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TETRAHEDRON

New Syntheses of Two Epimers of (+)-Castanospermine: (+)-8a-*Epi*- and (+)-1,8a-Di-*epi*-castanospermine

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Abstract: Two epimers of (+)-castanospermine, (1*S*,6*S*,7*R*,8*R*,8a*S*)-1,6,7,8-tetrahydroxyindolizidine [(+)-8a-*epi*-castanospermine] (**4**) and (1*R*,6*S*,7*R*,8*R*,8a*S*) derivative [(+)-1,8a-di-*epi*-castanospermine] (**5**) were synthesized from methyl α-D-glucopyranoside.

INTRODUCTION

(+)-Castanospermine [(1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine] (**1**) has been isolated from the toxic seeds of the Australian legume *Castanospermum australe*[1] and the dried pods of *Alexa leiopetala*[2]. This type of higher plant alkaloid is a potent reversible and competitive inhibitor of mammalian and insect glucosidases.[2] Castanospermine has been used in the treatment of several disorders, including cancer,[3-5] diabetes,[3] obesity,[6] and viral infections[7] (also HIV-1[8,9]). It was found that stereoisomers of **1**, isolated from natural sources, 6-*epi*-castanospermine[10] (**2**) and 6,7-di-*epi*-castanospermine[11] (**3**) also displayed useful biological activities.[10-13] These findings aroused considerable interest in the synthesis of castanospermine[14, 15] and also of its stereoisomeric forms.[15, 16]

We report herein new syntheses of (1*S*,6*S*,7*R*,8*R*,8a*S*)-1,6,7,8-tetrahydroxyindolizidine [(+)-8a-*epi*-

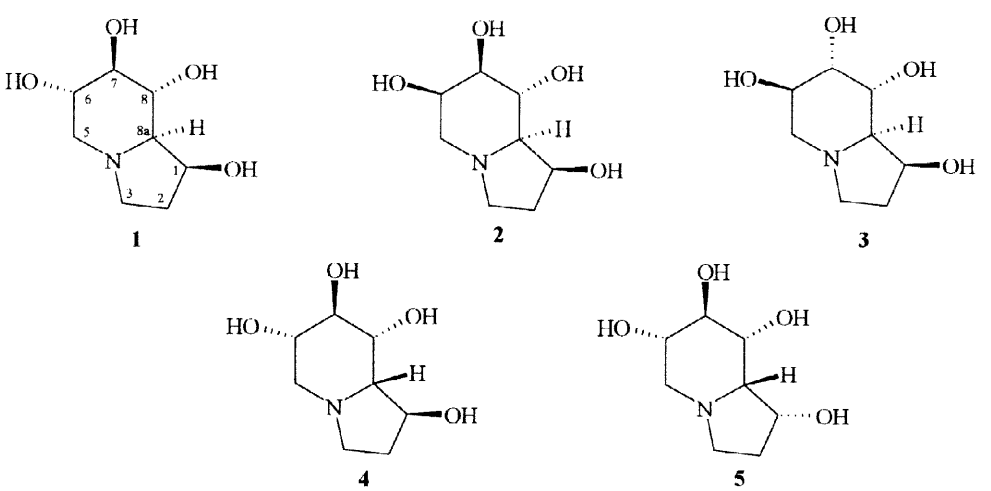

Fig. 1

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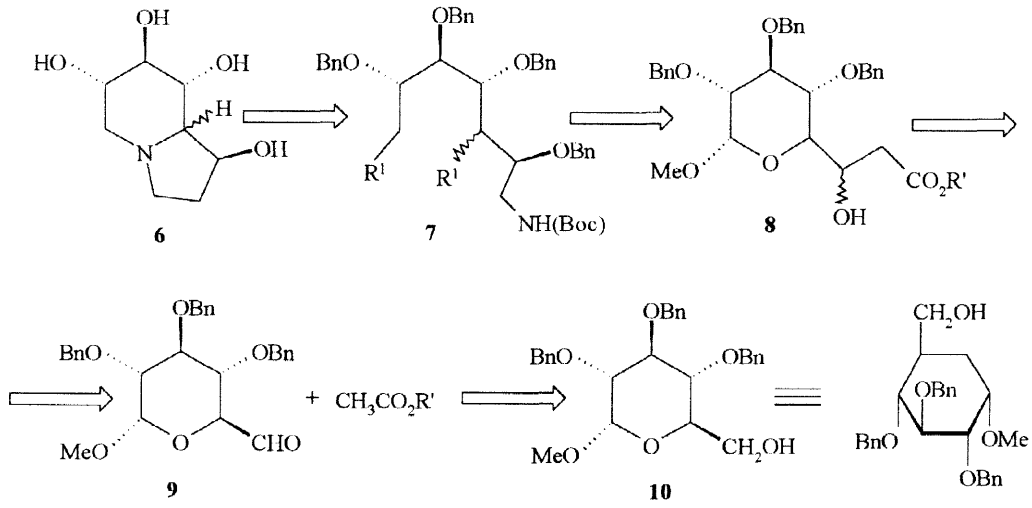
castanospermine] (**4**) and of the (1*R*,6*S*,7*R*,8*R*,8a*S*) stereoisomer [(+)-1,8a-di-*epi*-castanospermine] (**5**).

Three syntheses of **4** and **5** have been described in the literature. In 1992, Burgess[18] presented an approach to the enantiomer of **4**, (-)-8a-*epi*-castanospermine, *via* asymmetric allylation of 5-*N*-phthalyl-2,3,4-tri-*O*-benzyl-D-xylose. In 1995 Leeper[19] developed a new synthesis of (±)-**4** using *rac*-malic acid as the substrate. A synthesis of (+)-1,8a-di-*epi*-castanospermine (**5**) from 2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone was presented by Chamberlin and Miller[20] in 1990.

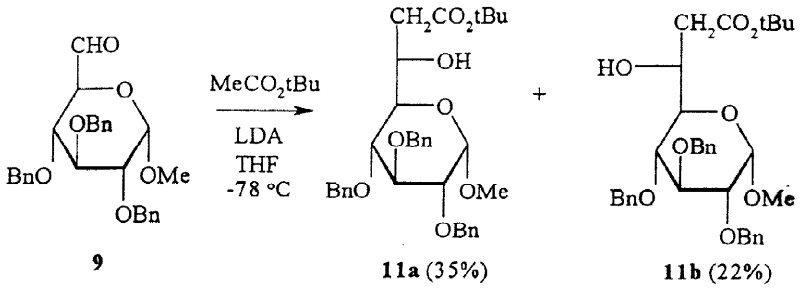
RESULTS AND DISCUSSION

Our studies in area of polyhydroxylated indolizidines have focused on the synthesis of two epimers of castanospermine (**1**). Our routes to 8a-*epi*- (**4**) and 1,8a-di-*epi*-castanospermines (**5**) started from the aldehyde **9**[21] readily available on a large scale. The retrosynthetic plan is shown in Scheme 1.



Scheme 1

Both 8a-*epi*- (**4**) and 1,8a-di-*epi*-castanospermines (**5**) possess the same stereochemistry at C-6, 7 and 8 as methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**10**) at positions C-2, 3 and 4. Derivative **10** was obtained from methyl α-D-glucopyranoside in three conventional steps. Swern oxidation of **10** furnished the stable aldehyde **9** which was reacted with *tert*-butyl lithioacetate, generated from lithium diisopropylamide and *tert*-butyl acetate at -78 °C. The aldol reaction resulted in a 3:2 mixture of diastereomers **11a** and **11b** which were separated by liquid chromatography (Scheme 2).



Scheme 2

On the basis of ^{1}H NMR, ^{13}C NMR, COSY ^{1}H-^{1}H and HETCOR ^{1}H-^{13}C data and, particularly, by employing the relation[22] linking coupling constants $J_{6,7A}$ and $J_{6,7B}$ with the configuration of the 6-CHOH grouping, the less polar epimer **11a** was assigned the structure of *tert*-butyl (methyl 2,3,4-tri-*O*-benzyl-7-deoxy-L-*glycero*-α-D-*gluco*-octopyranosid)uronate (35%) and the more polar **11b** was assigned that of *tert*-butyl (methyl 2,3,4-tri-*O*-benzyl-7-deoxy-D-*glycero*-α-D-*gluco*-octopyranosid)uronate (22%) (Scheme 2). Additionally, the structure of compound **11a** was confirmed independently by an X-ray structural determination (Fig. 2).

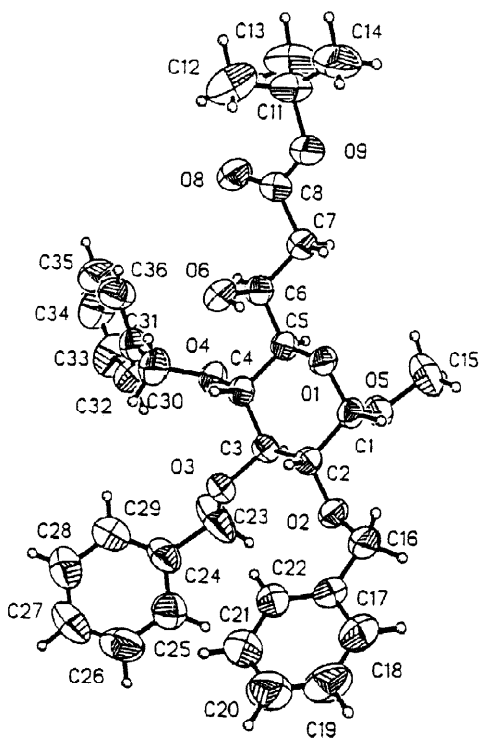
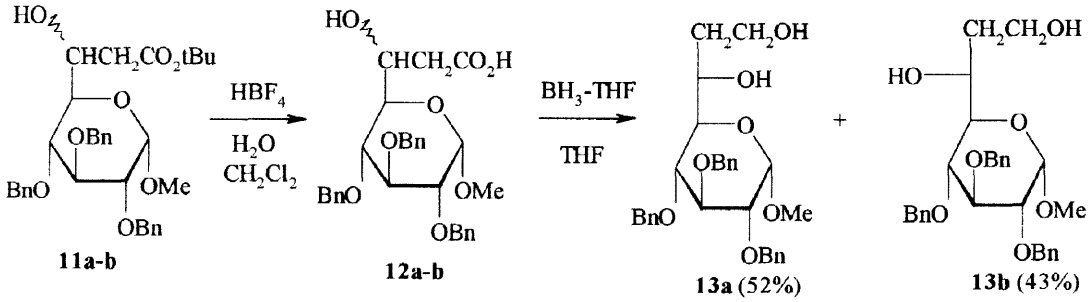


Fig. 2

The mixture of esters **11a** and **11b** was hydrolysed with aqueous 50% tetrafluoroboric acid to a mixture of free acids **12** (98%) which were subsequently reduced with borane-tetrahydrofuran complex to diols **13a** (52%) and **13b** (43%), separated by chromatography (Scheme 3).

The primary alcohol function in **13a** was protected with a *tert*-butyldiphenylsilyl group to form **14a** (97.4%). Compound **14a** was next benzylated at C-6 to give derivative **15a** (91%) (Scheme 4).

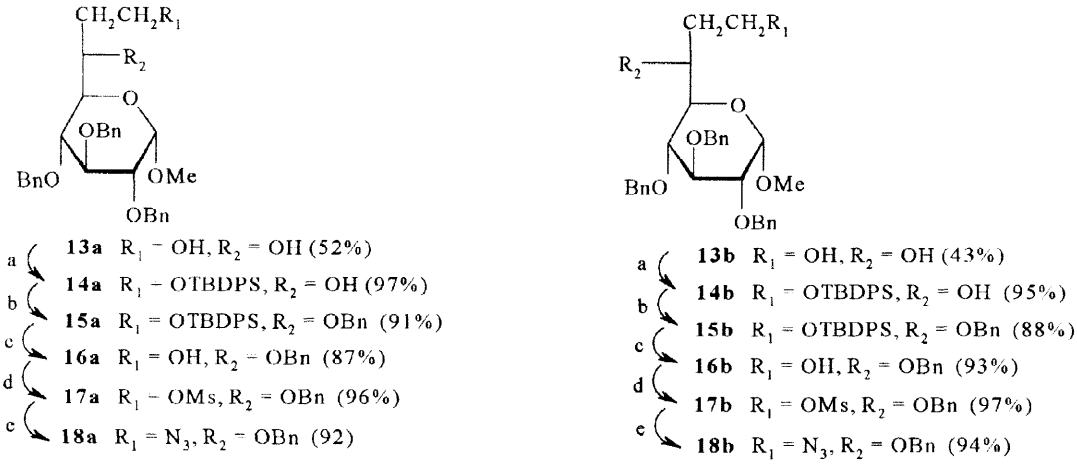
The *tert*-butyldiphenylsilyl group in **15a** was easily removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at room temperature to give alcohol **16a** (87%).



Scheme 3

Reaction of **16a** with methanesulfonyl chloride and DMAP in pyridine at -10 °C gave the corresponding mesylate **17a** (96%). Heating of **17a** with sodium azide in *N,N*-dimethylformamide afforded methyl 8-azido-2,3,4,6-tetra-*O*-benzyl-7,8-dideoxy-L-*glycero*-α-D-*gluco*-octopyranoside **18a** (92%).

Brief acetolysis (reaction time - only 5 min.) of the anomeric methoxyl group in **18a** led to **19a** (93%) (Scheme 5).

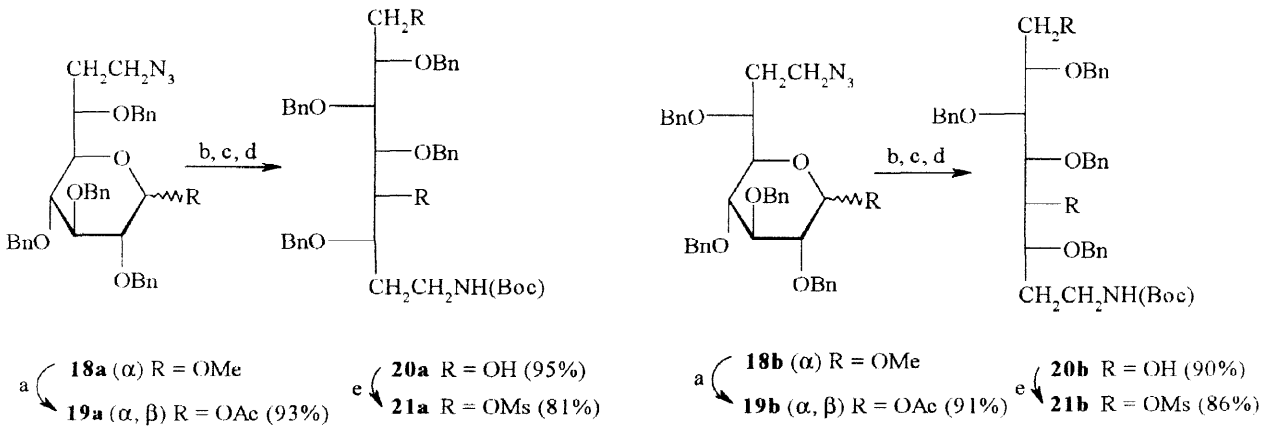


(a) TBDPSCl, imidazole, DMF; (b) BnBr, NaH, DMF; (c) Bu_4NF, THF; (d) MsCl, DMAP, Py -10 °C; (e) NaN_3, DMF, 60 °C.

Scheme 4

The next three synthetic steps were performed in one-pot. 1-O-Acetyl derivative **19a** was reduced with an excess of sodium borohydride (formation of primary-secondary diol), next, to the reacting mixture was added nickel chloride [$NiCl_2$-$NaBH_4$ reagent (Ni_2B):[17] reduction of the N_3 grouping] and then the amino group was protected as its Boc derivative to form **20a** (95% over three steps). Aminodiol **20a** was converted into dimesylate **21a** (81%).

Liberation of the amino group in the typical way with trifluoroacetic acid was unsuccessful. It was found eventually that treatment of **21a** with trimethylsilyl chloride and phenol furnished the desired amino-dimesylate, ready for the final ring closure step. Double-cyclization was effected by refluxing the amino-dimesylate with sodium acetate in anhydrous ethanol to give the fully protected (1*S*,6*S*,7*R*,8*R*,8a*S*)-1,6,7,8-tetra-*O*-benzylindolizidine **22a** in 55% yield (Scheme 6).

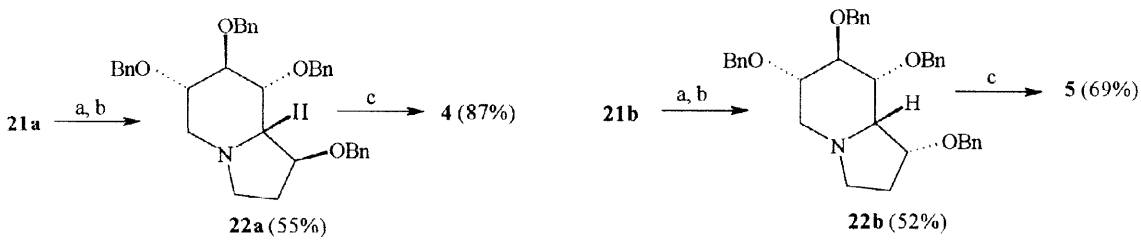


(a) Ac_2O, AcOEt, H_2SO_4; (b) $NaBH_4$, EtOH, reflux; (c) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, EtOH, r.t.; (d) $(Boc)_2O$, AcOEt/$NaHCO_3$aq, (e) MsCl, DMAP, Py, -10 °C.

Scheme 5

1,8a-Di-*epi*-castanospermine (**5**) was synthesized on a fully analogous way starting from methyl 2,3,4-tri-O-benzyl-7-deoxy-D-*glycero*-α-D-*gluco*-octopyranoside (**13b**) (cf Schemes 4, 5 and 6).

The structure assignment of **22a** was based on ^1H, ^{13}C NMR and 2D ^{13}C-^1H heteronuclear shift correlation spectra. Compound **22a** was then hydrogenated in the presence of palladium on activated carbon in methanol containing a few drops of concentrated hydrochloric acid. The suspension was stirred under hydrogen pressure (70 psi) at room temperature for 8 h. Purification on ion exchange resin afforded (+)-8a-*epi*-castanospermine (**4**) (87%) displaying optical rotation of the same magnitude but of opposite sign as the



(a) PhOH, Me_3SiCl, CH_2Cl_2; (b) AcONa, EtOH, reflux; (c) H_2, 10% Pd/C, MeOH, HCl.

Scheme 6

compound synthesized previously[18]. Similarly, deprotection of **22b** led to (+)-1,8a-di-*epi*-castanospermine (**5**) (69%) having optical rotation and ^{13}C NMR data identical with the compound synthesized by Chamberlin and Miller.[20]

CONCLUSION

We have conducted efficient syntheses of (+)-8a-*epi*-castanospermine (**4**) and (+)-1,8a-di-*epi*-castanospermine (**5**) *via* a carbohydrate-based strategy starting from the inexpensive methyl α-D-glucopyranoside.

Inversion of the configuration at the C-5 atom in diols **20a** and **20b** could lead to natural (+)-castanospermine and (+)-1-*epi*-castanospermine. However, in spite of many attempts (several versions of the Mitsunobu and Appel reactions, heating of C-5 mesylate with caesium acetate, oxidation of C-5 OH group to ketone with a range of oxidants and then reduction) we did not succeed in effecting the inversion. Nevertheless we are confident that using the route described a wide variety of castanospermine epimers or analogs should be available.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Solvents were purified and distilled under argon. ^1H NMR spectra were recorded with a Varian AC-200 (200 MHz) or Bruker AM-500 (500 MHz) spectrometers. High resolution mass spectra (HR-MS) were obtained with an AMD-604 mass spectrometer. Optical rotation were measured with a JASCO DIP-360 automatic polarimeter at 20 ± 2 °C. For column chromatography silica gel 70-230 mesh (Merck) was used.

***Tert*-butyl [methyl 2,3,4-tri-*O*-benzyl-7-deoxy-D(L)-*glycero*-α-D-*gluco*-octopyranosid]uronate (11a and 11b)**

Lithium diisopropylamide was generated by addition of butyllithium (7.6 ml, 18.9 mmol) to the solution of diisopropylamine (2.8 ml, 19.8 mmol) in tetrahydrofuran (20 ml) under argon. The reaction mixture was cooled to the -78 °C. *Tert*-butyl acetate (2.4 ml, 18.0 mmol) was added dropwise. After 30 min of stirring a solution of **9** (2.5 g, 5.4 mmol) in tetrahydrofuran (10 ml) was added and stirring was continued for 1 h at -78 °C. The mixture was allowed to warm to 25 °C. The solution was diluted with ether and washed with saturated NH_4Cl (40 ml) and brine (40 ml). The combined organic layers were dried. Removal of the volatiles *in vacuo* and purification of the residue by flash chromatography with hexane- diethyl ether, 7:3 gave **11a** (1.1 g, 35%)

and **11b** (0.7 g, 22%). The assignment of signals was confirmed by COSY ^{1}H-^{1}H and HETCOR ^{1}H-^{13}C experiments.

11a, as colorless crystals, m.p. 111 - 112 °C; $[\alpha]_D$ -2 (*c* 1.4, $CHCl_3$); IR (film): 3468 (OH), 1738 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.57 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.30 (ddd, 1 H, $J_{5,6}$ 0.9, $J_{6,7B}$ 4.0, $J_{6,7A}$ 9.1 Hz, H-6), 3.97 (dd, 1 H, $J_{3,4}$ 9.0, $J_{2,3}$ 9.6 Hz, H-3), 3.74 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 3.52 (dd, 1 H, H-2), 3.49 (dd, 1 H, H-5), 3.35 (s, 3 H, OMe), 2.90 (d, 1 H, *J* 6.2 Hz, OH), 2.67 (dd, 1 H, $J_{7A,7B}$ 16.1 Hz, H-7A), 2.35 (dd, 1 H, H-7B), 1.45 [s, 9H, Me (*t*-Bu)]. ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.81 (C-8), 137.68, 137.23, 137.00, 127.30, 127.26, 127.05, 126.86, 126.81, 126.45, 97.25 (C-1), 80.96 (C-3), 80.17 (C-2), 78.62 (C-4), 76.21 (CH_2Ph), 74.65 (CH_2Ph), 74.10 (CH_2Ph), 72.40 (CMe_3), 70.94 (C-5), 64.36 (C-6), 54.18 (OCH_3), 38.16 (C-7), 27.03 (Me). HR-MS/ LSIMS-NBA: for $C_{34}H_{42}O_8Na$ $(M+Na)^+$ calcd.: 601.2777. Found: 601.2780. MS/ LSIMS-NBA: 601 $(M+Na)^+$, 579 $(M+H)^+$, 547 $(M-OMe)^+$.

11b, oil, $[\alpha]_D$ +36 (*c* 0.4, $CHCl_3$); IR (film): 3491 (OH), 1728 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.55 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.24 (ddd, 1 H, $J_{5,6}$ 1.1, $J_{6,7B}$ 3.9, $J_{6,7A}$ 8.2 Hz, H-6), 4.05 (dd, 1 H, $J_{3,4}$ 8.9, $J_{2,3}$ 9.3 Hz, H-3), 3.76 (dd, 1 H, $J_{4,5}$ 9.9 Hz, H-5), 3.51 (dd, 1 H, H-2), 3.44 (dd, 1 H, H-4), 3.41 (s, 3 H, OMe), 3.35 (d, 1 H, *J* 4.4 Hz, OH), 2.45 (dd, 1 H, $J_{7A,7B}$ 16.2, H-7A), 2.28 (dd, 1 H, H-7B), 1.45 [s, 9 H, Me (*t*-Bu)]. HR-MS/ LSIMS-NBA: for $C_{34}H_{42}O_8Na$ $(M+Na)^+$ calcd.: 601.2777. Found: 601.2785. MS/ LSIMS-NBA: 601 $(M+Na)^+$, 547 $(M-OMe)^+$.

[Methyl 2,3,4-tri-*O*-benzyl-7-deoxy-D(L)-*glycero*-α-D-*gluco*-octopyranosid]uronic acids (12a and 12b)

A mixture of *tert*-butyl (methyl 2,3,4-tri-*O*-benzyl-7-deoxy-D(L)-*glycero*-α-D-*gluco*-octopyranoside)uronates **11a** and **11b** (9 g, 15.6 mmol) was dissolved in dichloromethane (60 ml), and aqueous 50% tetrafluoroboric acid (5.8 ml, 46.4 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The resulting solution was neutralised with triethylamine (15 ml) and washed with water (3x30 ml). The organic layer was dried, concentrated, and the residue was purified on a silica gel column with hexane-diethyl ether 9:1 to yield **12a** and **12b** in *ca* 1.2:1 proportion (8 g, 98.1 %). IR (film): 3454 (OH), 1714 (C=O). *Anal.*: for $C_{30}H_{34}O_8$ calcd.: C 68.95; H 6.56. Found: C 69.00; H 6.71. Spectral data of both components were taken from the ^{1}H NMR spectrum of the mixture.

12a, oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.62 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.36 (ddd, 1 H, $J_{5,6}$ 1.2, $J_{6,7B}$ 2.8, $J_{6,7A}$ 9.4 Hz, H-6), 4.05 (dd, 1 H, $J_{3,4}$ 9.2, $J_{2,3}$ 9.4 Hz, H-3), 3.50 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 3.55 (dd, 1 H, H-2), 3.53 (dd, 1 H, H-5), 3.39 (s, 3 H, OMe), 2.80 (dd, 1 H, $J_{7A,7B}$ 16.5 Hz, H-7A), 2.53 (d, 1 H, *J* 6.8 Hz, OH), 2.49 (dd, 1 H, H-7B).

12b, oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.58 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.30 (ddd, 1 H, $J_{5,6}$ 1.1, $J_{6,7B}$ 3.0, $J_{6,7A}$ 9.2 Hz, H-6), 4.05 (dd, 1 H, $J_{3,4}$ 9.2, $J_{2,3}$ 9.5 Hz, H-3), 3.74 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 3.73 (dd, 1 H, H-2), 3.50 (dd, 1 H, H-5), 3.41 (s, 3 H, OMe), 2.82 (dd, 1 H, $J_{7A,7B}$ 16.4 Hz, H-7A), 2.51 (dd, 1 H, H-7B), 2.50 (d, 1 H, J 4.2 Hz, OH).

Methyl 2,3,4-tri-*O*-benzyl-7-deoxy-D(L)-*glycero*-α-D-*gluco*-octopyranosides (13a and 13b)

A mixture of acids **12a** and **12b** (7.9 g, 15.1 mmol) was dissolved in tetrahydrofuran (15 ml), and borane-tetrahydrofuran complex (30.2 ml, 30.2 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and ethanol (40 ml) was added. The solution was concentrated under reduced pressure and the residue was purified by chromatography with hexane-diethyl ether, 8:2 to yield **13a** (4 g, 52%) and **13b** (3.3 g, 43%).

Eluted first was **13a,** colorless crystals, m.p. 125 - 126 °C; $[\alpha]_D$ +18 (*c* 0.5, $CHCl_3$); IR (KBr): 3480 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.62 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.08 (ddd, 1 H, $J_{5,6}$ 1.1, $J_{6,7B}$ 4.0, $J_{6,7A}$ 9.4 Hz, H-6), 4.03 (dd, 1 H, $J_{3,4}$ 9.1, $J_{2,3}$ 9.3 Hz, H-3), 3.87 (m, 3 H, OH, H-8A, H-8B), 3.68 (dd, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 3.54 (dd, 1 H, H-2), 3.51 (dd, 1 H, H-5), 3.39 (s,3 H, OMe), 2.10 (d, 1 H, J 8.2 Hz, OH), 2.00 (m, 1 H, H-7A), 1.63 (m, 1 H, H-7B). HR-MS/ LSIMS-NBA: for $C_{30}H_{36}O_7Na$ $(M+Na)^+$ calcd.: 531.2359. Found: 531.2322. MS/ LSIMS-NBA: 531 $(M+Na)^+$.

Eluted next was **13b**, oil, $[\alpha]_D$ +9 (*c* 0.2, $CHCl_3$); IR (film): 3445 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.57 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 3.97 (m, 1 H, H-6), 3.90 (dd, 1 H, $J_{3,4}$ 8.8, $J_{2,3}$ 9.5 Hz, H-3), 3.75 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 3.67 (m, 3 H, OH, H-8A, H-8B), 3.55 (dd, 1 H, $J_{5,6}$ 1.2 Hz, H-5), 3.50 (dd, 1 H, H-2), 3.41 (s, 3 H, OMe), 3.30 (d, 1 H, J 4.0 Hz, OH), 2.15 (m, 2 H, H-7A, H-7B). HR-MS/ LSIMS-NBA: for $C_{30}H_{36}O_7Na$ $(M+Na)^+$ calcd.: 531.2359. Found: 531.2387. MS/ LSIMS-NBA: 531 $(M+Na)^+$.

Methyl 2,3,4-tri-*O*-benzyl-8-*O*-*tert*-butyldiphenylsilyl-7-deoxy-L-*glycero*-α-D-*gluco*-octopyranoside (14a)

To a solution of diol **13a** (2.1 g, 4.1 mmol) in *N,N*-dimethylformamide (15 ml) were added *tert*-butyldiphenylsilyl chloride (1.1 ml, 4.1 mmol) and imidazole (0.3 g, 4.1 mmol). The reaction mixture was stirred for 12 h at room temperature, diluted with water (30 ml) and extracted with diethyl ether (3x30 ml). The combined extracts were washed with water (30 ml), dried, concentrated, and the residue was chromatographed with hexane-diethyl ether, 3:2 to afford **14a** (3 g, 97.4%), oil, $[\alpha]_D$ +1° (*c* 1.0, $CHCl_3$); IR (film): 3493 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.63 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.30 (ddd, 1 H, $J_{5,6}$ 1.1, $J_{6,7A}$ 7.0, $J_{6,7B}$ 7.3 Hz, H-6), 4.02 (dd, 1 H, $J_{3,4}$ 8.9, $J_{2,3}$ 9.3 Hz, H-3), 3.88 (m, 2 H, H-8A, H-8B), 3.77

(dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 3.57 (dd, 1 H, H-2), 3.52 (dd, 1 H, H-5), 3.35 (s, 3 H, OMe), 2.57 (d, 1 H, J 5.8 Hz, OH), 2.06 (m, 1 H, H-7A), 1.68 (m, 1 H, H-7B), 1.06 [s, 9 H, Me (*t*-Bu)]. HR-MS/ LSIMS-NBA: for $C_{46}H_{54}O_7Na$ $(M+Na)^+$ calcd.: 769.3536. Found: 769.3598. MS/ LSIMS-NBA: 769 $(M+Na)^+$, 715 $(M-OMe)^+$.

Methyl 2,3,4-tri-*O*-benzyl-8-*O*-*tert*-butyldiphenylsilyl-7-deoxy-D-*glycero*-α-D-*gluco*-octopyranoside (14b)

The procedure used was analogous to the one described for **14a**. Diol **13b** (2 g, 3.9 mmol) was silylated to **14b** (2.8 g, 95.3%), oil, $[\alpha]_D$ +10° (*c* 1.5, $CHCl_3$); IR (film): 3501 cm^{-1} (OH); ^1H NMR (200 MHz, $CDCl_3$): δ 4.60 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.15 (ddd, 1 H, $J_{5,6}$ 1.1, $J_{6,7A}$ 6.9, $J_{6,7B}$ 7.0 Hz, H-6), 4.05 (dd, 1 H, $J_{3,4}$ 8.8, $J_{2,3}$ 9.4 Hz, H-3), 3.80 (m, 2 H, H-8A, H-8B), 3.55 (dd, 1 H, $J_{4,5}$ 10.1 Hz, H-4), 3.50 (dd, 1 H, H-2), 3.49 (dd, 1 H, H-5), 3.39 (s, 3 H, OMe), 3.10 (d, 1 H, J 3.9 Hz, OH), 1.75 (m, 2 H, H-7A, H-7B), 1.09 [s, 9 H, Me (*t*-Bu)]. *Anal.:* for $C_{46}H_{57}O_7Si$ calcd.: C 73.97; H 7.29. Found: C 74.02; H 7.35.

Methyl 2,3,4,6-tetra-*O*-benzyl-8-*tert*-butyldiphenylsilyl-7-deoxy-L-*glycero*-α-D-*gluco*-octopyranoside (15a)

To a solution of alcohol **14a** (2.8 g, 3.8 mmol) in dry *N,N*-dimethylformamide (40 ml) was added sodium hydride (50% in oil, 0.2 g, 8.4 mmol). After 30 min of stirring at room temperature benzyl bromide was added (0.5 ml, 4.2 mmol). The reaction mixture was stirred for 3 h at room temperature, diluted with water (80 ml) and extracted with diethyl ether (3x60 ml). The combined extracts were washed with water (40 ml), dried, concentrated, and the residue was purified on a silica gel column with hexane-diethyl ether, 9:1 to yield **15a** (2.9 g, 91%), oil, $[\alpha]_D$ +17 (*c* 0.7, $CHCl_3$); ^1H NMR (200 MHz, C_6D_6): δ 4.64 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.35 (ddd, 1 H, $J_{5,6}$ 1.1, $J_{6,7A}$ 6.2, $J_{6,7B}$ 6.7 Hz, H-6), 4.14 (dd, 1 H, $J_{3,4}$ 8.8, $J_{2,3}$ 9.6 Hz, H-3), 3.95 (m, 2 H, H-8A, H-8B), 3.67 (dd, 1 H, $J_{4,5}$ 10.1 Hz, H-4), 3.62 (dd, 1 H, H-5), 3.61 (dd, 1 H, H-2), 3.07 (s, 3 H, OMe), 2.20 (m, 2 H, H-7A, H-7B), 1.15 [s, 9H, Me (*t*-Bu)]. HR-MS/ LSIMS-NBA: for $C_{53}H_{60}O_7SiNa$ $(M+Na)^+$ calcd.: 859.4006. Found: 859.4082. MS/ LSIMS-NBA: 859 $(M+Na)^+$.

Methyl 2,3,4,6-tetra-*O*-benzyl-8-*O*-*tert*-butyldiphenylsilyl-7-deoxy-D-*glycero*-α-D-*gluco*-octopyranoside (15b)

The procedure used was analogous to the one described for **15a**. Alcohol **14b** (2.8 g, 3.8 mmol) was converted to **15b** (2.8 g, 88%), oil, $[\alpha]_D$ +36 (c 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 4.63 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.24 (ddd, 1 H, $J_{5,6}$ 1.0, $J_{6,7A}$ 6.2, $J_{6,7B}$ 6.6 Hz, H-6), 4.08 (dd, 1 H, $J_{3,4}$ 8.9, $J_{2,3}$ 9.4 Hz, H-3), 4.04 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.79 (m, 2 H, H-8A, H-8B), 3.65 (dd, 1 H, H-5), 3.59 (dd, 1 H, H-2), 3.26 (s,

3 H, OMe), 2.10 (m, 2 H, H-7A, H-7B), 1.05 [s, 9H, Me (*t*-Bu)]. HR-MS/ LSIMS-NBA: for $C_{53}H_{60}O_7SiNa$ $(M+Na)^+$ calcd.: 859.4006. Found: 859.4054. MS/ LSIMS-NBA: 859 $(M+Na)^+$.

Methyl 2,3,4,6-tetra-*O*-benzyl-7-deoxy-L-*glycero*-α-D-*gluco*-octopyranoside (16a)

To a solution of compound **15a** (2.4 g, 2.9 mmol) in tetrahydrofuran (40 ml) was added tetrabutylammonium fluoride (0.98 g, 3.7 mmol). The reaction mixture was stirred for 12 h at room temperature and then concentrated to a residue that was chromatographed with hexane-diethyl ether, 1:1 to yield **16a** (1.5 g, 87%), oil, $[\alpha]_D$ +71 (c 1.0, $CHCl_3$); IR (film): 3486 cm^{-1} (OH); ^1H NMR (200 MHz, $CDCl_3$): δ 4.65 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.08 (dd, 1 H, $J_{3,4}$ 8.8, $J_{2,3}$ 9.6 Hz, H-3), 4.04 (dd, 1 H, $J_{5,6}$ 1.1, $J_{4,5}$ 10.3 Hz, H-5), 3.89 (ddd, 1 H, $J_{6,7A}$ 9.1 Hz, H-6), 3.57 (m, 2 H, H-8A, H-8B), 3.53 (dd. 1 H, H-2), 3.44 (s, 3 H, OMe), 3.40 (dd, 1 H, H-4), 1.85 (m, 1 H, H-7A), 1.73 (d, 1 H, *J* 5.5 Hz, OH), 1.46 (m, 1 H, H-7B). *Anal.*: for $C_{37}H_{42}O_7$ (598.74) calcd.: C 74.22; H 7.07. Found: C 74.18; H 7.25.

Methyl 2,3,4,6-tetra-*O*-benzyl-7-deoxy-D-*glycero*-α-D-*gluco*-octopyranoside (16b)

The procedure used was analogous to the one described for **16a**. Derivative **15b** (2.4 g, 2.9 mmol) was converted to **16b** (1.6 g, 93%), oil, $[\alpha]_D$ +26 (*c* 0.3, $CHCl_3$); IR (film): 3478 cm^{-1} (OH); ^1H NMR (200 MHz, C_6D_6): δ 4.32 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.19 (ddd, 1 H, $J_{5,6}$ 1.7, $J_{6,7A}$ 6.2 Hz, H-6), 4.07 (dd, 1 H, $J_{3,4}$ 8,7, $J_{2,3}$ 9.7 Hz, H-3), 3.89 (dd, 1 H, $J_{4,5}$ 9.8 Hz, H-5), 3.64 (m, 4H, OH, H-4, H-8A, H-8B), 3.59 (dd, 1 H, H-2), 3.21 (s, 3 H, OMe), 2.00 (m, 2 H, H-7A, H-7B). HR-MS/ LSIMS-NBA: for $C_{37}H_{42}O_7Na$ $(M+Na)^+$ calcd.: 621.2828. Found: 621.2840. MS/ LSIMS-NBA: 621 $(M+Na)^+$, 597 $(M+H)^+$, 567 $(M-OMe)^+$.

Methyl 2,3,4,6-tetra-*O*-benzyl-7-deoxy-8-*O*-methanesulfonyl-L-*glycero*-α-D-*gluco*-octopyranoside (17a)

To a solution of alcohol **16a** (1.5 g, 2.5 mmol) in pyridine (30 ml), cooled to -10 °C were added methanesulfonyl chloride (0.3 ml, 3.8 mmol) and DMAP. The reaction mixture was stirred at -10 °C. After 7 h the solution was brought to room temperature and concentrated. The solution was diluted with dichloromethane (40 ml), washed with 1M hydrochloric acid (40 ml) and saturated aq sodium hydrogencarbonate (40 ml). The combined extracts were dried and concentrated. The residue was purified by chromatography with hexane-diethyl ether 7:3 to yield **17a** (1.63 g, 96%), colorless crystals, m.p.: 100 -102 °C; $[\alpha]_D$ +58 (*c* 0.4, $CHCl_3$); ν_{max} (KBr) 1347, 1168, 1088 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$):δ 4.65 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.24 (m, 3 H, H-6, H-8A, H-8B), 4.08 (dd, 1 H, $J_{3,4}$ 9.0, $J_{2,3}$ 9.3 Hz, H-3), 3.90 (dd, 1 H, $J_{5,6}$ 1.1, $J_{4,5}$ 10.1 Hz, H-5), 3.53 (dd, 1 H, H-2), 3.43 (s, 3 H, OMe), 3.39 (dd, 1 H, H-4), 2.78 [s, 3 H, Me (Ms)], 2.04 (m, 1 H, H-7A), 1.84 (m, 1 H, H-7B). HR-MS/ LSIMS-NBA: for $C_{38}H_{44}O_9SNa$ $(M+Na)^+$ calcd.: 699.2604. Found: 699.2635. MS/ LSIMS-NBA: 699 $(M+Na)^+$, 675 $(M-H)^+$, 645 $(M-OMe)^+$.

Methyl 2,3,4,6-tetra-*O*-benzyl-7-deoxy-8-*O*-methanesulfonyl-D-*glycero*-α-D-*gluco*-octopyranoside (17b)

The procedure was analogous to the one described for **17a.** Alcohol **16b** (1.6 g, 2.7 mmol) was converted to **17b** (1.76 g, 97%), oil, $[\alpha]_D$ +10 (*c* 0.4, $CHCl_3$); ν_{max} ($CHCl_3$) 1357, 1174, 1090 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.68 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.06 (m, 2 H, H-3, H-6), 3.76 (m, 3 H, H-5, H-8A, H-8B), 3.67 (dd, 1 H, $J_{3,4}$ 8.9, $J_{4,5}$ 10,1 Hz, H-4), 3.61 (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 3.42 (s, 3 H, OMe), 2.92 [s, 3 H, Me (Ms)], 2.21 (m, 2 H, H-7A, H-7B). HR-MS/ LSIMS-NBA: for $C_{38}H_{44}O_9SNa$ $(M+Na)^+$ calcd.: 699.2604. Found: 699.2638. MS/ LSIMS-NBA: 699 $(M+Na)^+$, 675 $(M-H)^+$, 645 $(M-OMe)^+$.

Methyl 8-azido-2,3,4,6-tetra-*O*-benzyl-7,8-dideoxy-L-*glycero*-α-D-*gluco*-octopyranoside (18a)

To a solution of mesylate **17a** (1.4 g, 2.1 mmol) in *N,N*-dimethylformamide (30 ml) sodium azide (0.54 g, 8.3 mmol) was added and the mixture was heated at 60 °C for 1 h. The solution was cooled to room temperature, diluted with water (50 ml) and extracted with diethyl ether (3x40 ml). The combined extracts were washed with water (30 ml), dried and concentrated. The residue was chromatographed with hexane-diethyl ether, 9:1 to afford **18a** (1.2 g, 92%), colorless crystals, m.p.: 52 - 53 °C; $[\alpha]_D$ +59 (*c* 0.3, $CHCl_3$); ν_{max} (film): 2096 cm^{-1} (N_3); ^1H NMR (500 MHz, $CDCl_3$): δ 4.67 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.06 (dd, 1 H, $J_{3,4}$ 8.8, $J_{2,3}$ 9.5 Hz, H-3), 4.04 (ddd, 1 H, $J_{5,6}$ 1.1, $J_{6,7A}$ 10.3 Hz, H-6), 3.75 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-5), 3.52 (dd, 1 H, H-2), 3.43 (s, 3 H, OMe), 3.38 (m, 1 H, H-8A), 3.37 (dd, 1 H, H-4), 3.13 (m, 1 H, H-8B), 1.89 (m, 1 H, H-7A), 1.53 (m, 1 H, H-7B). HR-MS/ LSIMS-NBA: for $C_{37}H_{41}O_6N_3Na$ $(M+Na)^+$ calcd.: 646.2893. Found: 646.2931. MS/ LSIMS-NBA: 646 $(M+Na)^+$, 622 $(M-H)^-$, 592 $(M-OMe)^+$.

Methyl 8-azido-2,3,4,6-tetra-*O*-benzyl-7,8-dideoxy-D-*glycero*-α-D-*gluco*-octopyranoside (18b)

The procedure was analogous to the one described for **18a**. Mesylate **17b** (1.5 g, 2.2 mmol) was converted to **18b** (1.3 g, 94%), oil, $[\alpha]_D$ +12 (*c* 0.2, $CHCl_3$); ν_{max} (film): 2096 cm^{-1} (N_3); ^1H NMR (500 MHz, $CDCl_3$): δ 4.67 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.05 (dd, 1 H, $J_{3,4}$ 8.4, $J_{2,3}$ 9.7 Hz, H-3), 3.99 (ddd, 1 H, $J_{5,6}$ 1.1, $J_{6,7A}$ 8.3, $J_{6,7B}$ 9.9 Hz, H-6); 3.74 (dd, 1 H, $J_{4,5}$ 10.8 Hz, H-4), 3.65 (dd, 1 H, H-5), 3.61 (dd, 1 H, H-2), 3.42 (m, 2 H, H-8A, H-8B), 3.41 (s, 3 H, OMe), 2.11 (m, 1 H, H-7A), 2.03 (m, 1 H, H-7B). HR-MS/ LSIMS-NBA: for $C_{37}H_{41}O_6N_3Na$ $(M+Na)^+$ calcd.: 646. 2893. Found: 646.2915. MS/ LSIMS-NBA: 646 $(M+Na)^+$.

1-O-Acetyl-8-azido-2,3,4,6-tetra-*O*-benzyl-7,8-dideoxy-L-*glycero*-α(β)-D-*gluco*-octopyranose (19a)

To a solution of compound **18a** (1.2 g, 1.93 mmol) in ethyl acetate (13 ml) were added acetic anhydride (26 ml) and concentrated sulfuric acid (0.021 ml). After 5 min of stirring the reaction mixture was diluted with diethyl ether (50 ml) and washed with saturated aq sodium hydrogencarbonate (5x40 ml). The

organic extract was washed with water (40 ml), dried and concentrated. The residue was purified on a silica gel column hexane-ethyl acetate, 9:1 to yield **19a** (1.17 g, 93%), oil, $[\alpha]_D$ + 106 (*c* 0.6, $CHCl_3$); ν_{max} (film): 2098 (N_3), 1753 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 6.43 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1$_\alpha$), 5.68 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1$_\beta$), 4.10 (dd, 1 H, $J_{5,6}$ 1.0, $J_{4,5}$ 10.4 Hz, H-5), 4.02 (dd, 1 H, $J_{3,4}$ 9.0, $J_{2,3}$ 9.5 Hz, H-3), 3.79 (ddd, 1 H, $J_{6,7A}$ 8.2, $J_{6,7B}$ 10.7 Hz, H-6), 3.66 (dd, 1 H, H-2), 3.53 (dd, 1 H, H-4), 3.40 (m, 1 H, H-8A), 3.21 (m, 1 H, H-8B), 2.17 [s, 3 H, Me (Ac)], 1.95 (m, 1 H, H-7A), 1.58 (m, 1 H, H-7B). HR-MS/ LSIMS-NBA: for $C_{38}H_{41}O_7N_3Na$ $(M+Na)^+$ calcd.: 674.2842. Found: 674.2814. MS/ LSIMS-NBA: 674 $(M+Na)^+$.

1-O-Acetyl-8-azido-2,3,4,6-tetra-*O*-benzyl-7,8-dideoxy-D-*glycero*-α(β)-D-*gluco*-octopyranose (19b)

The procedure used was analogous to the one described for **19a**. Compound **18b** (1.3 g, 2.09 mmol) was converted to **19b** (1.23 g, 91%), oil, $[\alpha]_D$ +43 (*c* 0.8, $CHCl_3$);ν_{max} (film): 2097 (N_3), 1751 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 6.38 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1$_\alpha$), 5.52 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1$_\beta$), 4.10 (m, 2 H, H-5, H-6), 3.83 (m, 2 H, H-3, H-4), 3.73 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 3.37 (m, 2 H, H-8A, H-8B), 2.19 [s, 3 H, Me (Ac)], 2.05 (m, 2 H, H-7A, H-7B). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.28 (C=O), 128.46, 128.24, 128.13, 127.98, 127.88, 127.80, 127.76, 127.62, 127.53, 127.37, 89.83, 82.09, 78.79, 76.77, 75.73 (CH_2Ph), 74.76 (CH_2Ph), 73.52, 73.20 (CH_2Ph), 73.13, 71.87 (CH_2Ph), 47.91 (C-8), 29.04 (C-7), 21.04 (Me). HR-MS/ LSIMS-NBA: for $C_{38}H_{41}O_7N_3Na$ $(M+Na)^+$ calcd.: 674.2842. Found: 674.2820. MS/ LSIMS-NBA: 674 $(M+Na)^+$.

2,3,4,6-Tetra-*O*-benzyl-8-(*N*-*tert*-butoxycarbonyl)amino-7,8-dideoxy-L-*glycero*-D-*gluco*-octitol (20a)

To a solution of compound **19a** (1 g, 1.54 mmol) in ethanol (10 ml) was added sodium borohydride (0.2 g, 5.4 mmol). The reaction mixture was refluxed 1 h, then cooled to room temperature. To this mixture were added 10 drops of $NiCl_2 \cdot 6H_2O$ solution in ethanol (40 mmol of $NiCl_2 \cdot 6H_2O$ in 250 ml of ethanol). The reaction mixture was stirred for 20 min and then ethyl acetate (10 ml), saturated aq sodium hydrogencarbonate (20 ml) and di-*tert*-butyl dicarbonate (0.4 g, 1.7 mmol) were added. The reaction mixture was stirred for 15 min and extracted with ethyl acetate (3x10 ml). The extract was washed with 1M hydrochloric acid (20 ml) and brine (20 ml), dried, and evaporated to dryness. The crude product was chromatographed over silica gel column with hexane-ethyl acetate, 1:1 to give diol **20a** (1 g, 95%), oil, $[\alpha]_D$ +11 (*c* 0.6, $CHCl_3$); ν_{max} (film): 3430 (OH, NH), 1713 cm^{-1} (C=O, Boc); ^1H NMR (500 MHz, $CDCl_3$): δ 4.09 (m, 1H), 3.98 (dd, 1 H, *J* 3.3, *J* 6.2 Hz), 3.88 (m, 1 H), 3.74 (m, 2 H), 3,67 (m, 2 H, H-8A, H-8B), 3.20 (m, 2 H), 2.14 (d, 1 H, *J* 6.4 Hz, OH), 2.10 (d, 1 H, *J* 6.0 Hz, OH), 1.75 (m, 2 H, H-7A, H-7B), 1.55 [s, 9H, Me (*t*-Bu)]. HR-MS/ LSIMS-NBA: for $C_{41}H_{51}O_8NNa$ $(M+Na)^+$ calcd.: 708.3513. found: 708.3492. MS/ LSIMS-NBA: 708 $(M+Na)^+$, 692 $(M+Li)^+$, 686 $(M+H)^+$.

2,3,4,6-Tetra-*O*-benzyl-8-(*N-tert*-butoxycarbonyl)amino-7,8-dideoxy-D-*glycero*-D-*gluco*-octitol (20b)

The procedure used was analogous to the one described for **20a**. Octitol **19b** (1 g, 1.54 mmol) was converted to **20b** (0.95 g, 90%), oil, $[\alpha]_D$ +39 (*c* 0.5, $CHCl_3$); ν_{max} (film): 3428 (OH, NH), 1702 cm^{-1} (C=O, Boc); ^1H NMR (200 MHz, C_6D_6): δ 4.16 (dd, 1 H), 3.85 (m, 6H), 3.75 (ddd, 1 H, $J_{5,6}$ 1.5, $J_{6,7A}$ 6.2 Hz, H-6), 3.21 (m, 2 H, H-8A, H-8B), 2.29 (d, 1 H, *J* 6.1 Hz, OH), 1.83 (m, 2 H, H-7A, H-7B), 1.49 [s, 9H, Me (*t*-Bu)]. ^{13}C NMR (50 MHz, C_6D_6): δ 155.97 (C=O), 138.61, 138.54, 138.44, 138.13, 129.00, 128.60, 128.48. 128.30, 128.25, 128.10, 128.00, 127.86, 127.81, 127.78, 127.52, 80.67, 80.12, 77.50, 76.06, 74.88 (CH_2Ph), 73.10 (C-5), 73.09 (CH_2Ph), 72.53 (CH_2Ph), 71.80 (CH_2Ph), 62.15 (C-1), 37.55 (C-8), 31.21 (C-7), 28.53 (Me). HR-MS/ LSIMS-NBA: for $C_{41}H_{51}O_8NNa$ $(M+Na)^+$ calcd.: 708.3513. Found: 708.3498. MS/ LSIMS-NBA: 708 $(M+Na)^+$.

2,3,4,6-Tetra-*O*-benzyl-8-(*N-tert*-butoxycarbonyl)amino-7,8-dideoxy-1,5-di-*O*-methanesulfonyl-L-*glycero*-D-*gluco*-octitol (21a)

To a solution of octitol **20a** (0.9 g, 1.31 mmol) in pyridine (10 ml), cooled to -10 °C, were added methanesulphonyl chloride (0.24 ml, 1.65 mmol) and DMAP. The reaction mixture was stirred for 7 h, brought to room temperature, and concentrated. The residue was dissolved in chloroform (20 ml). The organic layer was washed with 0.5M hydrochloric acid (15 ml), then with saturated aq sodium hydrogencarbonate (15 ml), dried, and evaporated to dryness. The residue was purified by chromatography with hexane-ethyl acetate 9:1 to yield **21a** (0.89 g, 81%), oil, $[\alpha]_D$ +22 (*c* 0.3, $CHCl_3$); ν_{max} (film): 3426 (OH, NH), 1712 cm^{-1} (C=O, Boc); ^1H NMR (200 MHz, $CDCl_3$): δ 5.27 (dd, 1 H, *J* 3.2, *J* 5.5 Hz, H-5), 3.96 (m, 4H), 3.82 (m, 2 H, H-1A, H-1B), 3.17 (m, 2 H, H-8A, H-8B), 3.03 [s, 3 H, Me (Ms)], 2.83 [s, 3 H, Me (Ms)], 1.75 (m, 1 H, H-7A), 1.42 [s, 9 H, Me (*t*-Bu)], 1.38 (m, 1 H, H-7B). HR-MS/ LSIMS-NBA: for $C_{43}H_{55}O_{12}NS_2Na$ $(M+Na)^+$ calcd.: 864.3063. Found: 864.3045. MS/ LSIMS-NBA: 864 $(M+Na)^+$, 842 $(M+H)^+$.

2,3,4,6-Tetra-*O*-benzyl-8-(*N-tert*-butoxycarbonyl)amino-7,8-dideoxy-1,5-di-*O*-methanesulfonyl-D-*glycero*-D-*gluco*-octitol (21b)

The procedure used was analogous to the one described for **21a**. Octitol **20b** (0.9 g, 1.31 mmol) was converted to **21b** (0.95 g, 86%), oil, $[\alpha]_D$ -7 (*c* 0.2, $CHCl_3$); ν_{max} (film): 3424 (NH), 1709 cm^{-1} (C=O, BOC); ^1H NMR (200 MHz, $CDCl_3$): δ 5.15 (m, 1 H, H-5), 4.27 (m, 2 H), 3.96 (m, 2 H), 3.72 (m, 2 H, H-1A, H-1B), 3.20 (m, 2 H, H-8A, H-8B), 2.89 [s, 3 H, Me (Ms)], 2.83[s, 3 H, Me (Ms)], 1.75 (m, 2 H, H-7A, H-7B), 1.46 [s, 9 H, Me (*t*-Bu)]. HR-MS/ LSIMS-NBA: for $C_{43}H_{55}O_{12}NS_2Na$. $(M+Na)^+$ calcd.: 864.3063. Found: 864.3018. MS/ LSIMS-NBA: 864 $(M+Na)^+$, 842 $(M+H)^+$.

(1*S*,6*S*,7*R*,8*R*,8a*S*)-1,6,7,8-Tetra-*O*-benzylindolizidine (22a)

To a solution of **21a** (300 mg, 0.36 mmol) in dichloromethane (5 ml) were added phenol (134 mg, 1.43 mmol) and trimethylsilyl chloride (45 μL, 0.36 mmol). The reaction mixture was stirred for 8 h at room temperature and then concentrated. The residue was purified by chromatography with hexane-ethyl acetate, 1:9. The crude product (220 mg, 0.3 mmol) was dissolved in abs. ethanol (5 ml) and sodium acetate (74 mg, 0.90 mmol) was added to the solution. The reaction mixture was refluxed for 2 h, and then the solution was cooled to room temperature and ethyl acetate (20 ml) was added. The organic layer was washed with water (2x20 ml), dried, and evaporated to dryness. The residue was purified by chromatography with hexane-ethyl acetate, 3:2 to yield **22a** (108 mg, 55%), oil, $[\alpha]_D$ -18 (*c* 1.1, $CHCl_3$); ν_{max} (film): 1098 cm^{-1} (C-O-C); ^1H NMR (500 MHz, $CDCl_3$): δ 4.16 (m, 2 H, H-1, H-7), 3.96 (dd, 1 H, *J* 8.4, *J* 6.1 Hz, H-8), 3.60 (m, 1 H, H-6), 2.97 (m, 1 H, H-8a), 2.89 (m, 4 H, H-3A, H-3B, H-5A, H-5B), 2.07 (m, 1 H, H-2A), 1.97 (m, 1 H, H-2B). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.20, 139.07, 138.88, 138.86, 128.36, 128.28, 128.24, 128.15, 128.09, 127.70, 127.66, 127.62, 127.61, 127.43, 127.39, 127.20, 82.80 (C-1), 80.71 (C-7), 79.44 (C-8), 79.31 (C-6), 74.82 (CH_2Ph), 73.60 (CH_2Ph), 72.72 (CH_2Ph), 72.04 (CH_2Ph), 66.18 (C-8a), 53.23 (C-5), 53.14 (C-3), 31.04 (C-2). COSY ^1H-^1H and HETCOR ^1H-^{13}C experiments confirmed the spectral assignments. HR-MS/ LSIMS-NBA: for $C_{36}H_{39}O_4NNa$ $(M+Na)^+$ calcd.: 572.2777. Found: 572.2782. MS/ LSIMS-NBA: 572 $(M+Na)^+$, 550 $(M+H)^+$.

(1*R*,6*S*,7*R*,8*R*,8a*S*)-1,6,7,8-tetra-*O*-benzylindolizidine (22b)

The procedure used was analogous to the one described for **22a**. Compound **21b** (300 mg, 0.36 mmol) was cyclized to **22b** (101 mg, 52%), oil, $[\alpha]_D$ +10 (*c* 2.6, $CHCl_3$); ν_{max} (film): 1091, 1073 cm^{-1} (C-O-C); ^1H NMR (500 MHz, $CDCl_3$): δ 4.24 (m, 1 H, H-1), 3.67 (m, 1 H, H-8), 3.60 (t, 1 H, *J* 2.3 Hz, H-7), 3.46 (m, 1 H, H-6), 3.03 (m, 2 H, H-5A, H-5B), 2.42 (m, 2 H, H-3A, H-8a), 2.33 (m, 1 H, H-3B), 2.18 (m, 1 H, H-2A), 1.64 (m, 1 H, H-2B). ^{13}C NMR (125 MHz): δ 138.78, 138.64, 138.47, 138.16, 128.60, 128.34, 128.24, 128.23, 128.20, 127.90, 127.85, 127.67, 127.64, 127.49, 127.46, 77.73 (C-1), 73.73 (C-6), 73.58 (C-8), 72.29 (CH_2Ph), 72.11 (C-7), 71.75 (CH_2Ph), 71.64 (CH_2Ph), 71.25 (CH_2Ph), 67.49 (C-8a), 53.20 (C-5), 53.13 (C-3), 29.05 (C-2). COSY ^1H-^1H and HETCOR ^1H-^{13}C experiments confirmed the spectral assignments. HR-MS/ LSIMS-NBA: for $C_{36}H_{39}O_4NNa$ $(M+Na)^+$ calcd.: 572.2777. Found: 572.2752. MS/ LSIMS-NBA: 572 $(M+Na)^+$, 550 $(M+H)^+$.

(1*S*,6*S*,7*R*,8*R*,8a*S*)-1,6,7,8-Tetrahydroxyindolizidine [(+)-8a-*epi*-castanospermine] (4)

To a solution of **22a** (80 mg, 0.15 mmol) in methanol (9 ml) were added palladium on activated carbon catalyst (10%, 80 mg) and concentrated hydrochloric acid (0.2 ml). The solution was placed in a *Parr* medium-pressure hydrogenation apparatus under 70 psi of H_2. After 8 h TLC indicated the absence of starting material. Amberlite [Amberlite IRA-400(OH), 1 g] was added. After 4 h stirring the solution was filtered through Celite and concentrated. The crude product was purified by chromatography with chloroform-methanol 3:1 to yield **4** (24 mg, 87%), oil, $[\alpha]_D$ +28 (*c* 0.3, MeOH); [lit.[18]: for (1*R*,6*R*,7*S*,8*S*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine [(-)-8a-*epi*-castanospermine] $[\alpha]_D$ - 33 (*c* 0.31, MeOH)]; ν_{max} (film): 3353 cm^{-1} (OH); ^1H NMR (500 MHz, CD_3OD): δ 4.31 (m, 1 H, H-1), 4.10 (m, 1 H, H-8), 3.94 (m, 1 H, H-7), 3.70 (m, 1 H, H-6), 3.34 (m, 2 H, H-3A, H-5A), 3.21 (m, 1 H, H-5B), 3.12 (m, 1 H, H-3B), 2.50 (m, 1 H, H-8a), 2.01 (m, 1 H, H-2A), 1.53 (m, 1 H, H-2B). ^{13}C NMR (125 MHz, CD_3OD): δ 72.38, 72.37, 71.40, 69.66, 67.07, 56.03, 53.12, 33.18. HR-MS/ LSIMS-NBA: for $C_8H_{16}O_4N$ $(M+H)^+$ calcd.: 190.1079. Found: 190.1071. MS/ LSIMS-NBA: 190 $(M+H)^+$.

(1*R*,6*S*,7*R*,8*R*,8a*S*)-1,6,7,8-Tetrahydroxyindolizidine [(+)-1,8a-di-*epi*-castanospermine] (5)

The procedure used was analogous to the one described for **4**. Compound **22b** (80 mg, 0.15 mmol) was hydrogenated to product **5** (19 mg, 69%), oil, $[\alpha]_D$ -8 (*c* 0.4, MeOH); [lit.[20]: $[\alpha]_D$ - 9° (*c* 0.5, MeOH)]; ν_{max} (film): 3370 cm^{-1} (OH); ^{13}C NMR (50 MHz, D_2O): δ 74.96, 73.90, 73.83, 73.44, 72.73, 56.10 (C-5), 54.10 (C-3), 34.50 (C-2). HR-MS/ LSIMS-NBA: for $C_8H_{16}O_4N$ calcd.: 190.1079. Found: 190.1064. MS/ LSIMS-NBA: 190 $(M+H)^+$.

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