-/ethyl acetate (2/1)) to give **11a** (520 mg, 46%) and **11b** (110 mg, 9%).

D. To a solution of titantetraisopropylate (6.8 g, 23.9 mmol) in THF (120 mL) was added allylmagnesium chloride (0.95 M in THF, 20 mL, 19 mmol) at −78 °C and stirred for 30 min. Aldehyde **6a** (1.45 mmol) in THF (20 mL) was added dropwise, and the reaction mixture was allowed to reach rt overnight. A saturated solution of NH_4Cl was added, extracted with ether, washed with water and brine, dried ($MgSO_4$), and chromatographed (hexane/ethyl acetate (2/1)) to give **11a/11b** (615 mg, 73%) as a mixture of diastereomers (**11a:11b** (1:3.2)).

E. To a solution of aldehyde **6a** (0.73 mmol) in CH_2Cl_2 (2.5 mL) were added $MgBr_2$ (266 mg, 1.4 mmol) and allyltributyltin (430 μL, 1.22 mmol) at intervals of 10 min, and the solution was stirred overnight at that temperature and quenched with water. Work up as in D gave **11a/11b** (320 mg, 76%) as a mixture of diastereomers (**11a:11b** 5:95).

In the following description the detailed procedure is given only for one diastereomer of the **a** or **b** series, generally the one giving the better yield.

(2*R*,3*S*,4*R*,5*R*,6*S*)-2,3,4,6-Tetra-*O*-benzyl-1,5-bis-*O*-(methoxymethyl)-8-nonene-1,2,3,4,5,6-hexol (12b). **11b** (35.8 g, 61.7 mmol) was deprotonated with sodium hydride (60% in mineral oil, 4.4 g, 110 mmol) in DMF (260 mL). The dark brown solution of the alkoxide was treated dropwise with benzyl bromide (11 mL, 93 mmol) in DMF (20 mL) at 0 °C. After the solution was stirred at rt for 24 h, water was added and concentrated at reduced pressure and the residue diluted with a mixture of water/ether. The layers were separated, extracted with ether, washed with water and brine, and dried ($MgSO_4$). Chromatography (hexane/ethyl acetate (2/1)) provided **12b** (41.3 g, 98%) as a colorless oil: $[\alpha]^{20}_D$ +2.0 (*c* 2.6, $CHCl_3$); ^{1}H-NMR δ 7.32 (mc, 20 H), 5.66 (m, 1 H), 4.99 (dd, 1 H, *J* = 2.5, 12.5 Hz), 4.93 (dd, 1 H, *J* = 2.5, 5 Hz), 4.82–4.45 (m, 12 H), 3.96 (dd, 1 H, *J* = 5, 10 Hz), 3.91 (dd, 1 H, *J* = 3.5, 10 Hz), 3.86 (dd, 1 H, *J* = 6, 10 Hz), 3.74 (dd, 1 H, *J* = 5, 11 Hz), 3.67 (d, 1 H, *J* = 4.5 Hz), 3.57 (m, 2 H), 3.38 (s, 3 H), 3.28 (s, 3 H), 2.3 (m, 1 H), 2.15 (m, 1 H); ^{13}C-NMR δ 138.53 (C), 138.40 (C), 138.35 (C), 138.32 (C), 134.88 (CH), 128.44 (CH), 128.24 (CH), 127.90 (CH), 127.79 (CH), 127.58 (CH), 127.50 (CH), 117.14 (CH_2), 98.65 (CH_2), 96.57 (CH_2), 78.81 (CH), 78.05 (CH), 77.47 (CH), 77.00 (CH), 76.53 (CH), 74.43 (CH_2), 74.32 (CH_2), 72.72 (CH_2), 67.82 (CH_2), 56.16 (CH_3), 55.17 (CH_3), 35.30 (CH_2); IR 1150, 1100, 1040, 920. Anal. Calcd for $C_{41}H_{50}O_8$: C, 73.41; H, 7.51. Found: C, 73.16; H, 7.50.

(2*R*,3*S*,4*R*,5*R*,6*R*)-2,3,4,6-Tetra-*O*-benzyl-1,5-bis-*O*-(methoxymethyl)-8-nonene-1,2,3,4,5,6-hexol (12a). **12a** (67.5 g) was prepared from **11a** (75.33 g, 130 mmol) as described for the preparation of **12b** from **11b**: yield 77%; $[\alpha]^{20}_D$ +4.9 (*c* 2.3, $CHCl_3$); ^{1}H-NMR δ 7.06 (mc, 20 H), 6.85 (ddt, 1 H, *J* = 7, 10, 17 Hz), 5.07 (dd, 1 H, *J* = 17 Hz), 5.02 (dd, 1 H, *J* = 10 Hz), 4.82–4.67 (m, 6 H), 3 AB-systems (δ_A = 4.7, 4.52, 4.38; δ_B = 4.58, 4.46, 4.32; 6 H, *J* = 7, 11 Hz), 3.96 (m, 2 H), 3.9 (t, 1 H, *J* = 5 Hz), 3.82 (t, 1 H, *J* = 5 Hz), 3.64 (m, 3 H), 3.37 (s, 3 H), 3.28 (s, 3 H), 2.44 (m, 2 H); ^{13}C-NMR δ 138.67, 138.55, 138.45, 135.44, 128.23, 128.14, 128.04, 127.96, 127.54, 127.48, 127.40, 127.29, 116.69, 97.73, 96.68, 79.53, 79.33, 78.36, 78.10, 77.80, 74.63, 74.50, 72.83, 71.27, 67.75, 56.02, 55.23, 34.45; IR 1150, 1110, 1070, 1030, 920. Anal. Calcd for $C_{41}H_{50}O_8$: C, 73.41; H, 7.51. Found: C, 73.03; H, 7.54.

(2*R*,3*S*,4*R*,5*R*,6*S*)-2,3,4,6-Tetra-*O*-benzyl-1,5-bis-*O*-(methoxymethyl)octane-1,2,3,4,5,6,8-heptol (14b). To a suspension of $LiAlH_4$ (3.6 g, 93 mmol) in ether (120 mL) was added aldehyde **13b** (prepared from **12b** (30.28 g, 45.2 mmol) in CH_2Cl_2 (400 mL) and PPh_3 (14.0 g, 53.4 mmol) by ozonation) in ether (350 mL) at 0 °C and stirred for 24 h. Ethyl acetate, water, and 2 M HCl were added. The mixture was extracted with ether, washed with a solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and chromatographed (hexane/ethyl acetate (2/1)) to furnish **14b** (25.98 g, 86%, 2 steps) as a colorless oil: $[\alpha]^{20}_D$ −20.7 (*c* 2.1, $CHCl_3$); ^{1}H-NMR δ 7.29 (mc, 20 H), 4.88–4.46 (m, 12 H), 3.96 (m, 3 H), 3.72 (m, 4 H), 3.44 (m, 2 H), 3.38 (s, 3 H), 3.32 (s, 3 H), 1.68 (m, 1 H), 1.48 (m, 2 H); ^{13}C-NMR δ 138.31, 138.14, 138.01, 128.49, 128.26, 128.16, 127.97, 127.85, 127.73, 127.58, 127.54, 127.43, 98.54, 96.45, 79.16, 78.76, 77.89, 77.67, 77.00, 74.34, 74.18, 73.05, 72.52, 67.68, 59.75, 56.06, 55.09, 33.19; IR 3500, 1150, 1110, 1050. Anal. Calcd for $C_{40}H_{50}O_9$: C, 71.19; H, 7.47. Found: C, 71.10; H, 7.28.

(2*R*,3*S*,4*R*,5*R*,6*R*)-2,3,4,6-Tetra-*O*-benzyl-1,5-bis-*O*-(methoxymethyl)octane-1,2,3,4,5,6,8-heptol (14a). **14a** (18.7 g) was prepared from **12a** (31 g, 46.3 mmol) as described for **14b** from **12b** in 60% yield (2 steps): $[\alpha]^{20}_D$ +26.7 (*c* 2.1, $CHCl_3$); ^{1}H-NMR δ 7.29 (mc, 20 H), 4.84–4.4 (m, 11 H), 4.18 (m, 2 H), 3.93 (m, 1 H), 3.82–3.55 (m, 7 H), 3.36 (s, 3 H), 3.31 (s, 3 H), 2.26 (m, 1 H), 1.92 (m, 1 H), 1.76 (m, 1 H); ^{13}C-NMR δ 138.32, 128.23, 128.05, 128.00, 127.85, 127.62, 127.54, 127.47, 97.53, 96.68, 78.78, 78.69, 78.58, 77.99, 76.96, 74.38, 74.26, 72.72, 71.10, 67.46, 60.17, 55.94, 55.21, 32.32; IR 3500, 1150, 1100, 1070. Anal. Calcd for $C_{40}H_{50}O_9$: C, 71.19; H, 7.47. Found: C, 70.94; H, 7.36.

(2*R*,3*S*,4*R*,5*R*,6*S*)-2,3,4,6-Tetra-*O*-benzyl-1,2,3,4,5,6-hexahydroxy-1,5-bis-*O*-(methoxymethyl)-8-*N*-phthaloyloctan-8-amine (15b). To a stirred solution of **14b** (25.8 g, 38.2 mmol), phthalimide (7.7 g, 52.5 mmol), and PPh_3 (13.7 g, 52.4 mmol) in THF (250 mL) was added DEAD (10.8 mL, 69.4 mmol) in THF (50 mL) at 0 °C. The mixture was allowed to warm to rt and stirred for 24 h. After evaporation the residue was diluted with ether, extracted with 2 M NaOH, washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by chromatography (hexane/ethyl acetate (3/1)) gave **15b** (28.9 g, 93%) as a colorless oil: $[\alpha]^{20}_D$ −17.7 (*c* 2.0, $CHCl_3$); ^{1}H-NMR δ 7.72 (m, 2 H), 7.6 (m, 2 H), 7.22 (mc, 20 H), 4.86–4.44 (m, 12 H), 3.96 (m, 3 H), 3.8 (dd, 1 H), 3.72 (m, 1 H), 3.64 (m, 2 H), 3.56 (m, 2 H), 3.38 (s, 3 H), 3.28 (s, 3 H), 1.88 (m, 1 H), 1.62 (m, 1 H); ^{13}C-NMR δ 167.95, 138.38, 138.16, 133.57, 131.98, 128.10, 128.07, 127.90, 127.70, 127.60, 127.38, 127.35, 127.27, 122.82, 98.43, 96.47, 78.77, 78.49, 77.86, 77.62, 74.49, 74.30, 72.54, 67.74, 56.06, 55.07, 34.85, 29.55; IR 1710, 1155, 1105, 1035. Anal. Calcd for $C_{48}H_{53}NO_{10}$: C, 71.71; H, 6.64; N, 1.74. Found: C, 71.53; H, 6.43; N, 1.57.

(2*R*,3*S*,4*R*,5*R*,6*R*)-2,3,4,6-Tetra-*O*-benzyl-1,2,3,4,5,6-hexahydroxy-1,5-bis-*O*-(methoxymethyl)-8-*N*-phthaloyloctan-8-amine (15a). **15a** (35.56 g) was prepared from **14a** (35.12 g, 52.04 mmol) in the same manner as described for the preparation of **15b** from **14b** in 85% yield: $[\alpha]^{20}_D$ +20.9 (*c* 1.97, $CHCl_3$); ^{1}H-NMR δ 7.74 (m, 2 H), 7.64 (m, 2 H), 7.26 (mc, 20 H), 5 AB-systems (δ_{A1} = 4.81, δ_{B1} = 4.77, 2 H, J_{AB} = 6.5 Hz; δ_{A2} = 4.70, δ_{B2} = 4.64, 2 H, J_{AB} = 11 Hz; δ_{A3} = 4.66, δ_{B3} = 4.59, 2 H, J_{AB} = 11 Hz; δ_{A4} = 4.5, δ_{B4} = 4.46, 2 H, J_{AB} = 5.5 Hz; δ_{A5} = 4.41, δ_{B5} = 4.35, 2 H, J_{AB} = 11 Hz), 4.64 (s, 2 H), 4.08 (dd, 1 H, *J* = 3, 6 Hz), 3.91 (dd, 1 H, *J* = 5.5, 9.5 Hz), 3.86–3.53 (m, 7 H), 3.34 (s, 3 H), 3.28 (s, 3 H), 2.02 (m, 2 H); ^{13}C-NMR δ 168.24, 138.46, 138.33, 138.30, 133.66, 132.19, 128.22, 128.12, 128.07, 127.95, 127.85, 127.58, 127.45, 127.37, 127.21, 122.95, 97.60, 96.62, 78.89, 78.65, 78.19, 76.86, 74.42, 74.37, 72.74, 71.03, 67.62, 56.03, 55.18, 35.04, 28.91; IR 1710, 1150, 1110, 1025; HRMS calcd for $[C_{40}H_{42}NO_9]^+$ 680.285 96, found 680.286 77.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2,3,4,6-Tetra-*O*-benzyl-1,2,3,4,5,6-hexahydroxy-8-*N*-phthaloyloctan-8-amine (16a). **15a** (41.0 g, 51.0 mmol) was dissolved in methanol (100 mL) and 25% HCl (4 mL), and the solution was stirred at 60 °C for 2 h. Saturated aqueous $NaHCO_3$ was added at rt. The mixture was concentrated in vacuo, diluted with a mixture of ether/water, and extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. Chromatography (hexane/ethyl acetate (2/1)) furnished **16a** (35.4 g, 97%) as a colorless oil: $[\alpha]^{20}_D$ −18.2 (*c* 2.1, $CHCl_3$); ^{1}H-NMR δ 7.76 (m, 2 H), 7.64 (m, 2 H), 7.24 (mc, 20 H), 4 AB-systems (δ_A = 4.73, 4.71, 4.67, 4.52; δ_B = 4.62, 4.6, 4.38, 4.16; 8 H, *J* = 12 Hz), 4.06 (dd, 1 H), 3.98–3.64 (m, 7 H), 3.56 (m, 1 H), 2.81 (m, 1 H), 2.3 (m, 1 H), 2.21 (m, 1 H), 2.12 (m, 1 H); ^{13}C-NMR δ 168.26, 138.16, 133.63, 132.11, 128.24, 128.15, 127.86, 127.67, 127.53, 127.39, 122.95, 79.60, 79.06, 77.12, 76.74, 74.48, 74.17, 72.71, 71.06, 70.70, 61.69, 34.06, 27.74; IR 3460, 1705,

1086, 1070, 1026. Anal. Calcd for $C_{44}H_{45}NO_8$: C, 73.83; H, 6.34; N, 1.96. Found: C, 73.85; H, 6.41; N, 1.94.

(2*R*,3*S*,4*S*,5*R*,6*S*)-2,3,4,6-Tetra-*O*-benzyl-1,2,3,4,5,6-hexahydroxy-8-*N*-phthaloyloctan-8-amine (16b). **16b** (24.02 g, 92%) was prepared from **15b** (29.3 g, 36.4 mmol) analogously to the preparation of **16a** from **15a**: $[\alpha]^{20}_D$ −21.7 (*c* 1.9, $CHCl_3$); ^{1}H-NMR δ 7.8 (m, 2 H), 7.68 (m, 2 H), 7.27 (mc, 20 H), 3 AB-systems (δ_A = 4.83, 4.76, 4.63; δ_B = 4.69, 4.55, 4.54; 6 H, *J* = 11 Hz), 4.66 (s, 2 H), 4.04 (t, 1 H, *J* = 5.5 Hz), 3.97 (d, 1 H), 3.91 (dd, 1 H), 3.86 (m, 1 H), 3.77 (m, 2 H), 3.71 (m, 2 H), 3.58 (m, 1 H), 2.81 (m, 1 H), 2.33 (m, 1 H), 1.92 (m, 1 H), 1.64 (m, 1 H); ^{13}C-NMR δ 168.08 (C), 138.02 (C), 137.92 (C), 137.88 (C), 137.75 (C), 133.70 (CH), 131.90 (C), 128.21 (CH), 128.11 (CH), 128.06 (CH), 127.83 (CH), 127.65 (CH), 127.59 (CH), 127.52 (CH), 122.94 (CH), 78.77 (CH), 77.64 (CH), 77.47 (CH), 76.99 (CH), 74.35 (CH_2), 73.93 (CH_2), 72.38 (CH_2), 72.07 (CH_2), 71.10 (CH), 61.40 (CH_2), 34.24 (CH_2), 28.48 (CH_2); IR 1710, 1088, 1070, 1027. Anal. Calcd for $C_{44}H_{45}NO_8$: C, 73.83; H, 6.34; N, 1.96. Found: C, 73.64; H, 6.41; N, 1.85.

(2*R*,3*S*,4*S*,5*R*,6*S*)-2,3,4,6-Tetra-*O*-benzyl-1-*O*-(*tert*-butyldiphenylsilyl)-1,2,3,4,5,6-hexahydroxy-8-*N*-phthaloyloctan-8-amine (17b). To a stirred solution of **16b** (21.5 g, 30.0 mmol) in DMF (35 mL) and imidazole (6.2 g, 91 mmol) was added $BuSiPh_2Cl$ (8.4 mL, 32.7 mmol) in DMF (10 mL) at 0 °C and stirred for 18 h at rt. The mixture was quenched with aqueous $NaHCO_3$, concentrated, diluted with ether/water, and extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. Chromatography (hexane/ethyl acetate (3/1)) gave **17b** (26.2 g, 92%) as an oil: $[\alpha]^{20}_D$ −33.7 (*c* 2.3, $CHCl_3$); ^{1}H-NMR δ 7.78 (m, 2 H), 7.66 (m, 6 H), 7.48–7.08 (m, 26 H), 4.87–4.4 (m, 8 H), 4.10 (dd, 1 H), 3.91 (m, 3 H), 3.84 (m, 1 H), 3.72 (m, 1 H), 3.62 (m, 3 H), 2.7 (d, 1 H), 1.84 (m, 1 H), 1.6 (m, 1 H), 1.06 (s, 9 H); ^{13}C-NMR δ 167.95, 138.31, 138.26, 138.09, 135.57, 135.51, 133.65, 133.26, 133.21, 132.02, 129.59, 128.24, 128.14, 128.05, 127.87, 127.60, 127.52, 127.42, 127.39, 127.32, 122.92, 79.40, 78.68, 77.86, 77.79, 74.55, 74.26, 72.85, 72.36, 71.90, 63.18, 34.45, 28.93, 26.79, 19.01; IR 3560, 1710, 1110, 1090, 1070, 830. Anal. Calcd for $C_{60}H_{63}NO_8Si$: C, 75.52; H, 6.65; N, 1.47. Found: C, 75.27; H, 6.66; N, 1.37.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2,3,4,6-Tetra-*O*-benzyl-1-*O*-(*tert*-butyldiphenylsilyl)-1,2,3,4,5,6-hexahydroxy-8-*N*-phthaloyloctan-8-amine (17a). **17a** (20.2 g) was prepared from **16a** (18.7 g, 26.1 mmol) as described for **17b** from **16b** in 81% yield as a colorless oil: $[\alpha]^{20}_D$ −18.6 (*c* 2.8, $CHCl_3$); ^{1}H-NMR δ 7.76 (m, 2 H), 7.64 (m, 6 H), 7.46–7.1 (m, 26 H), 4 AB-systems (δ_A = 4.77, 4.73, 4.62, 4.50, δ_B = 4.62, 4.49, 4.31, 4.17, 8 H, J_{AB} = 11 Hz), 4.04 (m, 2 H), 3.89 (m, 1 H), 3.86 (m, 2 H), 3.78 (m, 2 H), 3.74 (m, 1 H), 3.56 (m, 1 H), 2.7 (d, 1 H, *J* = 8.6 Hz), 2.18 (m, 2 H), 1.06 (s, 9 H); ^{13}C-NMR δ 168.25, 138.46, 138.39, 138.33, 137.97, 135.65, 135.58, 134.75, 133.64, 133.38, 132.22, 129.63, 129.58, 128.16, 128.11, 127.95, 127.73, 127.65, 127.43, 127.36, 127.32, 122.98, 79.21, 77.34, 76.63, 74.72, 74.28, 73.13, 71.37, 70.60, 63.35, 34.11, 27.90, 26.88, 19.07; IR 3470, 1710, 1160, 1110, 1060, 1025, 825. Anal. Calcd for $C_{60}H_{63}NO_8Si$: C, 75.52; H, 6.65; N, 1.47. Found: C, 75.15; H, 6.67; N, 1.50.

(2*R*,3*S*,4*R*,5*R*,6*S*)-2,3,4,6-Tetra-*O*-benzyl-5-*O*-(methylsulfonyl)-1-*O*-(*tert*-butyldiphenylsilyl)-1,2,3,4,5,6-hexahydroxy-8-*N*-phthaloyloctan-8-amine (18b). To **17b** (21.98 g, 23.03 mmol) and DMAP (400 mg, 3.2 mmol) in pyridine (40 mL) was added mesyl chloride (2.4 mL, 30.8 mmol) in pyridine (3 mL) at 0 °C. The solution was stirred at 0 °C for 1 h, warmed to rt, and stirred for another 18 h. Aqueous $NaHCO_3$ was added, and the mixture was extracted with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and chromatographed (hexane/ethyl acetate (2/1)). **18b** (23.3 g) was obtained in 98% yield as a colorless oil: $[\alpha]^{20}_D$ −10.1 (*c* 2.0, $CHCl_3$); ^{1}H-NMR δ 7.79 (m, 2 H), 7.66 (m, 6 H), 7.42–7.08 (m, 26 H), 4.95 (t, 1 H, *J* = 6.5 Hz), 2 AB-systems (δ_{A1} = 4.74, δ_{B1} = 4.58, 2 H, J_{AB} = 10 Hz; δ_{A2} = 4.49, δ_{B2} = 4.42, 2 H, J_{AB} = 12 Hz), 4.62 (s, 2 H), 4.6 (s, 2 H), 4.11 (t, 1 H, *J* = 5.5 Hz), 4.04 (m, 1 H), 3.98 (m, 2 H), 3.86 (m, 1 H), 3.71 (m, 1 H), 3.57 (m, 2 H), 2.82 (s, 3 H), 1.88 (m, 2 H), 1.06 (s, 9 H); ^{13}C-NMR δ 168.01, 138.39, 137.83, 137.63, 137.48, 135.55, 133.73, 133.25, 133.17, 132.03, 129.56, 128.20, 128.14, 128.09, 127.89, 127.76, 127.61, 127.44, 127.33, 122.99, 81.20, 79.28, 77.83, 76.07, 75.63, 74.15, 73.99, 73.03, 71.90, 63.92, 38.39, 34.32, 28.65, 26.81, 19.03; IR 1710, 1350, 1175, 1110, 1090, 1030, 820. Anal. Calcd for $C_{61}H_{65}NO_{10}SSi$: C, 70.97; H, 6.35; N, 1.36. Found: C, 70.89; H, 6.31; N, 1.45.

(2*R*,3*S*,4*R*,5*R*,6*R*)-2,3,4,6-Tetra-*O*-benzyl-1-*O*-(*tert*-butyldiphenylsilyl)-1,2,3,4,5,6-hexahydroxy-5-*O*-(methylsulfonyl)-8-*N*-phthaloyloctan-8-amine (18a). **18a** (17.9 g, 91%) was prepared from **17a** (18.17 g, 19.0 mmol) as described for **18b** from **17b**: $[\alpha]^{20}_D$ +10.9 (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ 7.74 (m, 2 H), 7.62 (m, 6 H), 7.44–7.08 (m, 26 H), 5.36 (d, 1 H, *J* = 8 Hz), 4 AB-systems (δ_A = 4.72, 4.62, 4.54, 4.29, δ_B = 4.55, 4.49, 4.44, 4.04, 8 H, J_{AB} = 11 Hz), 4.00 (m, 1 H), 3.94–3.64 (m, 6 H), 3.56 (m, 1 H), 2.96 (s, 3 H), 1.95 (m, 2 H), 1.05 (s, 9 H); ^{13}C-NMR δ 168.23, 138.50, 137.86, 137.65, 135.68, 133.83, 133.36, 132.28, 129.76, 128.47, 128.41, 128.34, 128.30, 128.13, 127.99, 127.87, 127.79, 127.64, 127.59, 127.48, 123.09, 84.01, 78.89, 77.64, 76.84, 76.74, 74.55, 74.26, 73.06, 71.43, 63.26, 39.24, 35.11, 28.89, 27.02, 19.18; IR 1710, 1110, 1060, 1025, 825. Anal. Calcd for $C_{61}H_{65}NO_{10}SSi$: C, 70.97; H, 6.35; N, 1.36. Found: C, 70.37; H, 6.14; N, 1.25.

(2*S*,3*S*,1′*S*,2′*S*,3′*R*)-3-(Benzyloxy)-2-[1′,2′,3′-tris(benzyloxy)-4′-[(*tert*-butyldiphenylsilyl)oxy]butyl]pyrrolidine (19b). To a stirred solution of **18b** (21.4 g, 20.8 mmol) in ethanol (450 mL) was added hydrazine·hydrate (2 mL, 33 mmol), and the solution was refluxed for 5 h. After the solution was to rt concd acetic acid was added and the mixture was filtered over silica gel, washed with cold ether, and concentrated. The residue was diluted with ether, washed with 2 M NaOH, saturated $NaHCO_3$ solution, water, and brine, dried ($NaHCO_3$), and evaporated. Chromatography (ethyl acetate/methanol (6/1)) yielded **19b** (15.6 g, 94%) as a light yellow oil: $[\alpha]^{20}_D$ −16.2 (*c* 0.6, $CHCl_3$); ^{1}H-NMR δ 7.6 (m, 4 H), 7.24 (m, 26 H), 4 AB-systems (δ_A = 4.74, 4.73, 4.71, 4.43, δ_B = 4.60, 4.54, 4.53, 4.36, 8 H, J_{AB} = 12 Hz), 4.08 (q, 1 H, *J* = 3, 6 Hz), 3.94–3.79 (m, 4 H), 3.67 (t, 1 H, *J* = 6 Hz), 3.15 (dd, 1 H, *J* = 3, 5.6 Hz), 2.90–2.79 (m, 2 H), 1.89–1.64 (m, 3 H), 1.09 (s, 9 H); ^{13}C-NMR (DEPT) δ 138.80 (C), 138.63 (C), 135.64 (CH), 133.44 (C), 133.36 (C), 129.62 (CH), 128.23 (CH), 127.68 (CH), 127.54 (CH), 127.48 (CH), 127.36 (CH), 80.98 (CH), 79.77 (CH), 79.44 (CH), 74.84 (CH_2), 73.98 (CH_2), 73.16 (CH_2), 70.88 (CH_2), 65.63 (CH), 64.05 (CH_2), 45.26 (CH_2), 32.56 (CH_2), 26.90 (CH_3), 19.16 (C); HRMS calcd for $[C_{48}H_{50}NO_5Si]^+$ 748.345 83, found 748.345 76.

(2*S*,3*S*,1′*S*,2′*S*,3′*R*)-3-(Benzyloxy)-2-[1′,2′,3′-tris(benzyloxy)-4′-[(*tert*-butyldiphenylsilyl)oxy]butyl]-*N*-(trifluoroacetyl)pyrrolidine (20b). To a solution of **19b** (9.2 g, 11.4 mmol) and DMAP (200 mg, 1.6 mmol) in pyridine (20 mL) was added trifluoroacetic anhydride (2 mL, 14 mmol) at 0 °C and the solution stirred for 3 h at rt. After the solution was quenched with saturated $NaHCO_3$ solution, the product was extracted with CH_2Cl_2, washed with water and brine, dried ($NaHCO_3$), and purified by chromatography (hexane/ethyl acetate (2/1)) to give **20b** (9.4 g, 91%) as an oil: $[\alpha]^{20}_D$ −14.7 (*c* 2.1, $CHCl_3$); ^{1}H-NMR δ 7.64 (m, 2 H), 7.6 (m, 2 H), 7.44–7.08 (m, 26 H), 4 AB-systems: (δ_A = 4.75, 4.74, 4.70, 4.33, δ_B = 4.67, 4.54, 4.35, 4.27; 8 H, *J* = 11 Hz), 4.44 (dd, 2 H), 4.3 (m, 1 H), 3.92 (d, 2 H, *J* = 6.5 Hz), 3.78 (m, 3 H), 3.66 (m, 1 H), 2.34 (m, 1 H), 2.04 (m, 1 H), 1.04 (s, 9 H); ^{13}C-NMR (DEPT) δ 138.47 (C), 138.27 (C), 138.12 (C), 137.81 (C), 135.58 (CH), 133.31 (C), 129.66 (CH), 128.41 (CH), 128.34 (CH), 128.19 (CH), 127.93 (CH), 127.87 (CH), 127.71 (CH), 127.66 (CH), 127.49 (CH), 127.40 (CH), 79.80 (CH), 79.30 (CH), 78.13 (CH), 76.84 (CH), 75.48 (CH_2), 74.76 (CH_2), 73.59 (CH_2), 70.71 (CH_2), 67.60 (CH), 63.36 (CH_2), 45.37 (CH_2), 31.10 (CH_2), 26.94 (CH_3), 19.14 (C); IR 1685, 1150, 1120. Anal. Calcd for $C_{54}H_{56}NO_6SiF_3$: C, 71.90; H, 6.48; N, 1.55. Found: 71.59; H, 6.40; N, 1.74.

(2*S*,3*R*,1′*S*,2′*S*,3′*R*)-3-(Benzyloxy)-2-[1′,2′,3′-tris(benzyloxy)-4′-[(*tert*-butyldiphenylsilyl)oxy]butyl]-*N*-(trifluoroacetyl)pyrrolidine (20a). **20a** (9.8 g) was prepared from **18a** (17.86 g, 17.3 mmol) as described for the conversion of **18b** to **20b** (without characterization of **19a**) in 63% yield (two steps): $[\alpha]^{20}_D$ −16.9 (*c* 1.8, $CHCl_3$); ^{1}H-NMR δ 7.64 (m, 4 H), 7.49–7.1 (m, 26 H), 4 AB-systems (δ_A = 4.69, 4.64, 4.60, 4.36, δ_B = 4.60, 4.46, 4.28, 4.14, 8 H, J_{AB} = 11 Hz), 4.0 (m, 1 H), 3.89 (m, 3 H), 3.74 (m, 1 H), 3.66 (m, 1 H), 3.54 (m, 1 H), 3.36 (m, 1 H), 3.24 (m, 1 H), 1.94 (m, 2 H), 1.08 (s, 9 H); ^{13}C-NMR (DEPT) δ 137.97 (C), 137.86 (C), 137.78 (C), 137.47 (C), 135.59 (CH), 133.18 (C), 129.81 (CH), 129.76 (CH), 128.46 (CH), 128.40 (CH), 128.34 (CH), 128.30 (CH), 128.22 (CH), 127.98 (CH), 127.85 (CH), 127.79 (CH), 127.74 (CH), 78.64 (CH), 78.29 (CH), 77.37 (CH), 76.54 (CH), 74.42 (CH_2), 74.00 (CH_2), 72.89 (CH_2), 70.92 (CH_2), 70.75 (CH), 62.68 (CH_2), 36.13

(CH_2), 27.38 (CH_2), 26.85 (CH_3), 19.11 (C); IR 1690, 1150, 1120. Anal. Calcd for $C_{54}H_{58}NO_6SiF_3$: C, 71.90; H, 6.48; N, 1.55. Found: C, 71.31; H, 6.35; N, 1.48.

(2*S*,3*S*,1′*S*,2′*S*,3′*R*)-3-(Benzyloxy)-2-[1′,2′,3′-tris(benzyloxy)-4′-hydroxybutyl]-*N*-(trifluoroacetyl)pyrrolidine (21b). To a stirred solution of **20b** (9.5 g, 10.6 mmol) in THF (15 mL) was added a solution of TBAF in THF (1 M, 13.5 mL, 13.5 mmol) dropwise at 0 °C and stirred for 2 d at rt. Water was added, and the mixture was concentrated, diluted with water/ether, extracted with ether, dried ($MgSO_4$), and evaporated. Purification by column chromatography (hexane/ethyl acetate (2/1)) gave **21b** (6.2 g, 88%) as a colorless oil: $[\alpha]^{20}_D$ −25.0 (*c* 2.1, $CHCl_3$); ^{1}H-NMR δ 7.38–7.12 (m, 20 H), 4 AB-systems (δ_A = 4.78, 4.72, 4.60, 4.44, δ_B = 4.60, 4.42, 4.36, 4.32, 8 H, J_{AB} = 11 Hz), 4.38 (m, 2 H), 4.30 (m, 1 H), 3.84–3.70 (m, 3 H), 3.70–3.56 (m, 3 H), 2.32 (m, 1 H), 2.04 (m, 1 H), 1.9 (s, 1 H); ^{13}C-NMR (DEPT) δ 138.17 (C), 137.99 (C), 137.77 (C), 134.85 (C), 128.47 (CH), 128.35 (CH), 128.20 (CH), 128.08 (CH), 127.91 (CH), 127.85 (CH), 127.68 (CH), 118.57 (C), 79.95 (CH), 78.71 (CH), 77.57 (CH), 77.11 (CH), 75.83 (CH_2), 74.63 (CH_2), 73.02 (CH_2), 70.61 (CH_2), 67.37 (CH), 61.39 (CH_2), 45.62 (CH_2), 31.14 (CH_2); IR 3500, 1780, 1500, 1450, 1240, 1200, 1140, 1020. Anal. Calcd for $C_{38}H_{40}NO_6F_3$: C, 68.77; H, 6.07; N, 2.11. Found: C, 68.30; H, 5.95; N, 1.92.

(2*S*,3*R*,1′*S*,2′*S*,3′*R*)-3-(Benzyloxy)-2-[1′,2′,3′-tris(benzyloxy)-4′-hydroxybutyl]-*N*-(trifluoroacetyl)pyrrolidine (21a). **21a** (6.23 g, 93%) was prepared from **20a** (9.1 g, 10.1 mmol) as described for the preparation of **21b** from **20b**: $[\alpha]^{20}_D$ −42.1 (*c* 3.5, $CHCl_3$); ^{1}H-NMR δ 7.24 (mc, 20 H), 4 AB-systems (δ_A = 4.92, 4.77, 4.6, 4.56; δ_B = 4.52, 4.46, 4.44, 4.33; 8 H, J = 12 Hz), 4.64 (m, 1 H), 4.47 (m, 1 H), 4.36 (dd, 1 H), 4.12 (m, 1 H, J = 8, 9 Hz), 3.91 (d, 1 H, J = 7, 11 Hz), 3.8 (dd, 1 H, J = 5, 11 Hz), 3.67 (m, 1 H), 3.54 (m, 2 H), 2.44 (ddd, 1 H), 2.06 (m, 1 H), 1.9 (s, 1 H); ^{13}C-NMR δ 138.80, 138.24, 137.83, 128.34, 128.25, 128.14, 127.95, 127.75, 127.53, 127.42, 80.04, 79.07, 78.53, 76.40, 74.40, 72.07, 71.90, 61.15, 59.83, 44.41, 29.70; IR 3490, 1685, 1450, 1240, 1200, 1140, 1050; HRMS calcd for $[C_{38}H_{40}NO_6F_2]^+$ 644.282 37, found 644.283 33.

(1*S*,6*R*,7*S*,8*S*,8a*S*)-1,6,7,8-Tetra-*O*-benzyloctahydroindolizine (23b). To **21b** (2 g, 3 mmol) in methanol (24 mL) was added 0.1 M $Ba(OH)_2$ (24 mL), and the solution was refluxed for 3 h. At rt 2 M H_2SO_4 was added, the solution stirred for 30 min, filtered over Celite, washed with CH_2Cl_2, neutralized, extracted with CH_2Cl_2, and dried ($NaHCO_3$), and the light yellow oil **22b** (1.4 g, 84%) was obtained. Alternatively, **19b** (2.6 g, 4 mmol) in THF (4 mL) was treated with TBAF in THF (1 M, 5 mL, 5 mmol) overnight at rt. Workup as for **21b** and column chromatography (ethyl acetate/methanol (10/1)) yielded **22b** as an oil (1.95 g, 88%), which was subjected to cyclization according to version A or B without further purification.

A. To a solution of **22b** (2 g, 3.55 mmol), NEt_3 (0.34 g, 3.3 mmol), and CCl_4 (0.6 g, 4.3 mmol) in acetonitrile (5 mL) was added PPh_3 (1.03 g, 3.9 mmol) in small portions at 0 °C, and the reaction mixture was allowed to warm to rt and was stirred for 35 h. A saturated solution of $NaHCO_3$ was added. The mixture was extracted with ether, and the organic layer was dried ($NaHCO_3$), evaporated, and chromatographed (ethyl acetate/hexane (2/1)) followed by ethyl acetate). Crystallization gave **23b** (1.28 g, 66%): mp 99.5 °C; $[\alpha]^{20}_D$ +29.3 (*c* 1.9, $CHCl_3$); ^{1}H-NMR δ 7.7 (m, 20 H), 3 AB-systems (δ_{A1} = 4.96, δ_{B1} = 4.85; δ_{A2} = 4.91, δ_{B2} = 4.74; δ_{A3} = 4.71, δ_{B3} = 4.66; 6 H, J_{AB} = 11.25 Hz), 4.46 (s, 2 H), 3.92 (m, 1 H), 3.67 (ddd, 1 H, J = 5, 9.6, 10 Hz), 3.58 (dd, 1 H, J = 8.8, 10 Hz), 3.4 (t, 1 H, J = 9 Hz), 3.22 (dd, 1 H, J = 5, 10 Hz), 2.89 (dd, 1 H, J = 8.5, 10 Hz), 2.53 (dd, 1 H, J = 8.8, 10 Hz), 2.33 (dd, 1 H, J = 5.5, 10 Hz), 2.20 (t, 1 H, J = 10 Hz), 2.08 (m, 1 H), 1.84 (m, 1 H); ^{13}C-NMR δ 138.90, 138.72, 138.49, 138.33, 128.37, 128.27, 128.22, 127.97, 127.87, 127.75, 127.62, 127.55, 127.44, 127.40, 127.34, 87.56, 82.04, 81.68, 79.26, 75.68, 74.35, 72.85, 72.09, 71.33, 53.75, 51.59, 31.35; IR 1093, 1067. Anal. Calcd for $C_{36}H_{39}NO_4$: C, 78.66; H, 7.15; N, 2.55. Found: C, 78.35; H, 7.05; N, 2.52.

B. To a solution of **22b** (1.8 g, 3.2 mmol) and PPh_3 (1.3 g, 5 mmol) in THF (2.5 mL) was added DEAD (0.8 mL, 5.1 mmol) at 0 °C, and the mixture was stirred at rt for 24 h. Workup as in version A gave crystalline **23b** (395 mg, 23%).

(1*R*,6*R*,7*S*,8*S*,8a*S*)-1,6,7,8-Tetra-*O*-benzyloctahydroindolizine (23a). **22a** (1.42 g) was prepared from **21a** (2.2 g, 3.31 mmol) as described for **22b** from **21b** in 76% yield and was cyclized without further purification. The preparation of **23a** (1.54 g, 78%) was achieved from **22a** (2.1 g, 3.6 mmol) as described for **23b** to **22b**: $[\alpha]^{20}_D$ −60.8 (*c* 2.3, $CHCl_3$); ^{1}H-NMR δ 7.39–7.15 (m, 20 H), 4 AB-systems (δ_A = 4.98, 4.88, 4.70, 4.60; δ_B = 4.82, 4.65, 4.62, 4.32; 8 H; J = 11 Hz), 4.15 (dd, 1 H, J = 5, 8 Hz), 3.92 (t, 1 H, J = 9 Hz), 3.76 (m, 1 H, J = 5.5 Hz), 3.54 (t, 1 H, J = 9 Hz), 3.27 (dd, 1 H, J = 5, 10 Hz), 3.15 (m, 1 H), 2.23–1.91 (m, 5 H); ^{13}C-NMR δ 139.16, 138.93, 138.47, 137.92, 128.29, 128.24, 128.16, 127.91, 127.87, 127.77, 127.55, 127.41, 127.39, 127.34, 127.22, 87.57, 79.13, 77.38, 75.53, 74.38, 72.80, 71.67, 70.55, 54.53, 52.43, 29.92; IR 1097, 1068; HRMS calcd for $[C_{36}H_{39}NO_4]^+$, $[M]^+$ 549.287 909, found 549.288 264; HRMS calcd for $[C_{29}H_{32}NO_4]^+$ 458.233 134, found 458.232 766.

(1*S*,6*R*,7*S*,8*S*,8a*S*)-1,6,7,8-Tetrahydroxyoctahydroindolizine ((−)-1-*epi*-Castanospermine) (2). **23b** (600 mg, 1.1 mmol) was hydrogenated in methanol (40 mL) including 10% Pd/C (90 mg) and methanolic HCl (4%, 4 mL) for 2 d at 3 bar. Filtration over Celite, stirring over ion exchange resin, and chromatography (methanol/CH_2Cl_2/NH_4OH (10/5/1)) gave **2** (190 mg, 90%): $[\alpha]^{20}_D$ −21 (*c* 0.5, H_2O, pH 7.1), $[\alpha]^{20}_D$ −10 (*c* 0.4 H_2O, pH 6) and $[\alpha]^{20}_D$ +4 (*c* 0.3, H_2O, pH 5), $[\alpha]^{20}_D$ −4 (*c* 1.2, MeOH) (lit.[9a] $[\alpha]^{20}_D$ +6 (*c* 0.45, H_2O), lit.[9b] $[\alpha]^{20}_D$ −39.1 (*c* 0.4, H_2O)); ^{1}H-NMR (D_2O + TSP[26]) δ 4.6 (q, 1 H, J = 3, 3, 6.5 Hz), 3.91 (m, 1 H), 3.63 (m, 1 H), 3.58 (m, 1 H), 3.55 (m, 1 H), 3.52 (m, 1 H), 3.48 (m, 1 H), 3.23 (m, 1 H), 3.17 (dd, 1 H, J = 11, 12 Hz), 2.57 (m, 1 H), 2.07 (m, 1 H); ^{1}H-NMR (CD_3OD) δ 4.24 (m, 1 H), 3.91 (m, 1 H), 3.62 (m, 1 H), 3.36–3.12 (m, 3 H), 3.04 (m, 1 H), 2.78 (m, 1 H), 2.36 (m, 1 H), 2.32 (m, 1 H), 1.72 (dd, 1 H); ^{13}C-NMR (D_2O + TSP[26]; DEPT) δ 78.72 (CH), 74.27 (CH), 73.79 (CH), 71.33 (CH), 68.73 (CH), 53.78 (CH_2), 53.28 (CH_2), 33.37 (CH_2); HRMS calcd for $[C_8H_{15}NO_4]^+$, $[M]^+$ 189.100 109, found 189.100 031.

(1*R*,6*R*,7*S*,8*S*,8a*S*)-1,6,7,8-Tetrahydroxyoctahydroindolizine ((−)-Castanospermine) (1). **1** (310 mg) was prepared from **23a** (1 g, 1.8 mmol) by hydrogenation in the same manner as **2** from **23b**, yield 91%: mp 210–212 °C dec (lit.[1] mp 212–215 °C dec); $[\alpha]^{20}_D$ −81.1 (*c* 2.0, H_2O) (lit.[1] $[\alpha]^{25}_D$ +79.9 (*c* 0.93, H_2O), lit.[9b] $[\alpha]^{20}_D$ +81.9 (*c* 0.72, H_2O)); ^{1}H-NMR (D_2O + TSP[26]) δ 4.41 (m, 1 H), 3.70 (m, 1 H), 3.65 (m, 1 H), 3.37 (t, 1 H), 3.20 (m, 1 H), 3.11 (dd, 1 H), 2.41 (m, 1 H), 2.29 (m, 1 H), 2.08 (t, 1 H), 2.05 (dd, 1 H), 1.74 (m, 1 H); ^{13}C-NMR (D_2O + TSP[26]) δ 81.77, 74.18, 72.86, 72.34, 71.72, 58.15, 54.41, 35.52; IR 3362; HRMS calcd for $[C_8H_{15}NO_4]^+$, $[M]^+$ 189.100 109, found 189.100 031. HRMS calcd for $[C_8H_{14}NO_3]^+$ 172.097 369, found 172.097 892.

(2*R*,3*S*,4*R*,1′*R*,2′*S*)-2′,3,4-Tris(benzyloxy)-2-[1′-[(methylsulfonyl)oxy]-4′-phthalimidobutyl]tetrahydrofuran (24). To a solution of **16b** (1 g, 1.4 mmol) and DMAP (0.5 g, 4 mmol) in pyridine (10 mL) was added MsCl (0.3 mL, 3.8 mmol) in CH_2Cl_2 (3 mL) at −30 °C, and the solution was stirred for 1 h at that temperature and quenched with a saturated solution of $NaHCO_3$. The mixture was extracted with ether, washed with water and brine, dried ($MgSO_4$), and chromatographed (hexane/ethyl acetate (2/1)) to give **24** (867 mg, 89%) as a colorless oil: ^{1}H-NMR δ 7.8 (m, 2 H), 7.64 (m, 2 H), 7.26 (mc, 15 H), 5.0 (dd, 1 H, J = 2, 8 Hz), 2 AB-systems (δ_A = 4.6, 4.38; δ_B = 4.38, 4.2; 4 H; J = 11 Hz), 4.46 (s, 2 H), 4.4 (t, 1 H, J = 5.5 Hz), 4.12 (dd, 1 H, J = 4, 9.5 Hz), 4.04 (d, 1 H, J = 4 Hz), 3.82 (m, 2 H), 3.68 (m, 3 H), 3.1 (s, 3 H), 2.12 (m, 2 H); ^{13}C-NMR δ 137.60, 137.44, 136.93, 133.75, 132.00, 128.49, 128.43, 128.31, 128.04, 127.92, 127.83, 127.64, 127.44, 123.02, 82.60, 81.30, 81.09, 78.71, 75.40, 71.55, 71.33, 71.25, 70.81, 38.82, 34.49, 28.63; IR 1712, 1356, 1175, 910, 733; HRMS calcd for $[C_{38}H_{39}NO_9S]^+$ 685.234 56, found 685.234 71.

(2*S*,3*S*,1′*S*,2′*R*,3′*S*)-3-(Benzyloxy)-2-[1′,2′,3′-tris(benzyloxy)-4′-oxobutyl]-*N*-(trifluoroacetyl)pyrrolidine (25). To a solution of oxalyl chloride (3.1 mL, 35.5 mmol) in CH_2Cl_2 (30 mL) were added DMSO (3.5 mL, 48.6 mmol) in CH_2Cl_2 (8 mL) and **21b** (5.5 g, 8.2 mmol) in CH_2Cl_2 (30 mL) at intervals of 20 min at −78 °C, and the solution was stirred for 30 min. NEt_3 (14.8 mL, 106.3 mmol) was added, and the solution was stirred for 20 min at −78 °C and 20 min at 0 °C, quenched with water, and extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated: ^{1}H-NMR δ 9.68 (s, 1 H), 7.26 (mc, 20 H), 4.84–4.58 (m, 4 H), 4.5–4.36 (m, 3 H),

(26) TSP = 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt.

4.36–4.24 (m, 3 H), 4.2 (s, 1 H), 3.94 (dd, 1 H), 3.88 (d, 1 H), 3.72 (dd, 1 H), 3.58 (dt, 1 H), 2.2 (m, 1 H), (m, 1 H); ^{13}C-NMR 201.65, 137.64, 137.49, 137.25, 136.90, 128.65, 128.51, 128.42, 128.39, 128.20, 128.04, 127.98, 127.88, 127.77, 127.57, 81.41, 81.14, 77.63, 76.26, 75.38, 74.39, 73.66, 70.72, 67.49, 45.41, 30.77; IR 1728, 1685. Anal. Calcd for $C_{38}H_{38}NO_6F_3$: C, 68.98; H, 5.79; N, 2.12. Found: C, 68.38; H, 5.78; N, 2.06.

(2*S*,3*S*,1′*S*,2′*R*,3′*S*)-3-(Benzyloxy)-2-[1′,2′,3′-tris(benzyloxy)-3′-carboxypropyl]-*N*-(trifluoroacetyl)pyrrolidine (26). The crude aldehyde **25** was dissolved in 2-methyl-2-propanol (80 mL), buffer (50 mL, 1.25 M KH_2PO_4/0.244 M K_2HPO_4), and aqueous $KMnO_4$ (1%, 80 mL) and stirred for 30 min at rt. At intervals of 20 min were added a saturated solution of sodium sulfite and 2 M HCl. The aqueous layer was extracted with ether, dried ($MgSO_4$), and chromatographed to give **26** (2.8 g, 50%) along with unreacted aldehyde **25** (1.67 g, 31%). Anal. Calcd for $C_{38}H_{38}NO_7F_3$: C, 67.35; H, 5.65; N, 2.07. Found: C, 67.35; H, 5.58; N, 2.15.

(1*S*,6*S*,7*R*,8*S*,8a*S*)-1,6,7,8-Tetra-*O*-benzyloctahydroindolizin-5-one (28). **26** (810 mg, 1.2 mmol) in methanol (10 mL) and 0.1 M $Ba(OH)_2$ (10 mL) were stirred at 60 °C for 3 h, 1 M H_2SO_4 was added, and the solution was filtered and washed with CH_2Cl_2. The layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried ($NaHCO_3$), and evaporated to give **27** as a yellow oil (550 mg, 79%), which was cyclized according to version A or B without further purification.

A. A solution of **27** (270 mg, 0.46 mmol) in ether (3 mL) was treated with PCl_5 (97 mg, 0.47 mmol) at 0 °C for 2 h. Aqueous $NaHCO_3$ was added. The mixture was extracted with ether, and the ethereal layer was washed with $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The oily residue was chromatographed (ethyl acetate/hexane (2/1)) to give **28** (170 mg, 66%): $[\alpha]^{20}_D$ −123.3 (*c* 0.8, $CHCl_3$); ^{1}H-NMR δ 7.42–7.11 (m, 20 H), 4 AB-systems (δ_A = 4.88, 4.67, 4.66, 4.55, δ_B = 4.67, 4.47, 4.43, 4.42, 8 H, J_{AB} = 12 Hz), 4.1 (d, 1 H, J = 4.1 Hz), 4.0–3.68 (m, 4 H), 3.4 (dt, 1 H, J = 7, 11 Hz), 3.28 (dd, 1 H, J = 5.5, 9.5 Hz), 1.9 (m, 1 H), 1.76 (m, 1 H); ^{13}C-NMR (DEPT) δ 166.49 (C), 137.69 (C), 137.40 (C), 137.22 (C), 128.24 (CH), 128.16 (CH), 128.12 (CH), 128.04 (CH), 127.99 (CH), 127.81 (CH), 127.75 (CH), 127.68 (CH), 127.60 (CH), 127.41 (CH), 127.36 (CH), 82.32 (CH), 81.48 (CH), 80.46 (CH), 78.61 (CH), 72.40 (CH_2), 72.28 (CH_2), 70.44 (CH_2), 62.59 (CH), 43.22 (CH_2), 29.13 (CH_2); IR 1610, 1110, 1070. Anal. Calcd for $C_{36}H_{37}NO_5$: C, 76.71; H, 6.62; N, 2.48. Found: C, 76.26; H, 6.56; N, 2.53.

B. To a solution of **27** (390 mg, 0.57 mmol) in THF (7 mL) was added trifluoroacetic acid (1 mL), and the solution was stirred at rt for 2 d. The mixture was neutralized and extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and chromatographed (ethyl acetate/hexane (2/1)) to give **28** (240 mg, 74%).

(1*S*,6*R*,7*S*,8*S*,8a*S*)-1,6,7,8-Tetra-*O*-benzyloctahydroindolizine (23b). A stirred solution of **28** (127 mg, 0.22 mmol) in THF (2 mL) was refluxed with BH_3·THF (1 M, 0.5 mL, 0.5 mmol) for 3 h. 6 M HCl was added, and the solution was stirred for 1 h and neutralized. The aqueous layer was extracted with ether, and the ethereal layer was dried ($MgSO_4$), evaporated, and chromatographed (ethyl acetate/hexane (2/1)) to give **23b** (85 mg, 70%), identical in ^{1}H, ^{13}C-NMR, optical rotation with the material prepared from **21b**.

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Registry No. (*N*)-**1**, 140386-64-7; **2**, 140386-65-8; **3**, 58645-17-3; **4a**, 140201-51-0; **4b**, 140386-66-9; **5a**, 140201-52-1; **5b**, 140386-67-0; **6a**, 140201-53-2; **6b**, 140201-54-3; **7**, 140201-55-4; **8**, 140386-68-1; **9**, 6706-59-8; **10**, 79466-34-5; **11a**, 140201-56-5; **11b**, 140386-69-2; **12a**, 140201-57-6; **12b**, 140386-70-5; **13b**, 140201-58-7; **14a**, 140201-59-8; **14b**, 140386-71-6; **15a**, 140201-60-1; **15b**, 140386-72-7; **16a**, 140201-61-2; **16b**, 140386-73-8; **17a**, 140201-62-3; **17b**, 140387-56-0; **18a**, 140201-63-4; **18b**, 140386-74-9; **19a**, 140201-64-5; **19b**, 140386-75-0; **20a**, 140201-65-6; **20b**, 140386-76-1; **21a**, 140201-66-7; **21b**, 140386-77-2; **22a**, 140201-67-8; **22b**, 140386-78-3; **23a**, 140201-68-9; **23b**, 140386-79-4; **24**, 140201-69-0; **25**, 140201-70-3; **26**, 140201-71-4; **27**, 140201-72-5; **38**, 140201-73-6.

Supplementary Material Available: MS spectra of **1**, **2**, **4a/b**, **5a**, **5b**, **7**, **8**, **12a**, **14a–18a**, **20a–23a**, **11b**, **12b**, **14b–23b**, **24**, **25**, **28**, data of NOE experiments for **23a** and **23b**, tables of atomic coordinates, bond lengths/angles, and dihedral angles of **23b**, and NMR spectra of (−)-**1**, **2**, **15a**, **21a**, and **23a** (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.