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Note

Synthesis of methyl 3-*O*-α-D-galactopyranosyl-6-*O*-α-D-mannopyranosyl-α-D-mannopyranoside, methyl 3-*O*-α-D-glucopyranosyl-6-*O*-α-D-mannopyranosyl-α-D-mannopyranoside, methyl 6-*O*-α-D-galactopyranosyl-3-*O*-α-D-mannopyranosyl-α-D-mannopyranoside, and methyl 6-*O*-α-D-glucopyranosyl-3-*O*-α-D-mannopyranosyl-α-D-mannopyranoside

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The title trisaccharide glycosides were needed for studies of the interactions of lectins, receptor sites for bacteriophages with *Salmonella* lipopolysaccharide core-specificity, and correlation of n.m.r. chemical shifts and structure.

The methods used in the syntheses were conventional. Thus, 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide[1] was reacted with methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[2] in dichloromethane in the presence of silver triflate[3,4] to yield the (1→6)-linked disaccharide derivative, catalytic hydrogenolysis of which gave 89% of **1**. Treatment of **1**, first with trimethyl orthoacetate, then with acetic anhydride followed by acidic opening of the cyclic 2,3-orthoester[5], afforded 94% of methyl 2,4-di-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**2**). Glycosylation of the HO-3 of **2** with 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl bromide[6] under halide-assisted conditions[7] afforded 83% of the trisaccharide derivative **3**, whereas the corresponding reaction of **2** with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl bromide[7] afforded 79% of **4**. Deprotection of **3** and **4** then gave the first two of the title trisaccharides, **5** and **6**.

Similarly, methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[8,9] was glycosylated with tetra-*O*-benzoyl-α-D-mannopyranosyl bromide[1] in dichloromethane in the presence of silver triflate to yield 82% of the (1→3)-linked disaccharide derivative **7**. Removal of the 4,6-*O*-benzylidene group of **7** by acid hydrolysis afforded 92% of **8**. Selective glycosylation of HO-6 in **8** with 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl bromide[6] under halide-assisted conditions[7] gave 70% of the trisaccharide derivative **9** and glycosylation with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide[7] gave 78% of **10**. The "open" strategy was preferred to more circuitous routes involving, for example, regioselective reductive opening of the 4,6-*O*-benzylidene acetal ring of **8**, to

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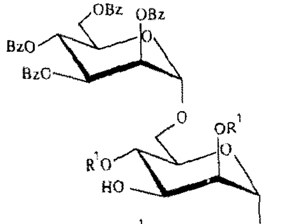
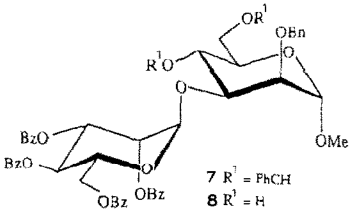
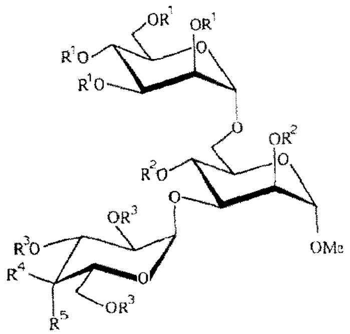


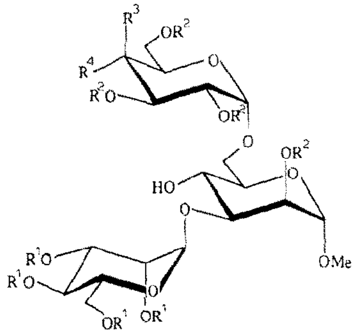
1 R^1 = H
2 R^1 = Ac



7 R^1 = PhCH
8 R^1 = H



3 R^1 = Bz, R^2 = Ac, R^3 = Bn, R^4 = H, R^5 = OBn
4 R^1 = Bz, R^2 = Ac, R^3 = Bn, R^4 = OBn, R^5 = H
5 R^1 = R^2 = R^3 = R^4 = H, R^5 = OH
6 R^1 = R^2 = R^3 = R^5 = H, R^4 = OH



9 R^1 = Bz, R^2 = Bn, R^3 = OBn, R^4 = H
10 R^1 = Bz, R^2 = Bn, R^3 = H, R^4 = OBn
11 R^1 = R^2 = R^4 = H, R^3 = OH
12 R^1 = R^2 = R^3 = H, R^4 = OH

EXPERIMENTAL

General methods. – These were the same as described[12,13]. ^{13}C-N.m.r. spectra for solutions in D_2O were obtained at 70° and referenced relative to internal acetone (δ 31.00).

Methyl 6-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**1**). — A solution of silver triflate (0.62 g) in toluene (4 mL) was added dropwise at 0° to a stirred mixture of methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[2] (0.74 g) and 2,3,4,6-tetra-*O*-benzoyl-D-mannopyranosyl bromide[1] (1.5 g) in dichloromethane containing molecular sieves. The mixture was allowed to attain room temperature, then filtered through Celite, diluted with toluene, and washed with saturated aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated. A solution of the residue in ethyl acetate (20 mL) was hydrogenolyzed in a Parr apparatus over 10% Pd–C (0.1g). After 2 days at 400 kPa pressure, the mixture was filtered and concentrated. Column chromatography (silica gel, 1:1 toluene–ethyl acetate) of the residue gave **1** (1.1 g, 89%), $[\alpha]_D$ −15° (*c* 1, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 55.0 (OMe), 62.8, 66.8, 67.6, 68.8, 70.4, 70.6, 70.9, 71.4, 72.2 (C-2,3,4,5,6, C-2′,3′,4′,5′,6′, one overlap), 97.6, 101.1 (C-1,1′), 128.3–133.4 (aromatic carbons), 165.5, 166.0, and 166.3 (carbonyl C).

Anal. Calc. for $C_{41}H_{40}O_{15}$: C, 63.7; H, 5.2. Found: C, 63.3; H, 5.5.

Methyl 2,4-di-O-acetyl-6-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**2**). — Trimethyl orthoacetate (1 mL) and *p*-toluenesulfonic acid (100 μL of a 5% solution in acetonitrile) were added to a solution of **1** (1.1 g) in acetonitrile (50 mL). After 5 min, pyridine (3 mL), acetic anhydride (3 mL), and a catalytic amount of 4-dimethylaminopyridine were added. When t.l.c. (toluene–ethyl acetate, 2:1) showed acetylation to be complete, the mixture was concentrated and co-concentrated twice with toluene. The residue was dissolved in acetonitrile (50 mL), aqueous 90% trifluoroacetic acid (100 μL) was added, and, after 15 min, the mixture was concentrated. Column chromatography (2:1 toluene–ethyl acetate) of the residue gave **2** (1.15 g, 94%), $[\alpha]_D$ −22° (*c* 1.3, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 20.9, 21.0 (CH_3CO), 55.3 (OMe), 62.8, 66.6, 66.8, 68.6, 69.0, 69.1, 69.6, 70.0, 70.4, 72.4 (C-2,3,4,5,6, C-2′,3′,4′,5′,6′), 97.6, 98.6 (C-1,1′), 125.8–133.5 (aromatic C), 165.3, 165.4, 165.5, 166.2, 170.8, and 171.1 (carbonyl C).

Anal. Calc. for $C_{45}H_{44}O_{17}$: C, 63.1; H, 5.2. Found: C, 62.9; H, 5.0.

Methyl 2,4-di-O-acetyl-3-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-6-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**3**) *and methyl 2,4-di-O-acetyl-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-6-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside* (**4**). — A solution of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl bromide[6] (1 g) in dichloroethane (1.5 mL) was added to a mixture of **2** (0.36 g) and tetraethylammonium bromide (0.12 g) in dichloroethane (2 mL) containing *N*,*N*-dimethylformamide (0.5 mL) and molecular sieves. The mixture was stirred for 24 h at 35°, then filtered through Celite onto the top of a column of silica gel, and eluted with 16:1 toluene–ethyl acetate to give **3** (0.48 g, 83%), $[\alpha]_D$ +4° (*c* 1, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 20.7, 20.9 (CH_3CO), 55.3 (OMe), 62.8 (C-6″), 66.8, 67.2, 68.5, 68.9, 69.4, 70.1, 70.4, 71.5, 72.9, 73.4, 73.6, 74.8, 74.9, 76.2, 76.6, 78.8 (C-2,3,4,5,6, C-2′,3′,4′,5′,6′, C-2″,3″,4″,5″, and 4 $PhCH_2$, overlap), 97.5, 98.1, 100.2 (C-1,1′,1″), 127.5–138.9 (aromatic C), 165.3, 165.5, 166.2, 170.0, 170.7 (carbonyl C).

Anal. Calc. for $C_{79}H_{78}O_{22}$: C, 68.8; H, 5.7. Found: C, 68.8; H, 5.7.

Compound **4** (0.46 g, 79%), prepared as described above for **3** except that the glucosyl bromide[7] was used and the reaction was worked-up after 48 h, had m.p. 78–79° [from toluene–light petroleum (b.p. 40–60°)], $[\alpha]_D$ +6° (*c* 1, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 20.7, 21.1 (CH_3CO), 55.4 (OMe), 62.8 (C-6″), 66.8, 66.9, 67.0, 68.2, 68.9, 69.5, 70.1, 70.4, 71.5, 71.7, 73.4, 73.5, 74.9, 75.6, 77.3, 77.5, 80.1, 81.5 (C-2,3,4,5,6, C-2′,3′,4′,5′,6′, C-2″,3″,4″,5″, and 4 $PhCH_2$), 97.4, 98.0, 100.0 (C-1,1′,1″), 127.5–138.8 (aromatic C), 165.3, 166.1, 169.9, 170.6 (carbonyl C).

Anal. Calc. for $C_{79}H_{78}O_{22}$: C, 68.8; H, 5.7. Found: C, 68.6; H, 5.7.

Methyl 3-O-α-D-galactopyranosyl-6-O-α-D-mannopyranosyl-α-D-mannopyranoside (**5**) *and methyl 3-O-α-D-glucopyranosyl-6-O-α-D-mannopyranosyl-α-D-mannopyranoside* (**6**). — A catalytic amount of methanolic sodium methoxide was added to a solution of **3** (135 mg) in methanol (5 mL). The mixture was stirred for 48 h at room temperature, then neutralised with Dowex (H^+) resin, and filtered. 10% Pd–C (40 mg) was added to the filtrate, and the mixture was hydrogenolyzed in a Parr apparatus (400 kPa) overnight, then filtered, and concentrated. A solution of the residue in water was washed with dichloromethane and ethyl acetate, then concentrated, and the residue was purified on a column of Bio-Gel P-2 and freeze-dried to give **5** (47 mg, 93%), $[\alpha]_D$ +118° (*c* 1.1, water). ^{13}C-N.m.r. data (D_2O): δ 55.0 (OMe), 61.2, 61.3 (C-6′,6″), 65.8, 66.0, 67.0, 68.9, 69.5, 69.6, 69.8, 70.2, 70.9, 71.1, 71.5, 72.9, 79.4 (C-2,3,4,5,6, C-2′,3′,4′,5′, C-2″,3″,4″,5″), 99.7 ($J_{C-1,H-1}$ 170 Hz), 100.9 ($J_{C-1,H-1}$ 171 Hz), and 101.1 ($J_{C-1,H-1}$ 171 Hz) (C-1,1′,1″).

Anal. Calc. for $C_{19}H_{34}O_{16}\cdot H_2O$: C, 42.5; H, 6.8. Found: C, 42.7; H, 6.5.

Compound **4** (160 mg) was deprotected, as described above for **3**, to give **6** (55 mg, 92%), $[\alpha]_D$ 111° (*c* 1.2, water). ^{13}C-N.m.r. data (D_2O): δ 55.2 (OMe), 61.1, 61.4 (C-6′,6″), 66.0, 66.2, 66.2, 67.3, 70.1, 70.5, 71.1, 71.4, 72.2, 72.8, 73.1, 73.4, 79.5 (C-2,3,4,5,6, C-2′,3′,4′,5′, C-2″,3″,4″,5″), 100.0 ($J_{C-1,H-1}$ 171 Hz), 100.9 ($J_{C-1,H-1}$ 171 Hz), and 101.3 ($J_{C-1,H-1}$ 171 Hz) (C-1,1′,1″).

Anal. Calc. for $C_{19}H_{34}O_{16}\cdot H_2O$: C, 42.5; H, 6.8. Found: C, 42.1; H, 6.5.

Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**7**). — Silver triflate (0.66 g) in toluene (4 mL) was added dropwise at 0° to a stirred mixture of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[8,9] (0.48 g) and 2,3,4,6-tetra-*O*-benzoyl-D-mannopyranosyl bromide[1] (1.7 g) in dichloromethane (10 mL) containing molecular sieves. The mixture was allowed to attain room temperature, and, after 1 h thereat, the mixture was filtered through Celite onto the top of a column of silica gel which was eluted with 19:1 toluene–ethyl acetate to give **7** (1.01 g, 82%), m.p. 203–205° (from ethanol–ethyl acetate), $[\alpha]_D$ −23° (*c* 1.3, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 54.9 (OMe), 63.0, 64.0, 67.2, 68.6, 69.3, 69.8, 70.3, 73.2, 74.1, 77.1, 78.8 (C-2,3,4,5,6, C-2′,3′,4′,5′,6′, and PhCH_2), 98.8, 99.8, 101.1 (C-1,1′, and Ph-*C*H), 125.9–137.8 (aromatic C), 165.0, 165.4, and 166.1 (carbonyl C).

Anal. Calc. for $C_{55}H_{49}O_{15}$: C, 69.5; H, 5.2. Found: 69.6; H, 5.2.

Methyl

mannopyranoside (**8**). — A solution of **7** (0.6 g) in aq. 70% acetic acid (15 mL) was stirred at 70° until t.l.c. (toluene–ethyl acetate, 3:1) showed complete reaction (3–4 h). The mixture was then concentrated and co-concentrated twice with toluene. Column chromatography (3:1 toluene–ethyl acetate) of the residue gave **8** (0.5 g, 92%), $[\alpha]_D$ −19° (*c* 1, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 54.9 (OMe), 62.5, 63.0, 66.9, 67.3, 69.3, 70.1, 70.4, 72.3, 72.5, 77.4, 79.7 (C-2,3,4,5,6, C-2′,3′,4′,5′,6′, and PhCH_2), 98.4, 99.5 (C-1,1′), 125.3–137.9 (aromatic C), 165.4, 165.7, and 166.2 (carbonyl C).

Anal. Calc. for $C_{48}H_{45}O_{15}$: C, 66.9; H, 5.3. Found: C, 66.5; H, 5.3.

Methyl 2-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-3-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**9**) *and methyl 2-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-3-O-*(2,3,4,6-tetra-*O-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranoside* (**10**). — A solution of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl bromide[6] (0.6 g) in dichloromethane (2 mL) was added at 0° to a mixture of **8** (0.36 g) and tetraethylammonium bromide (0.12 g) in dichloromethane (3 mL) containing *N*,*N*-dimethylformamide (0.5 mL) and molecular sieves (4 Å). The mixture was allowed to attain room temperature, stirred overnight, then filtered through Celite onto the top of a column of silica gel which was eluted with 14:1 toluene–ethyl acetate to give **9** (0.41 g, 70%), $[a]_D$ +10° (*c* 0.7, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 54.9 (OMe), 63.2 (C-6′), 67.2, 69.2, 69.6, 69.9, 70.1, 70.2, 70.4, 70.5, 72.5, 73.1, 73.5, 73.6, 74.6, 74.9, 76.2, 76.9, 77.7, 79.0 (C-2,3,4,5,6, C-2′,3′,4′,5′, C-2″,3″,4″,5″,6″, and 5 Ph*C*H_2, one overlap), 98.5 (2 C), 99.4 (C-1,1′,1″), 127.5–138.7 (aromatic C), 165.2, and 165.5 (carbonyl C). A satisfactory elemental analysis was not obtained for this compound, but its purity was established by t.l.c. (toluene–ethyl acetate, 9:1) and by ^{13}C-n.m.r. spectroscopy.

Compound **10** (0.53 g, 78%) [prepared from **8** (0.40 g), as described above for **9**, except that no ice-bath was used, and the glucosyl bromide[7] was used] was obtained after purification on a column of silica gel (chloroform–acetone, 50:1); $[a]_D$ +21° (*c* 0.8, chloroform). ^{13}C-N.m.r. data: δ 54.9 (OMe), 63.1 (C-6′), 67.1, 68.4, 69.2, 69.6, 70.0, 70.3, 70.4, 70.5, 72.5, 73.3, 73.4, 74.9, 75.6, 76.8, 77.4, 78.0, 79.6, 81.9 (C-2,3,4,5,6, C-2′,3′,4′,5′, C-2″,3″,4″,5″,6″, and 5 Ph*C*H_2, one overlap), 97.9, 98.5, 99.3 (C-1,1′,1″), 127.5–138.7 (aromatic C), 165.1, 165.4, and 166.1 (carbonyl C).

Anal. Calc. for $C_{82}H_{79}O_{20}$: C, 71.1; H, 5.85. Found: C, 71.5; H, 6.0.

*Mehyl 6-*O*-a-*D*-galactopyranosyl-3-*O*-a-*D*-mannopyranosyl-a-*D*-mannopyranoside* (**11**) *and methyl 6-*O*-a-*D*-glucopyranosyl-3-*O*-a-*D*-mannopyranosyl-a-*D*-mannopyranoside* (**12**). — Compound **9** (120 mg) was deprotected, as described above for **3** (except that 24 h was allowed for the deacylation), to give **11** (40 mg, 89%), $[a]_D$ +184° (*c* 0.9, water). ^{13}C-N.m.r. data (D_2O): δ 55.8 (OMe), 62.0 (2 C) (C-6′,6″), 66.7 (2 C), 67.8, 69.4, 70.2, 70.4, 70.5, 71.0, 71.4, 71.8, 72.1, 74.2, 79.4 (C-2,3,4,5,6, C-2′,3′,4′,5′, C-2″,3″,4″,5″), 99.0 ($J_{C-1,H-1}$ 171 Hz), 101.9 ($J_{C-1,H-1}$ 170 Hz), and 103.1 ($J_{C-1,H-1}$ 171 Hz) (C-1,1′,1″).

Anal. Calc. for $C_{19}H_{34}O_{16}\cdot 1.5H_2O$: C, 41.7; H, 6.9. Found: C, 41.6; H, 6.5.

Compound **10** (255 mg) was deprotected, as described above for **9**, to give **12** (85 mg, 89%), $[a]_D$ +122° (*c* 1.2, water). ^{13}C-N.m.r. data (D_2O): δ 55.1 (OMe), 61.0, 61.2 (C-6′,6″), 65.9, 66.0, 67.1, 69.7, 70.0, 70.3, 70.7, 71.3, 71.7, 72.0, 73.4, 73.5, 78.7 (C-2,3,4,5,6, C-2′,3′,4′,5′, C-2″,3″,4″,5″), 98.1 ($J_{C-1,H-1}$ 170 Hz), 101.2 ($J_{C-1,H-1}$ 171 Hz), and 102.4 ($J_{C-1,H-1}$ 171 Hz) (C-1,1′,1″).

Anal. Calc. for $C_{19}H_{34}O_{16}\cdot 0.5H_2O$: C, 43.2; H, 6.7. Found: C, 43.4; H, 6.7.

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