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Synthesis of C1- and C8a-epimers of (+)-castanospermine from D-glucose derived γ,δ-epoxyazide: intramolecular 5-*endo* epoxide opening approach

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ABSTRACT

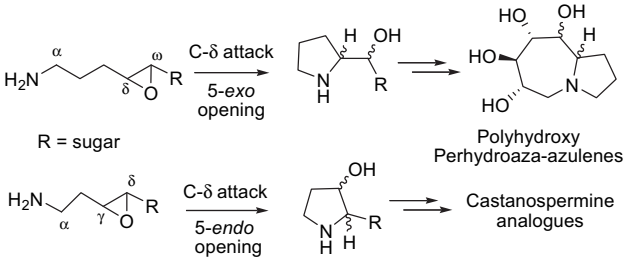
A concise synthesis of two diastereomers of (+)-castanospermine namely 1- and 8a-*epi*-castanospermine **1b** and **1c**, respectively, is reported from D-glucose. The methodology involves stereoselective cross metathesis of D-glucose derived alkene **2** with 4-bromo-1-butene followed by azide displacement and *m*-CPBA oxidation to afford diastereomeric γ,δ-epoxyazides **5a**/**5b**. The Staudinger reaction of epoxyazide **5a** followed by reaction with benzylchloroformate (CbzCl) unexpectedly furnished 1,3-oxazinan-2-one derivative **7** whose stereochemistry was established by single crystal X-ray. This helps to assign the stereochemistry in the epoxidation reaction. The reduction of **5a**/**5b** was then carried out by transfer hydrogenation to provide γ,δ-epoxyamine that concomitantly undergoes intramolecular 5-*endo*-tet cyclization to afford hydroxypyrrolidine ring skeleton with sugar framework-a precursor to castanospermine analogues **1b**/**1c**.

1. Introduction

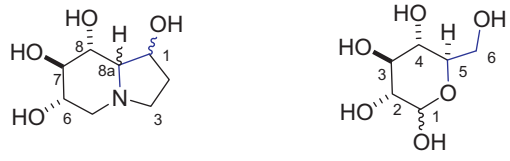
Common occurrence of hydroxypyrrolidine motif in biologically active natural products[1] and its applications in petidomimetics[2] along with its use as chiral auxiliary[3,4] in asymmetric synthesis led to the development of a number of inter- and intra-molecular pathways for its synthesis.[5,6] Among intramolecular cyclization strategies,[6] one of the widely used reaction is either 5-*endo*-tet cyclization[7] of γ,δ-epoxyamine or 5-*exo*-tet opening of δ,ω-epoxyamines to get hydroxypyrrolidine ring system.[8]

In this direction, we have recently reported an intramolecular 5-*exo*-tet opening of D-glucose derived δ,ω-epoxyamine (generated in situ) to afford sugar appended pyrrolidine ring that was explored in the synthesis of polyhydroxy perhydroaza-azulenes[8a] (Scheme 1). As a part of our interest in the synthesis of iminosugars,[9] we are now reporting regioselective intramolecular 5-*endo*-tet cyclization of sugar derived γ,δ-epoxyamine (generated in situ from epoxyazide) to provide 3-hydroxypyrrolidine ring[7] with sugar framework-a key synthon to castanospermine analogues.

Castanospermine **1a** (Fig. 1), isolated from the Australian legume *Castanospermum australae* and *Alexa leopetala*,[10] is of interest amongst synthetic organic chemist and biologists due to its potential utility in the treatment of cancer,[11] diabetes,[12] malaria[13] and AIDS.[14] It is predicted that castanospermine and its analogues may play a role in transplant surgery as they can inhibit the rejection of transplanted tissues.[15] In the search for



Scheme 1. Intramolecular cyclization to pyrrolidine-ring system.



1a α C8a–H, β C1–OH (+)–Castanospermine
1b α C8a–H, α C1–OH 1-*epi*-castanospermine
1c β C8a–H, β C1–OH 8a-*epi*-castanospermine

D-glucose

Fig. 1. (+)-Castanospermine/analogues.

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structure–activity relationship, a number of natural and unnatural analogues of **1a**; with variation in the number, position and stereochemistry of the hydroxyl groups on the indolizidine skeleton, have been synthesized and studied for their biological activity.[16]

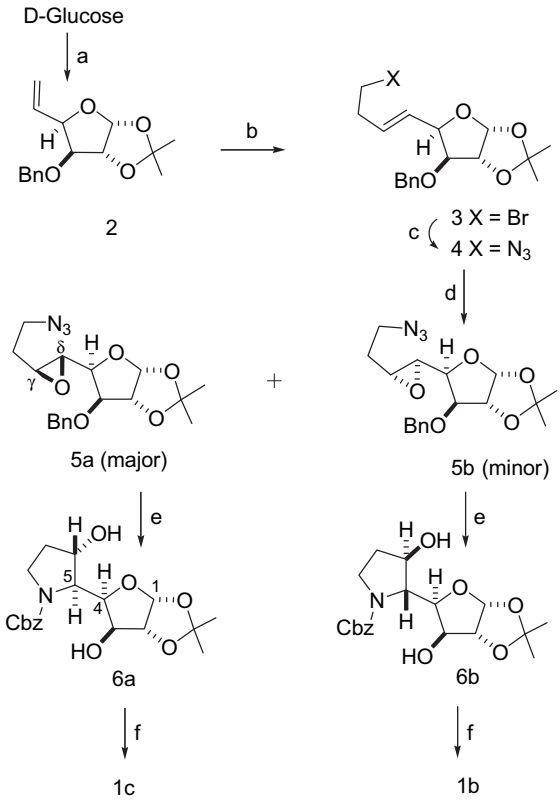
Amongst these analogues, the 1-*epi*-castanospermine **1b** was found to be a potential anti-AIDS therapeutic.[17f] A number of chiron and asymmetric approaches for **1a**–**c** are known in the literature.[17] Due to the sugar like (highly oxygenated) framework in **1**, commonly occurring sugars are appropriate starting material for their synthesis. In fact, the D-glucose type of hidden symmetry in **1** could be easily recognized in the trihydroxylated architect of the piperidine ring wherein; the C6, C7 and C8 of **1** match with that of C2, C3 and C4 of D-glucose as far as the position and stereochemical aspects are concerned. However, building of the hydroxypyrrolidine core, with stereochemically well-defined carbon centres at C1 and at ring-junction (C8a) of **1**, requires an asymmetric pathway. While working in the area of synthetic carbohydrate chemistry, we have investigated intramolecular 5-*endo*-tet cyclization of D-glucose derived γ,δ-epoxyamine. The reaction follows 5-*endo*-tet cyclization path to give of 3-hydroxypyrrolidine ring, which was elaborated towards synthesis of C1- and C8a-*epi*-castanospermine analogues **1b** and **1c**, respectively. Our results are described herein.

2. Result and discussion

The required 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuran-5-ene **2** was prepared from D-glucose in four steps as reported earlier by us and others.[18] As shown in Scheme 2, the cross metathesis reaction of **2** with 4-bromo-1-butene using the Grubb's second-generation catalyst afforded an alkenyl bromide **3** in 71% yield with exclusively *E*-selectivity ($J_{H5,\ H6}$=16 Hz).[19] The bromo compound **3** was subjected for the nucleophilic azide displacement with sodium azide in refluxing acetone to furnish γ,δ-alkenylazide **4** in 88% yield. Azide **4** on epoxidation with *m*-CPBA gave a diastereomeric mixture of epoxides in the ratio 3:1 (as evident from the ^{1}H NMR of crude product) that was separated by column chromatography to afford γ,δ-epoxyazide **5a** and **5b** in good yields. At this stage, we tried reduction of azide using the Staudinger conditions.[20] Thus, the major isomer **5a** was treated with triphenylphospine in THF/H_2O and after the complete disappearance of **5a** (as monitored by TLC) the reaction mixture was directly treated with benzylchloroformate in aq $NaHCO_3$ that afforded unexpected oxazinanone **7**, and not the expected *N*-Cbz protected pyrrolidine compound **A** (Scheme 3). Fortunately, compound **7** was obtained as a colourless solid and the single crystal X-ray analysis (Fig. 2) established the absolute configurations at newly generated stereocenters in **7** as 5*S* and 6*R*.[21] The plausible mechanism for the formation of **7** could be explained as follows (Scheme 3).

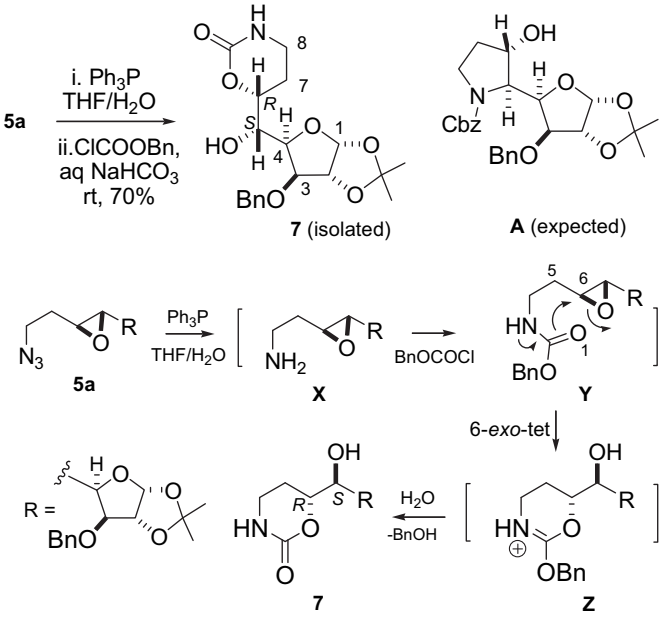
We believe that the Staudinger reduction of epoxyazide **5a** results initially in the formation of epoxyamine **X**, which on reaction with CbzCl gives *N*-Cbz protected epoxyamine **Y**.[22] Subsequently, the Ph_3P=O (generated in situ during the Staudinger reaction) activated oxirane ring undergoes epoxide opening via 6-*exo*-tet mode to give 1,3-oxazinium intermediate **Z** that on hydrolysis gives sugar substituted oxazinanone derivative **7**. The formation of **7** guided us to assign the absolute stereochemistry in the epoxidation reaction. Thus, as **7** is derived from the major epoxide **5a**, the absolute configurations at newly generated stereocenters in **5a** were assigned as 5*R*,6*S* and thus the minor epoxide **5b** was given the absolute configurations as 5*S*,6*R*.[23]

As an alternative pathway to target molecules, we thought of reduction of azide under transfer hydrogenation conditions.[24] Thus, reaction of **5a** using ammonium formate and 10% Pd/C in refluxing ethanol followed by treatment with benzylchloroformate in sodium bicarbonate afforded *N*-Cbz protected 3-hydroxypyrrolidine



[a]Reagents and conditions : (a) Ref–18 (b) 4-bromo-1-butene, Grubbs catalyst II gen (10 mol%), CH_2Cl_2, rt, 24h, 71%; (c) NaN_3, acetone, reflux, 8h, 88%; (d) *m*-CPBA, CH_2Cl_2, 0 °C to 25 °C, 24h; (e) (i) $HCOONH_4$, 10% Pd-C, EtOH, reflux, 26h; (ii) ClCOOBn, aq $NaHCO_3$, EtOH, 12h; (f) (i) TFA/H_2O (3:2), 0 °C to rt, 5h; (ii) H_2, $Pd(OH)_2$, aq MeOH, 90 psi, 15h.

Scheme 2. Synthesis of **1b** and **1c**. Reagents and conditions.



Scheme 3. Formation and plausible mechanism for oxazinanone **7**.

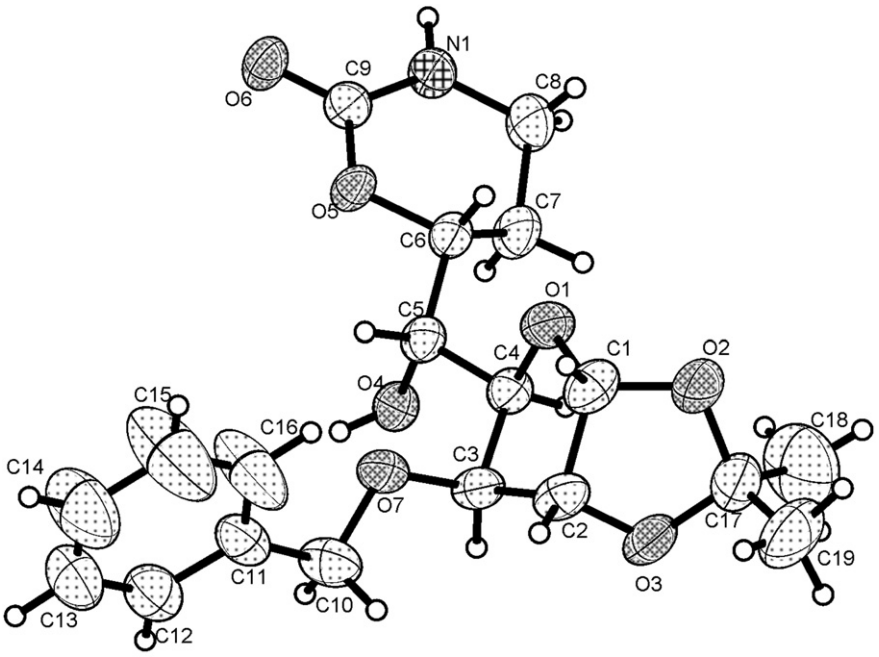


Fig. 2. ORTEP diagram of **7**. Ellipsoids are drawn at 40% probability.

compound **6a**. This reaction probably involves first reduction of azide to γ,δ-epoxyamine, which attacks the oxirane ring via 5-*endo*-tet epoxide opening at 80 °C to give pyrrolidine ring[25] that was protected as *N*-Cbz derivative. Finally, hydrolysis of 1,2-acetonide functionality in **6a** using TFA/water (3:2) furnished C1 anomeric mixture of hemiacetal, which on intramolecular reductive aminocyclization[26] under hydrogenation conditions (H_2, 10% $Pd(OH)_2/C$, 80 psi) afforded 8a-*epi*-castanospermine **1c** as a thick liquid. The spectroscopic and analytical data of **1c** were found to be in agreement with those reported; $[\alpha]_D^{25}$ +27 (*c* 0.5, MeOH), [lit[17r] $[\alpha]_D^{20}$ +28 (*c* 0.3, MeOH), lit[17p] for the antipode $[\alpha]_D^{25}$ −33 (*c* 0.31, MeOH)].

While targeting the synthesis of 1-*epi*-castanospermine **1b**, the epoxyazide **5b** was subjected to transfer hydrogenation using $HCOONH_4$ and 10% Pd/C in ethanol under reflux condition for 26 h followed by reaction with benzylchloroformate in aq $NaHCO_3$ to afford *N*-Cbz protected pyrrolidine **6b** in 55% yield. The 1,2 acetonide opening of **6b** using TFA/H_2O (6:4) and intramolecular reductive aminocyclization using H_2 and 10% $Pd(OH)_2$ in aq methanol afforded 1-*epi* isomer **1b** in overall 23% yield from epoxyazide **5b**. The spectral and analytical data of **1b** were found to be in consonance with that reported; $[\alpha]_D^{25}$ +8.4 (*c* 0.21, MeOH), [lit[17o] $[\alpha]_D^{22}$ +3.8 (*c* 0.54, MeOH)].

3. Conclusion

A short and convenient synthesis of two epimers of (+)-castanospermine **1b** and **1c** is reported using intramolecular 5-*endo*-tet cyclization approach with D-glucose derived γ,δ-epoxyazide. During the course of the synthesis we noticed an interesting formation of 1,3-oxazinan-2-one derivative **7**, in the Staudinger reduction and *N*-Cbz protection of γ,δ-epoxyazide **5a**. The structure of **7** was determined by X-ray crystallographic analysis that assisted us to decide absolute configuration at C5 and C6 in the epoxides **5a** and **5b**. Intramolecular 5-*endo*-tet epoxide opening to the pyrrolidine ring formation was however achieved under thermodynamically controlled condition in the presence of ammonium formate and Pd catalyst, which was further elaborated to the castanospermine stereoisomers **1b** and **1c**.

4. Experimental

4.1. General methods

Melting points were recorded with Thomas Hoover Capillary melting point apparatus and are uncorrected. IR spectra were recorded with Shimadzu FTIR-8400 as a thin film or in Nujol mull or using KBr pellets and are expressed in cm^{-1}. ^1H (300 MHz) and ^{13}C (75 or 100 MHz) NMR spectra were recorded with Varian Mercury instrument using $CDCl_3$ as solvent and Me_4Si (δ=0.0 ppm) is used an internal standard. When D_2O was used as NMR solvent internal standard for D_2O ^1H (δ=4.82 ppm) is used. *Bruker SMART APEX* CCD diffractometer was used for X-ray crystallographic analysis. Elemental analyses were carried out with Thermo-Electron Corporation CHNS analyzer Flash-EA-1112 at Department of Chemistry, University of Pune, Pune. Optical rotations were measured using Jasco P-1020 digital polarimeter at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60-F_{254}). Visualization was made by absorption of UV light or by thermal development after spraying with 3.5% solution of 2,4-dinitrophenylhydrazine in ethanol/H_2SO_4 and with basic aq potassium permanganate solution. Column chromatography was carried out with silica gel (100–200 mesh). The reactions were carried out in oven-dried glasswares under dry N_2 atmosphere. Acetone, dichloromethane, chloroform, ethanol and methanol were purified and dried before use. Distilled *n*-hexane, ethyl acetate, CH_2Cl_2 and methanol were used for column chromatography. After decomposition of the reaction with water, the workup involves washing of combined organic layer with water, brine, drying over anhydrous sodium sulfate and evaporation of solvent at reduced pressure using rotary evaporator.

*4.1.1. 8-Bromo-3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-α-D-xylo-oct-5-en-1,4-furanose (**3**).* To a stirred solution of compound **2** (0.5 g, 0.47 mmol) and 4-bromo-1-butene (0.16 mL, 0.95 mmol) in dry DCM (60 mL) at 30 °C was added the second-generation Grubb's catalyst (0.04 g, 0.047 mmol). The reaction mixture was stirred for 24 h at room temperature (27–30 °C). The solvent was evaporated and the crude product was purified by

column chromatography using *n*-hexane/ethyl acetate (95:5) as an eluent to give **3** (0.49 g, 71%) as viscous oil; R_f 0.50 (*n*-hexane/ethyl acetate, 75:25); $[\alpha]_D$ −26.44 (*c* 0.41, CH_2Cl_2); IR (neat): 1649, 1447, 1295, 1078 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3H, s, CH_3), 1.47 (3H, s, CH_3), 2.55–2.78 (2H, m, H-7), 3.35–3.45 (2H, m, H-8), 3.85 (1H, d, *J*=3.3 Hz, H-3), 4.54 (1H, d, *J*=12.3 Hz, *O*-CH_2Ph), 4.56–4.72 (3H, m, *O*-CH_2Ph, H-2 and H-4), 5.75 (1H, dd, *J*=16.0 and 6.4 Hz, H-5), 5.82–5.90 (1H, m, H-6), 5.95 (1H, d, *J*=3.8 Hz, H-1), 7.20–7.42 (5H, m, Ar–H); ^{13}C NMR ($CDCl_3$) δ 26.1 (CH_3), 26.7 (CH_3), 31.7(C7), 35.7 (C8), 72.1 (*O*-CH_2Ph), 80.9 (C2), 82.9 (C3), 83.3 (C4), 104.7 (C1), 111.5 (isopropylidene), 126.9, 127.5, 127.8, 128.4, 132.1, 137.5 (C5, C6 and Ar). Anal. Calcd for $C_{18}H_{23}BrO_4$: C, 56.41; H, 6.05. Found: C, 56.62; H, 5.95. The same experiment was repeated twice on 1.0 g of scale to get combined 1.96 g of product that was utilized for the subsequent step.

*4.1.2. 8-Azido-3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-α-D-xylo-oct-5-en-1,4-furanose (**4**).* To a stirred solution of **3** (1.9 g, 4.97 mmol) in acetone (35 mL) was added sodium azide (1.29 g, 19.9 mmol) and the reaction mixture was refluxed. After 8 h the solution was cooled to 25 °C, acetone was removed on rotary evaporator and the reaction mass was poured into EtOAc/H_2O (70 mL, 1:1). The organic layer was separated and aqueous phase was extracted with ethyl acetate (3×20 mL). Usual workup and column purification (*n*-hexane/ethyl acetate, 9:1) afforded **4** (1.51 g, 88%) as a thick liquid; R_f 0.54 (*n*-hexane/ethyl acetate, 8:2); $[\alpha]_D$ −62.4 (*c* 1.0, $CHCl_3$); IR (neat) 2096, 1648, 1456, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (3H, s, CH_3), 1.41 (3H, s, CH_3), 2.26–2.38 (2H, m, H-7), 3.23 (2H, t, *J*=6.8 Hz, H-8), 3.58 (1H, d, *J*=12.0 Hz, *O*-CH_2Ph), 3.76 (1H, d, *J*=3.0 Hz, H-3), 4.44 (1H, d, *J*=12.0 Hz, *O*-CH_2Ph), 4.50 (1H, dd, *J*=3.5 and 3.0 Hz, H-4), 4.54 (1H, d, *J*=3.8 Hz, H-2), 5.66 (1H, dd, *J*=16.0 and 3.4 Hz, H-5), 5.70–5.82 (1H, m, H-6), 5.85 (1H, d, *J*=3.8 Hz, H-1), 7.50–7.18 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$) δ 26.2 (CH_3), 26.8 (CH_3), 32.0 (C7), 50.5 (C8), 72.0 (*O*-CH_2Ph), 80.9, 82.8, 83.3 (C2, C3, C4), 104.6 (C1), 111.4 (isopropylidine), 126.8, 127.4, 127.7, 128.3, 131.1, 137.4 (C5, C6 and Ar). Anal. Calcd for $C_{18}H_{23}N_3O_4$: C, 62.49; H, 6.90; N, 12.29. Found: C, 62.59; H, 6.71; N, 12.17.

*4.1.3. 3-O-Benzyl-1,2-O-isopropylidene-7,8-dideoxy-8-azido-5,6-oxirano-β-L-glycero-D-gluco-oct-1,4-furanose (**5a**) and 3-O-benzyl-1,2-O-isopropylidene-7,8-dideoxy-8-azido-5,6-oxirano-α-D-glycero-L-ido-oct-1,4-furanose (**5b**).* To a solution of **4** (1.5 g, 4.34 mmol) in dichloromethane (40 mL) was added *m*-chloroperbenzoic acid (1.49 g, 8.69 mmol) at 0 °C. The resulting reaction mixture was stirred at 25 °C for 24 h. To the reaction mixture H_2O (30 mL) was added and the aqueous phase was extracted with dichloromethane (3×15 mL). The combined organic phase was washed with 2 N NaOH (2×10 mL) and worked up to afford a diastereomeric mixture of epoxides **5a**/**5b**. Purification by column chromatography and elution with *n*-hexane/ethyl acetate (97:3) afforded **5a** (0.86 g, 55%) as a thick liquid; R_f 0.53 (*n*-hexane/ethyl acetate, 8:2); $[\alpha]_D$ −53.1 (*c* 1.0, CH_2Cl_2); IR (neat): 2100, 1549, 1455, 1374 and 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.60–1.90 (1H, m, H-7a), 1.93–2.20 (1H, m, H-7b), 3.10–3.30 (2H, m, H-5 and H-6), 3.50 (2H, t, *J*=6.8 Hz, H-8), 3.90 (1H, dd, *J*=6.5 and 3.3 Hz, H-4), 4.12 (1H, d, *J*=3.3 Hz, H-3), 4.68 (1H, d, *J*=3.5 Hz, H-2), 4.74 (2H, ABq, *J*=11.8 Hz, *O*-CH_2Ph), 5.98 (1H, d, *J*=3.5 Hz, H-1), 7.25–7.56 (5H, m, Ar–H); ^{13}C NMR ($CDCl_3$) δ 26.3 (CH_3), 26.8 (CH_3), 31.3 (C7), 48.2 (C8), 54.3, 55.7 (C5 and C6), 72.3 (*O*-CH_2Ph), 80.9, 82.0, 82.5 (C2, C3 and C4), 105.3 (C1), 111.9 (isopropylidene), 127.5 (strong), 127.9, 128.4 (strong), 137.2 (Ar). Anal. Calcd for $C_{18}H_{23}N_3O_5$: C, 59.82; H, 6.41; N, 11.63. Found: C, 60.01; H, 6.38; N, 11.78. Further elution with *n*-hexane/ethyl acetate (96:4) afforded **5b** (0.31 g, 20%) as a thick liquid; R_f 0.50 (*n*-hexane/ethyl acetate, 8:2); $[\alpha]_D^{25}$ −45.1 (*c* 0.9, CH_2Cl_2); IR (neat): 2099, 1550, 1455, 1374 and 1078 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.60–1.95 (2H, m, H-7), 2.86–2.93 (1H, m, H-6), 3.09 (1H, dd, *J*=5.7 and 2.2 Hz, H-5), 3.37 (2H, t, *J*=6.8 Hz, H-8), 3.88 (1H, dd, *J*=5.7 and 3.6 Hz, H-4), 3.98 (1H, d, *J*=3.5 Hz, H-3), 4.49 (1H, d, *J*=12.0 Hz, *O*-CH_2Ph), 4.62 (1H, d, *J*=3.8 Hz, H-2), 4.72 (1H, d, *J*=12.0 Hz, *O*-CH_2Ph), 5.96 (1H, d, *J*=3.8 Hz, H-1), 7.25–7.41 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$) 26.4 (CH_3), 26.9 (CH_3), 31.2, (C7), 48.1 (C8), 52.0, 56.0 (C5 and C6), 71.8 (*O*-CH_2Ph), 81.0, 82.1, 82.8 (C2, C3 and C4), 105.3 (C1), 111.9 (isopropylidene), 127.6 (strong), 128.0, 128.4 (strong), 137.0 (Ar). Anal. Calcd for $C_{18}H_{23}N_3O_5$: C, 59.82; H, 6.41; N, 11.63. Found: C, 59.92; H, 6.51; N, 11.70.

*4.1.4. 1,2-O-Isopropylidene-5,7,8-trideoxy-5,8-imino (N-benzyloxycarbonyl)-6-(S)-hydroxy-β-L-glycero-L-ido-octafuranose (**6a**).* A solution of azido epoxide **5a** (0.61 g, 2.67 mmol), ammonium formate (0.63 g, 10.13 mmol) and 10% Pd/C (120 mg) in ethanol (20 mL) was vigorously refluxed for 26 h. The reaction mixture was filtered through Celite and the filtrate evaporated to give viscous oil. A solution of the above product (0.3 g, 1.22 mmol) in ethanol (10 mL) was added aq $NaHCO_3$ (0.51 g, 6.11 mmol in 3 mL water) followed by addition of 50% solution of benzylchloroformate in toluene (0.43 mL 3.06 mmol) and the reaction mixture was stirred at room temperature for 12 h. Ethanol was evaporated under reduced pressure and the residue was extracted with chloroform (3×10 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. Purification by column chromatography using *n*-hexane/ethyl acetate (7:3) gave **6a** (0.38 g, 59% overall two steps) as a white solid; mp 151–153 °C; R_f 0.40 (*n*-hexane/ethyl acetate, 2:8); $[\alpha]_D$ −67.0 (*c* 0.4, $CHCl_3$); IR (KBr) 3545–3140, 1692 cm^{-1}; ^1H NMR ($CDCl_3$+D_2O) δ 1.30 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.78–1.98 (1H, m, H-7a), 2.16–2.38 (1H, m, H-7b), 3.51 (1H, t, *J*=9.6 Hz, H-8a), 3.74 (1H, q, *J*=10.2 Hz, H-8b), 3.90–4.12 (1H, m, H-4), 4.15 (1H, d, *J*=2.7 Hz, H-3), 4.21 (1H, d, *J*=5.0 Hz, H-5), 4.25–4.34 (1H, m, H-6), 4.49 (1H, d, *J*=3.6 Hz, H-2), 5.12 (2H, ABq, *J*=12.4 Hz, NCO_2CH_2Ph), 5.88 (1H, d, *J*=3.6 Hz, H-1), 7.18–7.42 (5H, m, Ar–H); ^{13}C NMR ($CDCl_3$) δ 26.1 (CH_3), 26.8 (CH_3), 32.0 (C7), 45.4 (C8), 64.7 (C5), 67.6 (*O*-CH_2Ph), 75.2, 75.5, 80.6, 85.0 (C2, C3, C4 and C6), 104.5 (C1), 111.3 (isopropylidene), 127.7 (strong), 128.0, 128.4 (strong), 136.0 (Ar), 157.5 (NC=O). Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found: C, 60.30; H, 6.85; N, 3.83.

*4.1.5. (1S,6S,7R,8R,8aS)-1,6,7,8-Tetrahydroxy-indolizidine [(+)-8a-epi-castanospermine] (**1c**).* A solution of **6a** (0.12 g, 0. 31 mmol) in TFA/H_2O (8 mL, 3:2) was stirred at 0 °C for 30 min and at 25 °C for 5 h. TFA was co-evaporated with toluene to give viscous oil. A solution of the above product and 10% $Pd(OH)_2$/C (0.05 g) in aq methanol (12 mL, 9:1) was hydrogenated at 90 psi for 15 h at 25 °C. The catalyst was filtered through Celite and solvent was evaporated to afford thick liquid. Purification by column chromatography (CH_2Cl_2/MeOH/25%NH_4OH, 7:2:1) yielded **1c** (42 mg, 76%) as a thick liquid; R_f 0.40 (MeOH/CH_2Cl_2/NH_4OH, 5:3:2); $[\alpha]_D$ +27 (*c* 0.4, MeOH), [lit[17r] $[\alpha]_D^{20}$ +28 (*c* 0.3, MeOH); [lit[17p] for the antipode $[\alpha]_D^{25}$ −33 (*c* 0.31, MeOH)]; IR (neat) 3600–3200 cm^{-1}; ^1H NMR (D_2O) δ 1.62–1.78 (1H, m, H-2a), 2.22–2.40 (1H, m, H-2b), 2.53 (1H, dd, *J*=7.8 and 1.9 Hz, H-8a), 2.59–2.78 (2H, m, H-3a and H-5a), 2.92–3.12 (2H, m, H-3b and H-5b), 3.82–3.92 (1H, m, H-6), 3.98 (1H, t, *J*=7.4 and 3.8 Hz, H-7), 3.99–4.08 (1H, m, H-8), 4.42 (1H, dt, *J*=8.0 and 4.1 Hz, H-1); ^{13}C NMR (D_2O) δ 32.5 (C2), 54.3 (C3), 56.0 (C5), 70.3, 70.6, 71.1, 71.3, 71.5 (C1, C6, C7, C8 and C8a). The spectral data were found to be matching with that reported.[17p] Anal. Calcd for $C_8H_{15}NO_4$ C, 50.78; H, 7.99; N, 7.40. Found: C, 50.81; H, 8.11. N, 7.51.

*4.1.6. 1,2-O-Isopropylidene-5,7,8-trideoxy-5,8-imino-(N-benzyloxycarbonyl)-6-(R)-hydroxy-α-D-glycero-D-gluco-octafuranose (**6b**).* The reaction of epoxide **5b** (0.21 g, 0.58 mmol) with ammonium formate (0.22 g, 3.5 mmol) and 10% Pd/C (0.05 g) in ethanol at

reflux temperature (3 mL) and further reaction of resulted crude amino alcohol (0.082 g, 0.33 mmol) with aq sodium bicarbonate (0.14 g, 1.67 mmol in 2 mL water) and 50% solution of benzyl-chloroformate in toluene (0.12 mL, 0.83 mmol), was performed under similar reaction conditions as described for **6a**, and purification by column chromatography (*n*-hexane/ethyl acetate, 3:2) afforded **6b** (0.12 g, 55%, overall two steps) as a viscous oil; R_f 0.50 (*n*-hexane/ethyl acetate, 2:8); $[\alpha]_D$ −42.2 (*c* 0.5, $CHCl_3$); IR (neat) 3552–3135, 1688 cm^{-1}; ^1H NMR ($CDCl_3$+D_2O) δ 1.31 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.90–2.20 (2H, m, H-7), 3.48 (1H, dt, *J*=8.8 and 2.2 Hz, H-8a), 3.65 (1H, dd, *J*=10.45 and 1.92 Hz, H-4), 3.68 (1H, m, H-8b), 3.98 (1H, d, *J*=10.45 Hz, H-5), 4.15 (1H, d, *J*=1.92 Hz, H-3), 4.48 (1H, d, *J*=3.6 Hz, H-2), 4.61 (1H, d, *J*=2.7 Hz, H-6), 5.13 (2H, q, *J*=12.4 Hz, NCO_2CH_2Ph), 5.92 (1H, d, *J*=3.6 Hz, H-1), 7.21–7.41 (5H, m, Ar–H); ^{13}C NMR ($CDCl_3$) δ 26.0 (CH_3), 26.9 (CH_3), 31.1 (C7), 45.3 (C8), 64.2 (C5), 67.8 (NCO_2CH_2Ph), 73.1, 73.8, 81.0, 84.5 (C2, C3, C4 and C6), 104.7 (C1), 111.4 (isopropylidene), 127.8 (strong), 128.1, 128.4 (strong), 135.8 (Ar), 157.1 (NC=O). Anal. Calcd for C19H25NO7: C, 60.15; H, 6.64; N, 3.69. Found: C, 60.22; H, 6.78; N, 3.74.

*4.1.7. (1R,6S,7R,8R,8aR)-1,6,7,8-Tetrahydroxyindolizidine [(+)-1-epi-castanospermine] (**1b**).* Reaction of **6b** (0.95 g, 0.25 mmol) with TFA/H_2O (3:2, 4 mL) followed by hydrogenation with 10% $Pd(OH)_2$/C (50 mg) in aq methanol (10 mL, 9:1) as described for **1c** and column chromatography purification using CH_2Cl_2/MeOH/25% NH_4OH (4:1:0.2) afforded **1b** (35 mg, 74% overall) as a thick liquid; R_f 0.50 (methanol/CH_2Cl_2, 8:2); $[\alpha]_D$ +8.4 (*c* 0.21, MeOH), [lit[17o] $[\alpha]_D^{22}$ +3.8 (*c* 0.54, MeOH)]; IR (neat) 3600–3210 cm^{-1}; ^1H NMR (D_2O) δ 1.72–1.88 (1H, m, H-2a), 2.37 (1H, ddd, *J*=14.0, 9.0 and 3.5 Hz, H-2b), 2.42–2.58 (2H, m, H-3a and H-5a), 2.87 (1H, q, *J*=18.5 and 9.0 Hz, H-8a), 3.09 (1H, ddd, *J*=10.0 and 2.5 Hz, H-3b), 3.28 (1H, dd, *J*=11.5 and 5.2 Hz, H-5b), 3.33–3.50 (2H, m, *J*=15.4 and 9.0 Hz, H-8 and H-7), 3.62–3.78 (1H, m, H-6), 4.34 (1H, ddd, *J*=8.5, 5.5 and 3.3 Hz, H-1); ^{13}C NMR (D_2O) δ 32.1 (C2), 51.0 (C3), 53.8 (C5), 69.0 (C8a), 72.1, 72.5, 73.2, 78.0 (C1, C6, C7 and C8). The spectral data was found to be matching with that reported.[17m] Anal. Calcd for $C_8H_{15}NO_4$ C, 50.78; H, 7.99; N, 7.40. Found: C, 50.87; H, 8.19. N, 7.55.

*4.1.8. 3-O-Benzyl-(8-N,6-O-carbonyl)-7,8-dideoxy-1,2-O-isopropylidene-α-D-glycero-D-gluco-octafuranose (**7**).* To a solution of **5a** (0.12 g, 0.33 mmol) in THF/water (9:1, 8 mL) was added triphenyl phosphine (0.13 g, 0.5 mmol) and reaction mixture was stirred at room temperature for 15 h. To an ice cold solution of above product was added aq sodium bicarbonate solution (0.14 g, 1.66 mmol in 3 mL water) followed by 50% solution of benzyl-chloroformate in toluene (0.11 mL, 3.92 mmol) and the resulting reaction mixture was stirred at 30 °C for 15 h. Solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (3×10 mL). Usual workup and column purification using *n*-hexane/ethyl acetate (1:1) as an eluent gave **7** (0.087 g, 70%) as a white solid; mp 178–181 °C; R_f 0.40 (ethyl acetate); $[\alpha]_D$ −54.0 (*c* 1.3, $CHCl_3$); IR (Nujol): 2922, 1687, 1462 and 1376 cm^{-1}; ^1H NMR ($CDCl_3$+D_2O) δ 1.30 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.85–2.20 (2H, m, H-7), 3.22–3.47 (2H, m, H-8), 4.07–4.18 (2H, m, H-3 and H-5), 4.30 (1H, dd, *J*=8.0 and 3.6 Hz, H-4), 4.33–4.42 (1H, m, H-6), 4.58 (1H, d, *J*=12.0 Hz, *O*-CH_2Ph), 4.61 (1H, d, *J*=3.6 Hz, H-2), 4.70 (1H, d, *J*=12.0 Hz, *O*-CH_2Ph), 5.92 (1H, d, *J*=3.6 Hz, H-1), 7.21–7.43 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (C7), 26.3 (CH_3), 27.0 (CH_3), 38.6 (C8), 67.9 (C5), 72.6 (*O*-CH_2Ph), 78.94, 78.97 (C4 and C6), 81.7 (C3), 82.2 (C2), 105.3 (C1), 111.9 (isopropylidene), 127.9 (strong), 128.1, 128.6 (strong), 137.4 (Ar), 155.1 (NC=O). Previously when ^{13}C NMR of **7** was recorded on 75 MHz machine frequency, only one signal at δ=78.8 was observed, however when it was recorded on 100 MHz machine frequency showed two signals (very close) at δ=78.94 and 78.97. Assignment of ^1H and ^{13}C signals was confirmed by COSY and HETCOR experiments (spectra are given Supplementary data). Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found C, 59.95; H, 6.67; N, 3.75.

4.2. Crystal data for 7

Single crystals of the compound **7** were grown by slow evaporation of the solution mixture of methanol: water (9:1). Needles of approximate 0.46×0.18×0.09 mm^3, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo Kα radiation with fine focus tube with 50 kV and 30 mA. Crystal to detector distances 6.05 cm, 512×512 pixels/frame, hemisphere data acquisition. Total scans≡3, total frames≡1271, oscillation/frame −0.3°, exposure/frame≡7.0 s/frame, maximum detector swing angle≡−30.0°, beam center≡(260.2, 252.5), in plane spot width≡1.24, SAINT integration, θ range≡1.58–24.99°, completeness to θ of 25.0° is 100%. SADABS correction applied, $C_{19}H_{25}NO_7$, *M*≡379.40. Crystals belongs to Orthorhombic, space group $P2_12_12_1$, *a*≡12.3002(6) Å, *b*≡12.6031(7) Å, *c*≡25.807(1) Å, *V*≡4000.7(4) $Å^3$, *Z*≡8, D_c≡1.260 g/cc, μ (Mo K_α)≡0.096 mm^{-1}, *T*≡296(2) K, 20,322 reflections measured, 6997 unique [$I>2\sigma(I)$], *R* value 0.0493, w*R*2≡0.0957. All the data were corrected for Lorentzian, polarization and absorption effects. SHELX-97 (ShelxTL)[27] was used for structure solution and full matrix least squares refinement on F^2. There were two molecules in the asymmetric unit. Hydrogen atoms were included in the refinement as per the riding model. Data collection and refinement parameters are listed in Table 1 (see, Supplementary data). X-ray analysis revealed the conformation of the molecule and shows that C1, C2, C3, C4, C5 and C6 have *R*, *R*, *S*, *R*, *S* and *R* configurations, respectively.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra of compounds **3**, **4**, **5a**,**b**, **6a**,**b**, **7**, **1b**,**c** and copies of 2D NMR (COSY, HMBC and HSQC) spectra and X-ray crystal data of **7**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.02.030. These data include MOL files and InChIKeys of the most important compounds described in this article.

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22. The column purification of epoxyamine X led to the mixture of products and hence it was directly reacted further with benzylchloroformate.
23. The diastereoselectivity in the epoxidation reaction to get **5a** as the major product could be explained by the preferred hydrogen bonding of *m*-CPBA with the β-oriented C3–OBn oxygen; while the hydrogen bonding of *m*-CPBA with the α-oriented furanose-ring oxygen, which is sterically compressed due to C3–OBn group, affords α-epoxide **5b** as a minor product.
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