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STEREOSPECIFIC ACCESS TO β-MANNOSIDES FROM GLUCOSE-DERIVED 1,2-ORTHOESTERS AS GLYCOSYL DONORS

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Abstract - A new, stereospecific synthesis of β-mannosides from glucose-derived 1,2-orthoesters has been developed by a simple four step procedure, comprising β-specific glycosidation of the 1,2-orthoesters, 2'-*O*-deacetylation, 2'-*O*-triflation, and S$_N$2 type inversion of the triflyl group providing β-D-Man-(1→6)-D-Gal, and β-D-Man-(1→4)-D-Glc derivatives in reasonable yield.

β-Mannosides constitute the central core unit of *N*-linked glycoproteins,[1] bacterial capsular polysaccharides,[2] phosphomannans,[3] and lipopolysaccharides.[4] Biological and medicinal studies request synthetic oligosaccharide probes, with which the biological functions of β-mannoside-containing oligosaccharides are to be solved.[5]

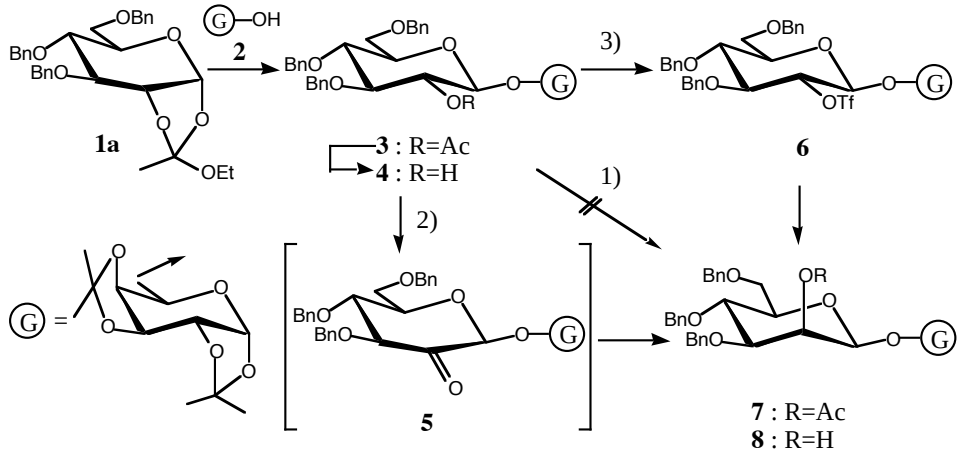
For the chemical synthesis of β-mannosides[6] many methods have been developed involving direct glycosylation with various mannosyl donors, either *via* S$_N$2 type displacement of the anomeric leaving group,[7] intramolecular aglycon derivery,[8] or through other means.[9] On the other hand, indirect methods have also been utilized, wherein a variety of building blocks, such as 2-ulosyl bromides[10,11] and glucosyl donors[12] possessing selectively protected 2-hydroxy group are available from glucose or galactose as mannosyl precursors. However, every method described to date has had some disadvantages in terms of stereoselectivity or practicality.

We report here an expedient route to β-mannosides which has both stereospecificity as well as practically useful capacities employing glucose 1,2-orthoester derivatives.[13] This method is based on the protocol that glycosidation of the orthoester would yield a significant level of β-glucosides, which are in turn readily epimerized to β-mannosides by several methods as depicted in Scheme 1.

First, we prepared various orthoesters (**1a**-**c**) as glycosyl donors in order to evaluate their reactivities with respect to electronic and stereochemical effect of the substituent R (cf. Scheme 2). According to Lichtenthaler's method,[10c] orthoesters (**1**) were prepared from acetobromoglucose (**9**) in two steps comprising orthoester formation, and acetyl to benzyl conversion in good yields.[14]

Subsequently, we attempted to synthesize β-D-mannosyl-(1→6)-D-galactose using **1a** in order to test the donor capacity for glycosylation of primary hydroxyl group of a glycosyl acceptor: 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**). Various coupling conditions employing several Lewis acids

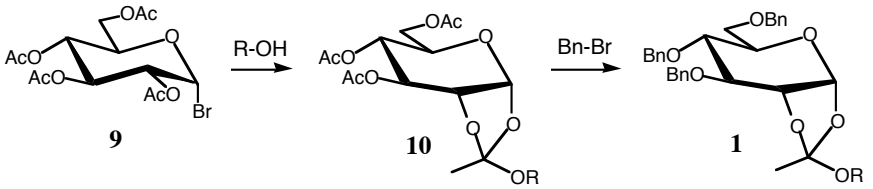
and protic acids were evaluated. As shown in Table 1, Lewis acids and trifluoromethanesufonic acid (TfOH)- promoted reactions were ineffective (Entries 1-4), whilst some sulfonic acid was found to be effective such that camphorsulfonic acid (CSA) employing a 0.04 molar equivalent to **2** in dichloroethane under reflux yielded the best result (Entry 8).



1) Mitsunobu inversion ; 2) oxidation - reduction ; 3) *via* O-Tf inversion

Scheme 1

In none of the tested conditions was β-(1→6)-isomer observed in the reaction mixture. The only byproduct isolated in this manner was determined to be ethyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**11a**) in moderate yield. Application of a stannyl ether-activated acceptor (**12**) (cf. Figure 1) to glycosylation with **1a** was found to be less effective, affording **3** in 39% yield. The disaccharide (**3**) was subjected to de-*O*-acetylation under Zemplen conditions (catalytic $NaOCH_3$ in CH_3OH) to yield 2'-OH free disaccharide (**4**) in 67% yield. The resulting compound (**4**) was considered to be a versatile precursor of β-mannoside by means of the following methods; 1) Mitsunobu inversion, 2) oxidation-reduction, and 3) S_N2 type inversion through 2'-*O*-triflate group of **6** (cf. Scheme 1).



a : R = - CH_2CH_3 ; **b** : R = - CH_2CF_3 ; **c** : R = - $CH(CH_3)_2$

Scheme 2

For Method 1 a variety of Mitsunobu conditions was applied to **4** in such a way that various combinations of the reagents, including phosphines, aliphatic and aromatic acids, and alkyl azodicarboxylates were employed.[15] However, the result was almost complete recovery of the starting materials. Since the Mitsunobu reaction is inherently hindered by bulky substituents near the reaction site, we concluded that Mitsunobu inversion cannot be applied in this case.

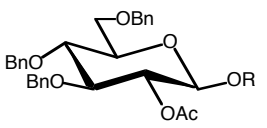
Next, an oxidation-reduction approach (Method 2) was examined for **4**. Although this reaction has been

reported by Danishefsky *et al*.[11] to give **7** in 60% yield, their access to **4** was completely different from that of the present study. First, we followed the above method, but only a 48% yield of **7** was attained. In order to improve the yield of **7**, we tried to isolate the intermediary 2-uloside (**5**) by oxidation of **4** with DMSO-Ac_2O in pyridine. Unexpectedly, the main product, isolable in 59%, was characterized to be 3,4-unsaturated 2-uloside (**13**) (cf. Figure 1). Although reaction conditions have not yet been optimized, it seemed inadvisable to apply an oxidation-reduction method to **4**, as compound (**5**) readily generates **13.**

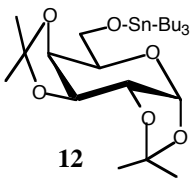
Table 1. Coupling Reactions of the Donor (**1a**) with the Acceptor (**2**)[a)]

Entry	**1** / **2** (mol.eq.)	Promoter[b)] (mol. eq.)	Additive	**3** (%)	**11a** (%)
1	1.5	$ZnCl_2$ (1.00)	Et_4NClO_4	27.2	33.3
2	2.0	TfOMe (0.03)	Et_4NClO_4	n. d.	n. d.
3	1.5	TfOH (0.02)	Et_4NClO_4	8.9	n. d.
4	1.5	TfOH (0.03)	Et_4NClO_4	7.2	n. d.
5	1.5	TsOH (0.03)	Et_4NClO_4	26.2	25.5
6	1.5	CSA (0.08)	Et_4NClO_4	45.2	42.0
7	1.5	CSA (0.06)	Et_4NClO_4	49.4	40.0
8	1.5	CSA (0.04)	Et_4NClO_4	54.6	39.2
9	1.5	CSA (0.03)	Et_4NClO_4	45.5	38.3
10	0.5	CSA (0.04)	Et_4NClO_4	40.5	18.5
11	1.5	CSA (0.04)	Bu_4NClO_4	47.3	39.2
12	1.5	CSA (0.04)	none	36.2	24.6

a) The reactions were carried out in refluxed 1,2-dichloromethane for 2 h in the presence of tetraalkyl-ammonium perchlorate of 1.0 molar equiv. to the promoter. b) Abbreviations: Tf = CF_3SO_2-; Ts = *p*-CH_3-C_6H_4-SO_2-; CSA = Camphorsulfonic acid.



11a : R = - CH_2CH_3
11b : R = - CH_2CF_3
11c : R = - $CH(CH_3)_2$



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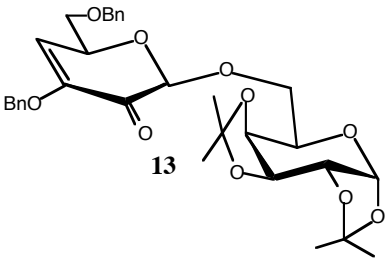

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Figure 1

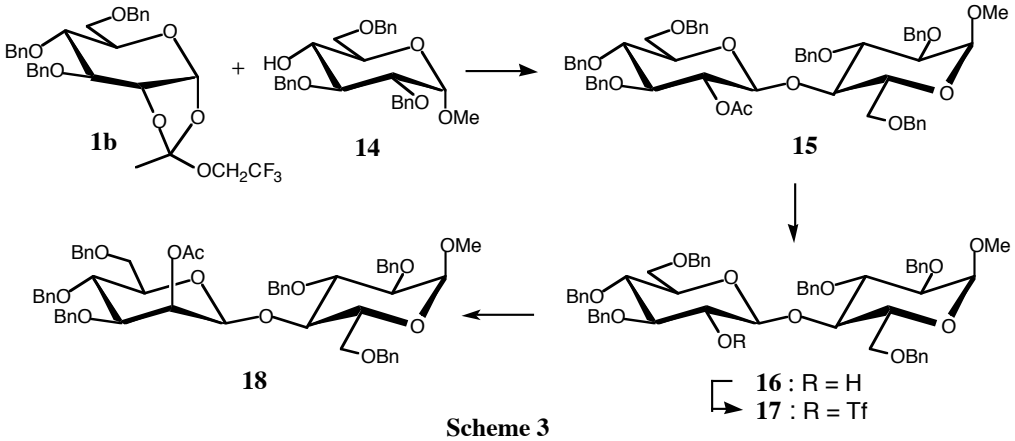
Lastly, we attempted the third method, namely 2'-*O*-triflate inversion, wherein the compound (**4**) was triflated with triflic anhydride in pyridine - CH_2Cl_2 to yield 2'-*O*-triflate (**6**) in 77% yield. Subsequently, S_N2 type inversion of the triflate (**6**) was subjected with either cesium acetate[16]/18-crown-6 or tetrabutyl-ammonium acetate to produce the desired mannoside (**7**) in 50% and 68% yield, respectively (c.f. Table 2). Accordingly, the latter conditions are recommended for the preparative purpose. Thus, β-mannoside (**7**) could be obtained in a simple four step procedure from the starting orthoester (**1a**) in 19% combined yield.

Table 2. SN 2 Displacement of 2'-*O*-Triflate (**6**) with Acetate Nucleophiles[a)]

Entry	**6** (mol.eq.)	Nucleophile	(mol.eq.)	18-Crown-6 (mol. eq.)	Bath Temp (°C)	**7** (%)
1	1.0	CsOAc	(3.0)	(3.0)	r. t.	n. d.
2	1.0	CsOAc	(3.0)	(3.0)	60	50.2
3	1.0	CsOAc	(3.0)	(3.0)	120	n. d.
4	1.0	Bu_4NOAc	(3.0)	none	60	68.0

a) The reactions were carried out under stirring in dry toluene for 5 h.

Next, we tried to synthesize β-mannoside interglycosidically (1→4)-linked disaccharide, for which methyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**14**)[17] was selected as an acceptor. Scheme 3 depicts the synthetic pathway to β-D-mannosyl-(1→4)-D-glucose disaccharide (**18**).



Scheme 3

Table 3. Coupling Reactions of the Donor (**1**) with the Acceptor (**14**)[a)]

Entry	Donor	**1** / **14** (mol. eq.)	Promoter	(mol. eq.)	Time (h)	**15** (%)	**11a-c** (%)
1	**1a**	0.5	$ZnCl_2$	(1.0)	1	n. d.	n. d.
2	**1a**	1.75	$Cu(OTf)_2$	(1.0)	1	n.d.	56.6
3	**1a**	1.0	CSA	(0.04)	2	20.0	48.0
4	**1a**	1.5	CSA	(0.04)	2	34.5	47.3
5	**1a**	2.0	CSA	(0.04)	2	36.0	40.4
6	**1a**	2.0	CSA	(0.08)	2	30.3	45.4
7	**1b**	1.0	CSA	(0.04)	2	27.0	25.2
8	**1b**	2.0	CSA	(0.04)	2	40.5	24.8
9	**1c**	1.0	CSA	(0.04)	2	23.5	40.6
10	**1c**	2.0	CSA	(0.04)	2	38.5	31.5

a) The reactions were carried out in refluxed 1,2-dichloroethane containing 1 molar equivalent tetraethyl-ammonium perchlorate to the promoter.

Glycosidation of **1a** with partially protected methyl glucopyranoside possessing a free C4-hydroxyl group was somewhat troublesome because of the low reactivity of the secondary hydroxyl group. After many attempts as shown in Table 3, the desired disaccharide (**15**) was obtained in 36% yield (Entry 5). At this stage we evaluated the donor reactivity of other alkoxyorthoesters, e.g. **1b**: R = $-CH_2CF_3$ and **1c**: R = $-CH(CH_3)_2$, which signify electronic and stereochemical effects of the leaving group on this glycosylation reaction. In fact, trifluoroethyl function (**1b**) gave rise to an increase of the disaccharide (**15**), and decrease of the byproduct (**11b**) (Entry 8). A similar tendency was observed in the case of isopropyl function (**1c**), although this was less effective than that of **1b** (Entry 10).

De-*O*-acetylation of **15** was carried out as described for **4**, to provide 2'-hydroxy free disaccharide (**16**) in 96% yield. Subsequent *O*-triflation of **16** in a similar fashion to that described for **6** was inadequate, since almost all of the educt was recovered. Accordingly, a large amount of the triflic anhydride (3 eq. 10 eq.) was used, and the resulting *O*-triflate (**17**) was subjected, in one pot, to SN2 displacement with tetraethyl-ammonium acetate providing the desired disaccharide, -D-mannosyl-(1 4)-D-glucose derivative (**18**) in 58% yield over two steps from **16**.

In summary, the easy accessibility of **1** (50-60% yield in only 2 steps from acetobromoglucose), and simple and efficient entry to -D-mannosyl-(1 6)-D-galactose and -D-mannosyl-(1 4)-D-glucose derivatives therefrom were exemplified through facile manipulations of -specific glycosidation, 2'-*O*-triflation, followed by epimerization of -Glc to -Man by SN 2 type inversion of the triflate in reasonable yields. Through all the reaction steps concerned, stereoselectivities were found to be complete, wherein no stereoisomers were observed. Various extensions of this method are under progress.

EXPERIMENTAL

Melting points were determined on a Yamato MP-1 apparatus and are uncorrected. Spectral data were recorded on the following instruments; Jasco P-1080 ($[\alpha]_D$), JMS-AX 505 H (MS), and Varian XL-400 and VXR-300 (NMR in chloroform-*d* solution). Column chromatography was carried out on silica gel (Kanto Kagaku Co.: up to 100 mesh) column. TLC was achieved on silica gel 60 F254 (Merck Art. 5735). The spots were detected by UV light (254 nm) or charring with 10% aq. sulfuric acid.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(*exo*-trifluoroethoxyethylidene)--D-glucopyranose (**10b**): To a stirred solution of 2,3,4,6-tetra-*O*-acetyl--D-glucopyranosyl bromide (**9**) (492 mg, 1.2 mmol) in dichloromethane (4 mL) were added 2,4,6-trimethylpyridine (0.5 mL), trifluoroethanol (0.6 mL), and tetrabutylammonium bromide (0.1 g, 3.1 mmol). The mixture was stirred at 50 °C for 14 h, and then diluted with chloroform (15 mL). The organic layer was washed with 1M HCl (5 mL), 5% aq. $NaHCO_3$ (15 mL), and water (15 mL). Drying (Na_2SO_4), filtration, and evaporation to dryness in vacuo gave a residue, which was dissolved into warm trifluoroethanol (3.0 mL) containing 2,4,6-trimethylpyridine (2-3 drops), triturated with water, and cooled to give 388 mg (75.2%) of **1b** as colorless crystals: mp 89-92 °C ; $[\alpha]_D^{25}$ +31.2 °(c 0.9, $CHCl_3$); MS (FAB) m/z 431 $[M+H]^+$, 453 $[M+Na]^+$; ^{1}H-NMR (in $CDCl_3$, 300 MHz): 1.73 (3H, s, CCH_3), 2.09 (6H, s, 2 x $COCH_3$), 2.11 (3H, s, $COCH_3$), 3.85-3.95 (2H, m, OCH_2CF_3), 3.89 (1H, m, H-5), 4.19 (2H, m, H-6), 4.35 (1H, td, H-2), 4.90 (1H, td, H-4), 5.18 (1H, dd, H-3), 5.73 (1H, d, H-1); $J_{1,2}$ = 5.0, $J_{2,3}$ = 3.0, $J_{3,4}$ = 3.0, $J_{4,5}$ = 10.0 Hz; ^{13}C-NMR (in $CDCl_3$, 75 MHz): 20.3

(CCH_3), 20.7 (3 x $COCH_3$), 60.8, 62.2 (CH_2CF_3), 61.3, 61.7 (CH_2CF_3), 63.0 (C-6), 67.2 (C-5), 68.1 (C-4), 69.9 (C-3), 73.2 (C-2), 97.1 (C-1), 121.1 ($CH_3\underline{C}OCH_2CF_3$), 169.0, 169.5, 170.5 (3 x $\underline{C}OCH_3$).

3,4,6-Tri-*O*-benzyl-1,2-*O*-(*exo*-trifluoroethoxyethylidene)-α-D-glucopyranose (**1b**): A mixture of **10b** (430 mg, 1.0 mmol), benzyl bromide (0.4 mL, 3.2 mmol), and potassium hydride (0.63 g, 11.3 mmol) in dry tetrahydrofuran (3 mL) was stirred under reflux for 3 h. Subsequent dilution with dry methanol (3 mL) and dichloromethane (25 mL) and washing with water (5 x 15 mL), 5% aq. $NaHCO_3$ (2 x 10 mL), water (2 x 15 mL) was followed by drying (Na_2SO_4) and evaporation to dryness. The residue was eluted through a silica gel column with toluene-ethyl acetate (8 : 1) containing triethylamine (0.1% v/v). Concentration of the major fraction gave 379 mg (66.0%) of **1b** as a colorless syrup: $[\alpha]_D^{25}$ +33.5 ° (c 1.0, $CHCl_3$); MS (FAB) m/z 574 $[M]^+$, 1171 $[2M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 300 MHz): 1.68 (3H, s, CCH_3), 3.63 (1H, d, H-6a), 3.65 (1H, d, H-6b), 3.76 (1H, td, H-5), 3.85 (1H, td, H-4), 3.89 (1H, dd, H-3), 4.45 (1H, dd, H-2), 5.78 (1H, d, H-1); $J_{1,2}$ = 5.0, $J_{2,3}$ = 3.5, $J_{3,4}$ = 3.5, $J_{4,5}$ = 9.0, $J_{5,6}$ = 2.5 and 3.5 Hz; ^{13}C-NMR (δ in $CDCl_3$, 75 MHz): 21.1 ($C\underline{C}H_3$), 61.0, 61.5 ($\underline{C}H_2CF_3$), 69.2 (C-6), 70.6 (C-5), 74.9 (C-4), 75.2 (C-2), 77.8 (C-3), 97.9 (C-1), 120.9 ($CH_3\underline{C}OCH_2CF_3$).

3,4,6-Tri-*O*-benzyl-1,2-*O*-(*exo*-isopropyloxyethylidene)-α-D-glucopyranose (**1c**): 3,4,6-Tri-*O*-acetyl-1,2-*O*-(*exo*-isopropyloxyethylidene)-α-D-glucopyranose[18] (**10c**) (780 mg, 2.0 mmol) was subjected to benzylation as described for **1b**. Aqueous workup followed by purification by elution from a silica gel column with toluene-ethyl acetate (8 : 1) containing triethylamine (0.1% v/v) gave 794 mg (73.4%) of **1c** as a colorless syrup: $[\alpha]_D^{25}$ +30.3 ° (c 1.0, $CHCl_3$); MS (FAB) m/z 535 $[M+H]^+$, 557 $[M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 300 MHz): 1.16, 1.17 (each 3H, d, $CH(C\underline{H}_3)_2$, 1.67 (3H, s, CCH_3), 3.62-3.75 (2H, m, H-6), 3.70 (1H, dd, H-4), 3.78 (1H, td, H-5), 3.87 (1H, dd, H-3), 3.93 (1H, dt, $OC\underline{H}(CH_3)_2$), 4.43 (1H, dd, H-2), 5.74 (1H, d, H-1); $J_{1,2}$ = 5.5, $J_{2,3}$ = 3.5, $J_{3,4}$ = 3.5, $J_{4,5}$ = 9.5, $J_{5,6}$ = 1.0 Hz; ^{13}C-NMR (δ in $CDCl_3$, 75 MHz): 22.4 ($C\underline{C}H_3$), 23.81, 23.84 ($CH(\underline{C}H_3)_2$), 66.2 ($\underline{C}H(CH_3)_2$), 69.3 (C-6), 70.4 (C-5), 75.1 (C-4), 75.4 (C-2), 78.6 (C-3), 97.7 (C-1), 121.1 ($CH_3\underline{C}OCH(CH_3)_2$).

6-*O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**3**) - **Method A**: (1S)-(+)-10-Camphorsulfonic acid (CSA) (4.5 mg, 19.2 μmol) was added to a mixture of orthoester (**1a**)[10c] (250 mg, 0.48 mmol), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**)[19] (83.3 mg, 0.32 mmol), and tetraethylammonium perchlorate (4.4 mg, 19.2 mol) in dry 1,2-dichloroethane (2 mL) under heating in an oil bath (ca. 115 °C). The mixture was stirred under reflux in the oil bath (*ca*. 115 °C) for 2 h. Dilution with dichloromethane (25 mL), washing with water (2 x 20 mL), 5% aq. $NaHCO_3$ (2 x 20 mL), water (2 x 20 mL), drying (Na_2SO_4), filtration, and evaporation to dryness in vacuo gave a residue, which was eluted from a silica gel column with hexane-ethyl acetate (2 : 1). The major fraction was concentrated to give 129 mg (54.6%) of the disaccharide (3) as a colorless syrup: $[\alpha]_{20}$ -28.2 (c 0.43, $CHCl_3$); MS (FAB) m/z 757 $[M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 300 MHz): 1.30-1.32, 1.43. 1.51 (each 3H, s, $CH(C\underline{H}_3)_2$), 2.02 (3H, s, $COCH_3$), 3.48 (1H, m, H-5'), 3.61 (1H, m, H-6a), 3.65-3.71 (2H, m, H-3',4'), 3.74 (2H, m, H-6'), 3.93 (1H, m, H-5), 4.06 (1H, dd, H-6b), 4.19 (1H, dd, H-4), 4.28 (1H, dd, H-2), 4.44 (1H, d, H-1'), 4.54-4.68 (each 2H, m, $PhC\underline{H}_2$), 4.56 (1H, m, H-3), 4.79 (2H, dd, $PhC\underline{H}_2$), 5.01 (1H, m, H-2'), 5.50 (1H, d, H-1), 7.10-7.40 (15H, m, C_6H_5); $J_{1,2}$ =

5.0, $J_{2,3}$ = 2.5, $J_{3,4}$ = 8.0, $J_{4,5}$ = 2.0, $J_{5,6a}$ = 7.8, $J_{5,6b}$ = 3.5, $J_{6a,6b}$ = 11.0, $J_{1',2'}$ = 8.0, $J_{2',3'}$ = 9.0 Hz; ^{13}C-NMR (δ in $CDCl_3$, 75 MHz): 20.93, 24.32, 25.09, 25.95, 25.06 (5 x CH_3), 67.84 (C-5), 68.65 (C-6'), 69.45 (C-6), 70.55 (C-2), 70.64 (C-3), 71.31 (C-4), 73.07 (C-2'), 77.96 and 82.82 (C-3' and 4'), 73.52, 74.95, 75.02 (3 x CH_2), 75.19 (C-5'), 96.21 (C-1), 101.82 (C-1'), 108.6 and 109.3 (2 x $\underline{C}(CH_3)_2$), 169.5 (C=O).

On concentration of the minor fraction, ethyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**11a**) was obtained as a colorless syrup in a yield of 98 mg (39.2%): $[\alpha]_D^{24}$ +5.77° (c 0.52, $CHCl_3$); MS (FAB) m/z 543 $[M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 300 MHz): 1.20 (3H, t, $CH_2C\underline{H}_3$), 1.98 (3H, s, $COCH_3$), 3.50 (1H, m, H-5), 3.56, 3.91 (each 1H, q, $CH_2\underline{C}H_3$), 3.65-3.76 (4H, m, H-3,4,6), 4.38 (H-1), 4.99 (1H, m, H-2); $J_{1,2}$ = 8.0 Hz; ^{13}C-NMR (δ in $CDCl_3$, 75 MHz): 15.13 ($CH_2\underline{C}H_3$), 20.89 ($CO\underline{C}H_3$), 65.02 ($\underline{C}H_2CH_3$), 68.85 (C-6), 73.19 (C-2), 75.20 (C-5), 78.08 and 83.02 (C-3 and C-4), 100.73 (C-1), 169.42 ($\underline{C}OCH_3$).

Method B: A mixture of diacetonegalactose (**2**) (78.1 mg, 0.30 mmol) and bis(tributyltin)oxide (0.12 mL, 0.23 mmol) in dry toluene (4.5 mL) was azeotropically refluxed for 4 h. After concentration in vacuo, dry 1,2-dichloroethane (4.4 mL), orthoester (**1a**) (234.3 mg, 0.45 mmol), tetraethylammonium perchlorate (102 mg, 0.45 mmol), and zinc chloride (61.3 mg, 0.45 mmol) were added to the residue containing stanyl ether (**12**), which was stirred under reflux for 1 h. The resulting mixture was diluted with dichloromethane (30 mL), washed with water (2 x 30 mL), 5% aq. $NaHCO_3$ (2 x 30 mL), and water (2 x 30 mL), dried (Na_2SO_4), and filtered. The filtrate was evaporated to dryness in vacuo, and the residue was purified by elution from a silica gel column with hexane-ethyl acetate (2 : 1), followed by concentration to give disaccharide (**3**) (85.4 mg, 38.7%) and ethyl glucoside (**11a**) (85.3 mg, 36.4%).

6-*O*-(3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-pyranose (**4**): A solution of **3** (70.2 mg, 95.6 μmol) in 0.05 M NaOMe in MeOH (4 mL) was stirred at ambient temperature for 4 h, and was subsequently neutralized with a dry acidic resin (Dowex 50W-X8) and filtered. The filtrate was evaporated to dryness and the residue was eluted through a silica gel column with hexane-ethyl acetate (3 : 2). Concentration of the major fraction gave 44.5 mg (67.2%) of **4** as a colorless syrup: $[\alpha]_D^{20}$ -40.5 ° (c 0.22, $CHCl_3$) (lit.,[20] $[\alpha]_D^{20}$ -44.4°); MS (FAB) m/z 715 $[M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 300 MHz): 1.33, 1.34, 1.46, 1.54 (each 3H, s, $C(CH_3)_2$), 3.14 (1H, OH), 3.49 (1H, m, H-5'), 3.58-3.66 (3H, m, H-2', 3', 4'), 3.67-3.79 (3H, m, H-6a, 6'), 4.03 (1H, m, H-5), 4.11 (1H, m, H-6b), 4.23 (1H, dd, H-4), 4.31-4.38 (2H, m, H-2, 1'), 4.48-4.65 (4H, m, H-3 and $PhC\underline{H}_2$), 4.82 (2H, dd, $PhC\underline{H}_2$), 5.03 (1H, d, $PhC\underline{H}_2$), 5.56 (1H, d, H-1), 7.20-7.45 (15H, m, C_6H_5); $J_{1,2}$ = 5.0, $J_{3,4}$ = 8.0, $J_{4,5}$ = 2.0, $J_{5,6a}$ = 7.6, $J_{5,6b}$ = 3.2 Hz; ^{13}C-NMR (δ in $CDCl_3$, 75 MHz): 24.38, 24.92, 25.95, 26.00, (4 x CH_3), 67.80 (C-5), 68.87 (C-6'), 69.37 (C-6), 70.42 (C-2), 70.69 (C-3), 71.23 (C-4), 73.49 (CH_2), 74.67 (C-2'), 74.99 (CH_2), 75.04 (C-5'), 77.29 (C-3'), 84.55 (C-4'), 96.26 (C-1), 103.92 (C-1'), 108.86 and 109.54 (2 x $\underline{C}(CH_3)_2$).

6-*O*-(3,4,6-Tri-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-β-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6**): Trifluoromethanesulfonic anhydride (38.4 μL) was added to a solution of 2'-OH free disaccharide (**4**) (52.4 mg, 76 μmol) in dry dichloromethane (1.0 mL) containing pyridine (0.23 mL) at - 20 °C under a nitrogen atmosphere. The mixture was stirred at rt for 3 h

and then partitioned between 5% aq. $NaHCO_3$ (20 mL) and dichloromethane (20 mL). The organic layer was washed with water (3 x 10 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. The resulting syrup was purified through a silica gel column eluted with hexane-ethyl acetate (2 : 1) to yield 48.4 mg (77.1%) of **6** as a colorless syrup: $[\alpha]_D^{20}$ - 38.0 ° (c 0.26, $CHCl_3$); MS (FAB) m/z 847 $[M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 300 MHz): 1.32, 1.33, 1.43. 1.53 (each 3H, s, $CH(C\underline{H}_3)_2$), 3.50 (1H, m, H-5'), 3.71-3.80 (5H, m, H-6a, 2', 3',6'), 4.03 (1H, m, H-5), 4.10 (1H, dd, H-6b), 4.27-4.32 (2H, m, H-2, 4), 4.51-4.89 (6H, m, $PhC\underline{H}_2$), 4.54-4.69 (3H, m, H-3, 1', 4'), 5.52 (1H, d, H-1), 7.26-7.37 (15H, m, C_6H_5); $J_{1,2}$ = 5.0, $J_{2,3}$ = 2.5, $J_{3,4}$ = 8.0, $J_{4,5}$ = 2.0, $J_{5,6a}$ = 5.5, $J_{6a,6b}$ = 10.5 Hz; ^{13}C-NMR (δ in $CDCl_3$, 75 MHz): 24.41, 24.95, 25.76, 25.98 (4 x CH_3), 67.00 (C-5), 67.91 (C-6'), 68.60 (C-6), 70.45 (C-2), 70.63 (C-3), 71.15 (C-4), 73.59, 75.07 ($PhC\underline{H}_2$), 75.37 (C-5'), 75.76 ($PhC\underline{H}_2$), 78.34, 81.73 (C-2', 3'), 84.75 (C-4'), 96.29 (C-1), 99.44 (C-1'), 108.66, 109.20 (2 x $\underline{C}(CH_3)_2$), 118.40 (CF_3).

6-*O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**7**) - **SN 2 Type Inversion Method**: A mixture of 2'-*O*-triflyl disaccharide (**6**) (61.8 mg, 75 μmol) and tetrabutylammonium acetate (67.8 mg, 1.7 mmol) in dry toluene (3 mL) was stirred at 60 °C for 5 h. After dilution with dichloromethane (20 mL), the mixture was washed with 5% aq. $NaHCO_3$ (25 mL) . The water layer was extracted with dichloromethane (2 x 20 mL) and the combined organic layer was dried (Na_2SO_4), filtered, and concentrated to dryness to give a residue, which was purified through a silica gel column eluted with hexane-ethyl acetate (2 : 1). The major fraction was concentrated to yield 37.5 mg (68.0%) of β-mannoside (**7**) as a colorless syrup: $[\alpha]_D^{20}$ -57.2 ° (c 0.60, $CHCl_3$) (lit.,[11] $[\alpha]_D^{20}$ -54.3 °) ; MS (FAB) m/z 757 $[M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 300 MHz): 1.30, 1.32, 1.43. 1.55 (each 3H, s, $C(CH_3)_2$), 2.17 (3H, s, $COCH_3$), 3.47 (1H, m, H-5'), 3.65 (1H, dd, H-3'), 3.71-3.80 (4H, m, H-6a, 4', 6'), 3.97-4.06 (2H, m, H-5, 6b), 4.21 (1H, dd, H-4), 4.29 (1H, dd, H-2), 4.46-4.89 (3 x 2H, m, $PhC\underline{H}_2$),4.57 (1H, dd, H-3), 4.69 (1H, d, H-1'), 5.51 (1H, d, H-1), 5.67 (1H, dd, H-2'), 7.30 (15H, m, C_6H_5); $J_{1,2}$ = 5.0, $J_{2,3}$ = 2.5, $J_{3,4}$ = 8.0, $J_{4,5}$ = 1.6, $J_{1',2'}$ = 1.0, $J_{2',3'}$ = 3.0, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.5 Hz; ^{13}C-NMR (δ in $CDCl_3$, 75 MHz): 21.06, 24.35, 25.04, 25.95, 26.01 (5 x CH_3), 68.16 and 68.22 (C-5 and C-2'), 69.06 and 69.16 (C-6 and C-6'), 70.52 (C-2), 70.68 (C-3), 71.34 ($PhC\underline{H}_2$), 71.37 (C-4), 73.50 ($PhC\underline{H}_2$), 74.30 (C-4'), 75.07 ($PhC\underline{H}_2$), 75.49 (C-5'), 80.28 (C-3'), 96.19 (C-1), 99.15 (C-1'), 108.75 and 109.35 (2 x $\underline{C}(CH_3)_2$), 170.41 (C=O).

Oxydation-Reduction Method: A solution of the 2'-hydroxy free disaccharide (**4**) (53.2 mg, 77 μmol) in DMSO-Ac_2O (2 : 1) (1.4 mL) was stirred at ambient temperature for 2 days. The resulting mixture was diluted with dichloromethane (10 mL), washed with water (15 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo to give a residue, which was dissolved into dichloromethane-methanol (1 : 1) (2.7 mL) and cooled to 0 °C. Sodium borohydride (13.3 mg, 0.35 mmol) was added to the solution, and the mixture was stirred at room temperature for 6 h. After dilution with dichloromethane (15 mL), sequential washing with water (15 mL), 5% aq. $NaHCO_3$ (15 mL), and brine (15 mL) was followed by drying (Na_2SO_4), filtration, and evaporation to dryness in vacuo to give a residue containing β-mannoside (**8**), which was *O*-acetylated with pyridine-Ac_2O (2 : 1) (2 mL) at room temperature for 14 h. A solution of 5% aq. $NaHCO_3$ (15 mL) was added to the mixture, which was extracted with ethyl acetate (3 x 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a residue, which was eluted

through a silica gel column with hexane-ethyl acetate (5 : 2). Concentration of the major fraction gave 26.8 mg (48%) of **7** as a colorless syrup, which identified in all respects with the authentic sample obtained by S_N2 type inversion method.

6-*O*-(3,6-Di-*O*-benzyl-β-D-*glycero*-hex-3-enopyranos-2-ulosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**13**) : A solution of the 2'-hydroxy free disaccharide (**4**) (89.0 mg, 0.13 mmol) in DMSO - Ac_2O (2 : 1) (2.0 mL) was stirred at ambient temperature for 2 days. The resulting mixture was diluted with dichloromethane (20 mL), washed with water (30 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo to give a residue, which was purified by elution from a silica gel column with hexane-ethyl acetate (5 : 2). The major fraction was concentrated to give 43.7 mg (58.5%) of **13** as a yellowish syrup: MS (FAB) m/z 605 $[M+Na]^+$; UV: λ_{max}^{MeOH} = 200 nm (log ε = 4.24), λ_{max}^{MeOH} = 258 nm (log ε = 3.82), ^{1}H-NMR (δ in $CDCl_3$, 400 MHz): 1.32 (6H, s, CH_3), 1.43, 1.54 (each 3H, s, $C(CH_3)_2$), 3.64 (1H, dd, H-6'a), 3.78-3.86 (2H, dd, H-6a, 6'b), 3.95 (1H, dd, H-6b), 4.03 (1H, m, H-5), 4.24 (1H, dd, H-4), 4.30 (1H, dd, H-2), 4.55 (2H, dd, $PhCH_2$), 4.59 (1H, dd, H-3), 4.73 (1H, m, H-5'), 4.87 (2H, dd, $PhCH_2$), 5.10 (1H, s, H-1'), 5.51 (1H, d, H-1), 6.01 (1H, d, H-4'), 7.28-7.39 (10H, m, C_6H_5); $J_{1,2}$ = 5.0, $J_{2,3}$ = 2.5, $J_{3,4}$ = 8.0, $J_{4,5}$ = 2.0, $J_{5,6a}$ = 6.2, $J_{6a,6b}$ = 11.0, $J_{4',5'}$ = 3.6, $J_{5',6'a}$ = 7.5, $J_{5',6'b}$ = 6.0, $J_{6'a,6'b}$ = 9.0 Hz; ^{13}C-NMR (δ in $CDCl_3$, 100 MHz): 24.48, 24.92, 24.93, 25.99, 26.08 (4 x CH_3), 66.80 (C-5), 67.22 (C-6), 69.88 ($PhCH_2$), 70.53 (C-2), 70.57 (C-3), 70.90 (C-4), 71.78 (C-5'), 73.14 (C-6'), 73.44 ($PhCH_2$), 96.23 (C-1), 98.79 (C-1'), 108.71, 109.23 (2 x $C(CH_3)_2$), 117.05 (C-4'), 184.40 (C-2').

Methyl 4-*O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**15**): A mixture of trifluoroethoxyethylideneglucose (**1b**) (506 mg, 0.88 mmol), methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**14**)[17] (204 mg, 0.44 mmol), tetraethyl ammonium perchlorate (8.3 mg, 36 μmol), and CSA (8.4 mg, 36 μmol) in dry 1,2-dichloroethane (5 mL) was refluxed (bath temp. 115 °C) for 2 h, followed by processing as described for **3**. Elution of the crude product from a silica gel column with toluene-ethyl acetate (5 : 1) and concentration in vacuo gave 167.5 mg (40.5%) of **15** as colorless crystals and 125.6 mg (24.8%) of **11b** as a colorless syrup. Compound (**15**): mp 82-85 °C (lit.,[21] mp 86-87 °C); $[\alpha]_D^{21}$ = +17.0 ° (c 0.9, chloroform) (lit.,[20] $[\alpha]_D$ = +17.0 ° (c 0.9, chloroform) ; MS (FAB) m/z : 938 $[M+H]^+$, 961 $[M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 400 MHz) : 1.87 (3H, s, $COCH_3$), 3.30 (1H, td, H-5'), 3.35 (3H, s, CH_3)3.44 (1H, dd, H-3'), 3.46 (1H, dd, H-2), 3.49 (1H, dd, H-6'-a), 3.58 (1H, dd, H-6-a), 3.65 (1H, dd, H-6'-b), 3.66 (1H, dd, H-4'), 3.67 (1H, td, H-5), 3.74 (1H, dd, H-6-b), 3.86 (1H, dd, H-4), 3.88 (1H, dd, H-3), 4.48 (1H, d, H-1'), 4.56 (1H, d, H-1), 4.94 (1H, td, H-2'); $J_{1,2}$ = 4.0, $J_{2,3}$ = 9.5, $J_{3,4}$ = 7.5, $J_{4,5}$ = 9.0, $J_{5,6}$ = 2.0 and 3.5, $J_{1',2'}$ = 8.0, $J_{2',3'}$ = 9.5, $J_{3',4'}$ = 9.0, $J_{4',5'}$ = 10.0, $J_{5',6'}$ = 5.0 and 2.0 Hz; ^{13} C- NMR (δ in $CDCl_3$, 100 MHz) : 21.2 ($COCH_3$), 55.5 (OCH_3), 68.1 (C-6), 69.0 (C-6'), 70.2 (C-4'), 73.9 (C-2'), 75.5 (C-5'), 77.1 (C-4), 78.3 (C-5), 79.3 (C-2), 80.4 (C-3), 83.4 (C-3'), 98.6 (C-1), 100.5 (C-1'), 169.5 ($COCH_3$).

Methyl 4-*O*-(3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**16**): 2'-*O*-Acetyl disaccharide (**15**) (94 mg, 0.1 mmol) was treated with 0.05 M NaOMe followed by workup as described for **4**. Purification by silica gel column chromatography afforded 88 mg (98%) of **16** as a colorless syrup: $[\alpha]_D^{20}$ + 15.5 ° (c 1.0, $CHCl_3$) (lit.,[21] $[\alpha]_D^{20}$ +14.5 ° (c 1.0, $CHCl_3$)) ; MS (FAB)

m/z : 898 $[M+H]^+$, 920 $[M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 400 MHz) : 3.22 (1H, td, H-5'), 3.27 (3H, s, CH_3), 3.43 (1H, dd, H-3'), 3.47 (1H, dd, H-2'), 3.48 (1H, dd, H-6'-a), 3.50 (1H, dd, H-6'-b), 3.50 (1H, dd, H-2), 3.60 (1H, dd, H-4'), 3.67 (1H, dd, H-6a), 3.79 (1H, td, H-5), 3.97 (1H, dd, H-3), 3.98 (1H, dd, H-4), 3.99 (1H, dd, H-6b), 4.56 (1H, d, H-1'), 4.58 (1H, d, H-1); $J_{1,2}$ = 3.5, $J_{2,3}$ = 10.0, $J_{3,4}$ = 10.0, $J_{4,5}$ = 10.0, $J_{5,6}$ = 2.0 and 3.5, $J_{1',2'}$ = 7.5, $J_{2',3'}$ = 9.0, $J_{3',4'}$ = 9.0, $J_{4',5'}$ = 9.5, $J_{5',6'}$ =2.5 and 3.5 Hz; ^{13}C-NMR (δ in $CDCl_3$, 100 MHz) : 55.2 (OCH_3), 68.5 (C-6'), 68.8 (C-6), 69.5 (C-5), 75.2 (C-5'), 75.6 (C-2')76.8 (C-4), 77.3 (C-4'), 79.6 (C-2), 80.9 (C-3), 84.4 (C-3'), 98.2 (C-1), 103.1 (C-1').

Methyl 4-*O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**18**): A solution of 2'-hydroxy free disaccharide (**16**) (89.6 mg, 0.1 mmol) in dichloromethane (2 mL) containing pyridine (0.16 mL) was treated with trifluoromethanesulfonic anhydride (0.168 mL, 1.0 mmol) and processed as described for **6**. The crude **17** was used for subsequent triflate inversion, without further purification, with tetrabutylammonium acetate (20 mg, 0.5 mmol). After stirring at 60 °C for 8 h, all the educt (**17**) was consumed (TLC). General aqueous workup followed by purification by silica gel column chromatography with hexane-ethyl acetate (2 : 1) as described for **7** gave 54.5 mg (58.1% over 2 steps from **16**) of β-mannoside (**18**) as a colorless syrup: $[\alpha]_D^{20}$ +23.2 ° (c 0.9, $CHCl_3$) ; MS (FAB) m/z : 937 $[M-H]^+$, 961 $[M+Na]^+$; ^{1}H-NMR (δ in $CDCl_3$, 400 MHz) : 2.12 (3H, s, CH_3), 3.24 (1H, td, H-5'), 3.37 (3H, s, $COCH_3$), 3.38 (1H, dd, H-3'), 3.46 (1H, dd, H-2), 3.51 (1H, dd, H-6'a), 3.54 (1H, dd, H-6'b), 3.62 (1H, dd, H-6a),3.73 (1H, dd, H-6b), 3.73 (1H, dd, H-4'), 3.74 (1H, td, H-5), 3.91 (1H, dd, H-3), 3.95 (1H, dd, H-4), 4.57 (1H, d, H-1), 4.60 (1H, d, H-1'), 5.41 (1H, td, H-2') ; $J_{1,2}$ = 3.5, $J_{2,3}$ = 9.0, $J_{3,4}$ = 8.5, $J_{4,5}$ = 9.0, $J_{5,6}$ = 5.0 and 3.0, $J_{1',2'}$ = 1.0, $J_{2',3'}$ = 3.0, $J_{3',4'}$ =9 .5, $J_{4',5'}$ = 9.5, $J_{5',6'}$ = 2.5 and 4.0 Hz;
^{13}C-NMR (δ in $CDCl_3$, 100MHz) : 21.1 ($COCH_3$), 55.2 (OCH_3), 68.4 (C-2'), 68.5(C-6), 68.9(C-6'), 69.3 (C-5), 74.2 (C-4'), 75.8 (C-5'), 77.3 (C-4), 79.2 (C-2), 80.4 (C-3'), 80.7 (C-3), 98.3 (C-1), 99.2 (C-1'), 170.6 ($\underline{C}OCH_3$).

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