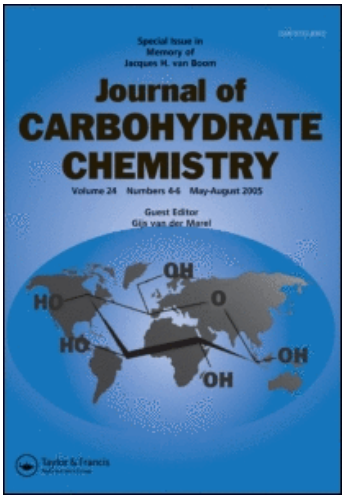

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REGIO- AND STEREOSELECTIVE SYNTHESIS OF 1→6 LINKED MANNO-, GLUCO-, AND GALACTOPYRANOSE DI-, TRI-, AND TETRASACCHARIDES VIA ORTHOESTER INTERMEDIATES

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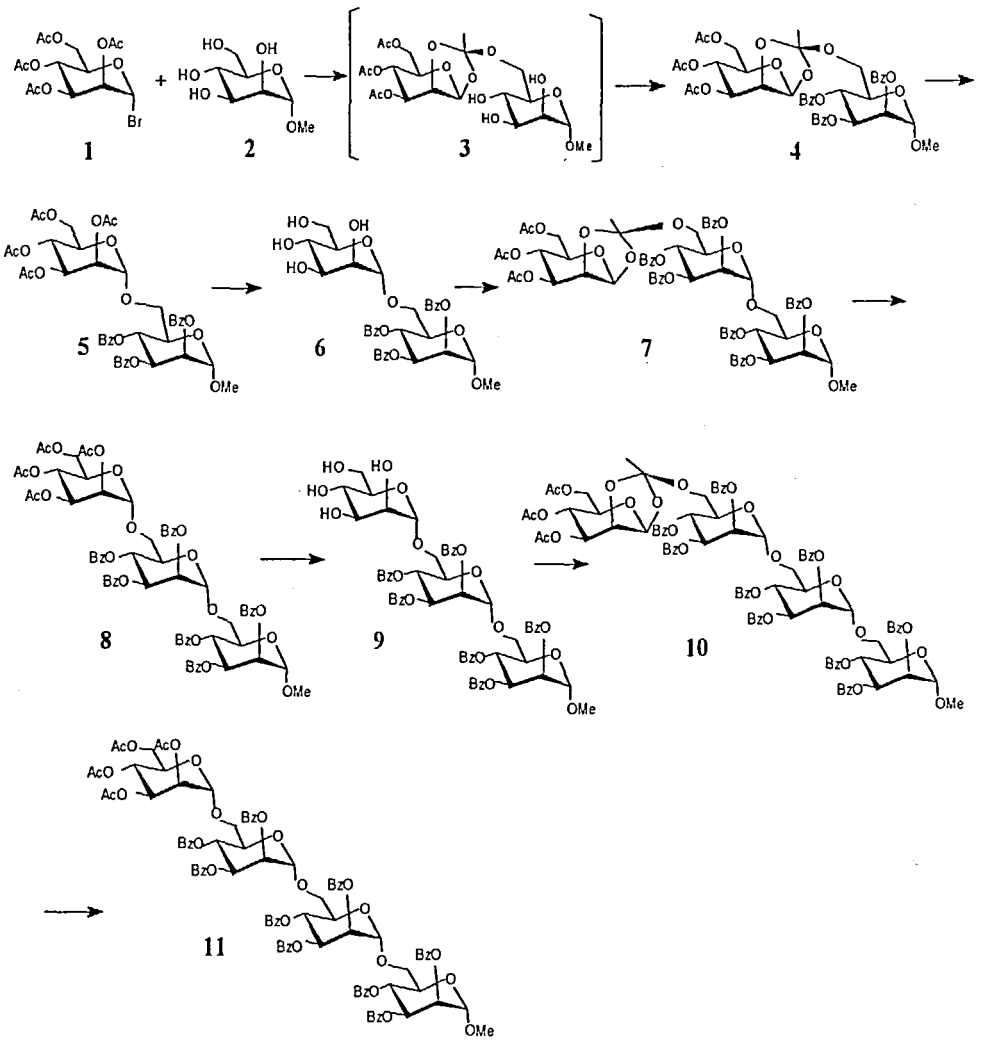
ABSTRACT

1→6 Linked manno-, gluco-, and galactopyranose di-, tri-, and tetrasaccharides with 1,2-*trans* glycosidic linkages were concisely and effectively synthesized using peracetylated glycosyl bromides as the donors and unprotected or partially protected glycopyranosides as the acceptors via orthoester intermediates.

INTRODUCTION

1→6 Linked glycopyranose oligosaccharides are widely distributed in nature; for instance, yeast cell wall polysaccharides contain 1→6 α-linked manno-oligosaccharide chains,[1] 1→6 β-linked gluco-oligosaccharides are known as gentiooligosaccharides, while 1→6 β-linked galacto-oligosacchrides occur in glycosphingolipids[2] of metacestodes of the parasite *Echinococcus multilocularis*, and exist in plant tissues and exudates. Stepwise synthesis of 1→6 β-linked galacto-oligosacchrides has been reported using 2,3,4-tri-*O*-benzoyl-6-*O*-bromoacetyl-α-D-galactopyranosyl chloride[3] or 6-*O*-acetyl-2-*O*-benzoyl-3,4-

di-*O*-benzyl-α-D-galactopyranosyl tosylate[4] as the glycosyl donor and protected galactose derivatives with only 6-free OH as the acceptors. In contrast to the synthesis of galacto-oligosaccharides, little attention[5] has been paid to the synthesis of 1→6 α-linked manno-oligosaccharides and 1→6 β-linked gluco-oligosaccharides. Here, we wish to report the use of unprotected or partially protected sugar pyranosides as the glycosyl acceptors for the synthesis of 1→6 linked manno-, gluco-, and galactopyranose di-, tri-, and tetrasaccharides.



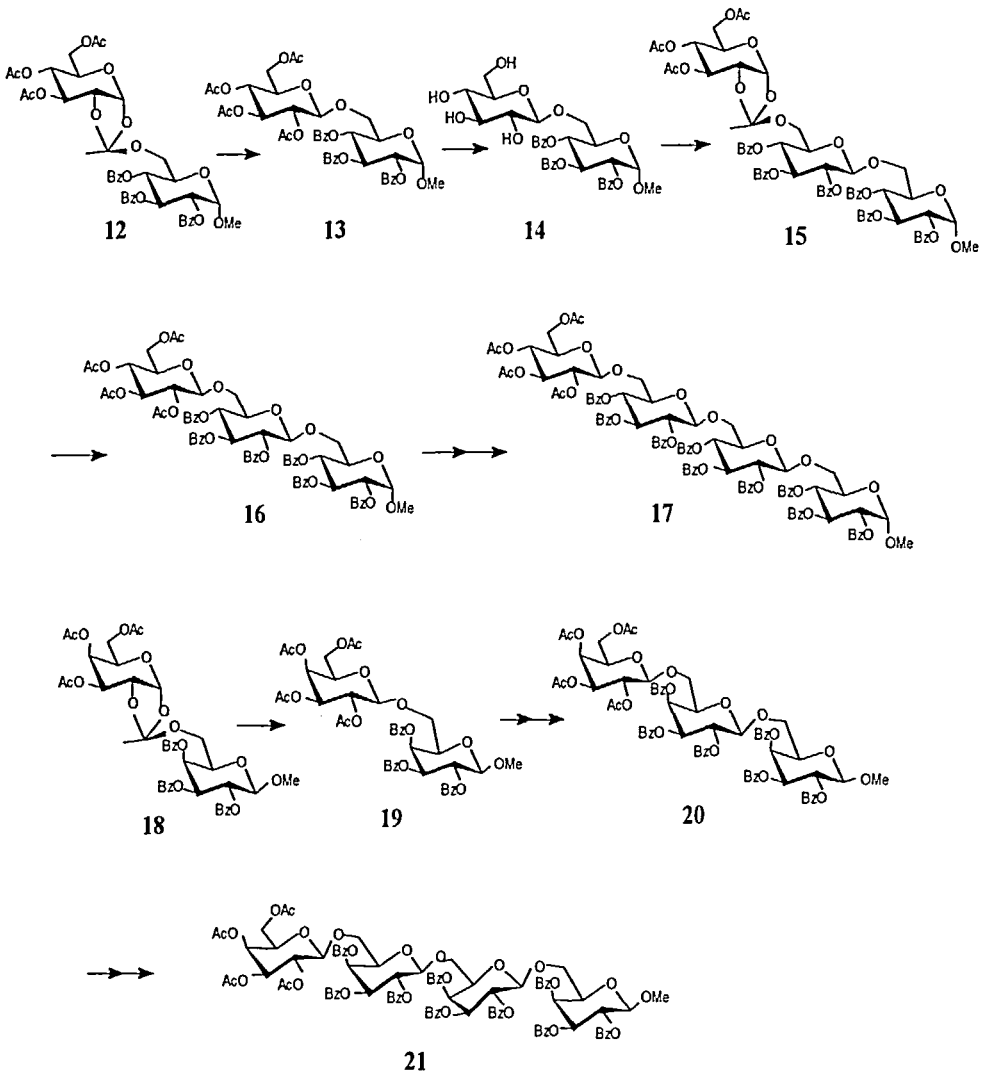
Scheme 1

RESULTS AND DISCUSSION

We have reported a new method[6] for regio- and stereoselective synthesis of oligosaccharides using unprotected or partially protected sugar pyranosides as the acceptors and simple peracetylated glycosyl bromides as the donors via orthoester intermediates. Based on the new strategy, we describe here, with a mannose series as a typical example, an effective and concise route for the synthesis of 1→6 linked glycopyranose oligosaccharides with 1,2-*trans* glycosidic linkages as shown in Scheme 1.

Coupling of acetobromomannose (**1**) with methyl α-D-mannopyranoside (**2**) in DMF in the presence of silver triflate and 2,4-lutidine[6a] afforded orthoester **3**, its benzoylation[7] with benzoyl chloride in pyridine (→**4**) followed by rearrangement[6,8] with TMSOTf gave methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (**5**) (72%, for 3 steps). Selective removal of acetyl groups[9] from **5** with CH_3COCl-MeOH furnished the disaccharide acceptor methyl α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (**6**) (90%). It was noted that the disaccharide acceptor **6** had much better solubility in dichloromethane than the corresponding monosaccharide acceptor **2**, thus its reaction with the donor **1** was carried out readily in dichloromethane to afford the orthoester that was benzoylated in situ with benzoyl chloride in pyridine to give fully protected orthoester **7** (72%, for 2 steps). Rearrangement of **7** with TMSOTf furnished methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside **8** (85%). The ^{1}H NMR spectrum of **8** showed 9 signals for H-2,3,4 of the 3 mannose residues at δ 6.16-5.13 indicating 1→6 linkages. Selective removal of acetyl groups from **8** was conducted smoothly to afford methyl α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside **9** in a high yield (89%). Coupling of **9** with **1** followed by benzoylation in situ, then rearrangement gave methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside **11** in satisfactory yield (60%, for 3 steps).

Gluco- and galactopyranose di-, tri- and tetrasaccharides were similarly synthesized in comparable yields by the same method (Scheme 2).



Scheme 2

In summary, here we describe a successful synthesis of 1→6 linked glycopyranose di-, tri-, and tetrasaccharides with 1,2-*trans* glycosidic linkages using unprotected or partially protected sugar pyranosides as the acceptors and peracetyl glycosyl bromides as the donors via orthoester intermediates. This method can also be used for the synthesis of 1→6 linked heterooligosaccharides.

EXPERIMENTAL

General methods. Optical rotations were determined at 20 °C with a Perkin-Elmer Model 241-Mc automatic polarimeter. ^{1}H NMR spectra were recorded with Varian XL-400 and Varian XL-200 spectrometers for solutions in $CDCl_3$. Chemical shifts are given in ppm downfield from internal Me_4Si. Thin-layer chromatography (TLC) was performed on silica gel HF with detection by charring with 30% (v/v) H_2SO_4 in MeOH or in some cases by a UV detector. Analytical samples were obtained by purification with a Gilson HPLC set consisting of two pumps (Model 306), Dynamic Mixer (Model 811c), RI Detector (Model 132), UV/VIS Detector (Model 118), stainless steel column packed with silica gel (10 × 300 mm or 4.6 × 250 mm), and an IBM computer installed with system control software 712. Ethyl acetate - petroleum ether (bp 60-90 °C) was used as the eluent at a flow rate of 1 to 4 mL min^{-1}. Column chromatography was conducted by elution of a column (16 × 240 mm, 18 × 300 mm, 35 × 400 mm) of silica gel (100-200 mesh) with EtOAc - petroleum ether (60-90 °C) as the eluent. Solutions were concentrated at < 60 °C under diminished pressure.

Orthoester 4. To a stirred mixture of **1** (411 mg, 1 mmol), **2** (194 mg, 1 mmol), 2,4-lutidine (158 μL, 1.4 mmol), and 4A molecular sieves (1 g) in DMF (dry, 20 mL) was added silver triflate (257 mg, 1 mmol) under a nitrogen atmosphere in a dark room. The reaction was carried out at rt and monitored by TLC (EtOAc). After completion of the reaction, the mixture was concentrated under reduced pressure. Freshly distilled benzoyl chloride (4.8 mL, 4 mmol) was added dropwise to the mixture in dry pyridine (20 mL) at 0 °C. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with MeOH (2 mL), and the mixture was poured into ice-water, extracted with dichloromethane, washed with satd aq $NaHCO_3$ (50 mL), and aq NaCl (50 mL). The aq phases were re-extracted with dichloromethane (30 mL), and the combined organic solutions were dried, concentrated, and purified by column chromatography with 2:1 petroleum ether-EtOAc as the eluent to give the title compound **4** as a colorless syrup (655 mg, 80%): $[\alpha]_D$ –22.6° (*c* 1.0, $CHCl_3$);.^{1}H NMR δ 8.12-7.22 (m, 15H, Bz-H), 5.91 (t, 1H, $J_{3,4}$ = 9.9 Hz, H-4'), 5.82 (d, 1H, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 9.9 Hz, H-3), 5.64 (m, 1H, $J_{1,2}$ = 1.6 Hz, H-2), 5.36 (d, 1H, $J_{1',2'}$ = 2.6 Hz, H-1'), 5.25 (t, 1H, $J_{3',4'}$ = 9.8 Hz, H-4'), 5.13 (dd, 1H, H-3'), 4.98 (d, 1H, H-1), 4.60 (m, 1H, $J_{2',3'}$ = 4.0 Hz, H-2'), 4.20 (m, 2H, H-6), 4.11

(m, 2H, H-6'), 3.77 (m, 2H, H-5, H-5'), 3.51 (s, 3H, OCH_3), 2.02 (d, 6H, $2CH_3CO$), 1.91 (s, 3H, CH_3CO), 1.72 (s, 3H, CH_3-C)

Anal. Calcd for $C_{42}H_{44}O_{18}$: C, 60.28; H, 5.30. Found: C, 60.27; H, 5.32.

Methyl 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (5). A solution of **4** (837 mg, 1 mmol) in anhydrous dichloromethane (20 mL) was cooled to -5 to -10 °C , then TMSOTf (5 μL) was added under N_2 flow. The mixture was stirred at this temperature for about 90 min, then neutralized with Et_3N. After concentration under diminished pressure, the residue was subjected to column chromatography to give **5** (753mg, 90%) as a colorless syrup: $[\alpha]_D$ – 12.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.12-7.22 (m, 15H, Bz-H), 5.90-5.88 (m, 2H, H-2, H-4), 5.70 (dd, 1H, $J_{1',2'}$ = 1.6 Hz, $J_{2',3'}$ = 2.9 Hz, H-2'), 5.42 (t, 1H, $J_{3,4}$ = 9.8 Hz, H-3), 5.33 (dd , 1H, $J_{3',4'}$ = 10.0 Hz, H-3'), 5.28 (t, 1H, H-4'), 5.12 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.85 (d, 1H, $J_{1',2'}$ = 1.5 Hz, H-1'), 4.36-4.33 (m, 2H, H-5, H-5'), 4.13-4.11 (m, 1H, H-6), 4.01-3.94 (m, 3H, H-6, H-6'), 3.62 (s, 3H, OCH_3), 2.12 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 1.94 (s, 3H, CH_3CO).

Anal. Calcd for $C_{42}H_{44}O_{18}$: C, 60.28; H, 5.30. Found: C, 60.30; H, 5.29.

Methyl α-D-Mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (6). To a solution of **5** (836 mg, 1 mmol) in anhydrous MeOH (50 mL) was added acetyl chloride (1.5 mL) at 0 °C. The solution was sealed in a flask and stirred for 10 h at room temperature, then another portion of acetyl chloride (1 mL) was added. The reaction was monitored by TLC until the starting material disappeared. The solution was neutralized with Et_3N, then concentrated to dryness. The residue was passed through a short silica gel column to give **6** (600 mg, 90%) which was directly used for the further reaction: $[\alpha]_D$ –12.8° (*c* 2.3, $CHCl_3$); ^{1}H NMR δ 8.04-7.21 (m, 15H, Bz-H), 5.95 (t, 1H, $J_{3,4}$ = 4.8 Hz, H-4), 5.88 (dd, 1H, $J_{2,3}$ = 3.1 Hz, H-3), 5.68 (s, 1H, H-2), 5.08 (s, 1H, H-1), 4.80 (s, 1H, H-1'), 4.30-4.28 (m, 2H), 4.25-4.23 (m, 1H), 3.92-3.45 (m, 9H).

Anal. Calcd for $C_{34}H_{36}O_{14}$: C, 61.07; H, 5.43. Found: C, 61.12; H, 5.23.

Orthoester 7. To a solution of **1** (411 mg, 1 mmol), **6** (669 mg, 1 mmol), and 2,4-lutidine (161 μL, 1.4 mmol) in dichloromethane (50 mL) was added molecular sieves (4A, 1 g) and the mixture was stirred for 1 h. Then AgOTf (257 mg, 1 mmol) was added and the reaction was monitored by TLC (1:2 petroleum ether-ethyl acetate). When the

starting materials disappeared, the reaction mixture was processed according to the procedure used in the preparation of orthoester 4 and orthoester 7 (944 mg, 72%) was obtained as a syrup: $[\alpha]_D$ –9.3° (*c* 2.0, $CHCl_3$); ^1H NMR δ 8.21-7.22 (m, 30H, Bz-H), 6.02 (t, 1H, $J_{3',4'}$ = 10.0 Hz, H-4'), 5.95-5.85 (m, 3H, H-4, H-1', H-3'), 5.75 (dd, 1H, $J_{1',2'}$ = 1.6 Hz, $J_{2',3'}$ = 3.3 Hz, H-2'), 5.70 (dd, 1H, $J_{1,2}$ = 1.7 Hz, $J_{2,3}$ = 2.8 Hz, H-2), 5.25-5.18 (m, 2H, H-4'', H-3), 5.15 (d, 1H, $J_{1',2'}$ = 1.6 Hz, H-1'), 5.09 (dd, 1H, $J_{2'',3''}$ = 4.0 Hz, $J_{3'',4''}$ = 9.8 Hz, H-3''), 5.04 (d, 1H, $J_{1,2}$ = 1.7 Hz, H-1), 4.52 (dd, 1H, $J_{1'',2''}$ = 1.7 Hz, H-2''), 4.38 (m, 1H, H-5'), 4.23 (m, 1H, H-5), 4.18 (m, 1H, H-5''), 4.08 (m, 2H, H-6'), 3.61 (s, 3H, OCH_3), 3.52 (m, 4H, H-6, H-6''), 2.03 (d, 6H, $2CH_3CO$), 1.90 (s, 3H, CH_3CO), 1.59(s, 3H, CH_3-C)

Anal. Calcd for $C_{69}H_{66}O_{26}$: C, 63.20; H, 5.08. Found: C, 63.31; H, 5.02.

Methyl 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (8). The same procedures as described in the preparation of 5 from 4 were used for the preparation of **8** (syrup, 558 mg, 85%) from 7 (656 mg, 0.5 mmol): $[\alpha]_D$ –12.3° (*c* 1.5, $CHCl_3$); ^1H NMR δ 8.20-7.26 (m, 30H, Bz-H), 6.16 (t, 1H, $J_{3',4'}$ = 10.2 Hz, H-4'), 5.99 (dd, 1H, $J_{2',3'}$ = 3.3 Hz, H-3'), 5.93 (m, 2H, H-3, H-4), 5.84 (dd, 1H, $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 3.3 Hz, H-2'), 5.76 (dd, 1H, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 3.3 Hz, H-2), 5.33 (dd, 1H, $J_{2'',3''}$ = 3.3 Hz, $J_{3'',4''}$ = 10.2 Hz, H-3''), 5.24 (t, 1H, H-4''), 5.13 (m, 2H, H-1', H-2'), 5.03 (d, 1H, H-1), 4.58 (d, 1H, $J_{1'',2''}$ = 1.4 Hz, H-1''), 4.45 (m, 1H, H-5'), 4.23 (m, 1H, H-5), 4.10 (m, 2H, H-6'), 3.89 (m, 3H, H-5'',H-6), 3.76 (m, 2H, H-6'), 3.60 (s, 3H, OCH_3), 2.10 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO), 1.92 (s, 3H, CH_3CO)

Anal. Calcd for $C_{69}H_{66}O_{26}$: C, 63.20; H, 5.08. Found: C, 63.33; H, 5.04.

Methyl α-D-Mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (9). Selective deacetylation of **8** (656 mg, 0.5 mmol) was carried out by the same method as described in the preparation of **6** from **5**. The trisaccharide **9** (509 mg, 89 %) was obtained as a solid: mp 141-144 °C; $[\alpha]_D$ –11.5° (*c* 1.1, $CHCl_3$); ^1H NMR δ 8.07-7.20 (m, 30H, Bz-H), 5.96-5.78 (m, 4H), 5.68 (s, 1H), 5.60 (s, 1H), 5.10 (s, 1H), 5.01 (s, 1H), 4.85 (s, 1H), 4.33-3.41 (m, 15H).

Anal. Calcd for $C_{61}H_{58}O_{22}$: C, 64.09; H, 5.12. Found: C, 64.02; H, 5.14.

Orthoester 10. Coupling of **9** (570 mg, 0.5 mmol) with **1** (204.5 mg, 0.5 mmol) followed by benzoylation using the same method as described for the preparation of 7 from

6 and **1** furnished the orthoester **10** (625 mg, 70%) as a syrup: $[\alpha]_D$ –13.3° (*c* 1.0, $CHCl_3$); ^1H NMR δ 8.19-7.28 (m, 45H, Bz-H), 6.25 (t, 1H, $J_{3'',4''}$ = 10.0 Hz, H-4''), 6.04 (dd, 1H, $J_{2'',3''}$ = 3.0 Hz, H-3''), 6.00-5.95 (m, 2H, H-4', H-3'), 5.93 (d, 1H, $J_{1''',2'''}$ = 1.5 Hz, H-1'''), 5.90-5.84 (m, 2H, H-4, H-3), 5.77 (dd, 1H, $J_{1'',2''}$ = 1.6 Hz, H-2''), 5.49 (dd, 1H, $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 3.1 Hz, H-2'), 5.23-5.18 (m, 3H, H-1'', H-2, H-4'''), 5.10 (dd, 1H, $J_{2''',3'''}$ = 3.0 Hz, $J_{3''',4'''}$ = 10.1 Hz, H-3'''), 5.05 (d, 1H, H-1'), 4.82 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.49 (dd, 1H, $J_{1''',2'''}$ = 1.6 Hz, H-2'''), 4.26 (m, 3H, H-5, H-6), 4,16-4.09 (m, 4H, H-5, H-6), 3.91-3.80 (m, 2H, H-6), 3.59 (s, 3H, OCH_3), 3.57-3.52 (m, 3H, H-6), 2.02 (d, 6H, $2CH_3CO$), 1.88 (s, 3H, CH_3CO), 1.58 (s, 3H, CH_3-C)

Anal. Calcd for $C_{96}H_{88}O_{34}$: C, 64.57; H, 4.97. Found: C, 64.51; H, 5.02.

Methyl 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (11). Rearrangement of **10** (537 mg, 0.3 mmol) promoted with TMSOTf was conducted as described for the rearrangement of **7**, and the tetrasaccharide **11** (456 mg, 85%) was obtained as a solid: mp 126-128 °C; $[\alpha]_D$ –6.9° (*c* 1.5, $CHCl_3$); ^1H NMR δ 8.16-7.26 (m, 45H, Bz-H), 6.17 (t, 1H, $J_{3'',4''}$ = 10.0 Hz, H-4''), 6.09 (t, 1H, $J_{3',4'}$ = 10.1 Hz, H-4'), 6.04 (dd, 1H, $J_{2'',3''}$ = 3.0 Hz, H-3''), 5.97-5.92 (m, 2H, H-3', H-4), 5.86 (d, 1H, $J_{1'',2''}$ = 1.5 Hz, H-2''), 5.76 (dd, 1H, $J_{1',2'}$ = 1.3 Hz, $J_{2',3'}$ = 3.0 Hz, H-2'), 5.66 (m, 1H, $J_{1,2}$ = 1.3 Hz, H-2), 5.34 (dd, 1H, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 10.2 Hz, H-3), 5.25-5.22 (m, 2H, H-3''', H-2'''), 5.20 (d, 1H, H-1''), 5.07 (d, 1H, H-1'), 4.83 (d, 1H, H-1), 4.63 (d, 1H, $J_{1''',2'''}$ = 1.3 Hz, H-1'''), 4.50 (m, 1H, H-5), 4.32 (m, 1H, H-5), 4.20-4.00 (m, 3H, H-5, H-6), 3.92-3.70 (m, 4H, H-6), 3.63 (s, 3H, OCH_3), 3.45-3.41 (m, 2H, H_6), 2.10 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 1.98 (s, 3H, CH_3CO), 1.89 (s, 3H, CH_3CO)

Anal. Calcd for $C_{96}H_{88}O_{34}$: C, 64.57; H, 4.97. Found: C, 64.53; H, 5.01.

Orthoester 12. The same procedures as described in the preparation of **4** starting from **1** and **2** were used for the preparation of **12** (syrup, 694 mg, 83%) starting from the condensation of acetobromoglucose (411 mg, 1 mmol) with methyl α-D-glucopyranoside (194 mg, 1 mmol): $[\alpha]_D$ +3.6° (*c* 1.4, $CHCl_3$); ^1H NMR δ 8.05-7.26 (m, 15H, Bz-H), 6.11 (t, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 5.75 (d, 1H, $J_{1',2'}$ = 5.2 Hz, H-1'), 5.58 (t, 1H, $J_{3,4}$ = 9.7 Hz, H-4), 5.29-5.22 (m, 3H, H-3', H-4', H-2), 5.12 (d, 1H, $J_{1,2}$ = 6.2 Hz, H-1), 4.89 (dd, 1H, $J_{2,3}$

= 9.7 Hz, H-2), 4.36-4.14 (m, 6H, H-5, H-6), 3.46 (s, 3H, OCH_3), 2.10 (d, 6H, $2CH_3CO$), 2.08 (s, 3H, CH_3CO), 1.69 (s, 3H, CH_3-C)

Anal. Calcd for $C_{42}H_{44}O_{18}$: C, 60.28; H, 5.30. Found: C, 60.31; H, 5.28.

Methyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (13). The same procedures as described in the preparation of **5** from **4** were used for the preparation of **13** (syrup, 591 mg, 90%) from **12** (656 mg, 0.78 mmol): $[\alpha]_D$ +1.4° (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 8.05-7.26 (m, 15H, Bz-H), 6.11 (t, 1H, $J_{3,4}$ = 9.6 Hz, $J_{2,3}$ = 9.5 Hz, H-3), 5.41 (t, 1H, H-4), 5.39-5.19 (m, 3H, H-1, H-2, H-3'), 5.08-5.02 (m, 2H, H-4', H-2'), 4.63 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 4.62-3.73 (m, 6H, H-5, H-6), 3.5 (s, 3H, OCH_3), 2.10 (s, 3H, CH_3CO), 2.00 (s, 9H, $3CH_3CO$)

Anal. Calcd for $C_{42}H_{44}O_{18}$: C, 60.28; H, 5.30. Found: C, 60.29; H, 5.27.

Methyl β-D-Glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (14). The same procedures as described in the preparation of **6** from **5** were used for the preparation of **14** (syrup, 770 mg, 92%) from **13** (837 mg, 1 mmol): $[\alpha]_D$ −18.6° (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 7.96-7.82 (m, 15H, Bz-H), 6.15 (t, 1H, J = 9.8 Hz), 5.79 (t, 1H, J = 9.8 Hz), 5.31-5.26 (m, 2H), 4.29 (d, 1H, J = 7.5 Hz), 4.24-4.17 (m, 2H), 3.87-3.82 (m, 2H), 3.70-3.51 (m, 6H), 3.48 (s, 3H, OCH_3), 3.40 (s, 4H, 4OH).

Anal. Calcd for $C_{34}H_{36}O_{14}$: C, 61.07; H, 5.43. Found: C, 61.10; H, 5.33.

Orthoester 15. The same procedures as described in the preparation of **7** from **6** and **1** were used for the preparation of **15** (syrup, 524 mg, 80%) from acetobromoglucose (205 mg, 0.5 mmol) and the disaccharide **14** (334 mg, 0.5 mmol): $[\alpha]_D$ +3.7° (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 8.03-7.25 (m, 30H, Bz-H), 6.09 (t, 1H, J = 9.8 Hz), 5.84 (t, 1H, J = 9.6 Hz), 5.72-5.60 (m, 2H), 5.46-5.20 (m, 4H), 5.12-4.96 (m, 2H), 4.86 (d, 1H, J = 7.6 Hz,), 4.65 (d, 1H, J = 7.8 Hz,), 4.24-4.19 (m, 3H), 4.09-3.97 (m, 3H), 3.79-3.67 (m, 3H), 3.17 (s, 3H, OCH_3), 2.04 (s, 3H, CH_3CO), 2.00 (s, 6H, $2CH_3CO$), 1.67 (s, 3H, CH_3-C)

Anal. Calcd for $C_{69}H_{66}O_{26}$: C, 63.20; H, 5.08. Found: C, 63.27; H, 5.04.

Methyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (16). The same procedures as described in the preparation of **8** from **7** were used for the preparation of **16** (syrup, 583 mg, 89%) from **15** (656 mg, 0.5 mmol): $[\alpha]_D$ +1.7° (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 8.01-7.27 (m, 30H, Bz-H), 6.09 (t, 1H, $J_{3,4} = J_{2,3}$ = 9.8 Hz, H-3), 5.84 (t, 1H, $J_{3',4'}$

= $J_{2',3'}$ = 9.6 Hz, H-3'), 5.43 (t, 1H, H-4'), 5.39 (t, 1H, H-4), 5.31(t, 1H, $J_{3'',4''} = J_{2'',3''}$ = 9.4 Hz, H-3''), 5.21 (t, 1H, H-4''), 5.11 (dd, 1H, $J_{1,2}$ = 8.0 Hz, H-2), 5.04-4.96 (m, 3H, H-2', H-2'', H-1), 4.92 (d, 1H, $J_{1',2'}$ = 7.6 Hz, H-1'), 4.63 (d, 1H, $J_{1'',2''}$ = 7.8 Hz, H-1''), 4.20-4.15 (m, 3H, H-5, H-6), 4.05-3.97 (m, 3H, H-5, H-6), 3.77-3.69 (m, 3H, H-6), 3.12 (s, 3H, OCH_3), 2.03 (s, 3H, CH_3CO), 2.00 (s, 9H, $3CH_3CO$)

Anal. Calcd for $C_{69}H_{66}O_{26}$: C, 63.20; H, 5.08. Found: C, 63.27; H, 5.06.

Methyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (17). Starting from selective removal of acetyl groups from **16** (588 mg, 0.44 mmol), then coupling of the obtained triol with **1** (196 mg, 0.48 mmol) followed by benzoylation, and subsequent rearrangement of the obtained orthoester afforded the tetrasaccharide **17** (600 mg, 70% for 4 steps) as a solid: mp 149-152 °C; $[\alpha]_D$ -2.8° (*c* 1.4, $CHCl_3$); ^1H NMR δ 7.94-7.26 (m, 45H, Bz-H), 6.09 (t, 1H, $J_{3,4} = J_{2,3}$ = 9.8 Hz, H-3), 5.95 (t, 1H, $J_{3',4'} = J_{2',3'}$ = 9.6 Hz, H-3'), 5.76 (t, 1H, $J_{3'',4''} = J_{2'',3''}$ = 9.6 Hz, H-3''), 5,47 (t, 1H, H-4), 5.37 (t, 1H, H-4'), 5.34 (t, 1H, H-4''), 5.35-5.26 (m, 5H, H-2, H-2', H-3''', H-4'', H-2''), 5.16 (dd, 1H, $J_{1''',2'''}$ = 7.6 Hz, H-2'''), 5.06 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.96 (d, 1H, H-1'''), 4.73 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.67 (d, 1H, $J_{1'',2''}$ = 8.0 Hz, H-1''), 4.20-4.02 (m, 8H, H-5, H-6), 3.89-3.82 (m, 2H, H-6), 3.76-3.71 (m, 2H, H-6), 3.11 (s, 3H, OCH_3), 2.04 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO), 1.99 (s, 3H, CH_3CO)

Anal. Calcd for $C_{96}H_{88}O_{34}$: C, 64.57; H, 4.97. Found: C, 64.50; H, 5.03

Orthoester 18. The same procedures as described in the preparation of **4** from **1** and **2** were used for the preparation of **18** (syrup, 686 mg, 82%) from acetobromogalactose (411 mg, 1 mmol) and methyl β-D-galactopyranoside (194 mg, 1 mmol): $[\alpha]_D$ +9.8° (*c* 1.5, $CHCl_3$); ^1H NMR δ 8.14-7.71 (m, 15H, Bz-H), 5.83 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-4), 5.76-5.71 (m, 2H), 5.58 (dd, 1H, H-3), 5.39 (d, 1H, J = 3.3 Hz), 5.36-5.01 (m, 5H), 4.70 (d, 1H, J = 7.9 Hz), 4.61 (d, 1H, J = 7.9 Hz), 4.15-3.68 (m, 9H), 3.64 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 2.09 (d, 3H, CH_3CO), 1.65 (s, 3H, CH_3-C)

Anal. Calcd for $C_{42}H_{44}O_{18}$: C, 60.28; H, 5.30. Found: C, 60.23; H, 5.36.

Methyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside (19). The same procedures as described in the preparation

of **5** from **4** were used for the preparation of **19** (syrup, 686 mg, 82%) from **18** (837 mg, 1 mmol): $[\alpha]_D$ +7.8° (*c* 1.4, $CHCl_3$), ^1H NMR δ 8.12-7.24 (m, 15H, Bz-H), 5.84 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-4), 5.75 (dd, 1H, $J_{2,3}$ = 10.4 Hz, H-2), 5.56 (dd, 1H, H-3), 5.36 (d, 1H, $J_{3',4'}$ = 3.3 Hz, H-4'), 5.21 (dd, 1H, $J_{1',2'}$ = 8.0 Hz, $J_{2',3'}$ = 10.5 Hz, H-2'), 4.98 (dd, 1H, H-3'), 4.69 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.53 (d, 1H, H-1'), 4.23-3.85 (m, 6H), 3.62 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 2.01 (d, 6H, $2CH_3CO$)

Anal. Calcd for $C_{42}H_{44}O_{18}$: C, 60.28; H, 5.30. Found: C, 60.22; H, 5.34.

Methyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside (20). Starting from selective removal of acetyl groups from **19** (447 mg, 0.54 mmol), then coupling of the obtained triol with acetobromogalactose (246 mg, 0.60 mmol) followed by benzoylation, and subsequent rearrangement of the orthoester obtained afforded **20** (402 mg, 75% for 4 steps) as a syrup: $[\alpha]_D$ +50.8° (*c* 1.4, $CHCl_3$); ^1H NMR δ8.07-7.75 (m, 12H, Bz-H), 7.50-7.21 (m, 18H, Bz-H), 5.90 (d, 1H, $J_{3,4}$ = 3.3 Hz, H-4), 5.84 (d, 1H, $J_{3',4'}$ = 3.3 Hz, H-4'), 5.74-5.66 (m, 2H, H-2, H-2'), 5.53 (dd, 2H, H-3, H-3',), 5.32 (d, 1H, $J_{3'',4''}$ = 3.4 Hz, H-4''), 5.11 (dd, 1H, $J_{1'',2''}$ = 7.9, $J_{2'',3''}$ = 2.5 Hz, H-2''), 4.94 (dd, 1H, H-3''), 4.83 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 4.57 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 4.32 (d, 1H, H-1''), 4.18-3.84 (m, 9H, H-5, H-6), 3.22 (s, 3H, OCH_3), 2.11 (s, 3H, CH_3CO), 2.04(s, 3H, CH_3CO), 1.91 (d, 6H, $2CH_3CO$)

Anal. Calcd for $C_{69}H_{66}O_{26}$: C, 63.20; H, 5.08. Found: C, 63.30; H, 5.05.

Methyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside (21). Starting from selective removal of acetyl groups from **20** (441 mg, 0.33 mmol), then coupling of the obtained triol with acetobromogalactose (147 mg, 0.36 mmol), and subsequent rearrangement of the orthoester obtained afforded **21** (375 mg, 70% for 4 steps) as a syrup: $[\alpha]_D$ +36.0° (*c* 1.4, $CHCl_3$); ^1H NMR δ 8.02-7.25 (m, 45H, Bz-H), 5.95 (d, 1H, $J_{3,4}$ = 3.1 Hz, H-4), 5.80 (d, 1H, $J_{3',4'}$ = 3.2 Hz, H-4'), 5.78 (d, 1H, $J_{3'',4''}$ = 3.0 Hz, H-4''), 5.72-5.44 (m, 6H, H-2, H-2', H-2'', H-3, H-3', H-3''), 5.30 (d, 1H, $J_{3''',4'''}$ = 3.1 Hz, H-4'''), 5.14 (dd, 1H, $J_{1''',2'''}$ = 7.9 Hz, H-2'''), 4.92 (dd, 1H, $J_{2''',3'''}$ = 10.4 Hz, H-3'''), 4.80 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 4.67 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.58 (d, 1H, $J_{1'',2''}$ = 7.8 Hz, H-1''), 4.43 (d, 1H, H-1'''),

4.13-3.42 (m, 12H, H-5, H-6), 3.30 (s, 3H, OCH_3), 2.11 (3H, CH_3CO), 2.01 (s, 3H, CH_3CO), 1.93 (s, 3H, CH_3CO), 1.81 (s, 3H, CH_3CO)

Anal. Calcd for $C_{96}H_{88}O_{34}$: C, 64.57; H, 4.97. Found: C, 64.52; H, 5.02.

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