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Note

Synthesis of some methyl 6-*O*-alkyl-α-D-glycopyranosides

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The 6-*O*-alkyl-glycosides **1**, **9**, **10**, and **15** were required as intermediates in model cell-membrane binding studies. None of them have been described previously. Attempts to use the methods employed traditionally [1,2] for the synthesis of the corresponding 6-*O*-methyl analogues were not successful. For example, when the tribenzoate **2** [3] in 1,2-dimethoxyethane was treated with 1-bromobutane in the presence of silver carbonate at room temperature for 4 days, analysis (TLC) indicated a complex mixture of products including a substantial amount of unreacted **2**. An alternative general approach was investigated. The synthesis of compounds **1**, **9** and **10** was achieved by appropriate alkoxide nucleophilic displacement reactions on the ethoxyethyl-protected derivatives **4** and **12** derived from the tosylates **3** and **11**. The displacement of primary sulfonate groups on hexopyranosides by alkoxide ions is uncommon [4,5]. It was necessary to obtain compound **15** by an alternative route. Some aspects of these reactions are now described.

Treatment of **3** [6] with ethyl vinyl ether in the presence of a catalytic quantity of pyridinium *p*-toluenesulfonate yielded the tri-*O*-(1-ethoxyethyl) derivative **4**. The product of this reaction, a mixture of diastereomers, was not characterised but was treated

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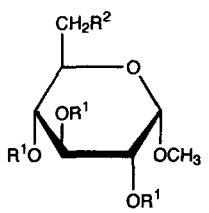
directly with a solution of sodium 1-butoxide in boiling 1-butanol. Hydrolysis of the product with aq 50% acetic acid yielded the required **1** as a syrup after column chromatography, which was characterised as the tris-*p*-nitrobenzoate **5**.

When the corresponding and uncharacterised ethoxyethyl derivative **12** of the tosylate **11** [19] was treated in a similar manner, compound **9** (38%) was obtained, also as a syrup, and was characterised as the tris-*p*-nitrobenzoate **13**.

Treatment of a solution of **12** in DMF with 2-benzyloxyethanol in the presence of potassium *tert*-butoxide at 100 °C for 72 h yielded the ether **10** (53%) as a thick oil, after deprotection. No suitable, crystalline, characterising derivative of **10** was obtained. Acetylation, benzoylation, *p*-nitrobenzoylation, and tosylation in the usual manner led only to syrupy products which were difficult to purify.

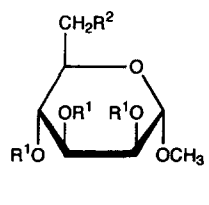
Attempts to convert the tosylate **16** [6] into the remaining required ether **15** in a similar sequence were unsuccessful indicating that nucleophilic displacement at C-6 is inhibited. Similar behaviour has been noted previously [7,8]. The difference between galactose 6-sulfonate derivatives and most other primary sulfonates in their reactivities towards nucleophiles is well-known [9]. The use of neutral nucleophiles greatly facilitates displacement. The behaviour has been rationalised in terms of polar repulsive forces in the transition states [10].

Compound **15** was obtained eventually by reaction of the diacetal **18** [20] with 1-bromobutane and finely powdered potassium hydroxide in Me_2SO, followed by treatment of the product with boiling 1% methanolic hydrogen chloride. Fractional crystallisation of the resulting mixture yielded crystalline **15** (51%), characterised as the tris-*p*-nitrobenzoate **17**.

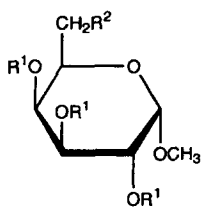


1 R^1 =H; R^2 = $O(CH_2)_3CH_3$
2 R^1 =Bz; R^2 = OH
3 R^1 =H; R^2 = OTs
4 R^1 =EE; R^2 = OTs
5 R^1 =*p*-nitrobenzoyl; R^2 = $O(CH_2)_3CH_3$
6 R^1 =H; R^2 = OH
7 R^1 =H; R^2 = Cl
8 R^1 =H; R^2 = I

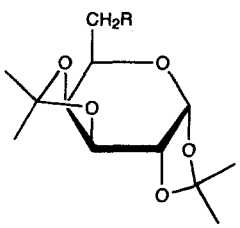
(EE = 1-ethoxyethyl)



9 R^1 =H; R^2 = $O(CH_2)_3CH_3$
10 R^1 =H; R^2 = OCH_2CH_2OBzl
11 R^1 =H; R^2 = OTs
12 R^1 =EE; R^2 = OTs
13 R^1 =*p*-nitrobenzoyl; R^2 = $O(CH_2)_3CH_3$
14 R^1 =H; R^2 = OH



15 R^1 =H; R^2 = $O(CH_2)_3CH_3$
16 R^1 =H; R^2 = OTs
17 R^1 =*p*-nitrobenzoyl; R^2 = $O(CH_2)_3CH_3$



18 R = OH

The syntheses of compounds **1**, **9**, and **10** were relatively successful but the method relies upon the selective tosylation of the C-6 hydroxyl groups of the appropriate glycosides **6** and **14**. With compound **6** this reaction proceeds only modestly (55%) [11]. It has been shown [12] that treatment of **6**, inter alia, with methanesulfonyl chloride in DMF gives the 6-chloro-6-deoxy derivative **7** in high yield (97%). It was decided to attempt to improve the overall yield of compound **1** by using this intermediate in a similar series of reactions. Compound **7** was treated with ethyl vinyl ether and the crude product treated with sodium 1-butoxide in 1-butanol for 56 h at 95 °C. Treatment of the resultant material with aq 50% acetic acid gave an inseparable (TLC) mixture of compounds **1** and **7**. ^{1}H NMR spectroscopy indicated that only ca. 10% of compound **1** was present in the mixture which was not investigated further. The result demonstrated the poor leaving-group activity of the 6-chloro group under these conditions.

Although 1-ethoxyethyl groups have been suggested as useful O-protecting functions [13,14] they have found limited applications, so far, in carbohydrate chemistry [15–17]. They are readily introduced in high yields and are very stable under strongly basic conditions. They are easily removed under very mild conditions, even in the presence of other acetal groups [16], and are possibly preferable to the better known tetrahydropyranyl group which requires more forcing conditions for complete removal [14]. The group was useful in the reactions described here since an easily removable, base-stable protecting function was required to prevent competitive 3,6-anhydride formation [6] during the displacement reactions.

During the course of this work a novel synthesis of a series of 6-*O*-alkyl derivatives of glycoside **6** was described [18]. Treatment of the 6-iodo derivative **8** with alcohols in the presence of chlorine gas yielded the corresponding ethers. The reactions were presumed to proceed by intermediate formation of an alkyl hypochlorite from the alcohol with subsequent attack on **8** to give the ether, together with iodine monochloride and hydrogen chloride as by-products. Compound **1** was not amongst those reported.

Treatment of **8** with 1-butanol in the reported manner [18] gave **1** in 42% yield, after chromatography, which was characterised as compound **5**. Although this route compares very favourably with the described alternative, difficulties were experienced in performing the reaction on a larger scale (> 400–500 mg).

1. Experimental

Optical rotations were determined on 1% solutions at 20 °C with a Perkin–Elmer model 241 polarimeter. TLC was performed on Kieselgel 60 (Merck) with 3:1 hexane–EtOAc and detection by charring with 3% H_2SO_4 in EtOH. Column chromatography (9:1 CH_2Cl_2–MeOH) was performed on Silica Gel 60. NMR spectra were recorded with a Bruker AM 400 spectrometer operating at 400 MHz for ^{1}H spectra [solutions in $CDCl_3$ (internal Me_4Si) or D_2O], and at 100.6 MHz for ^{13}C spectra [solutions in $CDCl_3$ (internal standard, Me_4Si) or D_2O (external standard, 1,4-dioxane at 67.8 ppm)].

Methyl 6-O-butyl-α-D-glucopyranoside (**1**).—*(a) From methyl 6-O-p-toluenesulfonyl-α-D-glucopyranoside* (**3**) [11]. A stirred mixture of **3** (2.68 g, 7.7 mmol) and pyridinium

p-toluenesulfonate (268 mg) in $CHCl_2$ (40 mL) was treated with ethyl vinyl ether (4.4 mL, 46.2 mmol) and set aside overnight at room temperature. The mixture was poured with stirring into cold (0 °C) saturated aq $NaHCO_3$ (100 mL) and then extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated aq NaCl, dried (Na_2SO_4), and concentrated in vacuo. A solution of the resultant oil (4.57 g) in 1-butanol (10 mL) was added dropwise to a stirred solution of sodium butoxide in 1-butanol (15 mL) from Na (354 mg). On completion of the addition the mixture was heated with stirring for 18 h at 90 °C. The cooled mixture was treated with Et_2O (175 mL) and H_2O (50 mL) and the separated aqueous layer extracted with Et_2O (50 mL). The combined organic layers were washed with saturated aq NaCl (2 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The resultant oil was dissolved in aq 50% AcOH (40 mL), the solution set aside overnight at room temperature, then concentrated in vacuo, and water (3 × 20 mL) distilled in vacuo from the residue. Column chromatography of the residue provided **1** (1.30 g, 67%); $[\alpha]_D$ +146° (acetone); ^{1}H NMR data: δ 4.97 (bs, 1 H, OH), 4.75 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.34 (bs, 1 H, OH), 4.5 (bs, 1 H, OH), 3.71 (m, 4 H), 3.5 (m, 4 H) 3.42 (s, 3 H, OCH_3), 1.58 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.36 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 0.92 (t, 3 H, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR data: δ 99.5 (C-1), 74.3 (C-3), 71.9, 71.7 (C-2, C-5), 70.9 (C-4), 70.3 × 2 (C-6, $OCH_2CH_2CH_2CH_3$), 55.1 (O-Me), 31.6 ($OCH_2CH_2CH_2CH_3$), 19.2 ($OCH_2CH_2CH_2CH_3$), 13.9 ($OCH_2CH_2CH_2CH_3$).

A cooled (0 °C), stirred solution of a portion (103 mg) of the product in dry pyridine (3 mL) was treated with *p*-nitrobenzoyl chloride (253 mg, 3.3 equiv), set aside at room temperature for 4 days, and processed in the usual manner. Recrystallisation (EtOH–CH_2Cl_2) of the crude product (292 mg) gave compound **5** (147 mg, 51%); mp 197–200 °C; $[\alpha]_D$ +40.3° ($CHCl_3$). Anal. Calcd for $C_{32}H_{31}N_3O_{15}$: C, 55.10; H, 4.48; N, 6.02. Found: C, 54.89; H, 4.41; N, 5.98.

*(b) From methyl 6-deoxy-6-iodo-α-*D*-glucopyranoside* (**8**) [18]. A slow stream of Cl_2 gas was bubbled through a stirred solution of **8** (410 mg, 1.35 mmol) in 1-butanol (40 mL) for 4 min, which was then set aside for 15 min at room temperature. The mixture was neutralised by addition of Amberlite IRA-400 ion-exchange resin (HCO_3^- form) and filtered, the resin was washed with 1-butanol (10 mL), and the combined filtrate and washings were concentrated in vacuo. Column chromatography of the residue gave **1** (143 mg, 42%); $[\alpha]_D$ +147° (acetone).

p-Nitrobenzoylation of the product, as described above, yielded **5**; mp 197–200 °C; $[\alpha]_D$ +39.5° ($CHCl_3$).

*Methyl 6-O-butyl-α-*D*-mannopyranoside* (**9**).—Compound **11** (7.71 g, 22 mmol) [19] was treated as described above in (*a*). Column chromatography of the resultant crude material yielded pure **9** (2.10 g, 38%) as a syrup; $[\alpha]_D$ +56.5° ($CHCl_3$); ^{1}H NMR data: δ 4.71 (s, 1 H, H-1), 4.42–4.07 (3 s, each 1 H, OH), 3.89 (s, 1 H, H-2), 3.72–3.64 (m, 5 H, H-3,4,5,6a,6b), 3.52 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 3.36 (s, 3 H, OCH_3), 1.58 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.36 (m, 2 H, $OCH_2CH_2CH_2CH_3$, 0.92 (t, 3 H, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR data: δ 101.0 (C-1), 71.7 × 2 (C-2, C-5), 70.6 × 2 (C-6, $OCH_2CH_2CH_2CH_3$), 70.5 (C-3), 68.5 (C-4), 54.9 (OCH_3), 31.5 ($OCH_2CH_2CH_2CH_3$), 19.2 ($OCH_2CH_2CH_2CH_3$), 13.9 ($OCH_2CH_2CH_2CH_3$).

A cooled (0 °C), stirred solution of **9** (117 mg, 0.47 mmol) in dry pyridine (3 mL)

was treated with *p*-nitrobenzoyl chloride (288 mg, 1.55 mmol), set aside at room temperature for 3 weeks, and processed in the usual manner to give **13** (174 mg, 53%); mp 159.5–161 °C (EtOH–EtOAc–H_2O); $[\alpha]_D$ −214° ($CHCl_3$). Anal. Calcd for $C_{32}H_{31}N_3O_{15}$: C, 55.10; H, 4.48; N, 6.02. Found: C, 54.64; H, 4.37; N, 5.96.

Methyl 6-O-benzyloxyethyl-α-D-mannopyranoside (**10**).—Compound **11** (12.3 g, 35 mmol) [19] was treated with ethyl vinyl ether (20 mL, 0.2 mol) and pyridinium *p*-toluenesulfonate (300 mg) and processed as described above in (*a*). A stirred solution of the resulting material (12.06 g) in DMF (75 mL) containing 2-benzyloxyethanol (26 g) was treated dropwise over 15 min with a solution of potassium *tert*-butoxide (12.0 g, 107 mmol) in DMF (100 mL), and then heated at 100 °C for 3 days. The cooled mixture was poured into cold (0 °C) saturated aq NaCl (600 mL) and extracted with Et_2O (3 × 250 mL). The combined extracts were washed with saturated aq NaCl and the aqueous layer then extracted with Et_2O (50 mL). The combined Et_2O solution was dried (Na_2SO_4), then concentrated in vacuo, and the crude product was chromatographed to give **10** (4.28 g, 53%) as an oil; $[\alpha]_D$ +41.7° ($CHCl_3$); ^1H NMR data: δ 7.29 (m, 5 H, Ph H), 4.67 (s, 1 H, H-1), 4.54 (s, 2 H, benzylic H), 4.22 (bs, 2 H, OH), 3.96 (bs, 1 H, OH), 3.86 (s, 1 H, H-2), 3.68 (m, 9 H, H-3,4,5,6a,6b, OCH_2CH_2), 3.31 (s, 3 H, OCH_3); ^{13}C NMR data: δ 137.9 (quaternary aromatic C), 128.3 × 2, 127.7 × 2, 127.6 (aromatic C), 101.0 (C-1), 73.06 ($PhCH_2$), 71.7 (C-2), 71.01 (C-3), 70.8, 70.77 (OCH_2CH_2O), 70.55 (C-6), 69.20 (C-4), 67.96 (C-5), 54.76 (OCH_3).

Methyl 6-O-butyl-α-D-galactopyranoside (**15**).—A stirred solution of the diacetal **18** [20] (5.0 g, 19.2 mmol) [17] in Me_2SO (25 mL) was treated with finely powdered KOH (3.30 g, 58 mmol), and 1-bromobutane (6.2 mL, 58 mmol) was added dropwise over 15 min to the mixture which was then maintained at 20 °C for 2.5 h. The mixture was treated with ice-cold water (100 mL) and extracted with ether (3 × 50 mL). The combined extracts were washed with saturated aq NaCl, dried (Na_2SO_4), and concentrated in vacuo. A solution of the resulting product (6.07 g) in methanolic 1% HCl (185 mL) was heated under reflux overnight, cooled, neutralised by addition of Amberlite IRA-400 resin (HCO_3^- form), and filtered. The filtrate was concentrated in vacuo, and EtOAc (20 mL) distilled from the residue. Crystallisation and recrystallisation (EtOAc–$CHCl_3$) of the residue provided pure **15** (1.47 g, 31%); mp 135.5–138 °C; $[\alpha]_D$ +141° (CH_2Cl_2); ^1H NMR data ($CDCl_3$ + D_2O): δ 4.81 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.00 (d, 1 H, $J_{4,3}$ 3.2 Hz, H-4), 3.87–3.68 (m, 5 H, H-2,3,5,6a,6b), 3.49 (t, 2 H, $OCH_2CH_2CH_2CH_3$), 3.41 (s, 3 H, OCH_3), 1.57 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.36 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 0.92 (t, 3 H, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR data: δ 99.8 (C-1), 71.6 (C-2), 70.7 × 2 (C-6, $OCH_2CH_2CH_2CH_3$), 70.0 (C-3), 69.0 (C-4), 68.7 (C-5), 55.3 (OCH_3), 31.6 ($OCH_2CH_2CH_2CH_3$), 19.2 ($OCH_2CH_2CH_2CH_3$), 13.9 ($OCH_2CH_2CH_2CH_3$). Anal. Calcd for $C_{11}H_{22}O_6$: C, 52.79; H, 8.86. Found: C, 52.72; H, 8.64.

The crystallisation mother liquors were concentrated in vacuo, and the residue was treated with methanolic 1% HCl and processed as described above to yield more **15** (0.94 g, 20%); mp 131.5–135 °C; $[\alpha]_D$ +132° (CH_2Cl_2).

Compound **15** (100 mg) in pyridine (3 mL) was treated with *p*-nitrobenzoyl chloride (473 mg), set aside at room temperature for 5 days, and processed in the usual manner to give **17** (104 mg, 37%); mp 126–130 °C (ether–isopropyl ether); $[\alpha]_D$ +274° ($CHCl_3$).

Anal. Calcd for $C_{32}H_{31}N_3O_{15}$: C, 55.10; H, 4.48; N, 6.02. Found: C, 54.99; H, 4.40; N, 6.01.

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