Pergamon

Bioorganic & Medicinal Chemistry, Vol. 4, No. 11, pp 1867–1871, 1996

PII: S0968-0896(96)00168-X
0968-0896/96 $15.00+0.00

Synthesis of Oligosaccharides Corresponding to Structures found in Capsular Polysaccharides of *Cryptococcus neoformans*—II

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Abstract—Formula **1** depicts a generalized structure of the capsular polysaccharides of four serotypes of the opportunistic microorganism *Cryptococcus neoformans*, which appears as one of the major infections in the late stages of development of AIDS. Syntheses are now described of two tetrasaccharides with corresponding structures. These are methyl *O*-α-D-mannopyranosyl-(1→3)-[*O*-β-D-xylopyranosyl-(1→2)]-*O*-α-D-mannopyranosyl-(1→3)-α-D-mannopyranoside and methyl *O*-α-D-mannopyranosyl-(1→3)-[*O*-β-D-glucopyranosyluronic acid-(1→2)]-*O*-α-D-mannopyranosyl-(1→3)-α-D-mannopyranoside. Copyright © 1996 Elsevier Science Ltd

Introduction

Cryptococcosis occurs in the late stages of the development of AIDS as one of the major lethal factors. It is caused by the opportunistic microorganism *Cryptococcus neoformans*. Its type specificity is determined by the structure of its capsular polysaccharide, which comprises at least four serotypes, A–D. The polysaccharides consist primarily of a (1→3)-linked α-D-mannopyranosyl backbone, to which are attached single (1→2)-linked β-D-xylopyranosyl and β-D-glucuronopyranosyl groups, and also acetyl groups to the

β-D-Xyl*p* β-D-Xyl*p* β-D-Glc*p*A
1 1 1
↓ ↓ ↓
2 2 2
3)-α-D-Man*p*-(1→3)-α-D-Man*p*-(1→3)-α-D-Man*p*-(1→
1

6-position of the mannopyranosyl units. In serogroups B and C (1→4)-linked β-D-xylopyranosyl groups are also found. The various structures were proposed on the basis of NMR studies.[1,2] In order to corroborate these, and for biomedical studies, oligosaccharides with structures corresponding to parts of the various antigenic capsular polysaccharides were needed. In Part 1[3] of this work we presented syntheses of the oligosaccharides **2**–**4**, each carrying a linking arm suitable, after conversion of the trifluoroacetamido group into an amino function, for attachment to proteins in order to obtain artificial antigens.

We now present the synthesis of structures **5** and **6**, with a xylosyl and a glucuronosyl group, respectively, attached to the central unit of the mannotriose backbone. Since these oligosaccharides are primarily to be used in inhibition and NMR experiments, where a conjugation to a carrier is not necessary, they were synthesized as methyl glycosides to simplify the synthesis. The synthesis permits the later introduction of the naturally occurring acetyl substituents, a feature which is believed to be of importance for the biological activity.

Results and Discussion

Thiomannosyl donor **7**[3] was condensed with the 3-OH mannosyl acceptor **8**[4] in the presence of dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST)[5] in dichloromethane to produce the disaccharide **9** (87%) (Scheme 1). Debenzoylation of compound **9** gave the 2′,3′-diol **10**. Since in compound **10** both the 2′- and the 3′-hydroxyl groups are to be glycosylated, a

β-D-Xyl*p*
1
↓
2
α-D-Man*p*-(1→3)-α-D-Man*p*-(1→O)$CH_2CH_2C_6H_4$-p-NHCOCF_3
2

β-D-Xyl*p*
1
↓
2
α-D-Man*p*-(1→3)-α-D-Man*p*-(1→O)$CH_2CH_2C_6H_4$-p-NHCOCF_3
3

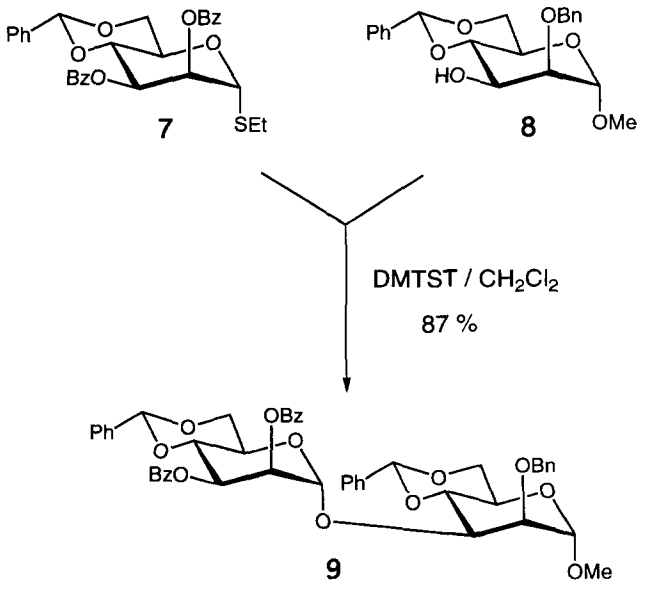
β-D-Xyl*p* β-D-Xyl*p*
1 1
↓ ↓
2 2
α-D-Man*p*-(1→3)-α-D-Man*p*-(1→O)$CH_2CH_2C_6H_4$-p-NHCOCF_3
4

β-D-Xyl*p*
1
↓
2
α-D-Man*p*-(1→3)-α-D-Man*p*-(1→3)-α-D-Man*p*-(1→O)CH3
5

β-D-GlcA*p*
1
↓
2
α-D-Man*p*-(1→3)-α-D-Man*p*-(1→3)-α-D-Man*p*-(1→O)CH3
6

regioselective mannosylation (using the same donor and promoter as above) of the more reactive equatorial 3′-OH was tried, to avoid laborious protecting group manipulations. To further enhance the nucleophilicity of the 3′-OH group stannylidene activation[6] was performed before glycosylation. Thus, **10** was treated with dibutyltin oxide and the crude stannylene derivative was glycosylated with **7** in the presence of DMTST in dichloromethane (Scheme 2). A 40% yield (53% based on aglycon consumed) of the desired 3′-*O*-linked trisaccharide **11** was obtained, with a free 2′-OH directly ready for the next glycosylation step. In the reaction the tetrasaccharide was also found and isolated (10–15%), but the 2′-*O*-linked trisaccharide was not detected. Experiments without prior tin activation indicate that in this coupling the same regioselectivity and yields of coupling products are obtained. Deprotection of **11** by debenzoylation followed by catalytic hydrogenolysis afforded the trimannoside **12**, whose correct structure was confirmed by methylation analysis and NMR data.

The remaining 2′-OH in **11** was xylosylated with benzobromoxylose **13** in the presence of silver trifluoromethanesulfonate to give the tetrasaccharide **14** (79%) (Scheme 3). Deprotection of **14** first by debenzoylation and then by catalytic hydrogenolysis produced the first target compound **5** (77%, two steps).



Scheme 1.

The key glycosyl acceptor **11** was also reacted with the thioglucuronosyl donor **15**[7] in the presence of DMTST in dichloromethane (Scheme 4). The yield of tetrasaccharide **16** (30%) was disappointing when compared with previous model experiments,[7] but 46% of the acceptor could be recovered from the reaction. The moderate yield is also offset by the short route from the monomers to the tetrasaccharide **16**. Deprotection of **16** by catalytic hydrogenolysis, followed by debenzoylation, saponification, and final isolation of the tetrasaccharide as the ammonium salt, produced the second target compound **6** (68%, three steps).

Experimental

General methods

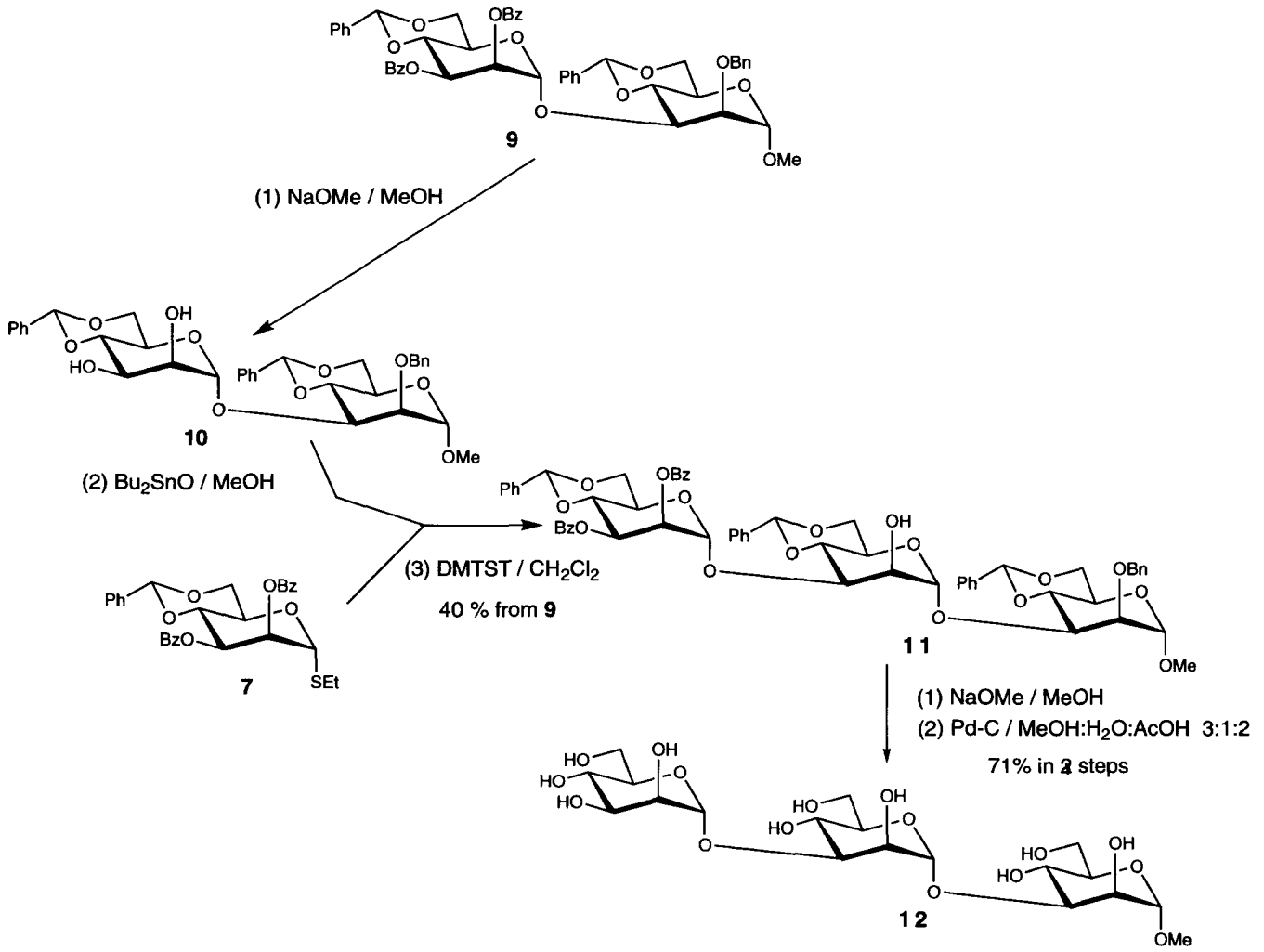
Melting points are corrected. Concentrations were performed under reduced pressure at <40 °C (bath). NMR spectra were recorded in $CDCl_3$ (internal Me_4Si, δ = 0.00) or D_2O (internal acetone δ = 31.0 ^{13}C, δ = 2.21 ^1H) at 25 °C unless otherwise stated, using a JEOL GX-270 instrument at 67.5 MHz (^{13}C) or 270 MHz (^1H). Optical rotations were recorded at room temperature with a Perkin–Elmer 241 polarimeter. TLC was performed on silica gel 60 F_{254} (Merck) with detection by UV light and/or by charring with 8% aq sulfuric acid. Silica gel (0.040–0.063 mm, Si 60A, Amicon) was used for column chromatography. Organic solutions were dried over $MgSO_4$ before concentration.

Methyl *O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→3)-2-*O*-benzyl-4, 6-*O*-benzylidene-α-D-mannopyranoside (9). Dimethyl(methylthio)sulfonium triflate (DMTST, 408 mg, 1.61 mmol) was added to a stirred mixture of **7** (315 mg, 0.60 mmol), **8** (150 mg, 0.40 mmol) and 4 Å molecular sieves (0.5 g) in dichloromethane (5 mL) at room temperature. Triethylamine (1 mL) was added after 2 h and stirring was continued for another 15 min. The mixture was then directly transferred to the top of a silica-gel column and eluted (flash chromatography, toluene:ethyl acetate 14:1) to give **9** (87%, 288 mg, 0.35 mmol), which crystallized from ethyl acetate–hexane, mp 155–157 °C, $[\alpha]_D$ −59° (*c* 1.0, $CHCl_3$). ^{13}C NMR data: δ 54.9 (CH_3—O), 63.9, 64.5, 68.7, 68.8 (2C), 70.7, 73.4, 73.7, 76.8, 77.0, 79.3 (C-2–6, O—CH_2—Ar), 99.5, 100.2, 101.1, 101.8 (C-1, O_2—CH—Ar), 125.8–129.8, 133.0, 133.4, 137.2, 137.2, 137.6 (aromatic C), 165.0, 165.4 (C=O benzoyl). Anal.: calcd for $C_{48}H_{46}O_{13}$: C, 69.39; H, 5.58.; found: C, 69.42 ; H, 5.72%.

Methyl*O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→3)-*O*-(4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (11). Methanolic sodium methoxide

(0.2 mL, 1 M) was added to compound **9** (542 mg, 0.65 mmol) in dichloromethane:methanol (1:1, 30 mL) and the mixture was stirred overnight. Dowex 50 (H^+) resin was added to neutralize the mixture which then was filtered, concentrated, and dried in vacuo. The debenzoylated residue **10** and dibutyltin oxide (163 mg, 0.65 mmol) in methanol (25 mL) were refluxed; 30 min after the reaction mixture became clear the solution was concentrated, and then dried in vacuo. The residue was glycosylated with **7** (375 mg, 0.72 mmol) promoted by DMTST (496 mg, 1.97 mmol) during 2.5 h as described for compound **9**. Flash chromatography (toluene:ethyl acetate 10:1) gave 282 mg of **11** (0.26 mmol, 40%) along with 98 mg (24%, 0.16 mmol) of the acceptor **10**. Compound **11** had $[\alpha]_D$ −42° (*c* 0.7, $CHCl_3$). ^{13}C NMR data: δ 54.9 (CH_3—O), 63.9, 64.0, 64.5, 68.7 (2C), 70.5, 71.0, 72.7, 73.0, 73.5, 76.7, 79.0, 79.1 (C-2–6, O—$\underline{C}H_2$—Ar), 99.2, 100.0, 101.1, 101.2, 101.5, 101.8 (C-1, O_2—$\underline{C}H$—Ar), 125.8–129.8, 133.1, 133.5, 136.9, 137.2, 137.3, 137.5 (aromatic C), 165.1, 165.5 (C=O benzoyl). Anal.: calcd for $C_{61}H_{60}O_{18}$: C, 67.76; H, 5.59; found: C, 67.50; H, 5.57%. Compound **10**, methyl *O*-(4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→3)-2-*O*-benzyl-4, 6-*O*-benzylidene-α-D-mannopyranoside, had ^{13}C NMR data: δ 54.7 (CH_3—O), 63.7, 68.2, 68.5, 70.5, 73.3, 73.6, 77.6, 78.7 (C-2–6, O—$\underline{C}H_2$—Ar), 99.6, 101.3, 101.5, 101.9 (C-1, O_2—$\underline{C}H$—Ar), 125.8–129.0, 137.1, 137.2, 137.5 (aromatic C).

Methyl *O*-α-D-mannopyranosyl-(1→3)-*O*-α-D-mannopyranosyl-(1→3)-α-D-mannopyranoside (12). Methanolic sodium methoxide (0.2 mL, 1M) was added to a solution of **11** (213 mg, 0.20 mmol) in methanol:dichloromethane (3:2, 10 mL). The solution was stirred overnight and then neutralized with Dowex 50 (H^+), filtered, concentrated, and dried in vacuo to give the debenzoylated intermediate, which had ^{13}C NMR data: δ 54.8 (CH_3—O), 63.8, 63.9, 68.2, 68.6, 68.7, 70.8, 70.9, 72.4, 72.9, 73.3, 77.5, 78.7, 78.8, 79.1 (C-2–6, O—$\underline{C}H_2$—Ar), 99.8, 101.1, 101.2, 101.4, 101.6, 102.1 (C-1, O_2—$\underline{C}H$—Ar), 126.0–129.5, 137.1, 137.3, 137.5 (aromatic C). This compound, in methanol:water:acetic acid (3:1:2, 13 mL), was hydrogenolysed over Pd/C (10%, 25 mg) in a Parr apparatus (120 psi) overnight, whereafter the mixture was filtered through Celite, concentrated, redissolved in water, washed with diethyl ether, and freeze-dried. After gel filtration on a



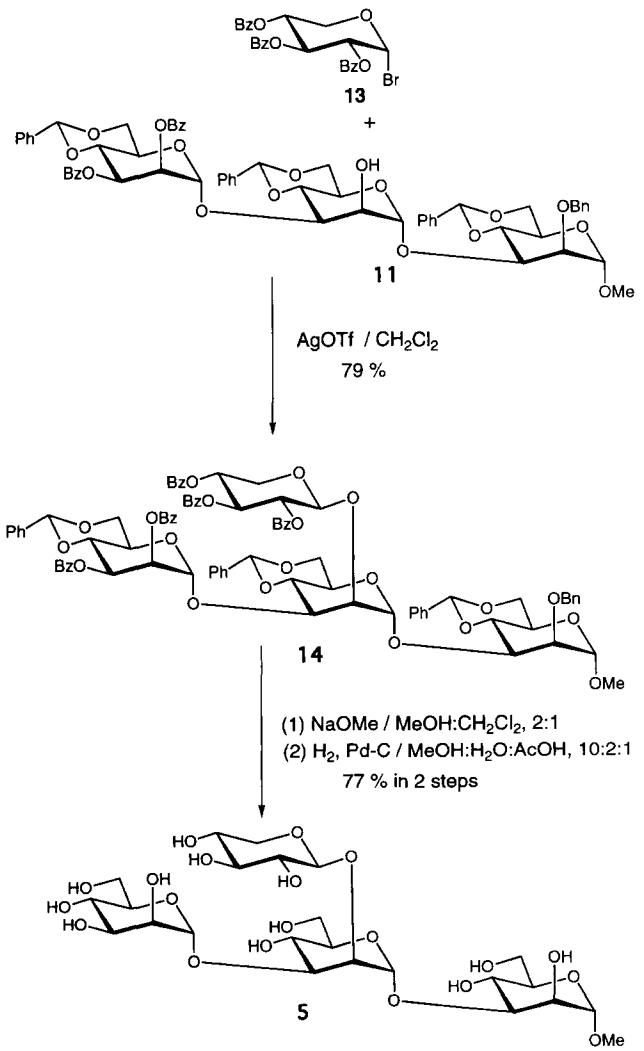
Scheme 2.

Bio-Gel P2-column eluted with water:*n*-butanol (99:1) compound **12** was obtained (71%, 73 mg, 0.14 mmol), $[\alpha]_D$ + 89° (*c* 0.9, water). NMR data (D_2O): ^{13}C: δ 55.8 (CH_3—O), 61.6 (2C), 61.9, 66.8 (2C) 67.6, 70.3, 70.4, 70.8, 71.1, 73.4, 74.1, 74.2, 78.8, 79.0 (C-2–6), 101.5 ($J_{C\text{-}1,H\text{-}1}$ = 172 Hz), 103.0 (two signals, $J_{C\text{-}1,H\text{-}1}$ = 172 Hz) (C-1); ^1H (70 °C): δ 4.73 (d, $J_{H\text{-}1,H\text{-}2}$ = 1.8 Hz, H-1), 5.09 (d, $J_{H\text{-}1,H\text{-}2}$ = 1.8 Hz, H-1), 5.13 (d, $J_{H\text{-}1,H\text{-}2}$ = 1.5 Hz, H-1). HRMS: calcd for $C_{19}H_{34}O_{16}$ (M-H): 517.1769; found: 517.1771.

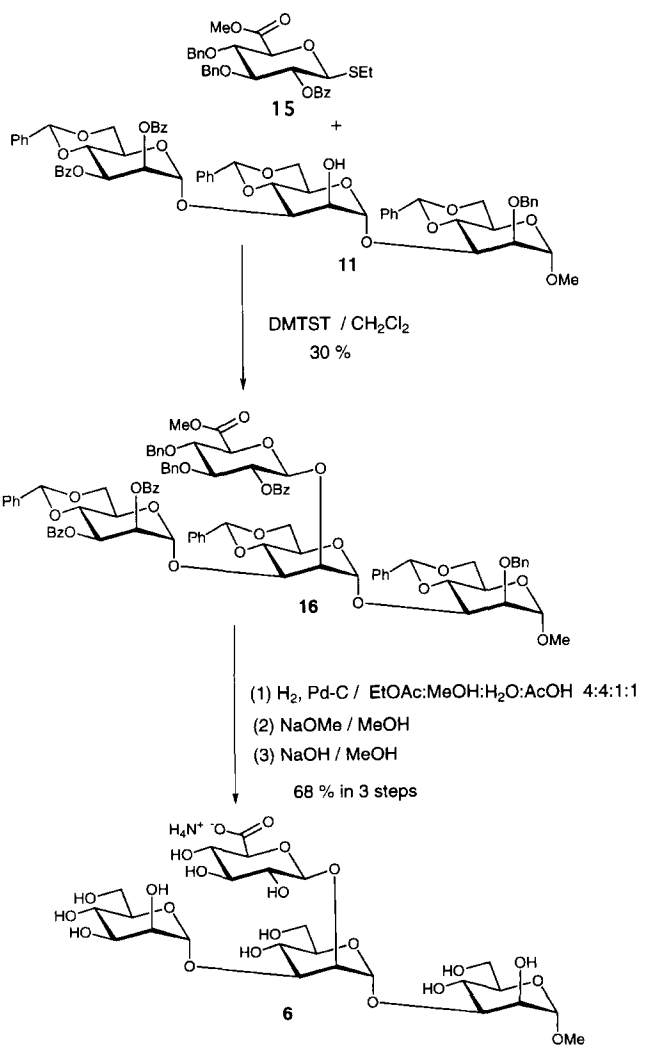
Methylation analysis of **12** showed the presence of 1,3,5-tri-*O*-acetyl-2,4,6-tri-*O*-methylhexitol and 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-methylhexitol in 2:1 ratio indicating one terminal mannopyranoside and two 3-*O*-substituted mannopyranosides, all in agreement with the postulated structure of **12**.

Methyl *O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→3)-[*O*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)-(1→2)]-*O*-(4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (14). A mixture of 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide[8] (**13**, 58 mg, 0.11 mmol), **11** (59 mg, 0.055 mmol), 2,6-di-*tert*-butylpyridine (12 μL, 0.055 mmol) and 4 Å molecular sieves in dichloromethane (5 mL) was cooled to −35 °C. Silver triflate (57 mg, 0.22 mmol) dissolved in toluene (1 mL) was added after 30 min. The mixture was stirred for 2 h, triethylamine (1 mL) was added, and the mixture was then allowed to attain room temperature before it was directly applied to flash chromatography (toluene:ethyl acetate 12:1) to give **14** (79%, 66 mg, 0.043 mmol). $[\alpha]_D$ −66° (*c* 1.1, $CHCl_3$). ^{13}C NMR data: δ 54.9 (CH_3—O), 59.9, 64.0, 64.5, 64.6, 68.1, 68.3 (2C), 68.5, 68.6, 68.8, 69.0, 71.0, 71.3, 73.4, 74.0, 74.9, 76.9, 77.4, 78.8, 79.1 (C-2–6, O—CH_2—Ar), 96.3, 98.8, 99.3, 100.1, 100.7, 101.8 (2C) (C-1, O_2—CH—Ar), 125.9–130.0, 132.9, 133.0, 133.2, 133.4, 133.5, 137.0, 137.3, 137.5 (aromatic C), 164.7, 165.1, 165.1, 165.3 (C=O benzoyl). Anal. calcd for $C_{87}H_{80}O_{25}$: C, 68.50; H, 5.28; found: C, 68.31; H, 5.31%.

Methyl *O*-α-D-mannopyranosyl-(1→3)-[*O*-β-D-xylopyranosyl-(1→2)]-*O*-α-D-mannopyranosyl-(1→3)-α-D-mannopyranoside (5). Methanolic sodium methoxide (0.2 mL, 1M) was added to a solution of **14** (105 mg, 0.069 mmol) in methanol:dichloromethane (2:1, 15 mL).



Scheme 3.



Scheme 4.

The mixture was stirred overnight and then neutralized with Dowex 50 (H^+) resin, filtered, concentrated, and dried in vacuo to give the debenzoylated intermediate. ^{13}C NMR data (CD_3OD): δ 55.5 (CH_3—O), 65.3, 65.4, 66.0, 66.8, 69.2, 69.5, 69.7, 70.9, 72.5, 73.9, 74.1, 74.5, 75.6, 77.4, 78.0, 79.1, 79.5, 80.2, 80.2 (C-2–6, O—CH_2—Ar), 100.9, 101.4, 102.9, 103.3 (2 C), 103.9, 104.4 (C-1, O_2—CH—Ar), 127.3–131.3, 139.0, 139.1, 139.3 (aromatic C). This compound in methanol: water:acetic acid (10:2:1, 13 mL) was hydrogenolysed over Pd/C (10%, 25 mg) in a Parr apparatus (60 psi) overnight, whereafter the mixture was filtered through Celite, concentrated, redissolved in water, washed with diethyl ether, and freeze-dried. After gel filtration on a Bio-Gel P2 column eluted with water:*n*-butanol (99:1) compound **5** was obtained (77%, 35 mg, 0.053 mmol); $[\alpha]_D$ + 56° (*c* 1.4, water). NMR data (D_2O): ^{13}C: δ 55.5 (CH_3—O), 61.0, 61.5, 62.0, 65.8, 66.9, 67.1, 67.5, 70.0, 70.3, 70.8, 71.1, 73.4, 74.1, 74.2, 76.3, 79.0, 79.1 (C-2–6), 101.2 ($J_{C\text{-}1,H\text{-}1}$ = 174 Hz), 101.5 ($J_{C\text{-}1,H\text{-}1}$ = 170 Hz), 103.1 ($J_{C\text{-}1,H\text{-}1}$ = 172 Hz), 104.1 ($J_{C\text{-}1,H\text{-}1}$ = 161 Hz) (C-1); ^1H (70 °C): δ 4.40 (d, $J_{H\text{-}1,H\text{-}2}$ = 7.3 Hz, H-1), 4.73 (d, $J_{H\text{-}1,H\text{-}2}$ = 1.6 Hz, H-1), 5.13 (d, $J_{H\text{-}1,H\text{-}2}$ = 1.5 Hz, H-1), 5,19 (d, $J_{H\text{-}1,H\text{-}2}$ = 1.5 Hz, H-1). HRMS: calcd for $C_{24}H_{42}O_{20}$ (M-H): 649.2191; found: 649.2142.

Methyl *O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→3)-[*O*-[methyl (2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1→2)]-*O*-(4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (16). Methyl (ethyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-1-thio-β-D-glucopyranosid)uronate **15** (306 mg, 0.57 mmol) and **11** (308 mg, 0.28 mmol) were coupled overnight, promoted by DMTST (433 mg, 1.709 mmol) as described for **9**. Flash chromatography twice (toluene:ethyl acetate 12:1, followed by hexane:ethyl acetate 3:1) gave **16** (30%, 135 mg, 0.087 mmol) and also unreacted **11** (46%, 142 mg, 0.13 mmol). Compound **16** had $[\alpha]_D$ −46° (*c* 1.0, $CHCl_3$). ^{13}C NMR data: δ 52.6, 54.9 (CH_3—O), 63.9, 64.0, 64.5, 68.4, 68.6, 68.9, 70.1, 71.0, 72.8, 72.9, 73.5, 74.5, 74.5, 74.7, 77.1, 77.5, 78.7, 79.6, 81.3 (C-2–6, O—CH_2—Ar), 98.5, 99.0, 100.2 (2C), 100.9, 101.8, 102.5 (C-1, O_2—CH—Ar), 125.9–130.3, 132.7, 133.2, 133.4, 137.2, 137.4, 137.5, 137.9, 138.0, 138.4 (aromatic C), 164.5, 164.6, 164.9 (C=O benzoyl), 167.9 (C=O uronate). Anal. calcd for $C_{89}H_{86}O_{25}$: C, 68.72; H, 5.57; found: C, 68.36; H, 5.66%.

Methyl *O*-α-D-mannopyranosyl-(1→3)-[*O*-(ammonium β-D-glucopyranosyluronate)-(1→2)]-*O*-α-D-mannopyranosyl-(1→3)-α-D-mannopyranoside (6). Compound **16** (135 mg, 0.087 mmol) in ethyl acetate:methanol: water (4:4:1, 20 mL) was hydrogenolysed over Pd/C (25 mg, 10%) in a Parr apparatus at 120 psi. Acetic acid (2 mL) was added after 5 h and the hydrogenolysis was continued for 15 h. The mixture was filtered through Celite, evaporated, and dried in vacuo to give an intermediate, which had ^{13}C NMR data (CD_3OD): δ 53.2, 55.2 (CH_3—O), 62.7, 63.1, 66.7, 67.2, 67.4, 71.0, 71.3, 71.8, 73.3, 74.5, 75.2, 75.4, 77,2, 79.2, 79.9, 80.5, 80.9 (C-2–6), 100.5, 101.7, 102.5, 102.6 (C-1), 129.3–131.5, 134.3, 134.7 (aromatic C), 166.8, 167.4, 167.6 (C=O benzoyl), 170.9 (C=O uronate). Methanolic sodium methoxide (0.2 mL, 1 M) was added to this compound in methanol (10 mL). After 2 h, water (1 mL) was added to cleave the methyl ester. The mixture was stirred for 3 h and then neutralized with 0.1 M HCl after which the solvent was evaporated. The residue was dissolved in water, washed with diethyl ether and freeze-dried. The residue was gel filtered (Bio-Gel P2, eluent: 0.07 M pyridinium acetate buffer at pH 5.4) and then purified by reversed-phase HPLC (semipreparative column, Dynamax 60-A C_{18}, eluted with 25 mM ammonium acetate buffer containing 2% acetonitrile). The product **6** was collected (68%, 42 mg, 0.59 mmol). $[\alpha]_D$ + 31° (*c* 1.0, water). NMR data (D_2O): ^{13}C: δ 55.5 (CH_3—O), 60.8, 61.5, 61.8, 66.8, 66.9, 68.2, 70.3, 70.9, 71.2, 72.5, 73.2, 73.4, 73.9, 74.2, 76.0, 76.8, 78.1, 78.2, 79.2 (C-2–6), 100.9 ($J_{C\text{-}1,H\text{-}1}$ = 170 Hz), 101.4 ($J_{C\text{-}1,H\text{-}1}$ = 170 Hz), 102.6 ($J_{C\text{-}1,H\text{-}1}$ = 161 Hz), 103.5 ($J_{C\text{-}1,H\text{-}1}$ = 167 Hz) (C-1), 176.6 (C=O uronate); ^1H (70 °C): δ 4.46 (d, $J_{H\text{-}1,H\text{-}2}$ 7.9 Hz, H-1), 4.73 (d, $J_{H\text{-}1,H\text{-}2}$ = 1.8 Hz, H-1), 5.13 (d, $J_{H\text{-}1,H\text{-}2}$ = 1.5 Hz, H-1), 5.20 (d, $J_{H\text{-}1,H\text{-}2}$ = 1.8 Hz, H-1). HRMS: calcd for $C_{25}H_{42}O_{22}$ (M-NH_4): 693.2090; found: 693.2076.

Acknowledgements

This work is a collaboration with Dr Robert Cherniak, Georgia State University, U.S.A. We thank the Swedish Natural Science Research Council for financial support.

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(*Received in U.S.A.* 26 *January* 1996; *accepted* 16 *May* 1996)