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Note

Syntheses of the octyl and tetradecyl glycosides of 3,6-di-*O*-α-D-mannopyranosyl-α-D-mannopyranose and of 3,4-di-*O*-α-D-mannopyranosyl-α-D-mannopyranose. A new way for 2,4-di-*O*-protection of mannopyranosides

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3,6-Di-*O*-α-D-mannopyranosyl-α-D-mannopyranose has been shown to be a very good inhibitor of the binding of phage G13 to its native receptor in the core region of lipopolysaccharides from *Salmonella* bacteria[1]. To study further this binding of the phage, especially when the carbohydrate structure is part of a membrane or membrane-like structures as the lipopolysaccharide is in the bacteria outer membrane, fatty chain glycosides of the trisaccharide were required. The octyl and tetradecyl glycosides were chosen as model substances.

The trisaccharide unit, being a part of both the complex type and the high mannose type of *N*-linked glycoproteins, is of great biological importance and has been synthesised a number of times. To achieve the appropiate protection pattern in the glycosyl acceptor, i.e., 2,4-di-*O*-protection, several approaches have been used. The most frequently used is tin activation followed by allylation to give the 3,6-di-*O*-allyl compound, which is benzylated and deallylated to give the required 2,4-di-*O*-benzyl derivative[2,3]. Other methods used are glycosylation of the unprotected mannoside followed by periodate degradation of unwanted trisaccharides[4] and the procedure described by El Ashry and Schuerch[5]. Our approach was to use ortho esters, which are opened regioselectively to give the required protection pattern. The 2,3 : 4,6-di-*O*-ethoxybenzylidene derivatives of the octyl and tetradecyl α-D-mannopyranosides (**2** and **4**, prepared via silver triflate-promoted[6,7] couplings between 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide[8] and 1-octanol or 1-tetradecanol to give **1** and **3**, respectively, followed by Zemplén deacylation) were prepared in almost quantitative yield (according to TLC) using triethyl orthoben-

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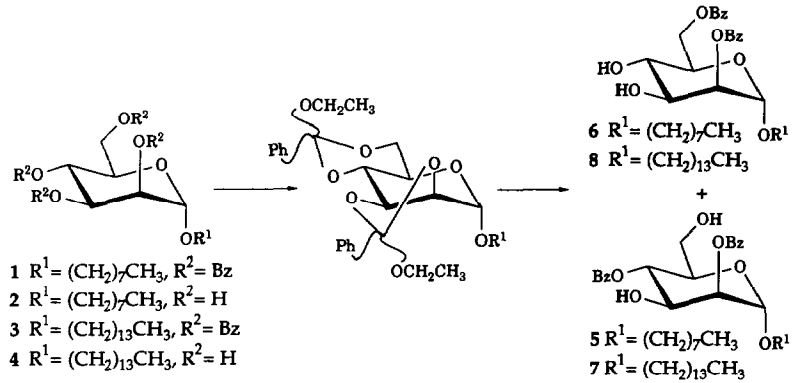
zoate and toluene-*p*-sulfonic acid–trifluoroacetic acid in acetonitrile. If the published conditions[9,10] (triethyl orthobenzoate, *p*TsOH, solvent) were used for the formation of the ortho esters, only small amounts of products were obtained, but the addition of trifluoroacetic acid as catalyst followed by evaporation forced the reaction to go to completion. These ortho esters were not isolated, but directly dissolved in acetonitrile and opened by treatment with aqueous trifluoroacetic acid. According to the literature, the 2,3-(ortho ester) should open up regiospecifically to the 2-*O*-acyl derivative[9], whereas the 4,6-(ortho ester) should give a mixture of the 4-*O*- and 6-*O*-acyl derivatives, the relative amount being difficult to predict[10]. This expectation was fulfilled; the opening of the di(ortho ester) compounds gave a mixture of the 2,4- and the 2,6-di-*O*-benzoyl derivatives, the former rather surprisingly with the higher R_f in TLC, together with some 2-*O*-benzoyl derivatives and non-benzoylated material. The substitution patterns were easily determined by 2D ^{1}H NMR because of the downfield shift of the ring protons due to benzoylation. This approach gave the wanted acceptors **5** and **7** in ca. 45% yield in a one-pot reaction after 1 h. It also gave the 2,6-protected derivatives **6** (32%) and **8** (39%); these can either be recycled after deacylation or used to synthesise the 3,4-trisaccharides, which can be used as standards in biological experiments. As found earlier[10], complete hydrolysis of the 4,6-(ortho ester) competed more with the opening to the 6-benzoate than with the corresponding opening to the 4-benzoate. Thus, in the opening of the ortho esters, the yields of the 2,4-di-*O*-benzoyl derivatives were always ca. 45%, whereas the yields of the 2,6-di-*O*-benzoyl derivatives were diminished by ca. 10% (and the yield of the 2-*O*-benzoyl derivative was raised by the same amount) if optimised conditions were not used.

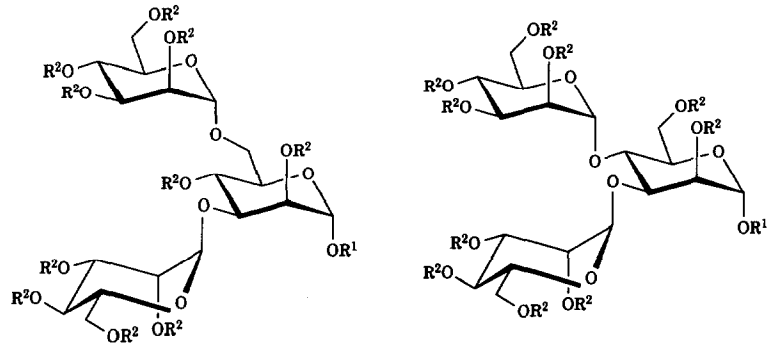
Silver triflate-promoted[6,7] couplings between 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide and octyl 2,4-di-*O*-benzoyl-α-D-mannopyranoside (**5**), octyl 2,6-di-*O*-benzoyl-α-D-mannopyranoside (**6**), tetradecyl 2,4-di-*O*-benzoyl-α-D-mannopyranoside (**7**), and tetradecyl 2,6-di-*O*-benzoyl-α-D-mannopyranoside (**8**) gave the wanted trisaccharides **9** (86%), **10** (98%), **11** (100%), and **12** (86%), respectively. Deprotection via Zemplén deacylation then gave the four title trisaccharides **13** (89%), **14** (78%), **15** (88%), and **16** (75%).

EXPERIMENTAL

General methods.—These were the same as those reported earlier[11].

Octyl α-D-mannopyranoside (**2**).—Silver triflate (2.6 g, 10 mmol) in toluene (10 mL) was added dropwise at 0°C to a stirred solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide[8] (4.8 g, 7.3 mmol) and 1-octanol (2.5 mL, 16 mmol) in CH_2Cl_2 (25 mL) containing 4A molecular sieves. The mixture was allowed to attain room temperature and then filtered through Celite onto the top of a silica gel column which was eluted with toluene to give octyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (**1**; 4.5 g, 87%); ^{13}C NMR data ($CDCl_3$): δ 14.1, 22.7, 26.1, 29.3, 29.4, 31.8, 63.0, 67.1, 68.8, 70.2, 70.7, 97.6, 128.3–133.4, 165.5 and 166.2.





Scheme 1.

A catalytic amount of NaOMe was added to a solution of **1** (2.6 g) in MeOH (30 mL) and the mixture was left overnight. Dowex (H^+) ion-exchange resin was added, and the mixture filtered and concentrated. Purification of the residue on a silica gel column (6:1 $CHCl_3$–MeOH) gave **2** (0.93 g, 87%); $[\alpha]_D$ +56° (*c* 0.85, H_2O); ^{13}C NMR data (D_2O): δ 13.4, 22.2, 25.8, 28.8, 29.1, 31.5, 60.7, 66.4, 67.4, 70.4, 71.0, 72.6, and 100.0. Anal. Calcd for $C_{14}H_{28}O_6$: C, 57.5; H, 9.7. Found: C, 57.8; H, 9.8.

Tetradecyl α-D-*mannopyranoside* (**4**).—2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (4.5 g, 6.8 mmol) and 1-tetradecanol (2.7 g, 13 mmol) were coupled as described above for **1**, to give tetradecyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (**3**; 4.5 g, 83%); ^{13}C NMR data ($CDCl_3$): δ 14.2, 22.8, 26.3, 29.5, 29.8, 32.0, 63.1, 67.2, 68.9, 70.3, 70.8, 97.7, 128.4–133.5, 165.6, and 166.2.

Compound **3** (2.8 g) was deacylated as described above for **2**, to yield **4** (1.2 g, 91%); $[\alpha]_D$ +50° (*c* 1.0, MeOH); ^{13}C NMR data (CD_3OD): δ 14.5, 23.7, 27.4, 30.5, 30.6, 30.8, 33.1, 62.9, 68.6, 72.3, 72.7, 74.5, and 101.5. Anal. Calcd for $C_{20}H_{40}O_6$: C, 63.8; H, 10.7. Found: C, 63.6; H, 10.9.

*Octyl 2,4-di-*O*-benzoyl-α-*D*-mannopyranoside* (**5**) *and octyl 2,6-di-*O*-benzoyl-α-*D*-mannopyranoside* (**6**).—Toluene-*p*-sulfonic acid (0.5 mL, 5% solution in MeCN, 0.10 mmol) and CF_3CO_2H (10 μL, 0.13 mmol) were added to a stirred suspension of **2** (0.5 g, 1.7 mmol) and triethyl orthobenzoate (1 mL, 4.4 mmol) in MeCN (33 mL). After 15 min, the clear solution was evaporated and the residue dissolved in MeCN (22 mL). Trifluoroacetic acid (0.61 mL, 90% aq) was added and the mixture stirred for 10 min, whereafter evaporation and column chromatography of the residue on silica gel (toluene–EtOAc, 9:1 and then 3:1) yielded, first, **5** (0.39 g, 45%); $[\alpha]_D$ −32° (*c* 1.1, $CHCl_3$); and then **6** (0.27 g, 32%); $[\alpha]_D$ +17° (*c* 1.7, $CHCl_3$); NMR data ($CDCl_3$) for **5**: ^{13}C, δ 14.0, 22.5, 26.0, 29.1, 29.2, 31.7, 61.4, 68.1, 68.3, 70.4, 70.6, 73.0, 97.3, 128.1–133.3, 165.9 and 166.9; ^1H, δ 3.72 (2 H, H-6), 3.93 (H-5), 4.42 (H-3), 5.00 (H-1), 5.38 (H-2), and 5.48 (H-4); and for **6**: ^{13}C, δ 14.1, 22.7, 26.1, 29.2, 29.3, 31.8, 63.8, 68.0, 70.1, 70.7, 72.7, 77.2, 97.6, 128.2–133.2, 166.2, and 166.9; ^1H, δ 3.92 (2 H, H-4,5), 4.17 (H-3), 4.55 (H-6a), 4.73 (H-6b), 4.92 (H-1), and 5.34 (H-2). Anal. Calcd for $C_{28}H_{36}O_8$: C, 67.2; H, 7.25. Found for **5**: C, 67.0; H, 7.28. Found for **6**: C, 67.1; H, 7.24.

*Tetradecyl 2,4-di-*O*-benzoyl-α-*D*-mannopyranoside* (**7**) *and tetradecyl 2,6-di-*O*-benzoyl-α-*D*-mannopyranoside* (**8**).—Compound **4** (0.4 g, 1.1 mmol) was treated as described above for **2**, to give, first, **7** (0.27 g, 44%); $[\alpha]_D$ −27° (*c* 2.3, $CHCl_3$); and then **8** (0.24 g, 39%); $[\alpha]_D$ +15° (*c* 2.5, $CHCl_3$); NMR data ($CDCl_3$) for **7**: ^{13}C, δ 14.2, 22.7, 26.2, 29.4, 29.7, 32.0, 61.5, 68.4, 68.6, 70.5, 70.6, 73.1, 97.5, 128.3–133.5, 166.1, and 167.1; ^1H, δ 3.73 (2 H, H-6), 3.93 (H-5), 4.43 (H-3), 5.02 (H-1), 5.39 (H-2), and 5.49 (H-4); and for **8**: ^{13}C, δ 14.1, 22.7, 26.1, 29.4, 29.7, 31.9, 63.8, 68.0, 68.3, 70.2, 70.8, 72.7, 97.6, 128.3–133.2, 166.2, and 167.0; ^1H, δ 3.92 (2 H, H-4,5), 4.17 (H-3), 4.54 (H-6a), 4.76 (H-6b), 4.91 (H-1), and 5.35 (H-2). Anal. Calcd for $C_{34}H_{48}O_8$: C, 69.8; H, 8.27. Found for **7**: C, 69.8; H, 8.19. Found for **8**: C, 69.5; H, 8.11.

*Octyl 2,4-di-*O*-benzoyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**9**).—Silver triflate (0.17 g, 0.66 mmol) dissolved in toluene (2 mL) was added at 0°C to a stirred solution of **5** (0.14 g, 0.28 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide[8] (0.4 g, 0.6 mmol) in CH_2Cl_2 (10 mL) containing crushed 4A molecular sieves. After 2 h, the mixture was put on top of a silica gel column and eluted (30:1 toluene–EtOAc) to give **9** (0.39 g, 86%); $[\alpha]_D$ −52° (*c* 0.97, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 14.2, 22.8, 26.3, 29.4, 29.6, 29.6, 32.0, 62.5, 62.8, 66.5, 66.7, 68.6, 68.8, 69.0, 69.5, 69.7, 70.2, 70.4, 72.2, 97.6 (2 C), 99.8, 128.2–133.7, 164.8, 165.2, 165.3, 165.6, 165.8, 166.2, and 166.4. Anal Calcd for $C_{96}H_{88}O_{26}$: C, 69.6; H, 5.09. Found: C, 69.7; H, 5.27.

*Octyl 2,6-di-*O*-benzoyl-3,4-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**10**).—Compound **6** (0.18 g, 0.35 mmol) and 2,3,4,6-tetra-*O*-

benzoyl-α-D-mannopyranosyl bromide (0.93 g, 1.4 mmol) were coupled as described above for **5**, to give **10** (0.58 g, 98%); $[\alpha]_D$ −20° (*c* 1.0, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 14.1, 22.7, 26.1, 29.2, 29.4, 29.5, 31.8, 62.3, 62.7, 63.6, 66.7, 68.9, 69.4, 69.7, 69.9, 70.4, 71.0, 71.4, 72.8, 75.7, 80.5, 96.8, 100.1, 100.2, 128.0–133.6, 165.0, 165.4, 165.5, 166.0, 166.1, and 166.2. Anal. Calcd for $C_{96}H_{88}O_{26}$: C, 69.6; H, 5.09. Found: C, 69.8; H, 5.46.

*Tetradecyl 2,4-di-*O*-benzoyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**11**).—Compound **7** (0.22 g, 0.38 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (1.03 g, 1.56 mmol) were coupled as described above for **5**, to give **11** (0.74 g, 100%); $[\alpha]_D$ −46° (*c* 1.6, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 14.3, 22.8, 26.4, 29.5, 29.6, 29.8, 32.1, 62.6, 62.8, 66.5, 66.8, 67.0, 68.6, 68.8, 69.0, 69.6, 69.8, 70.3, 70.5, 72.2, 79.2, 97.6 (2 C), 99.8, 128.3–133.7, 164.8, 165.3, 165.7, 165.9, 166.3, and 166.4. Anal. Calcd for $C_{102}H_{100}O_{25}$: C, 71.0; H, 5.84. Found: C, 70.8; H, 5.80.

*Tetradecyl 2,6-di-*O*-benzoyl-3,4-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**12**).—Compound **9** (0.18 g, 0.31 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (0.83 g, 1.3 mmol) were coupled as described above for **5**, to give **12** (0.47 g, 86%); $[\alpha]_D$ −17° (*c* 1.5, $CHCl_3$); ^{13}C NMR data ($CDCl_3$): δ 14.1, 22.7, 26.1, 29.4, 29.5, 29.6, 31.9, 62.3, 62.7, 63.6, 66.6, 66.8, 68.9, 69.4, 69.6, 69.8, 70.3, 70.9, 71.3, 72.7, 75.6, 80.5, 96.8, 100.1, 100.2, 128.0–133.6, 165.0, 165.4, 165.5, 166.0, 166.0, and 166.2. Anal. Calcd for $C_{102}H_{100}O_{25}$: C, 71.0; H, 5.84. Found: C, 70.8; H, 5.88.

*Octyl 3,6-di-*O*-α-*D*-mannopyranosyl-α-*D*-mannopyranoside* (**13**).—Sodium methoxide (1 mL, 1 M) was added to **9** (0.22 g, 0.13 mmol) in MeOH (30 mL) and left overnight. Dowex (H^+) ion-exchange resin was added, and the mixture filtered and evaporated. A solution of the residue in water was washed with Et_2O, and gel filtration on a Bio-Gel P2 column then gave **13** (71.5 mg, 89%); $[\alpha]_D$ +90° (*c* 0.48, H_2O); ^{13}C NMR data (D_2O): δ 14.3, 22.9, 26.4, 29.4, 29.6, 32.1, 61.8 (2 C), 66.3, 66.5, 67.6, 68.8, 70.7, 70.9, 71.0, 71.4, 71.6, 72.1, 73.4, 74.0, 79.7, 100.5 ($J_{C\text{-}1,H\text{-}1}$ 170 Hz), 100.8 ($J_{C\text{-}1,H\text{-}1}$ 170 Hz), and 103.0 ($J_{C\text{-}1,H\text{-}1}$ 167 Hz). Anal. Calcd for $C_{26}H_{48}O_{16} \cdot 2.5\ H_2O$: C, 47.2; H, 8.05. Found: C, 47.3; H, 7.36.

*Octyl 3,4-di-*O*-α-*D*-mannopyranosyl-α-*D*-mannopyranoside* (**14**).—Compound **10** (0.50 g, 0.30 mmol) was deacylated as described above for **9**, to yield **14** (146 mg, 78%); $[\alpha]_D$ +100° (*c* 0.50, H_2O); ^{13}C NMR data (D_2O): δ 14.3, 22.9, 26.4, 29.5, 29.6, 32.1, 61.4, 61.6, 61.8, 67.2, 67.5, 68.7, 70.6, 71.3, 71.4, 71.5, 72.4, 73.5, 74.1, 74.6, 81.5, 100.5 ($J_{C\text{-}1,H\text{-}1}$ 170 Hz), 102.6 ($J_{C\text{-}1,H\text{-}1}$ 170 Hz), and 102.9 ($J_{C\text{-}1,H\text{-}1}$ 167 Hz). Anal. Calcd for $C_{26}H_{48}O_{16} \cdot 1.5\ H_2O$: C, 48.5; H, 7.99. Found: C, 48.1; H, 7.60.

*Tetradecyl 3,6-di-*O*-α-*D*-mannopyranosyl-α-*D*-mannopyranoside* (**15**).—Compound **11** (0.53 g, 0.31 mmol) was deacylated as described above for **9**, to give **15** (192 mg, 88%); $[\alpha]_D$ +89° (*c* 0.51, MeOH); ^{13}C NMR data (CD_3OD): δ 14.8, 24.0, 27.7, 30.7, 30.9, 31.1, 33.3, 63.0, 67.4, 67.7, 68.8, 68.9, 69.1, 71.7, 72.3, 72.7, 72.9, 73.5, 74.5, 75.1, 81.2, 101.6 ($J_{C\text{-}1,H\text{-}1}$ 170 Hz), 101.9 ($J_{C\text{-}1,H\text{-}1}$ 170 Hz), and 104.2

($J_{C\text{-}1,H\text{-}1}$ 169 Hz). Anal. Calcd for $C_{32}H_{60}O_{16} \cdot 1.5\ H_2O$: C, 52.8; H, 8.72. Found: C, 52.8; H, 8.31.

Tetradecyl 3,4-di-O-α-D-mannopyranosyl-α-D-mannopyranoside (**16**).—Compound **12** (0.39 g, 0.22 mmol) was deacylated as described above for **9**, to yield **16** (118 mg, 75%); $[\alpha]_D$ +86° (*c* 0.49, MeOH); ^{13}C NMR data (CD_3OD): δ 14.8, 24.0, 27.6, 30.7, 30.8, 31.0, 33.3, 63.0 (3 C), 68.6, 68.8, 69.2, 71.6, 72.6, 72.7, 73.6, 74.6, 75.3, 75.9, 83.4, 101.7 ($J_{C\text{-}1,H\text{-}1}$ 168 Hz), 103.9 ($J_{C\text{-}1,H\text{-}1}$ 173 Hz), and 104.4 ($J_{C\text{-}1,H\text{-}1}$ 169 Hz). Anal. Calcd for $C_{32}H_{60}O_{16}$: C, 54.8; H, 8.63. Found: C, 54.6; H, 8.75.

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