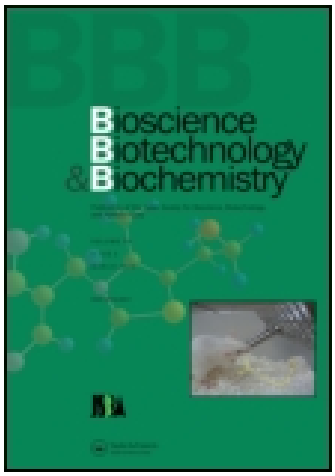

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The BC-ring system of ciguatoxin was stereoselectively synthesized by 12 steps from methyl α-D-glucopyranoside.

Key words: ciguatoxin; chiral synthesis; D-glucose

Ciguatoxin (**1**) and its congeners are the toxic principles of ciguatera, which is one of the largest-scale food poisonings of non-bacterial origins.[1] The structure of ciguatoxin has become an attractive target for synthetic organic chemists.[2] Recently, its absolute configuration has been reported.[3] In the course of our synthetic studies of the ABC-ring system of ciguatoxins for both identification of the absolute stereochemistry of ciguatoxins and development of specific immunoassay for their detection, we have already reported[4] the preparation of a chiral ABC-ring system starting from D-glucose, in which the C-ring was constructed using C-1 and C-2 of D-glucose.

In this paper, we describe a preparation of the enantiomeric BC-ring system of the previous one where the C-ring was constructed using the C-4 and C-6 of D-glucose.

Results and Discussion

The starting material for our synthesis was methyl 2,3-di-*O*-benzyl-4,6-*O*-(4-methoxybenzylidene)-α-D-glucopyranoside (**2**). Although regioselective reductive cleavage of the *p*-methoxybenzylidene group of **2** using sodium cyanoborohydridetrimethylsilyl chloride to give the 4-*O*-(**3**) (76%) and 6-*O*-(4-methoxybenzyl) ether (**4**) (13%) have been reported,[5a] we found that **3** can be prepared from **2** with complete regioselectivity by reduction with lithium aluminum hydride (LAH) in the presence of 1.3 eq of aluminum chloride in ether/dichloromethane using the conditions of the stereoselective ring-cleavage of benzylidene acetal.[5b] Swern oxidation of **3** followed by Wittig reaction of the resulting aldehyde **5** with methoxycarbonylmethylidenetriphenylphosphorane gave the (*E*)-unsaturated ester **6** in 97% yield. Diisobutylaluminum hydride (DIBAL) reduction of **6** gave allyl alcohol **7** in 94% yield. Epoxidation of **7** with *m*-chloroperbenzoic acid afforded two epoxides **8a** and **8b** in a ratio of 2.2:1 (by ^{1}H-NMR analysis). They could not be separated by chromatographic methods and therefore the mixture was next reduced by DIBAL. Although the structures were not determined at this stage, the major **8a** was later found to be the one with the desired stereochemistry at C-7. The DIBAL reduction of the mixture gave three products **9a**, **9b**, and **9c** in a ratio of 12:4.5:1. Compound **9b** was isolated in pure form by column chromatography, however, **9a** and **9c** could not be separated.

Therefore, **9a** and **9c** were separated as the corresponding acetonides **9a′** and **9c′**. The 1,3-dioxolane structure of **9a′** and the 1,3-dioxane structure of **9c′** were identified on the basis of their ^{1}H-NMR data, thereby the one which had a methylene proton coupled with H-5 was assigned to 1,3-dioxolane **9a′** and the other, with no methylene proton coupled with H-5 to 1,3-dioxane **9c′**.

The structures of **9a′** and **9c′** were further confirmed by a sequence of reactions. Thus, **9a′** and **9c′** were respectively restored to **9a** and **9c** by acid hydrolysis and submitted to periodate oxidation. The vicinal diol structures were assigned to **9a** and **9b** being oxidized with sodium periodate, and the 1,3-diol structure to **9c** being not oxidized by sodium periodate.

The stereochemistry of secondary alcohols of **9a** and **9b** was identified by our CD (circular dichroism) method for terminal vicinal diols.[6] Compounds **9a** and **9b** were benzoylated to the terminal vicinal di-*O*-benzoates **9a″** and **9b″**, respectively.

Compound **9a″**, with a positive sign at a long wavelength (237 nm) in its CD spectrum was assigned to havd (*S*)-stereochemistry at C-8 and **9b″**, which had a negative sign at the same wavelength to be (*R*)-configurated at C-8. These stereochemical assignments were later confirmed by

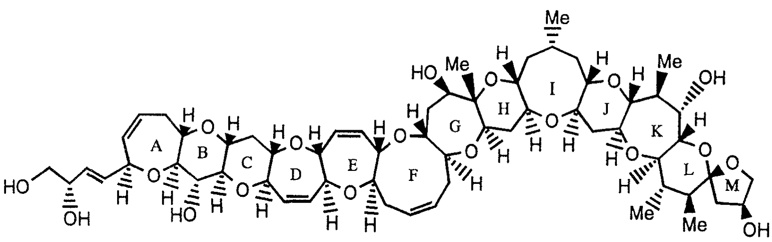

Fig. 1. The Structure of Ciguatoxin (**1**).

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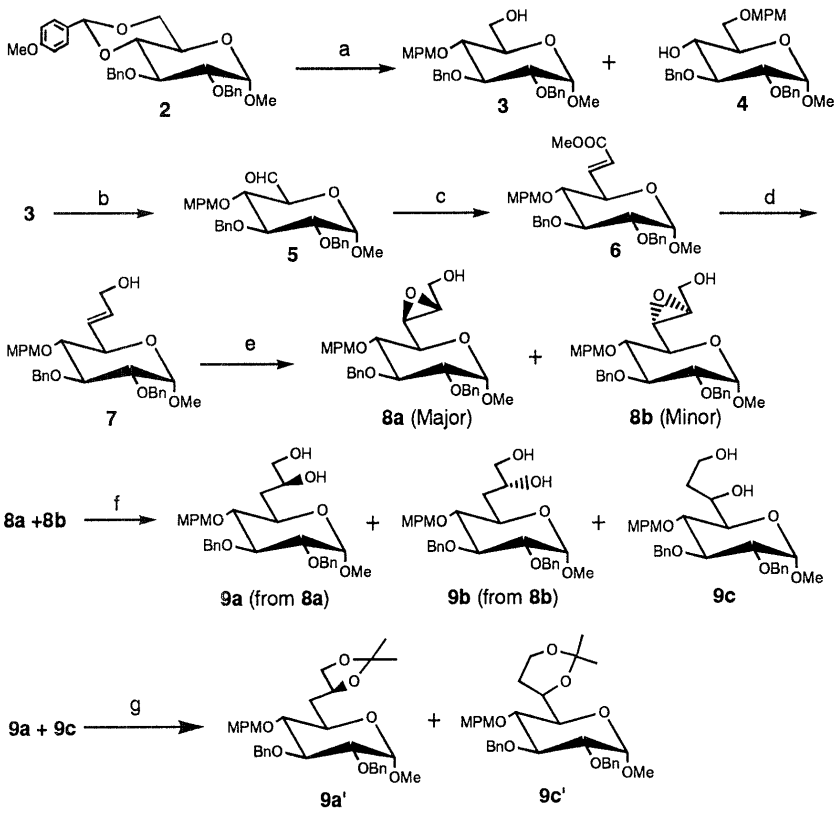


Scheme 1. Synthesis of **9a′**.

Reagents and conditions: a) LAH (2.0 eq), $AlCl_3$ (1.3 eq), Et_2O, CH_2Cl_2, reflux (93%). b, c) DMSO (2.0 eq), $(COCl)_2$ (1.1 eq), Et_3N (5.0 eq), CH_2Cl_2, N_2, −78°C then, $Ph_3P{=}CHCOOMe$, ~rt, (97% from **3**). d) DIBAL (2.7 eq), CH_2Cl_2, N_2, 0°C (94%). e) mCPBA (4.0 eq), CH_2Cl_2, N_2, rt (mix. 90% **8a**:**8b** = 2.2:1). f) DIBAL (3.9 eq), CH_2Cl_2, N_2, 0°C (93%). g) 2,2-Dimethoxypropane, TsOH, rt (96%).

converting **9a** and **9b** to the BC-ring systems.

According to our previous approach of building the tetrahydropyrane ring C,[2] **9a** was first converted into the acetonide **9a′**. The selective deprotection of the *p*-methoxybenzyl group at C-4 of **9a′** with dichlorodicyanobenzoquinone (DDQ) followed by acetylation of the resulting alcohol **10** gave **11** in 92% yield.

De-*O*-isopropylidenation of **11** with 70% acetic acid gave diol **12** in 93% yield. Tosylation of **12** with 1.1 equivalent of tosyl chloride in pyridine gave mono-*O*-tosylate **13** in 67% yield, the hydroxy group of which was protected as a methoxymethyl ether to afford **14**. Zemplen de-*O*-acetylation of **14** afforded **15** quantitatively. Compound **15** was treated with NaH in the presence of 15-crown-5 in *N*,*N*-dimethylformamide to give the bicyclic **16** in 98% yield.

The equatorial stereochemistry of the methoxymethyl protected alcohol of **16** was analyzed by ^{1}H-NMR study. The proton at C-7 position showed a multiplet, which mean it difficult to obtain the coupling constants directly between the proton at C-7 and the axial protons at C-6 and C-8 from the signal. The axial proton at C-6 showed one proton quartet (J = 11.4 Hz) at 1.45 ppm and the one at C-8 did one proton triplet (J = 10.6 Hz) at 3.16 ppm, which indicated the proton at C-7 was axially oriented. These results supported the (*S*)-configuration identified by the CD method.

To simplify the synthetic pathway, a different route to **16** from **9a** was examined. Thus, **9a** was converted into 4-*O*-*p*-methoxybenzyl-7-*O*-methoxymethyl-8-*O*-tosylderivative **18** by mono-tosylation followed by methoxymethyl protection. The de-*O*-*p*-methoxybenzylation of **18** with DDQ gave **15**

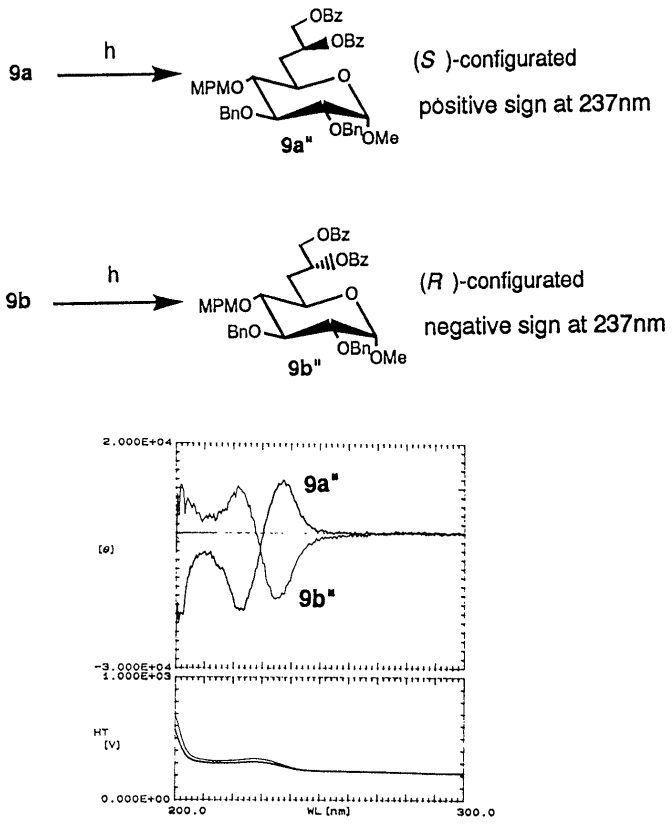
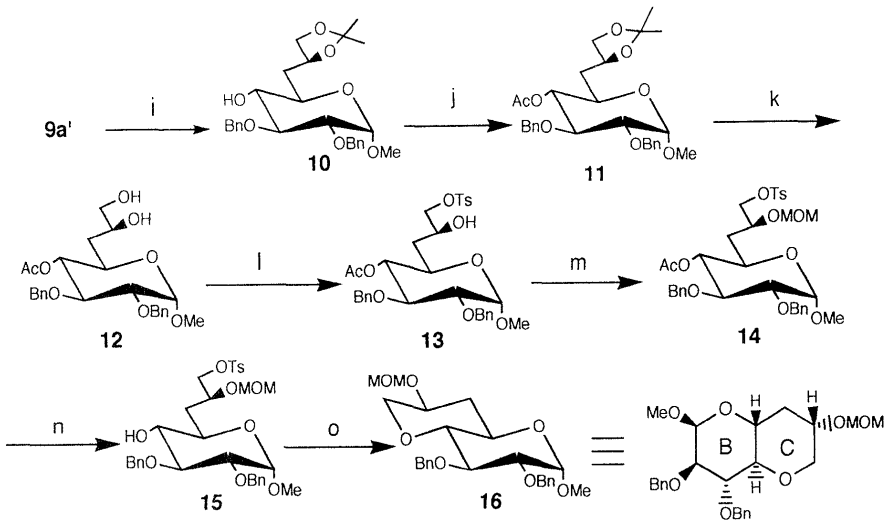


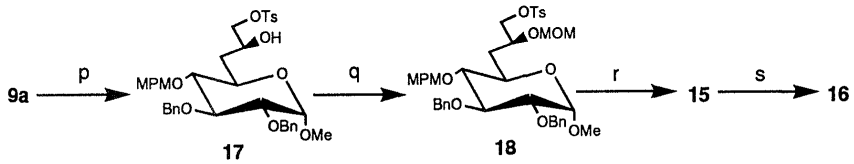
Fig. 2. The Identification of the Configuration by the CD Method.

Reagents and conditions: h) BzCl, py, **9a″** (87%), **9b″** (80%).



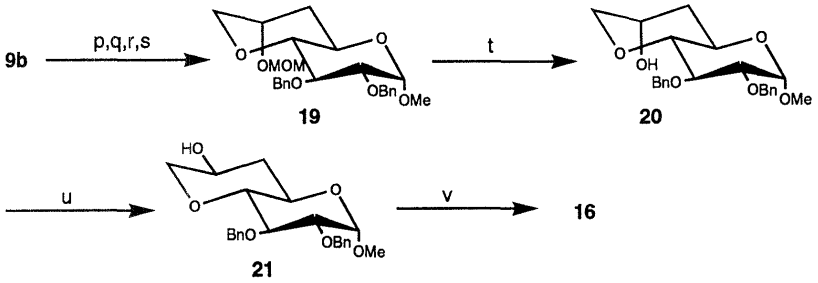
Scheme 2. Synthesis of BC-Ring System (**16**).

Reagents and conditions: i) DDQ, CH_2Cl_2, 2 h, rt (72%). j) Ac_2O, py, 3 h, rt (92%). k) AcOH, H_2O (93%). l) TsCl, DMAP, py, 30 min, rt (67%). m) MOMCl, *N,N*-diisopropylethylamine, CH_2Cl_2, rt (79%). n) MeOH, NaOMe (71%). o) NaH, 15-crown-5, DMF, rt (98%).



Scheme 3. A Different Route to **16**.

Reagents and conditions: p) TsCl, DMAP, py, 30 min, rt (72%). q) MOMCl, *N,N*-diisopropylethylamine, CH_2Cl_2, rt (90%). r) DDQ, CH_2Cl_2, 2 h, rt (80%). s) NaH, 15-crown-5, DMF, rt (98%).



Scheme 4. A Conversion of **9b** to **16**.

Reagents and conditions: p) TsCl DMAP, py, 30 min, rt (72%). q) MOMCl, *N,N*-diisopropylethylamine, CH_2Cl_2, rt (89%). r) DDQ, CH_2Cl_2, 2 h, rt (80%). s) NaH, 15-crown-5, DMF, rt (87%). t) AcOH/HCl, reflux (55%). u) i) DEAD/Ph_3P, $CH_2ClCOOH$, ether, rt (59%). ii) NaOMe/MeOH, rt (78%). v) MOMCl, *N,N*-diisopropylethylamine, CH_2Cl_2, rt (80%).

in 80% yield. Thus, the overall yield of **15** starting from **2**, was improved to 24% from 11% in our earlier approach.

On the other hand, **9b** was converted to a bicyclic **19** by a similar sequence of reactions as those described for **9a**. The axial proton at C-6 of **19** showed a double triplet ($^3J_{H\text{-}7,H\text{-}6ax} = 2.5$ Hz) supporting the axial stereochemistry of the methoxymethyl protected hydroxy group.

Deprotection of the methoxymethyl group of **19** with MeOH–HCl gave **20**. The stereochemistry of the hydroxy group of **20** was inverted by the Mitsunobu reaction[7] to afford **21** in 47% yield, which was converted to **16** by methoxymethyl protection of the hydroxy group at C-7.

Thus, we have prepared the enantiomeric BC-ring system of our previously synthesized BC-ring system of ciguatoxin from methyl α-D-glucopyranoside in 24% yield. Currently we are investigating the synthesis of the ABC-ring system from the BC-compound **16**.

Experimental

General methods. Melting points were recorded on a Yanaco melting point apparatus and are not corrected. ^{1}H-NMR spectra were recorded on a JEOL GSX-270 (270 Hz) and a Varian Gemini 2000/300 (300 Hz) at 21—23°C in $CDCl_3$ with Me_4Si as an internal standard. $[\alpha]_D$ were measured with a JASCO DIP-4 spectometer at 20°C. MS spectra were obtained with a JEOL JMS-DX303HF. CD spectra were obtained on a JASCO J-720 spectrometer. Silica gel column chromatography was done on Meck silica gel (Art. 7734), and analytical TLC was done on Merck silica gel (Art. 5554). The usual workup refers to dilution with an organic solvent ($CHCl_3$), washing with water to neutrality, drying with $MgSO_4$, filtering, and evaporation under reduced pressure.

Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-α-D-glucopyranoside (**3**). To a refluxed mixture of lithium aluminum hydride (1.55 g 40.8 mmol 2.0 eq) and **2** (10.0 g 20.4 mmol) in ether–dichloromethane (1 : 1, 200 ml) was added dropwise a solution of aluminum chloride (anhydorous) (3.54 g 26.5 mmol 1.3 eq) in ether (50 ml) under N_2, and stirred for 5 min. The reaction mixture was cooled, and the excess of lithium alminum hydride was decomposed with ethyl acetate (50 ml) and water (50 ml). The pre-

cipitates were removed by Celite, and the organic phase was worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 3 : 1) to provide **3** (9.34 g 93%). **3**: mp 60.5°C, $[\alpha]_D^{20} = +18.1$ ($c = 1.0$ in $CHCl_3$) lit.[5a] $[\alpha]_D^{22} = +19.3$ ($c = 1.0$ in $CHCl_3$), ^{1}H-NMH DATA (270 MHz/$CDCl_3$) δ (ppm): 7.39–6.81 (m, 14H, aromatic protons), 5.00–4.59 (m, 6H, benzyl protons), 4.55 (d, 1H, H-1, $J = 3.7$ Hz), 3.99 (t, 1H, H-3, $J = 9.5$ Hz), 3.76 (s, 3H, –OMe from MPM), 3.73–3.59 (m, 3H, H-5, H-6, H-6′), 3.53–3.46 (m, 2H, H-2, H-4), 3.34 (s, 3H, –OMe from anomeric position), 1.87 (s, 1H, OH). HRMS *m/z*; Calcd. for $C_{29}H_{34}O_7$ 494.2303 (M^+), 493.2224 ($M^+ - H$), Found: 493.2244. *Anal.* Calcd. for $C_{29}H_{34}O_7$: C, 70.41; H, 6.93%, Found: C, 70.63; H, 6.93%.

*Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-6-(E)-methoxycarbonyl methylidine-α-*D*-glucopyranoside* (**6**). To a mixture of oxalyl chloride (6.0 ml 47.2 mmol 1.1 eq) and dimethyl sulfoxide (6.0 ml 82.0 mmol 2.0 eq) in dichloromethane (100 ml) was added dropwise a solution of **3** (20.0 g 40.4 mmol) in dichoromethane (50 ml) under N_2 at −78°C and stirred for 30 min. Triethyl amine (20 ml 197.6 mmol 5.0 eq) was added to the solution and the temperature was raised to room temperature. Ph_3PCH = COOMe (14.8 g 45.7 mmol 1.1 eq) was added to the mixture. The organic phase was worked up to give a syrup that solidified with time, which was purified by column chromatography (hexane–ethyl acetate = 3 : 1) to provide **6** (21.5 g 97%). **6**: mp 41–42°C, $[\alpha]_D^{20} = +40.8$ ($c = 1.0$ in $CHCl_3$), ^{1}H-NMR DATA (300 MHz/$CDCl_3$) δ (ppm): 7.37–6.82 (m, 14H, aromatic protons), 6.97 (dd, 1H, H-7, $J = 4.7$, 15.7 Hz), 6.07 (dd, 1H, H-6, $J = 4.7$, 15.7 Hz), 4.99–4.48 (m, 6H, benzyl protons), 4.60 (d, 1H, H-1, $J = 3.6$ Hz), 4.20 (m, 1H, H-5), 3.97 (t, 1H, H-3, $J = 9.3$ Hz), 3.79 (s, 3H, –OMe from MPM), 3.74 (s, 3H, methyl ester), 3.49 (dd, 1H, H-2, $J = 3.6$ Hz), 3.35 (s, 3H, –OMe from anomeric position), 3.18 (dd, 1H, H-4, $J = 8.8$ Hz). HRMS *m/z*; Calcd. for $C_{32}H_{36}O_8$ 548.2408 (M^+) 547.2330 ($M^+ - H$), Found: 547.2338. *Anal.* Calcd. for $C_{32}H_{36}O_8$: C, 70.04; H, 6.62%, Found: C, 70.15; H, 6.51%.

*6-(E)-Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-6,7-didehydro-6,7-dideoxy-α-*D*-gluco-octapyranoside* (**7**). To a solution of **6** (2.00 g 3.60 mmol) in dichloromethane (50 ml) was added DIBAL (diisobutylalminum hydride in *n*-hexane, 0.95 M) 10 ml 9.5 mmol 2.6 eq) under N_2 at 0°C, and stirred for 5 min. Excess of DIBAL was decomposed with methanol (30 ml). The solution was worked up to give a residue, which was purified by column chromatography (hexane–ethyl acetate = 1 : 1) to provide **7** (1.75 g 94%). **7**: mp 92°C, $[\alpha]_D^{20} = +19.3$ ($c = 1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.37–6.82 (m, 14H, aromatic protons), 6.00–5.91 (m, 1H, H-7), 5.69–5.61 (m, 1H, H-6), 4.98–4.50 (m, 6H, benzyl protons), 4.56 (d, 1H, H-1, $J = 3.7$ Hz), 4.13–4.03 (m, 3H, H-5, H-8, H-8′), 4.01–3.94 (t, 1H, H-3, $J = 9.5$ Hz), 3.79 (s, 3H, –OMe from MPM), 3.54–3.49 (dd, 1H, H-2, $J = 3.7$, 9.6 Hz), 3.37 (s, 3H, –OMe from anomeric position), 3.25–3.18 (t, 1H, H-4, $J = 9.5$ Hz), 1.46 (s, 1H, –OH). HRMS *m/z*; Calcd. for $C_{31}H_{36}O_7$ 520.2459 (M^+), 519.2381 ($M^+ - H$), Found: 519.2397. *Anal.* Calcd. for $C_{31}H_{36}O_7$: C, 71.51; H, 6.97%, Found: C, 71.79; H, 6.98%.

*Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-6,7-anhydro-8-hydroxy-*D*-threo-α-*D*-gluco-octapyranoside* (**8**). To a solution of **7** (0.30 g 0.58 mmol) in dichloromethane (10 ml) was added *m*-chloroperbenzoic acid (0.40 g 2.30 mmol 4.0 eq) at 0°C, and stirred for 5 h. Saturated sodium hydrogen carbonate was added to the solution to quench *m*-chlorobenzoic acid. The organic phase was worked up to give a residue, which was purified by column chromatography (hexane–ethyl acetate = 1 : 1) to provide **8** as a mixture of **8a** and **8b**. (0.28 g 90% as a mixture **8a** : **8b** = 2.2 : 1 by ^{1}H-NMR analysis).

*Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-6-deoxy-*D*-glycero-α-*D*-gluco-octapyranoside* (**9a**). To a solution of **8** (a mixture of **8a** and **8b**) (27.5 g 51.5 mmol) in dichloromethane (300 ml) was added DIBAL (diisobutylalminum hydride in *n*-hexane, 0.95 M) (200 ml 190 mmol 3.7 eq) under N_2 at 0°C and stirred for 5 min. The mixture was quenched with methanol, filtered to remove the precipiate, and worked up to give a syrup, which was purified by column chromatography (chloroform–methanol = 100 : 1) to provide a mixture of **9a**, **9c**, and **9c**. **9a** and **9c** could not be separated (total 25.7 g 93%, the mixture of **9a** and **9c**: 19.0 g **9b**: 6.70 g). **9a**: mp 62°C, $[\alpha]_D^{20} = +12.4$ ($c = 1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.36–6.83 (m, 14H, aromatic protons), 5.05–4.50 (m, 6H, benzyl protons), 4.52 (d, 1H, H-1, $J = 3.4$ Hz), 4.02–3.82 (m, 3H, H-3, H-7, H-8), 3.80 (s, 3H, –OMe from MPM), 3.61–3.32 (m, 3H, H-2, H-5, H-8′), 3.39 (s, 3H, –OMe from anomeric position), 3.18 (t, 1H, H-4, $J = 9.5$ Hz), 1.97–1.45 (m, 4H, H-6, H-6′, –OH, –OH). HRMS *m/z*; Calcd. for $C_{31}H_{38}O_8$ 538.2564 (M^+), 561.2462 ($M^+ + Na$), Found: 561.2466. *Anal.* Calcd. for $C_{31}H_{38}O_8$:C, 69.11; H, 7.12%, Found: C, 69.24; H, 7.14%.

*Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-6-deoxy-7,8-O-isopropylidene-*D*-glycero-α-*D*-gluco-octapyranoside* (**9a′**). to a solution of *p*-toluenesulfonic acid (22 mg) in 2,2-dimethoxypropane (20 ml) was added the mixture of **9a** and **9c** (3.51 g 6.52 mmol) at room temperature, and stirred for 3 h. The solution was worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 4 : 1) to provide **9a′** and **9c′** (total 3.61 g 96%, **9a′**: 3.32 g **9c′**: 0.29 g). **9a′**: mp 91°C, $[\alpha]_D^{20} = +14.9$ ($c = 1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.37–6.83 (m, 14H, aromatic protons), 5.01–4.59 (m, 6H, benzyl protons), 4.53 (d, 1H, H-1, $J = 3.7$ Hz), 4.24 (m, 1H, H-7), 4.04–3/89 (m, 2H, H-3, H-8), 3.79 (s, 3H, –OMe from MPM), 3.63 (m, 1H, H-5), 3.53–3.40 (m, 2H, H-2, H-8′), 3.35 (s, 3H, –OMe from anomeric position), 3.20 (t, 1H, H-4, $J = 8.8$ Hz), 1.90 (t, 2H, H-6, H-6′, $J = 5.6$ Hz), 1.40 (s, 3H, –Me), 1.33 (s, 3H, –Me). HRMS *m/z*; Calcd. for $C_{34}H_{42}O_8$ 578.2877 (M^+), 577.2799 ($M^+ - H$), Found 577.2805. *Anal.* Calcd. for $C_{34}H_{42}O_8$: C, 70.03; H, 7.32% Found: C, 69.79; H, 7.39%. **9c′**: ^{1}H-NMR DATA (270 MHz/$CHCl_3$) δ (ppm); 7.41–6.83 (m, 14H, aromatic protons), 5.02–4.63 (m, 6H, benzyl protons), 4.59 (d, 1H, H-1, $J = 3.4$ Hz), 4.05–3.95 (m, 2H, H-3, H-6), 3.79 (s, 3H, –OMe from MPM), 3.75–3.71 (m, 2H, H-8, H-8′), 3.60 (dd, 1H, H-5, $J = 1.7$, 10.3 Hz), 3.50–3.37 (m, 2H, H-2, H-4), 3.35 (s, 3H, –OMe from anomeric position), 1.93 (m, 1H, H-7), 1.42 (s, 3H, –Me), 1.38 (s, 3H, –Me), 0.90 (dd, 1J, H-7′, $J = 2.7$, 12.9 Hz).

*Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-6-deoxy-7,8-di-O-benzoyl-*D*-glycero-α-*D*-gluco-octapyranoside* (**9a″**). To a solution of **9a** (200 mg 0.37 mmol) in pyridine (10 ml) was added benzoyl chloride (1.0 ml, 8.59 mmol, 23 eq) at the room temperature and stirred for 3 h. The solution was worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 4 : 1) to provide **9a″** (240 mg 87%). **9a″**: syrup, ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 8.05–6.75 (m, 24H, aromatic protons), 5.65 (m, 1H, H-7), 5.00–4.46 (m, 9H, benzyl protons, H-1, H-8, H-8′), 3.96 (t, 1H, H-3, $J = 9.3$ Hz), 3.81 (1H, H-5), 3.74 (s, 3H, –OMe from MPM), 3.50 (dd, 1H, H-2, $J = 3.7$, 9.7 Hz), 3.39 (s, 3H, –OMe from anomeric position), 3.21 (t, 1H, H-4, $J = 9.3$ Hz), 2.34 (m, 1H, H-6), 1.85 (m, 1H, H-6′). CD (MeOH) λ_{ext} 237 nm (θ +12,000), 230 (0), 222 (−18.000).

*Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-6-deoxy-7,8-di-O-benzoyl-*L*-glycero-α-*D*-gluco-octapyranoside* (**9b″**). **9b″** was prepared from **9b** in 80% according to the procedures described for **9a″**. **9b″**: syrup, ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 8.02–6.75 (m, 24H, aromatic protons), 5.64 (m, 1H, H-7), 5.00–4.53 (m, 7H, benzyl protons, H-8), 4.48 (d, 1H, H-1, $J = 3.7$ Hz), 4.40 (dd, 1H, H-8′, $J = 5.6$, 11.8 Hz), 3.93 (t, 1H, H-3, $J = 9.3$ Hz), 3.78 (m, 1H, H-5), 3.75 (s, 3H, –OMe from MPM), 3.48 (dd, 1H, H-2, $J = 3.7$, 9.7 Hz), 3.22 (t, 1H, H-4, $J = 9.3$ Hz), 3.15 (s, 3H, –OMe from anomeric position), 2.44 (m, 1H, H-6), 1.56 (m, 1H, H-6′). CD (MeOH) λ_{ext} 234 nm (θ −14.000), 227 (0), 222 (+10,000).

*Methyl 2,3-di-O-benzyl-6-deoxy-7,8-O-isopropylidene-*D*-glycero-α-*D*-gluco-octapyranoside* (**10**). To a solution of **9a** (3.28 g 5.67 mmol) in dichloromethane–water (10 : 1, 110 ml) was added DDQ (1.63 g 7.18 mmol 1.3 eq) at the room temperature and stirred for 3 h. The solution was worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 4 : 1) to provide **10** (1.87 g 72%). **10**: syrup, $[\alpha]_D^{20} = +24.9$ ($c = 1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.37–7.26 (m, 10H, aromatic protons), 5.02–4.57 (m, 4H, benzyl protons), 4.54 (d, 1H, H-1, $J = 3.7$ Hz), 4.28 (m, 1H, H-7), 4.03 (dd, 1H, H-8, $J = 5.9$, 7.8 Hz), 3.76 (t, 1H, H-3, $J = 9.5$ Hz) 3.65–3.47 (m, 3H, H-2, H-5, H-8′) 3.36 (s, 3H, –OMe from anomeric position), 3.28 (t, 1H, H-4, $J = 9.5$ Hz), 2.18 (s, 1H, –OH), 1.93 (t, 2H, H-6, H-6′, $J = 5.9$ Hz), 1.40 (s, 3H, –Me), 1.34 (s, 3H, –Me). HRMS *m/z*; Calcd. for $C_{26}H_{34}O_7$ 458.2303 (M^+), 459.2381 ($M^+ + H$), Found: 459.2403. *Anal.* Calcd. for $C_{26}H_{34}O_7$: C, 68.09; H, 7.48%, Found: C, 68.04; H, 7.43%.

*Methyl 2,3-di-O-benzyl-4-O-acetyl-6-deoxy-7,8-O-isopropylidene-*D*-glycero-α-*D*-gluco-octapyranoside* (**11**). To a solution of pyridine (40 ml) and acetic anhydride (20 ml) was added **10** (3.01 g 7.00 mmol) at room temperature and stirred for 1 h. The solution was evaporated with toluene and worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 3 : 1) to provide **11** (1.87 g 72%). **11**: mp

90°C, $[\alpha]_D^{20} = +13.2$ ($c=1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.37–7.26 (m, 10H, aromatic protons), 4.90–4.61 (m, 5H, benzyl protons H-4), 4.54 (d, 1H, H-1, $J=3.7$ Hz), 4.21 (m, 1H, H-7), 4.00 (dd, 1H, H-8, $J=5.9$, 7.8 Hz), 3.85 (t, 1H, H-3, $J=9.5$ Hz), 3.68 (m, 1H, H-5), 3.58–3.51 (m, 2H, H-2, H-8′), 3.38 (s, 3H, –OMe from anomeric position), 1.92 (s, 3H, Ac), 1.85 (m, 1H, H-6), 1.65 (m, 1H, H-6′), 1.38 (s, 3H, –Me), 1.32 (s, 3H, –Me). HRMS *m/z*; Calcd. for $C_{28}H_{36}O_8$ 500.2408 (M^+), 523.2306 (M^+ + Na), Found: 523.2351. *Anal.* Calcd. for $C_{28}H_{36}O_8$: C, 67.17; H, 7.25%, Found: C, 67.28; H. 7.28%.

Methyl 2,3-di-O-benzyl-4-O-acetyl-6-deoxy-D-*glycero*-α-D-*gluco-octapyranoside* (**12**). To a solution of **11** (2.06 g 4.12 mmol) in dichloromethane (50 ml) was added a mixture of trifluoroacetic acid–water (1 : 1, 1 ml), and stirred for 1 day. The solution was evaporated with toluene and worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 1 : 1) to provide **12** (1.77 g 93%). **12**: syrup, $[\alpha]_D^{20} = +12.2$ ($c=1.0$ in $CHCl_3$). ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.37–7.26 (m, 10H, aromatic protons), 4.91–4.61 (m, 5H, benzyl protons, H-4), 4.56 (d, 1H, H-1, $J=3.7$ Hz), 3.93–3.84 (m, 3H, H-3, H-7, H-8), 3.58–3.46 (m, 3H, H-2, H-5, H-8′), 3.42 (s, 3H, –OMe from anomeric position), 3.18 (s, 1H, –OH), 2.03 (s, 1H, –OH), 1.91 (s, 3H, Ac), 1.61 (m, 2H, H-6, H-6′). HRMS *m/z*: Calcd. for $C_{25}H_{32}O_8$ 460.2095 (M^+), 483.1993 (M^+ + Na), Found: 483.1997. *Anal.* Calcd. for $C_{25}H_{32}O_8$: C, 65.19; H, 7.01%, Found: C, 65.14; H, 6.95%.

Methyl 2,3-di-O-benzyl-4-O-acetyl-6-deoxy-8-O-tosyl-D-*glycero*-α-D-*gluco-octapyranoside* (**13**). To a solution of **12** (0.38 g 0.83 mmol) in pyridine (5 ml) was added tosyl chloride (180 mg 0.94 mmol 1.1 eq) at room temperature and stirred for 30 min. The solution was worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 1 : 1) to provide **13** (0.34 g 67%). **13**: syrup, $[\alpha]_D^{20} = +9.0$ ($c=1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.78–7.26 (m, 14H, aromatic protons), 4.90–4.60 (m, 5H, benzyl protons, H-4), 4.51 (d, 1H, H-1, $J=3.7$ Hz9, 4.22 (m, 1H, H-7), 3.99–3.80 (m, 4H, H-3, H-5, H-8, H-8′), 3.50 (dd, 1H, H-2, $J=3.7$, 9.5 Hz), 3.35 (s, 3H, –OMe from anomeric position), 2.44 (s, 3H, Me from tosyl), 2.02 (s, 1H, –OH), 1.91 (s, 3H, Ac), 1.56 (m, 2H, H-6, H-6′). *Anal.* Calcd. for $C_{32}H_{38}O_{10}S$: C, 62.52; H, 6.24; S, 5.21%, Found: C, 62.54; H, 6.28; S, 5.24%.

Methyl 2,3-di-O-benzyl-4-O-acetyl-6-deoxy-7-O-methoxymethyl-8-O-tosyl-D-*glycero*-α-D-*gluco-octapyranoside* (**14**). To a solution of **13** (730 mg 1.19 mmol) in dichloromethane (20 ml) and *N,N′*-diisopropylethylamine (0.90 ml) was added methoxymethyl chloride (0.30 ml 4.40 mmol 3.7 eq) at 0°C, and stirred for 1 h. The solution was worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 4 : 1) to provide **14** (620 mg 79%). **14**: syrup, $[\alpha]_D^{20} = +10.7$ ($c=1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.78–7.26 (m, 14H, aromatic protons), 4.89–4.56 (m, 7H, benzyl protons methylenes from MOM, H-4), 4.47 (d, 1H, H-1, $J=3.7$ Hz), 4.13–4.02 (m, 2H, H-7, H-8), 3.94–3.67 (m, 3H, H-3, H-5, H-8′), 3.49 (dd, 1H, H-2, $J=3.7$, 9.5 Hz), 3.31 (s, 3H, –OMe from MOM), 3.28 (s, 3H, –OMe from anomeric position), 2.44 (s, 3H, –Me from tosyl), 1.91 (s, 3H, Ac), 1.75 (m, 1H, H-6), 1.65 (m, 1H, H-6′). *Anal.* Calcd. for $C_{34}H_{42}O_{11}S$: C, 61.98; H, 6.43; S, 4.86%, Found: C, 61.87; H, 6.36; S, 4.77%.

Methyl 2,3-di-O-benzyl-6-deoxy-7-O-methoxymethyl-8-O-tosyl-D-*glycero*-α-D-*gluco-octapyranoside* (**15**). To a solution of **14** (60 ml 0.09 mmol) in methanol (20 ml) was added sodium methoxide (30 mg) at room temperature and stirred for 1 day. The solution was worked up to give a residue, which was purified by column chromatography (hexane–ethyl acetate = 4 : 1) to provide **15** (50 mg 71%). **15**: syrup, $[\alpha]_D^{20} = +18.9$ ($c=1.0$ in $CHCl_3$), ^{1}H-NMR DATA (300 MHz/$CDCl_3$) δ (ppm); 7.89–7.34 (m, 14H, aromatkc protons), 5.02–4.58 (m, 6H, benzyl protons, methylenes from MOM), 4.50 (d, 1H, H-1, $J=3.6$ Hz), 4.12–3.98 (m, 2H, H-8, H-8′), 3.67 (t, 1H, H-3, $J=9.1$ Hz), 3.60 (m, 1H, H-5), 3.44 (dd, 1H, H-2, $J=3.6$, 9.6 Hz), 3.31 (s, 3H, –OMe from MOM), 3.28 (s, 3H, OMe from anomeric position), 3.19 (t, 1H, H-4. $J=9.1$ Hz), 2.44 (s, 3H, –Me from Ts), 2.21 (s, 1H, –OH), 2.05 (m, 1H, H-6), 1.65 (m, 1H, H-6′). *Anal.* Calcd. for $C_{32}H_{40}O_{10}S$: C, 62.31; H, 6.54; S, 5.19%, Found: C, 62.23; H, 6.45; S, 5.08%.

Methyl 2,3-di-O-benzyl-6-deoxy-7-O-methoxymethyl-4,8-anhydro-D-*glycero*-α-D-*gluco-octapyranoside* (**16**). To a solution of **15** (550 mg 0.89 mmol) and 15-crown-5 (250 mg 1.25 mmol 1.4 eq) in *N,N*-dimethylformamide (50 ml) was added sodium hydride (25 mg 1.04 mmol 1.2 eq) at room temperature, and stirred for 10 min. The solvent was evaporated and worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 1 : 1) to provide **16** (362 mg 98%). **16**: syrup, $[\alpha]_D^{20} = +24.1$ ($c=1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.37–7.26 (m, 10H, aromatic protons), 4.89–4.62 (m, 6H, benzyl protons, methylenes from MOM), 4.52 (d, 1H, H-1, $J=3.7$ Hz), 4.10 (m, 1H, H-8eq), 3.81 (t, 1H, H-3, $J=9.2$, 9.5 Hz), 3.72 (m, 1H, H-7), 3.54–3.46 (m, 2H, H-5), 3.38 (s, 8H, –OMe), 3.35 (s, 3H, –OMe), 3.16 (t, 1H, H-8ax, $^3J_{H\text{-}8ax,H\text{-}8eq}=10.4$ Hz, $^3J_{H\text{-}8ax,H\text{-}7ax}=10.6$ Hz), 3.01 (t, 1H, H-4, $J=9.2$, 9.5 Hz), 2.37 (m, 1H, H-6eq), 1.45 (q, 1H, H-6ax, $^3J_{H\text{-}6ax,H\text{-}6eq}=10.4$ Hz, $^3J_{H\text{-}6ax,H\text{-}7ax}=11.4$ Hz). HRMS *m/z*; Calcd. for $C_{25}H_{32}O_7$ 444.2146 (M^+), 433.2068 ($M^+ - H$), found 433.2089. *Anal.* Calcd. for $C_{25}H_{32}O_7$: C, 67.54; H, 7.26%, Found: C, 67.12; H, 7.11%.

Methyl 2.3-di-O-benzyl-4-O-(4-methoxybenzyl)-6-deoxy-8-O-tosyl-D-*glycero*-α-D-*gluco-octapyranoside* (**17**). **17** was prepared from **9a** in 72% according to the procedures described for **13**. **17**: syrup, $[\alpha]_D^{20} = +19.0$ ($c=1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz/$CDCl_3$) δ (ppm); 7.78–6.83 (m, 18H, aromatic protons), 5.00–4.51 (m, 6H, benzyl protons), 4.48 (d, 1H, H-1, $J=3.7$ Hz), 3.98–3.69 (m, 5H, H-3, H-5, H-7, H-8, H-8′), 3.80 (s, 3H, –OMe from MPM), 3.46 (dd, 1H, H-2, $J=3.7$, 9.5 Hz), 3.32 (s, 3H, –OMe), 3.17 (t, 1H, H-4, $J=9$ Hz), 2.44 (s, 3H, –Me from Tosyl), 2.03 (m, 1H, H-6), 1.90 (s, 1H, –OH), 1.45 (m, 1H, H-6′). FAB-MS (+) *m/z*; 693 (M^+ + H).

Methyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-6-deoxy-7-O-methoxymethyl-8-O-tosyl-D-*glycero*-α-D-*gluco-octapyranoside* (**18**). **18** was prepared from **17** in 90% according to the procedures described for **14**. **18**: syrup, $[\alpha]_D^{20} = +21.9$ ($c=1.0$ in $CHCl_3$), ^{1}H-NMR DATA (270 MHz.$CDCl_3$) δ (ppm); 7.78—6.83 (m, 18H, aromatic protons), 4.98–4.49 (m, 8H, benzyl protons, methylenes from MOM), 4.47 (d, 1H, H-1, $J=3.7$ Hz), 4.09–4.01 (m, 2H, H-8, H-8′), 3.97 (m, 1H, H07), 3.87 (t, 1H, H-3, $J=9.1$ Hz), 3.78 (s, 3H, –OMe from MPM), 3.59 (m, 1H, H-5), 3.43 (dd, 1H, H-2, $J=3.7$, 9.5 Hz), 3.28 (s, 3H, –OMe from MOM), 3.23 (s, 3H, –OMe from anomeric position), 3.12 (t, 1H, H-4, $J=9.3$ Hz), 2.44 (s, 3H, Me from Ts), 2.05 (m, 1H, H-6), 1.55 (m, 1H, H-6′). HRMS *m/z*; Calcd. for $C_{40}H_{48}O_{11}S$ 736.2914 (M^+), Found: 736.2922. *Anal.* Calcd. for $C_{40}H_{48}O_{11}S$: C, 65.19; H, 6.57 S; 4.34%, Found: C, 64.90; H, 6.44; S, 4.21%.

Methyl 2,3-di-O-benzyl-6-deoxy-7-O-methoxymethyl-4,8-anhydro-L-*glycero*-α-D-*gluco-octapyranoside* (**19**). **19** was prepared from **9b** in 45% according to the procedures described for **14**, **15**, **10**, and **16**. **19**: mp 80–81°C, $[\alpha]_D^{20} = +20.1$ ($c=1.0$ in $CHCl_3$), ^{1}H-NMR DATA (300 MHz/$CHCl_3$) δ (ppm); 7.42–7.24 (m, 10H, aromatic protons), 4.94–4.64 (m, 6H, benzyl protons, methylenes from MOM), 4.54 (d, 1H, H-1, $J=3.6$ Hz), 4.09–3.85 (m, 4H, H-3, H-7, H-8ax H-8eq), 3.51–3.47 (m, 2H, H-2, H-5), 3.40 (s, 3H, –OMe), 3.38 (s, 3H, –OMe), 3.08 (t, 1H, H-4, $J=9.3$ Hz), 2.23 (m, 1H, H-6eq), 1.57 (m, 1H, H-6ax, $^3J_{H\text{-}7,H\text{-}6ax}=2.5$ Hz). HRMS *m/z*; Calcd. for $C_{25}H_{32}O_7$ 444.2146 (M^+), 443.2068 ($M^+ - H$), Found: 443.2114. *Anal.* Calcd. for $C_{25}H_{32}O_7$: C, 67.54; H, 7.26%, Found: C, 67.75; H, 7.27%.

Methyl 2,3-di-O-benzyl-6-deoxy-4,8-anhydro-D-*threo*-α-L-*glycero-octapyranoside* (**20**). **19** (1.50 g 3.8 mmol) was dissolved in a mixture of acetic acid (10 ml) and water (10 ml). The mixture was heated to 120°C and stirred for 1 h. The solution was cooled and saturated ammonium chloride was added. The solution was worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 4 : 1) to provide **20** (740 mg 55%). **20**: syrup, $[\alpha]_D^{20} = +12.5$ ($c=1.0$ in $CHCl_3$), ^{1}H-NMR DATA (300 MHz/$CDCl_3$) δ (ppm); 7.42—7.24 (m, 10H, aromatic protons), 4.92–4.62 (m, 4H, benzyl protons), 4.54 (d, 1H, H-1, $J=3.9$ Hz), 4.00–3.85 (m, 4H, H-3, H-7, H-8ax, H-8eq), 3.57–3.47 (m, 2H, H-2, H-5), 3.37 (s, 3H, –OMe from anomeric position), 3.05 (t, 1H, H-4, $J=9.3$ Hz), 2.12 (m, 2H, H-6eq, –OH), 1.57 (m, 1H, H-6ax). HRMS *m/z*; Calcd. for $C_{23}H_{28}O_6$ 400.1884 (M^+), 399.1806 ($M^+ - H$), Found: 399.1821. *Anal.* Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05%, Found: C, 68.76; H, 6.92%.

Methyl 2,3-di-O-benzyl-6-deoxy-4,8-anhydro-D-*glycero*-α-D-*gluco-octapyranoside* (**21**). To a solution of **20** (340 mg 0.87 mmol), triphenylphosphine (460 mg 1.74 mmol), and monochloroacetic acid (170 mg 1.74 mmol) in ether (8 ml) was added azodicarboxylic acid diethyl ester (0.30 ml 1.72 mmol) at room temperature and stirred for 12 h. The solution was worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 4 : 1) to provide a monochloroethylester com-

pound (240 mg 59%). The compound (38 mg 0.08 mmol) was added to the solution of sodium methoxide (10 mg) in methanol (5 ml), and stirred for 10 min. The solution was worked up to give a syrup, which was purified by column chromatography (hexane–ethyl acetate = 4 : 1) to provide **21** (25 mg 78%). **21**: syrup, ^{1}H-NMR DATA (300 MHz/$CDCl_3$) δ (ppm); 7.42–7.24 (m, 10H, aromatic protons), 4.89–4.63 (m, 4H, benzyl protons), 4.54 (d, 1H, H-1, J = 3.6 Hz), 4.05 (m, 1H, H-8eq), 3.84 (m, 1H, H-7), 3.82 (t, 1H, H-3, J = 9.3 Hz), 3.55–3.47 (m, 2H, H-2, H-5), 3.38 (s, 3H, –OMe from anomeric position), 3.10 (t, 1H, H-8ax, J = 10.7 Hz), 3.00 (t, 1H, H-4, J = 9.3 Hz), 2.35 (m, 1H, H-6eq), 1.58 (s, 1H, –OH), 1.42 (q, 1H, H-6ax, J = 11.3 Hz). HRMS m/z; Calcd. for $C_{23}H_{28}O_6$ 400.1884 (M^+), 399.1806 ($M^+ - H$), Found: 399.1816. *Anal.* Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05%, Found: C, 68.83; H, 6.88%.

Preparation of **15** *from* **18**. **18** was prepared from **15** in 80% according to the procedures described for **10**.

Preparation of **16** *from* **21**. **21** was converted to **16** according to the procedures described for **14** (80% yield). **16**: HRMS m/z; Calcd. for $C_{25}H_{32}O_7$ 444.2146 (M^+), 433.2068 ($M^+ - H$), found 433.2089. *Anal.* Calcd. for $C_{25}H_{32}O_7$: C, 67.54; H, 7.26%, Found: C, 67.23; H, 7.17%.

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