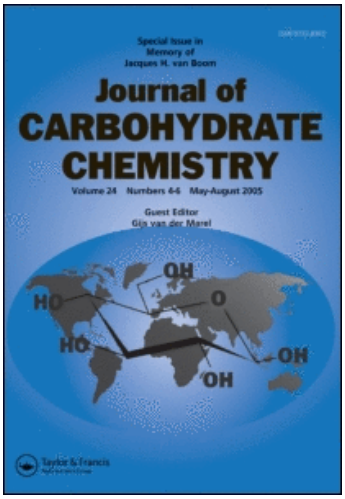

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SYNTHESIS OF THE REPEATING UNIT OF THE CAPSULAR POLYSACCHARIDE OF *STREPTOCOCCUS PNEUMONIAE* TYPE 3 AS A BUILDING BLOCK SUITABLE FOR FORMATION OF OLIGOMERS

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ABSTRACT

The synthesis of a cellobiouronic thioglycoside donor **12**, protected with a selectively removable 3´-*O*-benzyl group is described. The donor **12** is suitable as a monomer building block in the construction of oligomer structures corresponding to the capsular polysaccharide of *Streptococcus pneumoniae* type 3. The carboxyl function was introduced through regioselective TEMPO-oxidation of a 4´,6´-diol cellobiose derivative. If the oxidation was performed on a 2,3,2´,3´,4´,6´-hexaol derivative, oxidation also of the secondary 2- and 3-hydroxyl groups was observed to give a tricarboxyl derivative as one of the major products. The thioglycoside was formed by acidic mercaptolysis of a 1,6-anhydro bridge. The donor **12** was transformed into a suitable starting monomer acceptor through glycosylation with a spacer alcohol and subsequent debenzylation.

INTRODUCTION

In a program directed towards synthesis of uronic acid-containing oligosaccharides, the repeating unit of the capsular polysaccharide of *Streptococcus pneumoniae* type 3 was choosen as a suitable target structure of biological relevance. The polysaccharide is formed by cellobiouronic acid residues linked β-(1→3) to each other (Fig.1).[1,2]

The repeating unit and dimers thereof have earlier been synthesised by Chernyak *et al.*.[3,4] In our approach two different pathways were pursued, one including the use of reactive β-selective glucuronic acid donors[5] and the other, described below, a

$$[\rightarrow 3)\text{-}\beta\text{-D-Glc}p\text{A-}(1\rightarrow 4)\text{-}\beta\text{-D-Glc}p\text{-}(1\rightarrow]_n$$

Figure 1 Repeating unit of *Streptococcus pneumoniae* type 3 capsular polysaccharide.

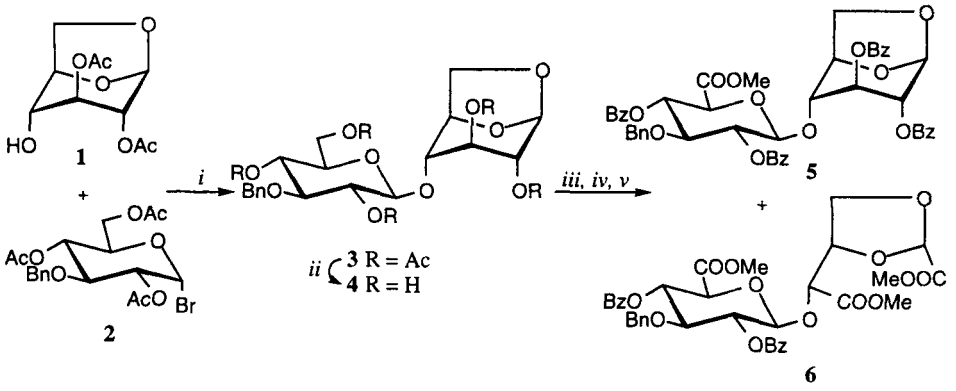
regioselective oxidation of a cellobiose derivative, to obtain a suitable cellobiouronic acid intermediate for the formation of oligomers of the repeating unit.

Due to the presence of the carboxyl group, uronic acid glycosyl donors are often unreactive and give low yields in coupling with hindered acceptors. Therefore, an often used alternative route to uronic acid-containing oligosaccharides is to use a non-acidic glycosyl donor with a temporary primary protecting group, which can be removed after the coupling reaction to allow the oxidation to the uronic acid derivative. Another similar strategy, which requires less protecting group manipulations, is the use of regioselective oxidation methods, which oxidize primary hydroxyl groups in the presence of secondary ones. Recently, an efficient such method has been described and applied on both mono- and polysaccharides,[6,7] using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as oxidant. The application of this method to the present synthesis is investigated and discussed.

RESULTS AND DISCUSSION

Desired requirements for the intermediate building block to be synthesised were the presence of a temporary protecting group at 3′-OH, to allow subsequent formation of new acceptors for further elongation, and the ability to function as a β-selective glycosyl donor, *i.e.*, a 2-*O*-participating group and a good anomeric leaving group at the reducing end is necessary.

As a precursor for the reducing end part of the cellobiouronic acid intermediate, a 1,6-anhydroglucose derivative was choosen. The anhydro-bridge protects this primary hydroxyl group from oxidation, but can later in the synthesis conveniently be opened by mercaptolysis or by acetolysis to give donor derivatives or donor precursor derivatives. The syntheses of the 2,3-protected 1,6-anhydro derivatives **1** and **7**, are described in the literature.[8,9] As donor, later to become the uronic acid part of the intermediate, the known derivative 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-D-glucopyranose,[10] easily obtained from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was selected. Transformation into the bromide **2** using titanium tetrabromide was almost quantitative. Coupling of **1** and **2** using silver triflate as promoter gave the cellobiose derivative **3** (71%) (Scheme 1). From **3** all acetyl groups were removed to give the pentaol **4**, on which selective TEMPO-oxidation[7] was tried. The desired cellobiouronic ester derivative **5** was obtained, after esterification

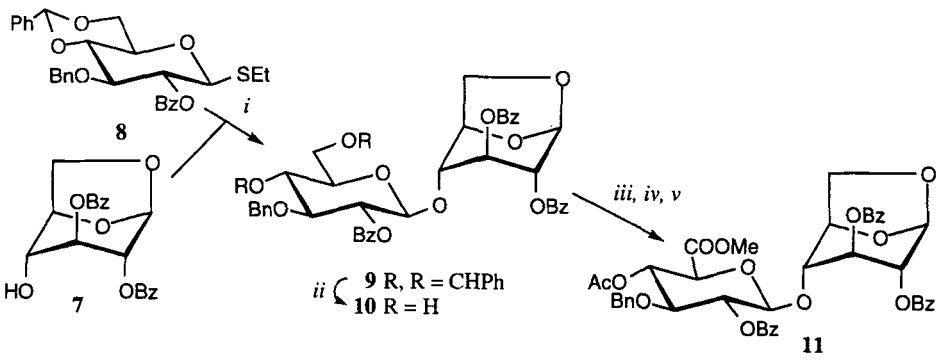


Scheme 1. (*i*) AgOTf, -35 °C; (*ii*) MeO^-; (*iii*) NaOCl, TEMPO; (*iv*) Dowex H^+, MeOH; (*v*) BzCl, Pyridine

with acidic methanol and benzoylation, but only in a 33% yield. Along with **5** another product was also formed in about the same amount. This product was isolated and its structure elucidated by NMR and found to be the over-oxidised derivative **6** with three carboxyl groups. Different conditions, various solvents and pHs, during the oxidation were tried but with similar results. The same type of by-product have been described in oxidations of octyl β-D-glucopyranoside using ruthenium complexes,[11] but to our knowledge not in connection with TEMPO oxidations. Apparently, the *trans*-diaxial glycol system of the 1,6-anhydroglucose residue is unusually susceptible to TEMPO oxidation.

To avoid this by-product an alternative pathway, which involved a protected 2,3-glycol system was constructed (Scheme 2). The thioglycoside donor **8**[12] was coupled to the 1,6-anhydro acceptor **7**[9] in a DMTST-promoted reaction[13,14] to give the disaccharide **9** (86%), from which the benzylidene acetal was removed to yield the 4,6-diol **10**. TEMPO-oxidation[6] of compound **10**, followed by esterification and acetylation now gave the desired cellobiouronic acid derivative **11** in 61% yield. Another advantage of the latter strategy is that various 4′-OH protecting groups can be introduced selectively to modulate the reactivity of the 3′-hydroxyl group in subsequent coupling reactions.

The 1,6-anhydro bridge in **5** was opened by a Lewis acid in the presence of a silylated mercaptan to give the target intermediate building block **12** (Scheme 3).[15] Different mercaptans were tried, the best result was obtained using cyclohexylthio-trimethylsilane which, after benzoylation of 6-OH, gave **12** in a 68% yield. Thioglycoside **12** can now be used as a donor, both in oligomer synthesis and for the construction of a suitable starting monomer acceptor. A spacer arm, 2-(4-trifluoroacetamidophenyl)ethanol,



Scheme 2. (*i*) AgOTf, -35 °C; (*ii*) HOAc (aq) (*iii*) NaOCl, TEMPO; (*iv*) Dowex H^+, MeOH; (*v*) AcCl, Pyridine

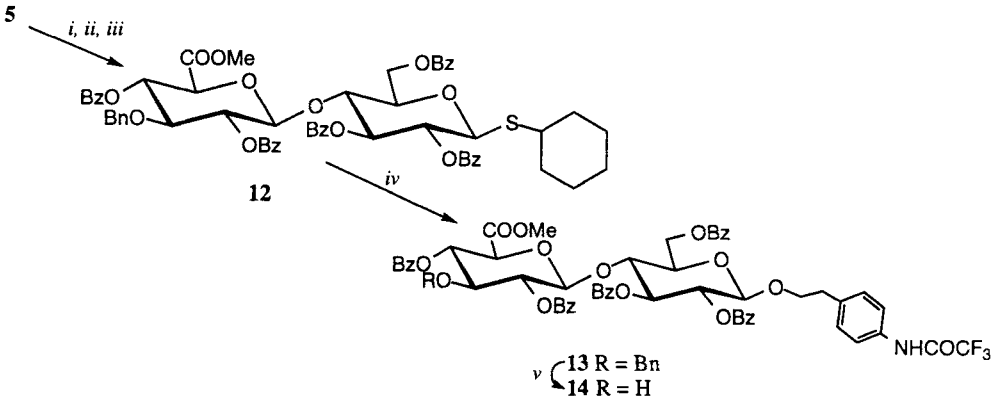
was thus coupled to donor **12** in a DMTST-promoted reaction to give the spacer disaccharide **13** (84%) (Scheme 3). Removal of the 3′-*O*-benzyl group by catalytic hydrogenation then gave the 3-OH compound **14** (86%), ready for use as an acceptor together with donor **12** in the synthesis of oligomer structures.

EXPERIMENTAL

General methods: Organic solutions were dried over $MgSO_4$ before concentrating, which was performed under reduced pressure at <40 °C (bath temp). NMR spectra were recorded at 25 °C at 270 MHz (^1H) or 67.5 MHz (^{13}C) in $CDCl_3$ with Me_4Si as internal standard ($\delta = 0$ ppm). TLC was performed on Silica Gel F_{254} (E. Merck) with detection by UV light and/or by charring with 8% sulfuric acid. Silica gel (0.040-0.063 mm, Amicon) was used for column chromatography.

2,3-Di-*O*-acetyl-1,6-anhydro-4-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranosyl)-β-D-glucopyranose (3). Silver triflate (1.2 g, 4.67 mmol) dissolved in toluene (10 mL) was added dropwise at -35 °C to a stirred solution of 2,3-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose[8] (**1**) (680 mg, 2.76 mmol) and 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide[10] (**2**) (1.85 g, 4.04 mmol) in CH_2Cl_2 (240 mL). After 15 h, NEt_3 (1.0 mL) was added and the mixture was filtered, concentrated and purified on a silica gel column (toluene- EtOAc 4:3) to give **3** (1.22 g, 1.95 mmol, 71%), $[\alpha]_D$ -27.3° (*c* 0.75, $CHCl_3$). ^{13}C NMR data ($CDCl_3$) : δ 20.6-21.0 (*Me*CO), 62.3, 64.9, 68.5, 69.1, 69.4, 72.3, 72.5, 73.6, 73.7, 76.7, 80.1 (C-2-6, C-2′-6′, Ph*C*H_2), 99.0, 100.8 (C-1, 1′), 127.9-137.7 (aromatic C), 168.8-170.8 (acetyl CO).

Anal. Calcd for $C_{29}H_{36}O_{15}$: C, 55.77; H, 5.81. Found: C, 55.94; H, 5.73.



Scheme 3. (*i*) C_6STMS, ZnI_2; (*ii*) 70% TFA (aq); (*iii*) BzCl, Pyr; (*iv*) DMTST, 2-(*p*-trifluoroacetamidophenyl)ethanol; (*iv*) H_2, Pd-C.

1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(methyl 2,4-di-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-β-D-glucopyranose (5). A catalytic amount of NaOMe was added to a solution of **3** (470 mg, 0.75 mmol) in MeOH (10 mL), after 3 h Dowex H^+ resin was added and the mixture filtered, concentrated and dried in vacuum for 1 h. The residue, **4**, was dissolved in water (15 mL) containing NaBr (15 mg, 0.15 mmol) at 0 °C and the pH was adjusted to 10 before 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (1 mg, 6.4 μmol) and NaOCl (3.0 mL, 5%) were added in one portion. The reaction was started by adding 1 drop of 4 M HCl and the pH was maintained at 10 by adding aliquots of 0.5 M NaOH (total 3 mL). After 30 min an additional amount of NaOCl (3 mL) was added. TLC (EtOAc-HOAc-MeOH-water 12:3:3:1) showed a slower moving product after 50 minutes, MeOH (3 mL) was added and the pH was adjusted to 6. After evaporation of the solvent and the coevaporation of added MeOH, the residue was dissolved in MeOH (15 mL), Dowex H^+ resin (0.8 g) was added and the mixture was stirred overnight. When TLC ($CHCl_3$-MeOH 9:1) showed complete reaction, the mixture was filtered, the filter washed with MeOH and CH_2Cl_2, and the filtrate concentrated and purified on a short silica gel column ($CHCl_3$-MeOH 12:1). The residue was treated with benzoyl chloride (675 μL) and pyridine (10 mL) overnight. The mixture was diluted with toluene and concentrated, coevaporated with toluene twice and purified on a silica gel column (toluene-EtOAc 9:1) to give **5** (214 mg, 0.25 mmol, 33%). $[\alpha]_D$ +27.1° (*c* 1.40, $CHCl_3$). ^{13}C NMR data ($CDCl_3$): δ 52.5 (OMe), 65.1, 68.8, 70.1, 71.3, 73.1, 73.3, 73.8, 74.1, 77.0, 78.9 (C-2-6, C-2′-5′, $PhCH_2$), 98.9, 101.4 (C-1, 1′), 127.7-137.1 (aromatic C), 164.8-165.6 (benzoyl CO), 167.3 (CO methyl ester).

Anal. Calcd for $C_{48}H_{42}O_{15}$: C, 67.13; H, 4.93. Found: C, 67.00; H, 5.00.

The byproduct, methyl 2-*O*-(methyl 2,4-di-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-3,4-*O*-(2-(*R*)-carboxymethylmethylidene)-D-threonate (**6**), had ^{13}C NMR data ($CDCl_3$) : δ 52.5, 52.6, 52.7 (3xMeO), 68.1 (C-6), 71.1 (C-4′), 2x72.6 (C-2′, 5′), 73.7 (Ph*C*H_2), 75.9 (C-5), 78.6 (C-3′), 79.2 (C-4), 98.9 (C-1), 100.9 (C-1′), 127.7-137.0 (aromatic C), 164.7, 165.1 (benzoyl CO), 167.1, 168.1, 169.4 (3xCO methyl ester). ^1H NMR data ($CDCl_3$) : δ 3.62, 3.73, 3.76 (3xMeO), 3.89 (t, 2H, 2xH-6), 4.04 (t, 1H, $J_{3',4'}$ 8.8 Hz, H-3′), 4.16 (d, 1H, H-5′), 4.26 (d, 1H, $J_{4,5}$ 8.1 Hz, H-4), 4.45 (ddd, 1H, H-5), 4.62 (s, 2H, PhCH_2), 4.95 (d, 1H, $J_{1',2'}$ 7.7 Hz, H-1′), 5.21 (s, 1H, H-1), 5.44 (t, 1H, $J_{2',3'}$ 8.0 Hz, H-2′), 5.62 (t, 1H, $J_{4',5'}$ 9.1 Hz, H-4′).

FABMS Calcd for $C_{36}H_{36}O_{15}$ [M+Na]$^+$: 731; Found: 731.3

1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-benzyl-β-D-glucopyranosyl)-β-D-glucopyranose (9). Ethyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-benzyl-1-thio-β-D-glucopyranoside[12] (**8**) (290 mg, 0.57 mmol), 1,6-anhydro-2,3-di-*O*-benzoyl-β-D-glucopyranose[9] (**7**) (140 mg, 0.38 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (39 mg, 0.19 mmol) were dissolved in CH_2Cl_2 (10 mL) containing crushed MS (4Å) and stirred for 30 min before DMTST (195 mg, 0.76 mmol) was added. After 2.5 h NEt_3 (1 mL) was added and the mixture was concentrated and purified on a silica gel column (toluene-EtOAc 12:1) to give **9** (265 mg, 0.35 mmol, 86%), $[\alpha]_D$ +43.2° (*c* 1.0, $CHCl_3$). ^{13}C NMR data ($CDCl_3$): δ 64.9, 66.3, 68.3, 2x69.0, 73.6, 74.0, 76.6, 77.9, 81.4 (C-2-6, C-2′-6′, Ph*C*H_2), 99.0, 101.2, 101.7 (C-1, 1′, Ph*C*H), 125.2-137.7 (aromatic C), 164.8, 165.0, 165.4 (benzoyl CO).

Anal. Calcd for $C_{47}H_{42}O_{13}$: C, 69.28; H, 5.20. Found: C, 69.43; H, 5.12.

1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyl)-β-D-glucopyranose (10). Compound **9** (245 mg, 0.30 mmol)was dissolved in CH_2Cl_2 (6 mL) and aqueous TFA (3 mL, 70%) was added. After 15 min the mixture was diluted with CH_2Cl_2 (15 mL) and the phases were separated. The organic phase was washed with aqueous $NaHCO_3$ twice, dried ($MgSO_4$), concentrated and purified on a silica gel column (toluene-EtOAc 4:3) to give **10** (141 mg, 0.19 mmol, 65%), $[\alpha]_D$ +0.5° (*c* 0.94, $CHCl_3$). ^{13}C NMR data ($CDCl_3$): δ 62.5, 64.9, 68.8, 69.6, 70.5, 73.6, 74.2, 74.4, 76.1, 76.4, 82.3 (C-2-6, C-2′-6′, Ph*C*H_2), 98.9, 101.7 (C-1, 1′), 125.2-137.8 (aromatic C), 165.0, 165.3, 165.9 (benzoyl CO).

FABMS Calcd for $C_{40}H_{38}O_{13}$ [M+Na]$^+$: 749; Found: 749.1.

1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(methyl 4-*O*-acetyl-2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-β-D-glucopyranose (11). Compound **10** (120 mg, 0.17 mmol) was added to a mixture of NaBr (3 mg, 0.03 mmol), tetrabutylammonium bromide (3 mg, 9.3 μmol), and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (1 mg, 6.4 μmol) in CH_2Cl_2/H_2O (3.5 mL, 6:1) at 0 °C and then a solution of NaOCl (1.3 mL, 5%) and saturated $NaHCO_3$ (1.0 mL). After 10 min the reaction was

quenched with MeOH (1 mL), diluted with CH_2Cl_2 (10 mL) and the phases were separated. The aqueous phase was acidified with 1M HCl and extracted with CH_2Cl_2 (3 mL) and EtOAc (3 mL). The combined organic phases were dried (Na_2SO_4), concentrated and dissolved in MeOH (15 mL), whereafter Dowex H^+ ion exchange resin (1 g) was added. When TLC (toluene-EtOAc 3:1) showed complete reaction, the mixture was filtered, the filter washed with MeOH and CH_2Cl_2, and the filtrate concentrated and purified on a short silica gel column ($CHCl_3$-MeOH 12:1). The residue was treated with Ac_2O (100 µL) and pyridine (3 mL) overnight. The mixture was diluted with toluene and concentrated, coevaporated with toluene twice and purified on a silica gel column (toluene-EtOAc 9:1) to give **11** (80 mg, 0.10 mmol, 61%), $[\alpha]_D$ +46.7° (*c* 1.45, $CHCl_3$). ^{13}C NMR data ($CDCl_3$): δ 20.5 (*Me*CO), 52.5 (OMe), 65.0, 68.8, 70.1, 70.8, 73.0, 73.1, 73.9, 74.1, 77.1, 79.2 (C-2-6, C-2′-5′, Ph*C*H_2), 98.9, 101.3 (C-1, 1′), 127.7-137.4 (aromatic C), 164.8-165.5 (benzoyl CO), 167.3 (CO methyl ester), 169.3 (acetyl CO).

Anal. Calcd for $C_{43}H_{40}O_{15}$: C, 64.82; H, 5.06. Found: C, 64.96; H, 4.92.

Cyclohexyl 2,3,6-Tri-*O*-benzoyl-4-*O*-(methyl 2,4-di-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-1-thio-β-D-glucopyranoside (12). ZnI_2 (95 mg, 0.30 mmol) was added to a stirred solution of **5** (85 mg, 0.10 mmol) and cyclohexylthiotrimethylsilane[15] (93 µL, 0.50 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred overnight, filtered through Celite and the filter washed with CH_2Cl_2. Aqueous TFA (3 mL, 70%) was added and when TLC showed complete reaction, the mixture was diluted with CH_2Cl_2 (15 mL) and washed with $NaHCO_3$ (aq., 5 mL) twice, dried and concentrated. The residue was dissolved in pyridine (5 mL) and treated with benzoyl chloride (100 µL). After 30 min the reaction mixture was diluted with toluene (50 mL), concentrated and purified on a silica gel column (toluene-EtOAc 9:1) to give **12** (73 mg, 67.6 µmol, 68%), $[\alpha]_D$ +38.7° (*c* 0.87, $CHCl_3$). ^{13}C NMR data ($CDCl_3$) : δ 25.5, 25.9, 26.0, 33.9, 34.0 (cyclohexyl CH_2), 43.8 (cyclohexyl CH), 52.4 (OMe), 63.0, 71.2, 73.1, 73.3, 73.8, 74.4, 76.9, 78.8 (C-2-6, C-2′-5′, Ph*C*H_2), 83.1 (C-1), 101.1 (C-1′), 127.6-137.0 (aromatic C), 164.6-165.7 (benzoyl CO), 166.5 (CO methyl ester).

Anal. Calcd for $C_{61}H_{56}O_{16}S$: C, 67.88; H, 5.42. Found: C, 67.74; H, 5.31.

2-(*p*-Trifluoroacetamidophenyl)ethyl 2,3,6-Tri-*O*-benzoyl-4-*O*-(methyl 2,4-di-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-β-D-glucopyranoside (13). DMTST (35 mg, 0.14 mmol) was added to a stirred solution of **12** (60 mg, 56 µmol) and 2-(*p* -trifluoroacetamidophenyl)ethanol (19 mg, 82 µmol) in CH_2Cl_2 (5 mL) containing crushed MS (4Å). After 30 min, NEt_3 (1 mL) was added, the mixture was diluted with toluene (5 mL), concentrated and purified on a silica gel column (toluene-EtOAc 5:1) to give **13** (56 mg, 47 µmol, 84%), $[\alpha]_D$ +41.1° (*c* 1.40, $CHCl_3$). ^{13}C NMR data ($CDCl_3$) : δ 35.3 (OCH_2CH_2Ph), 52.4 (OMe), 62.4, 70.2, 71.4, 72.1,

72.9, 2x73.2, 73.8, 78.8 (C-2-6, C-2′-5′, $PhCH_2$, OCH_2CH_2Ph), 100.6, 101.0 (C-1, 1′), 120.2-137.0 (aromatic C), 164.6-165.8 (benzoyl CO), 166.5 (CO methyl ester).

Anal. Calcd for $C_{65}H_{56}NO_{18}F_3$: C, 65.27; H, 4.72. Found: C, 65.06; H, 4.85.

2-(*p*-Trifluoroacetamidophenyl)ethyl 2,3,6-Tri-*O*-benzoyl-4-*O*-(methyl 2,4-di-*O*-benzoyl-β-D-glucopyranosyluronate)-β-D-glucopyranoside (14). Compound **13** (87 mg, 72.7 μmol) was dissolved in EtOAc (10 mL) and hydrogenolysed over Pd-C (cat) at 90 psi overnight. The mixture was filtered through Celite and concentrated to dryness to give **14** (69 mg, 62.4 μmol, 86%), $[\alpha]_D$ +34.6° (*c* 1.00, $CHCl_3$). ^{13}C NMR data ($CDCl_3$) : δ 35.3 (OCH_2CH_2Ph), 52.5 (OMe), 62.5, 70.2, 72.0, 72.5, 72.9, 2x73.1, 73.3, 74.4 (C-2-6, C-2′-5′, OCH_2CH_2Ph), 100.7, 100.8 (C-1, 1′) 120.2-137.0 (aromatic C), 164.6-165.8 (benzoyl CO), 166.5 (CO methyl ester).

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