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Note

A convenient etherification of the primary hydroxyl group of glucopyranosides

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Benzyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**5**) has been used[1–3] as the aglycon in high-yield syntheses of various disaccharides and in Koenigs–Knorr-type condensations[4]. The corresponding allyl glycoside was an intermediate in the synthesis of derivatives of di-*N*-acetylchitobiose and various syntheses[5–8] of 2-methyl-(2-acetamido-4-*O*-acetyl-3,6-di-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline. Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[9] has been used[10] as a precursor of methyl α-maltoside.

We have stressed[11–13] the usefulness of benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**7**) for the synthesis of branched oligosaccharides.

The foregoing glycosides have generally been obtained[2,5,9] after selective partial benzylation of HO-6, but the yields were moderate and purification was troublesome. We now report a more practical, two-step procedure based on regiospecific tosylation of HO-6 followed by SN2 displacement with a suitable sodium alkoxide.

Treatment of benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**1**) with an excess of tosyl chloride in pyridine gave 94% of crude benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-6-*O*-tosyl-α-D-glucopyranoside (**2**). T.l.c. revealed faster-migrating impurities, and pure **2** (84%) was obtained by chromatography on silica gel. However, an almost quantitative yield of pure **2** was obtained when a solution of **1** in anhydrous dichloromethane was treated with one equiv. of tosyl chloride in the presence of triethylamine and dimethylaminopyridine. Treatment (90°, 1 h) of **2** in *N*,*N*-dimethylformamide with M sodium benzylate in benzyl alcohol gave 88% of crystalline benzyl 2-acetamido-3,6-di-*O*-benzyl-α-D-glucopyranoside[14] (**5**). The conversion **1**→**2**→**5** gave an 84% yield without column chromatography. Selective benzylation[2] of **1** gave only 60% of **5**; furthermore, the yield was not reproducible and direct crystallisation was possible only when the yield was high. Likewise, **2** was converted into the 6-*O*-allyl

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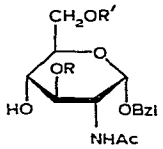
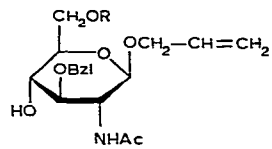
derivative **6**, and benzyl 2,3-di-*O*-benzyl-6-*O*-tosyl-β-D-glucopyranoside (**13**) into the crystalline 6-*O*-methyl derivative **16**. For the preparation of a large amount of allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**11**) from the tosylate of **10**, benzene was a more convenient solvent than *N*,*N*-dimethylformamide. Other examples are described in the Experimental section, illustrating the generality of this reaction for *gluco* compounds.

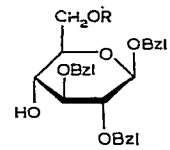
The reaction is not applicable to D-galactopyranosides, due to participation[15] of HO-4.



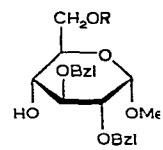
1 R = Bzl, R' = H
2 R = Bzl, R' = Ts
3 R = CH_2–CH=CH_2, R' = H
4 R = CH_2–CH=CH_2, R' = Ts
5 R = R' = Bzl
6 R = Bzl, R' = CH_2–CH=CH_2
7 R = CH_2–CH=CH_2, R' = Bzl
8 R = R' = CH_2–CH=CH_2



9 R = H
10 R = Ts
11 R = Bzl



12 R = H
13 R = Ts
14 R = Bzl
15 R = CH_2–CH=CH_2
16 R = Me



17 R = H
18 R = Bzl

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes using a Büchi apparatus and are uncorrected. Optical rotations were measured on solutions in chloroform with a Perkin–Elmer Model 141 polarimeter. ^{1}H-N.m.r. spectra (90 MHz, internal Me_4Si) were measured with a Perkin–Elmer R-32 instrument. Purity of products was determined by t.l.c. on Silica Gel 60 F 254 (Merck) with detection by charring with sulphuric acid. Column chromatography was performed on Silica Gel 60 (Merck, 0.063–0.200 mm). Elemental analyses were obtained from the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique.

*Benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-6-*O*-tosyl-α-D-glucopyranoside* (**2**). — (*a*) To a solution of benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside[14] (**1**; 1.605 g, 4 mmol) in anhydrous pyridine (15 ml) at 0° was added freshly crystallised tosyl chloride (1.114 g, 6 mmol). After 6 h, the mixture was stirred for 1 h in the presence of ice (10 g), and concentrated. A solution of the residue in chloroform (50 ml) was washed with water, dilute aqueous potassium hydrogen sulphate, conc. aqueous sodium hydrogencarbonate, and water, dried, and concentrated. The crude, syrupy residue (2.089 g, 94%) may be used directly for the next reaction. A portion (350 mg) was eluted from a column of silica gel (25 g), using chloroform–acetone (11:5), to give syrupy **2** (312 mg, 84%), $[\alpha]_D^{20}$ +98° (*c* 1). N.m.r. data (acetone-d_6): δ 1.80 (s, 3 H, Ac), 2.39 (s, 3 H, Me), 2.68 (s, 1 H, OH), 7.03 (d, 1 H, *J* 9 Hz, NH), and 7.25–7.83 (m, 14 H, aromatic protons).

Anal. Calc. for $C_{29}H_{33}NO_8S$: C, 62.69; H, 5.99; N, 2.52; S, 5.76. Found: C, 62.61; H, 5.91; N, 2.39; S, 5.85.

(*b*) A mixture of **1** (3.21 g, 8 mmol), freshly crystallised tosyl chloride (1.60 g, 8.4 mmol), dimethylaminopyridine (48 mg), triethylamine (2 ml), and anhydrous dichloromethane (40 ml) containing *N,N*-dimethylformamide (4 ml) was stirred at room temperature under nitrogen for 4 h. The mixture was then stirred for 1 h in the presence of ice, diluted with dichloromethane (50 ml), washed with ice-cold 2M hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water, dried (Na_2SO_4), and concentrated. The residue (4.271 g, 96%), which was homogeneous in t.l.c. (ethyl acetate–hexane, 4:1), had $[\alpha]_D^{20}$ +98° (*c* 1).

*Benzyl 2-acetamido-3-*O*-allyl-2-deoxy-6-*O*-tosyl-α-*D*-glucopyranoside* (**4**). — Tosylation of benzyl 2-acetamido-3-*O*-allyl-2-deoxy-α-D-glucopyranoside[12] (**3**; 2.81 g, 8 mmol), as in (*b*) above, gave **4** (3.742 g, 93%), m.p. 136–137° (from ethyl acetate–hexane), $[\alpha]_D^{20}$ +95° (*c* 1). N.m.r. data ($CDCl_3$): δ 1.93 (s, 3 H, Ac), 2.46 (s, 3 H, Me), 3.25 (d, 1 H, OH), 4.80 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.80 (d, 1 H, *J* 9 Hz, NH), and 7.35–7.95 (m, 9 H, aromatic protons).

Anal. Calc. for $C_{25}H_{31}NO_8S$: C, 59.39; H, 6.18; N, 2.77; S, 6.34. Found: C, 59.42; H, 6.28; N, 2.77; S, 6.39.

*Allyl 2-acetamido-3-*O*-benzyl-2-deoxy-6-*O*-tosyl-β-*D*-glucopyranoside* (**10**). — Tosylation of allyl 2-acetamido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside[18] (**9**), by method (*a*) above, gave (starting from 1.053 g, 3 mmol) a crude, syrupy residue that was eluted from a column of silica gel (60 g) with chloroform–methanol (20:1), to give **10** (1.241 g, 82%), $[\alpha]_D^{20}$ −7° (*c* 1). N.m.r. data ($CDCl_3$): δ 1.83 (s, 3 H, Ac), 2.38 (s, 3 H, Me), 3.08 (s, 1 H, OH), 6.19 (d, 1 H, *J* 8.5 Hz, NH), and 7.20–7.82 (m, 9 H, aromatic protons).

Anal. Calc. for $C_{25}H_{31}NO_8S$: C, 59.39; H, 6.18; N, 2.77; S, 6.34. Found: C, 59.22; H, 6.28; N, 2.56; S, 6.41.

Method (*b*) gave, directly (starting from 17 g, 48.5 mmol), **10** (23.61 g, 96%), $[\alpha]_D^{20}$ −7° (*c* 1).

*Benzyl 2,3-di-*O*-benzyl-6-*O*-tosyl-β-*D*-glucopyranoside* (**13**). — Tosylation of benzyl 2,3-di-*O*-benzyl-β-D-glucopyranoside[16] (**12**, 2 g), according to method (*a*), gave crude **13** (2.83 g, 89%). A portion was eluted from a column of silica gel with ether–light petroleum (2:1), to give **13**, $[\alpha]_D^{20}$ −36° (*c* 2). N.m.r. data (CCl_4): δ 2.29 (s, 3 H, Me), 2.77 (s, 1 H, OH), and 7.20–7.90 (m, 19 H, aromatic protons).

Anal. Calc. for $C_{34}H_{36}O_8S$: C, 67.54; H, 6.00; S, 5.29. Found: C, 67.56; H, 5.78; S, 5.45.

*Benzyl 2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**14**). — A solution of crude **13** (300 mg) in *N,N*-dimethylformamide (3 ml) containing 1.5 ml of M sodium benzylate in benzyl alcohol was kept for 2 h at 90°, cooled, diluted with cold water (10 ml), and concentrated. The residue was diluted with chloroform, washed with 2M hydrochloric acid and water, and concentrated. The residue was eluted from a column of silica gel (10 g), using ether–light petroleum (1:1.5), to give **14** (235 mg, 88%),

m.p. 66–67° (from ethanol–water), $[\alpha]_D^{20}$ −44° (*c* 0.94); lit.[17] m.p. 66–67°, $[\alpha]_D^{20}$ −42° (*c* 1.07).

Benzyl 6-O-allyl-2,3-di-O-benzyl-β-D-glucopyranoside (**15**). — A solution of crude **13** (300 mg) in *N,N*-dimethylformamide (3 ml) containing 1.5 ml of M sodium allylate in allyl alcohol was kept for 2 h at 85° and then treated as described above for **14**, to give **15** (197 mg, 81%), m.p. 66–67° (from ether–light petroleum), $[\alpha]_D^{20}$ −46° (*c* 0.74). N.m.r. data (CCl_4): δ 2.60 (s, 1 H, OH), 5.65–6.10 (m, 1 H, $-CH_2-CH=CH_2$), and 7.22 (s, 15 H, aromatic protons).

Anal. Calc. for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.53; H, 6.94.

Benzyl 2,3-di-O-benzyl-6-O-methyl-β-D-glucopyranoside (**16**). — A solution of crude **13** (300 mg) in *N,N*-dimethylformamide (3 ml) containing 0.75ml of 2M sodium methoxide in methanol was kept for 3 h at 85° and treated as described above for **14**, to give **16** (187 mg, 82%), m.p. 72.5–73.5° (from carbon tetrachloride–light petroleum), $[\alpha]_D^{20}$ −51° (*c* 0.76). N.m.r. data (CCl_4): δ 3.33 (s, 3 H, OMe) and 7.20–7.25 (3 s, 15 H, aromatic protons).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.42; H, 6.91.

Benzyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside (**5**). — A solution of **2** (1.32 g) in *N,N*-dimethylformamide (10 ml) containing 6 ml of M sodium benzylate in benzyl alcohol was kept for 1 h at 90°, and then cooled, concentrated, diluted with chloroform (100 ml), washed with saturated aqueous sodium hydrogencarbonate, saturated aqueous sodium chloride, and water, dried (Na_2SO_4), and concentrated. Benzyl alcohol was distilled off at 120° *in vacuo*. A solution of the residue in ethanol–water (4:1) was treated with charcoal, to give **5** (1.024 g, 88%), m.p. 144–145° (from ethanol–water, 4:1); lit.[14] m.p. 145–145.5°.

Benzyl 2-acetamido-6-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranoside (**6**). — A solution of **2** (1.85 g) in *N,N*-dimethylformamide (20 ml) containing 8 ml of M sodium allylate in allyl alcohol was kept for 1 h at 90°, and then worked-up as described above, to give **6** (1.289 g, 86%), m.p. 124–125° (from ethyl acetate–hexane), $[\alpha]_D^{20}$ +122° (*c* 1). N.m.r. data ($CDCl_3$): δ 1.83 (s, 3 H, Ac), 3.15 (s, 1 H, OH), 4.92 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.55 (d, 1 H, *J* 9 Hz, NH), 5.96 (m, 1 H, $-CH_2-CH=CH_2$), and 7.35 (m, 10 H, aromatic protons).

Anal. Calc. for $C_{25}H_{31}O_6$: C, 68.00; H, 7.16; N, 3.17. Found: C, 67.83; H, 7.07; N, 3.16.

Benzyl 2-acetamido-3-O-allyl-6-O-benzyl-2-deoxy-α-D-glucopyranoside (**7**). — Treatment of **4** (1.635 g) as described above for the conversion **2**→**5** gave **7** (1.269 g, 89%), m.p. 149–150° (from ethyl acetate–hexane); lit.[12] m.p. 149–150°.

Benzyl 2-acetamido-3,6-di-O-allyl-2-deoxy-α-D-glucopyranoside (**8**). — Treatment of **4** (810 mg) as described above for the conversion **2**→**6**, with elution of the product from a column of silica gel (50 g), using ethyl acetate–hexane (4:1) as eluant, gave **8** (558 mg, 89%), m.p. 103–105°, $[\alpha]_D^{20}$ +110° (*c* 1). N.m.r. data ($CDCl_3$): δ 1.96 (s, 3 H, Ac), 3.30 (s, 1 H, OH), 4.91 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), and 7.36 (s, 5 H, aromatic protons).

Anal. Calc. for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.14; H, 7.70; N, 3.41.

Allyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside (**11**). — A solution of **10** (2.422 g) in benzene (50 ml) containing 5 ml of 2M sodium benzylate in benzyl alcohol was kept for 1.5 h at 85°, and then cooled, filtered, washed with saturated aqueous sodium hydrogencarbonate, and water, dried (Na_2SO_4), and concentrated. Benzyl alcohol was distilled off at 120° *in vacuo*. A solution of the residue in ethanol–water (4:1) was treated with charcoal, to give **11** (1.816 g, 86%), m.p. 141–142° (from ethyl acetate–hexane); lit.[8] m.p. 140–142°.

Methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside (**18**). — Tosylation of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[18] (**17**, 374 mg), by method (*b*) above, gave methyl 2,3-di-*O*-benzyl-6-*O*-tosyl-α-D-glucopyranoside (514 mg, 97%). This compound was then treated with sodium benzylate in benzene, as described above, to give **18** (400 mg, 86%), identical with the compound prepared by Küster and Dyong[9].

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