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Note

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Synthesis of *β*-*C*-glycopyranosyl aldehydes and 2,6-anhydro-heptitols

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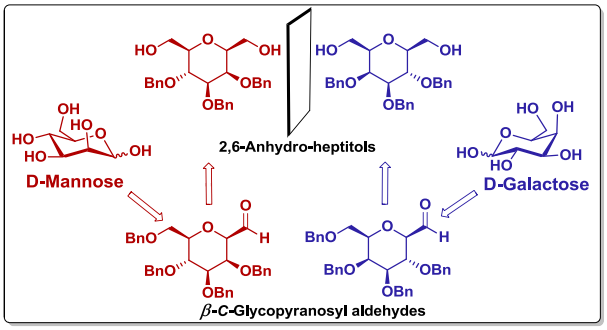
Abstract:



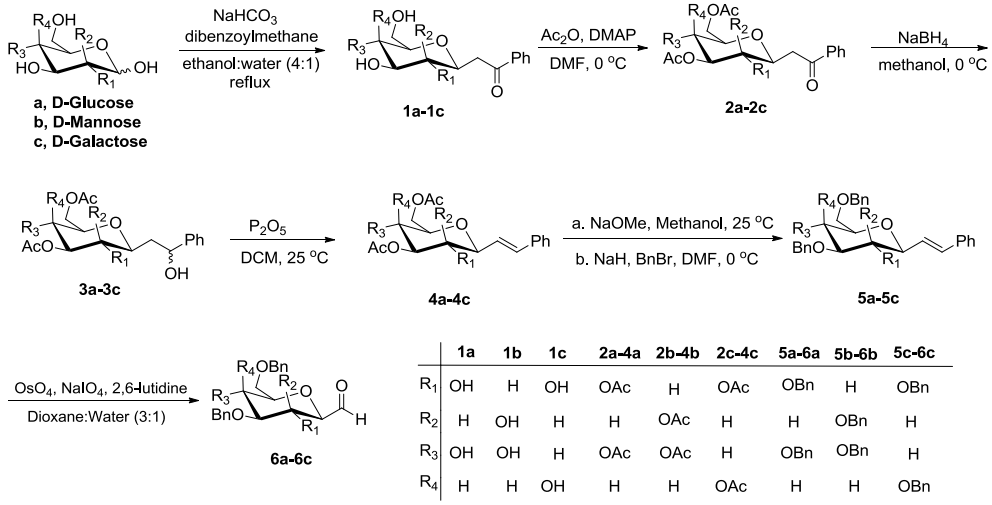
A convenient route has been developed for the diastereoselective synthesis of *β*-*C*-glycopyranosyl aldehydes from D-glucose, D-mannose and D-galactose. The key step in the synthesis of *C*-glycosyl aldehydes is the aryl driven reductive dehydration on 1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glycopyranosyl)ethanone to afford alkenes, which on oxidation afford the desired compounds in good yield. *β*-*C*-Glycopyranosyl aldehydes have been converted to 2,6-anhydro-heptitols in quantitative yields. The 2,6-anhydro-heptitols derived from D-mannose and D-galactose are enantiomeric and useful linker for the synthesis of macrocycles/amphiphiles of complimentary chirality.

Keywords: *β*-*C*-Glycosides, *β*-*C*-glycopyranosyl aldehydes, 2,6-anhydro-heptitols, linker.

The *β*-*C*-glycosides are important stable class of carbohydrate derivatives that possess interesting biological properties.[1-3] They are mainly used as synthetic intermediates to prepare amino acids,[4] *C*-linked disaccharides,[5-6] heterocycles of biological importance[7] and as models in enzymatic and metabolic studies because of the fact that the conformations of the native sugars and their *C*-linked analogs have little difference.[8] The pursuit for the introduction of formyl group during the synthesis of *β*-*C*-glycosides is quite demanding which further leads towards the development of a variety of biologically active compounds.[9,10] Till date, very limited synthetic approaches have been reported for the preparation of *β*-*C*-glycosyl aldehydes.[11,12] Genet, *et al.*[11a] has reported the synthesis of *β*-*C*-glycopyranosyl aldehydes from sugar lactone either using dithiane or phenyl acetylene in presence of butyl lithium at low temperature, whereas Lubineau, *et al.*[12b] has used acetyl acetone with the formation of mixture of enol ethers that requires oxidation by dimethyldioxirane making the whole synthesis cumbersome and inefficient. In most of the other synthesis of *β*-*C*-glycosyl aldehydes either the *α*-anomer has to be isomerized or the *β*-isomer has to be separated from the anomeric mixture formed during the synthesis.[13] Here in, we report a convenient and efficient method for the diastereoselective synthesis of *β*-*C*-glycopyranosyl aldehydes and their corresponding 2,6-anhydro-3,4,5-tri-*O*-benzyl-heptitols & 2,6-anhydro-heptitols starting from D-glucose, D-mannose and D-galactose sugars. These 2,6-anhydro-heptitols could find expedient utility as bidendate ligand/linkers due to the presence of two primary hydroxyl groups and can be used for the synthesis of macrocycles/amphiphilic polymers by transesterification reaction with different hydrophilic PEG-dimethyl esters.[14] It is also noteworthy that the 2,6-anhydro-heptitols to be derived from D-mannose and D-galactose will be enantiomeric to each other and can be used for the generation of amphiphiles leading to micelles having core with complimentary chirality.[15]

Natural, readily available, inexpensive starting materials, *i.e.* D-glucose, D-mannose and D-galactose has been used for the synthesis of *β*-*C*-glycopyranosyl aldehydes and 2,6-anhydro-heptitols. Thus the peracetates of *β*-*C*-glycosyl benzoylmethane **2a-2c** were synthesized from D-glucose, D-mannose and D-galactose in 85, 82 and 62% yields, respectively in two steps, *i.e.* conversion of the native sugar to *β*-*C*-glycosyl benzoylmethane **1a-1c** on reaction with dibenzoylmethane-sodium bicarbonate in aqueous-alcoholic solution followed by their peracetylation with acetic anhydride-DMAP in dimethylformamide (Scheme 1). The reduction of peracetylated *β*-*C*-glycosides **2a-2c** with $NaBH_4$ led to the formation of alcohols **3a-3c** in 96, 93 and 95% yields, respectively. Although the reduction of compounds **2a** and **2c** afforded only one diastereomeric alcohol each, *i.e.* **3a** and **3c**, the reduction of **2b** afforded diastereomeric mixture of alcohols **3b** (11:9, determined by ^{1}H NMR); this may be due to the stereochemical difference at C-2′ position of the precursor ketone. The optimization of the reaction for tandem mesylation followed by base catalyzed elimination with different bases or direct dehydration reaction on alcohol **3a** were tried in dichloromethane and also in bulk under microwave reactor condition to afford the desired alkene (*E*)-1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)ethene **4a** (entries 1-6, Table 1). The mesylation-elimination reaction using mesyl chloride with different bases in dichloromethane resulted in the formation of the desired product **4a** in very poor yields/no reaction (entries 1-3, Table 1) due to the competition between elimination and substitution reaction affected by the chloride ion generated in the reaction to form 1-chloro-1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)ethane as major side product.[16] Although the yield of bulk reaction on **3a** under microwave condition to form the alkene **4a** enhanced from 0-20% to 30-50% (entries 4-6, Table 1); this was also not up to the mark for practical purposes because of the lower reaction efficiency and the generation of HCl gas in the microwave reactor.

The direct dehydration reaction on alcohol **3a** in the presence of sulfuric acid, orthophosphoric acid and phosphorus pentaoxide in dichloromethane led to the formation of alkene **4a** in 70, 75 and 95% yields, respectively (entries 7-9, Table 1). The observation of moderate yields in the case of sulfuric acid and orthophosphoric acid as dehydrating agent could be due to charring of starting material **3a** under highly acidic condition. The use of P_2O_5 as dehydrating agent for the conversion of compound **3a** to **4a** was found to be a very effective method due to its non-nucleophilic nature. Thus P_2O_5 in dichloromethane was used for the dehydration of **3b** and **3c** to obtain **4b** and **4c** in 91 and 94% yields, respectively (Scheme 1).



Scheme 1

Table 1. Optimization of synthesis of *E*-alkene **4a** from alcohol **3a**

Entry	Solvent	Temp (^{o}C)	Time	Reagents	% Yield[a] of **4a**
1	DCM	40	24h	MsCl, TEA	20
2	DCM	40	24h	MsCl, DBU	10

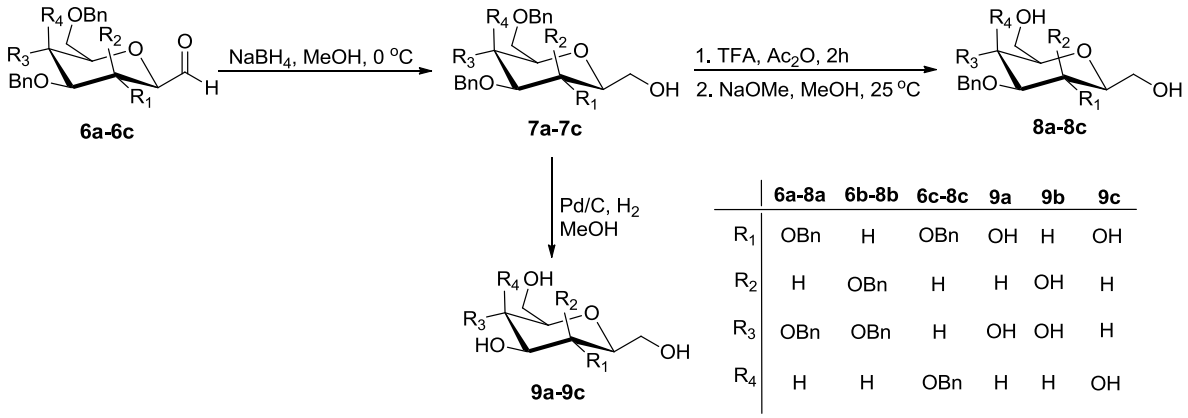
3	DCM	40	24h	MsCl, DIPEA	0
4	Neat*	80	5 min	MsCl, DIPEA	50
5	Neat*	80	5 min	MsCl, DBU	40
6	Neat*	80	5 min	MsCl, TEA	30
7	DCM	25	3h	H_2SO_4	70
8	DCM	25	30h	H_3PO_4	75
9	DCM	25	6h	P_2O_5	95

*Microwave reactor was used at 80 ^{o}C at a power of 100 W, [a]isolated yield.

The oxidation of acylated sugar alkenes **4a**-**4c** afforded a very unstable product which could not be isolated in pure form. This prompted us to convert the peracetylated *C*-glycosides **4a**-**4c** to their corresponding perbenzylated analogs **5a-5c** in one pot two steps reaction, *i.e.* by deacetylation using sodium methoxide followed by perbenzylation using benzyl bromide in the presence of sodium hydride in 90, 80 and 92% overall yields, respectively (Scheme 1). The oxidation of perbenzylated *C*-glycopyranosides **5a-5c** with OsO_4-$NaIO_4$ in the presence of 2,6-lutidine in dioxane/water successfully afforded the three corresponding *β*-*C*-glycopyranosyl aldehydes **6a-6c** in 80, 78 and 81% yields, respectively.[17]

The *β*-*C*-glycopyranosyl aldehydes **6a-6c** were further converted to 2,6-anhydro-3,4,5-tri-*O*-benzyl-heptitol and then to 2,6-anhydro-heptitol which can be used as a chiral linker involving its two primary hydroxyl groups for various applications. Thus, *β*-*C*-glycopyranosyl aldehydes **6a-6c** on reaction with sodium borohydride-methanol afforded the glycosyl carbinols **7a-7c** which in turn on selective removal of primary *O*-benzyl group using TFA-acetic anhydride/sodium methoxide-methanol led to the formation of 2,6-anhydro-3,4,5-tri-*O*-benzyl-heptitols **8a-8c** in 78, 72 and 79% overall yield, respectively (Scheme 2). The 2,6-anhydro-

heptitols, *i.e.* 2,6-anhyro-gluco-heptitol (**9a**), 2,6-anhydro-manno-heptitol (**9b**) and 2,6-anhydro-galacto-heptitol (**9c**) were synthesized by debenzylation of tetra-*O*-benzylated compounds **7a-7c** using Pd/charcoal under H_2 atmosphere in methanol in 90, 87 and 85% yields, respectively.



	6a-8a	6b-8b	6c-8c	9a	9b	9c
R_1	OBn	H	OBn	OH	H	OH
R_2	H	OBn	H	H	OH	H
R_3	OBn	OBn	H	OH	OH	H
R_4	H	H	OBn	H	H	OH

Scheme 2

Generally, enantiomers are either synthesized by enantioselective reactions or by chiral resolution of the racemic product formed in the classical reaction. In the present synthesis of heptitols, it has been observed that 2,6-anhydro-manno-heptitol (**9b**) derived from D-mannose and 2,6-anhydro-galacto-heptitol (**9c**) derived from D-galactose or their tri-*O*-benzylated derivatives **8b** and **8c** are enantiomeric to each other. The specific rotation value $[\alpha]_D^{26}$ for anhydro-manno-heptitol (**8b**) and anhydro-galacto-heptitol (**8c**) were found to be -47.0 (*c* 1, methanol) and +47.6 (*c* 1, methanol), respectively and for 2,6-anhydro-manno-heptitol **9b** and 2,6-anhydro-galacto-heptitol **9c** were found to be -32.4 (*c* 1, H_2O) and +33.0 (*c* 1, H_2O), respectively. The structures of all synthesized compounds, *i.e.* **1a**-**9a**, **1b**-**9b** and **1c**-**9c** were unambiguously established on the basis of their spectral data (^1H, ^{13}C NMR, IR spectra and HRMS) analysis. The structure of known compounds **1a**-**1c**, **4a**, **6a**-**6c**, **7a**, **8c** and **9a**-**9c** were

further confirmed on the basis of comparison of their physical and spectral data with those reported in the literature.[18-21]

Conclusion: In summary, a simple and efficient route has been developed for the synthesis of *β*-*C*-glycopyranosyl aldehydes, corresponding 2,6-anhydro-3,4,5-tri-*O*-benzyl-heptitols and 2,6-anhydro-heptitols in excellent to good overall yields. The P_2O_5 has been found to be the excellent dehydrating reagent for the synthesis of (*E*)-1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glycopyranosyl)ethene from 1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glycopyranosyl)ethanol. The process is highly selective and straightforward for the synthesis of *β*-*C*-glycosyl aldehydes and 2,6-anhydro-heptitols which have wide scope in the synthesis of various kinds of biologically important *β*-*C*-glycosides and amphiphiles. The enantiomeric anhydro-heptitols derived from D-mannose and D-galactose may be an expedient linker for the development of a wide variety of biocompatible polymers/macromolecules with complimentary chirality.

Experimental Section

General

All solvents were distilled before use. The IR spectra were recorded by making KBr disk for solid samples and thin film for oils. The optical rotations were measured using light of 589 nm wavelength. ^{1}H NMR and ^{13}C NMR spectra were recorded using tetramethylsilane (TMS) as internal standard. The chemical shift values were observed on *δ* scale and the coupling constant (*J*) are in Hz. Signals from OH group(s) in ^{1}H NMR spectra recorded in $CDCl_3$ were verified by D_2O exchange method. HRMS analysis was carried out using Q-TOF mass spectrometer. Analytical TLCs were performed on precoated fluorescent plates; visualization of the developed

plates was performed by UV light and charring with 5% alcoholic sulfuric acid. Silica gel (100-200 mesh) was used for column chromatography.

General procedure for the synthesis of 1-phenyl-2-(*β*-D-glycopyranosyl)ethanone (1a-1c)[18a]

Compounds **1a-1c** were synthesized as per the literature procedure and obtained in 65 to 90% yields. These compounds are identified on the basis of their spectral data (^{1}H, ^{13}C NMR spectra and HRMS) analysis. The structure was further confirmed by comparison of its physical and spectral data with those reported in the literature.[18a]

General procedure for the synthesis of 1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glycopyranosyl)ethanone (2a-2c)

To a solution of **1a-1c** (13 g, 46.09 mmol) in DMF (100 mL) was added DMAP (1.40 g, 11.52 mmol) and acetic anhydride (21.75 mL, 230.45 mmol) at 0 ^{o}C. The solution was stirred for 1 h at 0 ^{o}C and quenched by addition of ice-cold water (150 mL). The reaction mixture was extracted with ethyl acetate (2 x 150 mL) and combined organic layer was washed with saturated solution of $NaHCO_3$ (1 x 150 mL) followed by saturated solution of NaCl (1 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and then concentrated at reduced pressure to give the crude product, which was purified over silica gel column using 30% ethyl acetate in petroleum ether as eluent to afford the pure product (**2a-2c**).

1-Phenyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)ethanone (**2a**)

It was obtained as a white solid (19.49 g) in 94% yield; m.pt. 104-106 ^{o}C; IR (KBr, cm^{-1}): 1751, 1741, 1684, 1381, 1263, 1224; $[\alpha]^{26}_{D}$ -25.9 (*c* 0.4, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3H), 1.99 (s, 6H), 2.01 (s, 3H), 2.93 (dd, 1H, *J* = 2.9 & 16.8 Hz), 3.34 (dd, 1H, *J* = 8.0 &

16.8 Hz), 3.73-3.75 (m, 1H), 3.99 (d, 1H, *J* = 12.4 Hz), 4.20-4.26 (m, 2H), 5.02 (t, 1H, *J* = 9.5 Hz), 5.07 (t, 1H, *J* = 9.5 Hz), 5.24 (t, 1H, *J* = 9.5 Hz), 7.43-7.47 (m, 2H), 7.55-7.58 (m, 1H), 7.92 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.5, 20.6, 40.4, 61.9, 68.4, 71.6, 73.9, 74.1, 75.6, 128.2, 128.6, 133.4, 136.6, 169.5, 169.9, 170.2, 170.6, 196.1; HRMS (ESI): *m/z* = 473.1431 (calculated for $C_{22}H_{26}NaO_{10}$ $[M+Na]^+$ = 473.1418).

1-Phenyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-mannopyranosyl)ethanone (**2b**)

It was obtained as a white solid (20.12 g) in 97% yield; m.pt. 83-85 ^{o}C; IR (KBr, cm^{-1}): 1747, 1726, 1688, 1369, 1249, 1217, 1054; $[\alpha]^{26}_{D}$ -32.3 (*c* 0.4, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.18 (s, 3H), 2.99 (dd, 1H, *J* = 5.3 & 17.4 Hz), 3.38 (dd, 1H, *J* = 6.9 & 17.3 Hz), 3.70-3.74 (m, 1H), 4.04 (dd, 1H, *J* = 2.3 & 12.3 Hz), 4.28 (dd, 1H, *J* = 5.6 & 12.3 Hz), 4.40 (dd, 1H, *J* = 5.6 & 6.6 Hz), 5.17 (dd, 1H, *J* = 3.0 & 9.7 Hz), 5.25 (t, 1H, *J* = 9.7 Hz), 5.46-5.47 (m, 1H), 7.43-7.47 (m, 2H), 7.55-7.59 (m, 1H), 7.89-7.91 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.6, 20.8, 39.4, 62.7, 66.1, 70.1, 72.2, 73.2, 76.4, 128.1, 128.7, 133.5, 136.5, 169.8, 170.0, 170.5, 170.7, 195.9; HRMS (ESI): *m/z* = 473.1421 (calculated for $C_{22}H_{26}NaO_{10}$ $[M+Na]^+$ = 473.1418).

1-Phenyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosyl)ethanone (**2c**)

It was obtained as a white crystalline solid (19.91 g) in 96% yield; m.pt. 113-115 ^{o}C; IR (KBr, cm^{-1}): 1746, 1686, 1369, 1221, 1048; $[\alpha]^{26}_{D}$ +1.43 (*c* 0.1, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3H), 1.99 (s, 6H), 2.16 (s, 3H), 2.95 (dd, 1H, *J* = 3.3 & 16.5 Hz), 3.40 (dd, 1H, *J* = 8.1 & 16.5 Hz), 3.92-4.08 (m, 3H), 4.18-4.24 (m, 1H), 5.09 (dd, 1H, *J* = 3.2 & 10.0 Hz), 5.23 (t, 1H, *J* = 10.0 Hz), 5.44 (d, 1H, *J* = 3.3 Hz), 7.47 (t, 2H, *J* = 7.6 Hz), 7.58 (t, 1H, *J* = 7.6 Hz),

7.94 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.6, 20.7, 40.7, 61.2, 67.6, 69.1, 72.0, 74.2, 74.5, 128.2, 128.6, 133.4, 136.7, 170.1, 170.2, 170.4, 196.5; HRMS (ESI): *m/z* = 451.1608 (calculated for $C_{22}H_{27}O_{10}$ $[M+H]^+$ = 451.1599).

General procedure for the synthesis of 1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glycopyranosyl)ethanol (3a-3c)

To a solution of **2a-2c** (12.4 g, 27.54 mmol) in methanol (100 mL) was added $NaBH_4$ (1.22 g, 33.05 mmol) and seralite acidic resin (10 g) at 0 ^{o}C. The solution was stirred for 1 h at 0 °C. The seralite resin was removed from the reaction by filteration followed by the removal of methanol under reduced pressure to give the semi-solid residue which was extracted with ethyl acetate (3 x 125 mL). The combined organic layer was washed with saturated solution of NaCl (1 x 150 mL), dried over anhydrous Na_2SO_4, filtered and then concentrated at reduced pressure. The crude product thus obtained was purified over silica gel column with 40% ethyl acetate in petroleum ether as eluent to afford pure product (**3a-3c**).

1-Phenyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)ethanol (**3a**)

It was obtained as a white solid (11.95 g) in 96% yield; m.pt. 87-89 ^{o}C; IR (KBr, cm^{-1}): 3509, 1751, 1743, 1380, 1216, 1033; $[\alpha]^{26}_D$ -10.1 (*c* 0.6, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79-1.84 (m, 1H), 1.96-1.98 (m, 7H), 2.02 (s, 3H), 2.11 (s, 3H), 3.15 (brs, 1H), 3.51 (t, 1H, *J* = 9.2 Hz), 3.63-3.68 (m, 1H), 4.13 (dd, 1H, *J* = 6.5 & 12.4 Hz), 4.21 (dd, 1H, *J* = 2.2 & 12.4 Hz), 4.88-4.93 (m, 2H), 5.02 (t, 1H, *J* = 9.5 Hz), 5.12 (t, 1H, *J* = 9.2 Hz), 7.27-7.35 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.7, 20.8, 40.4, 62.6, 68.7, 71.8, 73.2, 74.0, 75.9, 77.6, 125.9,

127.9, 128.6, 143.5, 169.5, 169.6, 170.4, 170.8; HRMS (ESI): *m/z* = 475.1571 (calculated for $C_{22}H_{28}NaO_{10}$ $[M+Na]^+$ = 475.1575).

1-Phenyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-mannopyranosyl)ethanol (**3b**)

It was obtained as diastereomeric mixture (11:9) as a semi-solid (11.58 g) in 93% yield; IR (thin film, cm^{-1}): 3511, 1747, 1369, 1230, 1054; $[\alpha]^{26}_D$ -30.1 (*c* 0.6, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64-1.75 (m, 1H) 1.94-2.13 (m, 13H), 2.67 (brs, 0.45H), 2.93 (brs, 0.55H), 3.58-3.66 (m, 1H), 3.71-3.81 (m, 1H), 4.13-4.24 (m, 2H), 4.86 (dd, 0.55H, *J* = 4.6 & 8.6 Hz), 4.92 (dd, 0.45H, *J* = 2.3 & 7.9 Hz), 4.96-5.01 (m, 1H), 5.14-5.20 (m, 1H), 5.25 (d, 0.45H, *J* = 3.3 Hz), 5.31 (d, 0.55, *J* = 3.3 Hz), 7.24-7.33 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.6, 20.7, 20.8, 39.2, 39.8, 63.0, 66.2, 66.3, 69.8, 70.5, 70.8, 72.1, 72.3, 72.6, 74.2, 76.3, 76.4, 77.3, 125.4, 127.6, 127.9, 128.6, 143.5, 143.9, 169.8, 170.2, 170.5, 170.6, 170.8; HRMS (ESI): *m/z* = 475.1573 (calculated for $C_{22}H_{28}NaO_{10}$ $[M+Na]^+$ = 475.1575).

1-Phenyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosyl)ethanol (**3c**)

It was obtained as a semi-solid (11.83 g) in 95% yield; IR (thin film, cm^{-1}): 3462, 1749, 1370, 1225, 1051; $[\alpha]^{26}_D$ +7.48 (*c* 0.1, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (ddd, 1H, *J* = 2.1, 4.2 & 14.6 Hz), 1.97 (s, 3H), 2.01 (s, 3H), 2.04-2.13 (m, 4H), 2.18 (s, 3H), 3.25 (brs, 1H), 3.56 (t, 1H, *J* = 10.0 Hz), 3.92 (t, 1H, *J* = 6.5 Hz), 4.14 (d, 2H, *J* = 6.3 Hz), 4.94 (dd, 1H, *J* = 4.9 & 9.1 Hz), 4.98 (dd, 1H, *J* = 3.3 & 9.9 Hz), 5.15 (t, 1H, *J* = 9.9 Hz), 5.43 (d, 1H, *J* = 3.2 Hz), 7.28-7.37 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.5, 20.6, 20.7, 40.3, 62.1, 67.5, 68.9, 71.6, 73.4, 74.5, 78.2, 125.8, 127.7, 128.5, 143.3, 169.6, 170.1, 170.2, 170.5; HRMS (ESI): *m/z* = 475.1590 (calculated for $C_{22}H_{28}NaO_{10}$ $[M+Na]^+$ = 475.1575).

General procedure for the synthesis of (*E*)-1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glycopyranosyl)ethene (4a-4c)

To a solution of compound **3a-3c** (5 g, 11.05 mmol) in dichloromethane (300 ml) P_2O_5 (4.70 g, 33.17 mmol) was added and the reaction mixture was stirred for 6 h at 25 ^oC. The reaction mixture was decanted and ice-cold water was added in the decanted solution to completely quench the reaction. The reaction mixture was extracted with dichloromethane (3 x 100 mL) and the combined organic layer was washed with saturated solution of $NaHCO_3$ (1 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and then concentrated at reduced pressure. The crude product, thus obtained was purified over silica gel column with 20% ethyl acetate in petroleum ether to afford the pure product **4a-4c**.

(E)-1-Phenyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)ethene (**4a**)[18b]

Compound **4a** was obtained as a white solid (4.56 g) in 95% yield and identified on the basis of its spectral data (^1H, ^{13}C NMR spectra and HRMS) analysis. HRMS (ESI): *m/z* = 435.1670 (calculated for $C_{22}H_{27}O_9$ $[M+H]^+$ = 435.1650) (^1H- and ^{13}C NMR spectra has been given in the supporting information). The structure was further confirmed by comparison of its physical and spectral data with those reported in the literature.[18b]

(E)-1-Phenyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-mannopyranosyl)ethene (**4b**)

It was obtained as a semi-solid (4.36 g) in 91% yield; IR (thin film, cm^{-1}): 1747; 1369, 1227, 1054; $[\alpha]^{26}_D$ -37.2 (*c* 0.5, methanol); ^1H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.01 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 3.68-3.73 (m, 1H), 4.14 (dd, 2H, *J* = 2.9 & 12.4 Hz), 4.27 (dd, 1H, *J* = 5.1 & 12.4 Hz), 4.31 (d, 1H, *J* = 5.1 Hz), 5.10 (dd, 1H, *J* = 2.9 & 10.2 Hz), 5.26 (t, 1H, *J* = 10.2

Hz), 5.43 (d, 1H, *J* = 3.6 Hz), 6.01 (dd, 1H, *J* = 5.8 & 16.1 Hz), 6.63 (d, 1H, *J* = 16.1 Hz), 7.18-7.30 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.7, 20.8, 20.9, 63.0, 66.2, 70.3, 72.4, 76.4, 77.5, 123.3, 126.7, 128.2, 128.7, 133.4, 136.1, 169.8, 170.3, 170.5, 170.9; HRMS (ESI): *m/z* = 435.1649 (calculated for $C_{22}H_{27}O_9$ $[M+H]^+$ = 435.1650).

(E)-1-Phenyl-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosyl)ethene (**4c**)

It was obtained as a white solid (4.51 g) in 94% yield; m.pt. 121-123 ^{o}C; IR (film, cm^{-1}): 1749, 1373, 1226, 1054; $[\alpha]^{26}_D$ -20.8 (*c* 0.1, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.01 (s, 3H), 2.06 (s, 3H), 2.19 (s, 3H), 3.97-4.03 (m, 2H), 4.15 (d, 1H, *J* = 6.5 Hz), 5.12 (dd, 1H, *J* = 3.81 & 10.2 Hz), 5.26 (t, 1H, *J* = 9.9 Hz), 5.48 (d, 1H, *J* = 3.0 Hz), 6.12 (dd, 1H, *J* = 7.8 & 15.9 Hz), 6.64-6.68 (d, 1H, *J* = 15.8 Hz), 7.27-7.38 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.6, 20.7, 61.7, 67.6, 68.6, 71.6, 74.0, 80.2, 124.1, 126.7, 128.2, 128.5, 135.1, 135.8, 169.6, 170.2, 170.3, 170.4; HRMS (ESI): *m/z* = 435.1634 (calculated for $C_{22}H_{27}O_9$ $[M+H]^+$ = 435.1650).

General procedure for the synthesis of (*E*)-1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-benzyl-*β*-D-glycopyranosyl)ethene (5a-5c)

To a solution of **4a-4c** (4.7 g, 10.82 mmol) in methanol (50 mL) was added NaOMe (1.75 g, 32.47 mmol) at 25 ^{o}C. The solution was stirred for 2 h and it was neutralized with seralite acidic resin which was further removed by filtration. Methanol was evaporated under reduced pressure, the residue was taken in DMF (50 mL) followed by the addition of NaH (2.16 g, 90.18 mmol) in it at 0 °C. The reaction mixture was allowed to stir at 0 ^{o}C for 30 min followed by the addition of benzyl bromide (6.61 mL, 56.36 mmol) after half an hour. On completion, reaction mixture was poured into ice cold water and extracted with chloroform (2 x 100 mL). The combined organic

layer was washed with saturated NaCl (1 x 100 mL), dried over anhydrous Na_2SO_4, filtered and then concentrated at reduced pressure. The crude product thus obtained was purified over silica gel column with 5% ethyl acetate in petroleum ether as eluent to afford the pure product **5a-5c**.

(E)-1-Phenyl-2-(2′,3′,4′,6′-tetra-O-benzyl-β-D-glucopyranosyl)ethene (**5a**)

It was obtained as a white solid (6.1 g) in 90% yield; m.pt. 107-109 ^oC; IR (KBr, cm^{-1}): 1636, 1402, 1060; $[\alpha]^{26}_D$ +64.5 (*c* 0.1, chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ 3.42 (t, 1H, *J* = 9.1 Hz), 3.50-3.54 (m, 1H), 3.66-3.77 (m, 4H), 3.94 (dd, 1H, *J* = 7.3 & 9.1 Hz), 4.56 (d, 2H, *J* = 9.7 Hz), 4.62 (d, 1H, *J* = 8.1 Hz), 4.65 (d, 1H, *J* = 9.7 Hz), 4.74 (d, 1H, *J* = 10.3 Hz), 4.84 (d, 1H, *J* = 10.9 Hz), 4.90 (d, 1H, *J* = 10.9 Hz), 4.95 (d, 1H, *J* = 10.9 Hz), 6.23 (dd, 1H, *J* = 7.0 & 16.0 Hz), 6.74 (d, 1H, *J* = 16.0 Hz), 7.14-7.37 (m, 25H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 69.0, 73.6, 75.1, 75.3, 75.7, 78.2, 78.8, 80.4, 82.5, 86.9, 126.6, 127.7, 127.8, 128.0, 128.4, 128.5, 128.6, 133.4, 136.7, 137.8, 138.1, 138.2, 138.7; HRMS (ESI): *m/z* = 649.2917 (calculated for $C_{42}H_{42}NaO_5$ $[M+Na]^+$ = 649.2924).

(E)-1-Phenyl-2-(2′,3′,4′,6′-tetra-O-benzyl-β-D-mannopyranosyl)ethene (**5b**)

It was obtained as a gel (5.4 g) in 80% yield; IR (thin film, cm^{-1}): 2917, 1719, 1452, 1095; $[\alpha]^{26}_D$ -23.0 (*c* 0.2, chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ 3.51-3.55 (m, 1H), 3.67 (dd, 1H, *J* = 2.8 & 9.4 Hz), 3.72-3.80 (m, 2H), 3.85 (d, 1H, *J* = 2.1 Hz), 3.96 (t, 1H, *J* = 9.6 Hz), 4.00 (d, 1H, *J* = 6.2 Hz), 4.57 (dd, 2H, *J* = 7.5 & 11.4 Hz), 4.63-4.74 (m, 4H), 4.90 (dd, 2H, *J* = 6.6 & 11.4 Hz), 6.20 (dd, 1H, *J* = 6.1 & 16.1 Hz), 6.60 (d, 1H, *J* = 16.1 Hz), 7.15-7.36 (m, 25H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 69.8, 72.5, 73.6, 74.5, 75.3, 75.4, 76.7, 79.4, 79.8, 85.0, 126.7, 127.1,

127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 131.7, 136.9, 138.5, 138.6; HRMS (ESI): *m/z* = 649.2923 (calculated for $C_{42}H_{42}NaO_5$ $[M+Na]^+$ = 649.2924).

(E)-1-Phenyl-2-(2′,3′,4′,6′-tetra-O-benzyl-β-D-galactopyranosyl)ethene (**5c**)

It was obtained as a gel (6.23 g) in 92% yield; IR (thin film, cm^{-1}): 1635, 1457, 1097, 1027; $[\alpha]^{26}_D$ -31.1 (*c* 0.6, chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ 3.53-3.66 (m, 4H), 3.82 (t, 1H, *J* = 9.1 Hz), 3.90 (dd, 1H, 6.8 & 9.1Hz), 4.01 (d, 1H, *J* = 3.0 Hz), 4.42 (d, 1H, *J* = 11.9 Hz), 4.47 (d, 1H, *J* = 11.9 Hz) 4.62 (d, 1H, *J* = 10.6 Hz), 4.66 (d, 1H, *J* = 11.7 Hz), 4.72-4.76 (m, 2H), 4.81 (d, 1H, *J* = 10.6 Hz), 4.97 (d, 1H, *J* = 11.6 Hz), 6.25 (dd, 1H, *J* = 6.8 & 16.0 Hz), 6.71 (d, 1H, *J* = 16.0 Hz), 7.22-7.39 (m, 25H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 69.0, 72.7, 73.6, 74.0, 74.7, 75.5, 77.0, 79.0, 80.8, 84.4, 126.7, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 133.4, 136.9, 137.9, 138.2, 138.5, 138.8; HRMS (ESI): *m/z* = 627.3087 (calculated for $C_{42}H_{43}O_5$ $[M+H]^+$ = 627.3105).

General procedure for the synthesis of 1-formyl-2,3,4,6-tetra-*O*-benzyl-*β*-D-glycopyranoside (6a-6c)[17]

To a suspension of **5a-5c** (5 g, 7.98 mmol) in dioxane-water (3:1, 100 mL) was added 2,6-lutidine (0.41 mL, 15.97 mmol), OsO_4 (38.1 mg, 0.15 mmol) and $NaIO_4$ (6.78 g, 31.92 mmol). The reaction mixture was stirred at 25 ^oC for 8 h and after completion it was extracted with dichloromethane (2 x 75 mL) and combined organic layer was first washed with saturated solution of $NaHCO_3$ (1 x 75 mL) and then with saturated NaCl solution (1 x 75 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and then concentrated at reduced pressure to afford the crude products **6a**, **6b** and **6c** in 80, 78 and 81% yields, respectively. The crude

product as such was used for spectral studies, because an effort of purification of compounds over silica gel column led to the partial decomposition of the aldehyde function present in the molecule. Compounds **6a**, **6b** and **6c** were identified on the basis of their spectral data (^{1}H, ^{13}C NMR spectra and HRMS) analysis. HRMS (ESI) of **6a**: *m/z* = 575.2414 (calculated for $C_{35}H_{36}NaO_6$ $[M+Na]^+$ = 575.2404); HRMS (ESI) of **6b**: *m/z* = 553.2556 (calculated for $C_{35}H_{37}O_6$ $[M+H]^+$ = 553.2585) and HRMS (ESI) of **6c**: *m/z* = 575.2413 (calculated for $C_{35}H_{36}NaO_6$ $[M+Na]^+$ = 575.2404). The ^{1}H- and ^{13}C NMR spectra of the three compounds have been given in the supporting information. The structure was further confirmed by comparison of its physical and spectral data with those reported in the literature.[17,20]

General procedure for the synthesis of (2,3,4,6-tetra-*O*-benzyl-*β*-D-glycopyranosyl)methanol (7a-7c)

To a solution of **6a-6c** (4 g, 7.21 mmol) in methanol (40 mL) was added $NaBH_4$ (0.275 g, 7.21 mmol) at 0 ^{o}C and the mixture was stirred for 1 h at 0 ^{o}C. After completion of the reaction methanol was removed under reduced pressure and the residue was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with saturated NaCl solution (1 x 50 mL), dried over anhydrous Na_2SO_4, filtered and then concentrated at reduced pressure. The crude product thus obtained was purified over silica gel column with 20% ethyl acetate in petroleum ether as eluent to afford pure product **7a-7c**.

(*2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)methanol* (**7a**)[19a]

Compound **7a** was obtained as a white solid (3.68 g) in 92% yield and identified on the basis of its spectral data (^{1}H, ^{13}C NMR spectra and HRMS) analysis. HRMS (ESI): *m/z* = 577.2567

(calculated for $C_{35}H_{38}NaO_6$ $[M+Na]^+$ = 577.2561) (^{1}H- and ^{13}C NMR spectra have been given in the supporting information). The structure of the pure compound was further confirmed by comparison of its physical and spectral data with those reported in the literature.[19a]

(2,3,4,6-Tetra-O-benzyl-β-D-mannopyranosyl)methanol (**7b**)

It was obtained as a gel (3.6 g) in 90% yield; IR (thin film, cm^{-1}): 3437, 3030, 2859, 1365, 1092; $[\alpha]^{26}_D$ -23.0 (*c* 0.6, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (brs, 1H), 3.41-3.49 (m, 3H), 3.60-3.81 (m, 4H), 3.86-3.92 (m, 2H), 4.54 (dd, 2H, *J* = 6.1 & 10.3 Hz), 4.60 (d, 1H, *J* = 12.2 Hz), 4.67 (d, 1H, *J* = 11.6 Hz), 4.73 (d, 1H, *J* = 11.6 Hz), 4.78 (d, 1H, *J* = 11.6 Hz), 4.89 (d, 1H, *J* = 10.3 Hz), 4.97 (d, 1H, *J* = 11.6 Hz), 7.15-7.39 (m, 20H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 62.5, 69.6, 72.5, 73.4, 74.1, 75.2, 75.4, 78.7, 79.4, 84.9, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 138.0, 138.2, 138.3; HRMS (ESI): *m/z* = 577.2555 (calculated for $C_{35}H_{38}NaO_6$ $[M+Na]^+$ = 577.2561).

(2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl)methanol (**7c**)

It was obtained as a gel (3.8 g) in 95% yield; IR (thin film, cm^{-1}): 3448, 1454, 1104; $[\alpha]^{26}_D$ +33.8 (*c* 0.1, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (brs, 1H), 3.36 (ddd, 1H, *J* = 2.2, 4.5 & 7.6 Hz), 3.49-3.60 (m, 3H), 3.64 (dd, 1H, *J* = 2.6 & 9.5 Hz), 3.71 (dd, 1H, *J* = 5.2 & 11.8 Hz), 3.86 (dd, 1H, *J* = 2.6 & 11.8 Hz), 3.94 (t, 1H, *J* = 9.5 Hz) 3.99 (d, 1H, *J* = 2.6 Hz), 4.43 (d, 1H, *J* = 11.8 Hz), 4.48 (d, 1H, *J* = 11.8 Hz), 4.61 (d, 1H, *J* = 11.6 Hz), 4.66 (d, 1H, *J* = 10.8 Hz), 4.71 (d, 1H, *J* = 11.8 Hz), 4.78 (d, 1H, *J* = 11.7 Hz), 4.95 (dd, 2H, *J* = 8.4 & 11.1 Hz), 7.27-7.39 (m, 20H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 62.4, 68.8, 72.2, 73.4, 73.6, 74.4, 75.1, 75.2, 79.4, 84.5,

127.4, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 137.6, 138.1, 138.2, 138.5; HRMS (ESI): *m/z* = 577.2560 (calculated for $C_{35}H_{38}NaO_6$ $[M+Na]^+$ = 577.2561).

General procedure for the synthesis of 2,6-anhydro-3,4,5-tri-*O*-benzyl-glyco-heptitol (8a-8c)

To a solution of **7a-7c** (3.8 g, 6.85 mmol) in acetic anhydride (36 mL) was added trifluoroacetic acid (9 mL) and the solution was stirred for 2 h at 25 ^oC. The reaction mixture was evaporated under reduced pressure, coevaporated twice with toluene and dried under high vacuum. The residue obtained was taken in methanol (50 mL) and sodium methoxide (1.84 g, 34.25 mmol) was added into it. The reaction mixture was stirred for 1 h at 25 ^oC, methanol was removed under reduced pressure and the residue was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with saturated aqueous NaCl solution (1 x 50 mL), dried over anhydrous Na_2SO_4, filtered and then concentrated at reduced pressure. The crude product thus obtained was purified over silica gel column with 50% ethyl acetate in petroleum ether as eluent to afford the pure product **8a-8c**.

2,6-Anhydro-3,4,5-tri-O-benzyl-gluco-heptitol (**8a**)

It was obtained as a white solid (2.7 g) in 85% yield; m.pt. 142-144 ^oC; IR (KBr, cm^{-1}): 3432, 1453, 1348, 1102, 1065; $[\alpha]^{26}_D$ +0.01 (*c* 0.5, methanol); ^1H NMR (400 MHz, $CDCl_3$): δ 2.58 (brs, 2H), 3.36-3.40 (m, 2H), 3.56 (t, 2H, *J* = 9.3 Hz), 3.67-3.70 (m, 2H), 3.75 (t, 1H, *J* = 9.3 Hz), 3.85 (d, 2H, *J* = 11.7 Hz), 4.67 (d, 2H, *J* = 10.9 Hz), 4.87 (d, 2H, *J* = 10.9 Hz), 4.93 (s, 2H), 7.27-7.34 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 61.7, 75.0, 75.6, 77.7, 79.1, 86.8, 127.7, 127.9, 128.0, 128.4, 128.5, 137.9, 138.4; HRMS (ESI): *m/z* = 487.2101 (calculated for $C_{28}H_{32}NaO_6$ $[M+Na]^+$ = 487.2091).

2,6-Anhydro-3,4,5-tri-O-benzyl-manno-heptitol (**8b**)

It was obtained as a gel (2.54 g) in 80% yield; IR (thin film, cm^{-1}): 3437, 2922, 1104; $[\alpha]^{26}_{D}$ -47.0 (*c* 1.0, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (brs, 2H), 3.33-3.37 (m, 1H), 3.40-3.46 (m, 2H), 3.63 (dd, 1H, *J* = 2.6 & 9.5 Hz), 3.71 (dd, 1H, *J* = 5.4 & 11.9 Hz), 3.77 (dd, 1H, *J* = 4.2 & 9.4 Hz), 3.85 (dd, 2H, *J* = 2.2 & 5.8 Hz), 3.92 (t, 1H, *J* = 9.5 Hz), 4.65 (t, 2H, *J* = 11.6 Hz), 4.75 (d, 1H, *J* = 11.9 Hz), 4.79 (d, 1H, *J* = 11.9 Hz), 4.93 (d, 1H, *J* = 10.8 Hz), 4.97 (d, 1H, *J* = 11.8 Hz), 7.28-7.40 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 62.2, 62.6, 72.5, 74.0, 74.2, 75.1, 75.2, 78.4, 79.8, 84.5, 127.4, 127.6, 127.9, 128.0, 128.3, 128.4, 137.9, 138.0, 138.1; HRMS (ESI): *m/z* = 487.2094 (calculated for $C_{28}H_{32}NaO_6$ $[M+Na]^+$ = 487.2091).

2,6-Anhydro-3,4,5-tri-O-benzyl-galacto-heptitol (**8c**)[19b]

Compound **8c** was obtained as a gel (2.63 g) in 83% yield and identified on the basis of its spectral data (^{1}H, ^{13}C NMR spectra and HRMS) analysis. HRMS (ESI): *m/z* = 465.2271 (calculated for $C_{28}H_{33}O_6$ $[M+H]^+$ = 465.2272) (^{1}H- and ^{13}C NMR spectra has been given in the supporting information). The structure was further confirmed by comparison of its physical and spectral data with those reported in the literature.[19b]

General procedure for the synthesis of 2,6-anhydro-glyco-heptitol (9a-9c)

To a solution **7a-7c** (600 mg, 1.08 mmol) in methanol (5 mL) was added 10% Pd/C (100 mg) and the suspension was stirred for 12 h at 25 ^{o}C under H_2 atmosphere. The Pd/C was removed from reaction by filtration followed by the removal of methanol under reduced pressure to give the crude product. The crude product thus obtained was purified over silica gel column with 20% methanol in chloroform as eluent to afford the pure product **9a**, **9b** and **9c** in 90, 87 and 85%

yields, respectively. Compounds **9a**, **9b** and **9c** were identified on the basis of their spectral data (^{1}H, ^{13}C NMR spectra and HRMS) analysis. HRMS (ESI) of **9a**: *m/z* = 195.0858 (calculated for $C_7H_{15}O_6$ $[M+H]^+$ = 195.0863); HRMS (ESI) of **9b**: *m/z* = 195.0861 (calculated for $C_7H_{15}O_6$ $[M+H]^+$ = 195.0863); HRMS (ESI) of **9c**: *m/z* = 195.0860 (calculated for $C_7H_{15}O_6$ $[M+H]^+$ = 195.0863). ^{1}H- and ^{13}C NMR spectra has been given in supporting information. The structure was further confirmed by comparison of their physical and spectral data with those reported in the literature.[21]

Supporting Information: ^{1}H and ^{13}C NMR spectra of compounds **2a**-**9a**, **2b**-**9b**, **2c**-**9c** and 1-chloro-1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)ethane have been given in supporting information. This material is available free of charge via internet at http://pubs.acs.org.

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16. The ^{1}H-, ^{13}C-NMR spectra and HRMS data of 1-chloro-1-phenyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)ethane is given in supporting information.

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