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Note

Synthesis of benzyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside and benzyl 6-*O*-allyl-2,4-di-*O*-benzyl-β-D-galactopyranoside*

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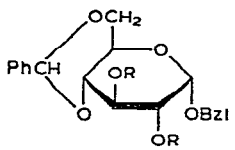
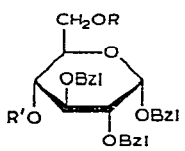
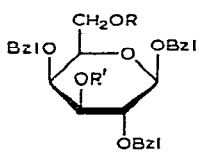
Gent and Gigg[2] have described recently a general method of oligosaccharide synthesis in which *O*-benzyl groups are used for "persistent" blocking and *O*-allyl groups for "temporary" blocking. The *O*-benzyl group is well suited to protect the positions that will not be involved in glycoside bond formation, since it is stable and not prone to migration under the conditions of the Koenigs–Knorr reaction. The *O*-allyl group offers the same advantages, but can be selectively removed from benzylated derivatives by isomerisation to the *cis*-1-propenyl group and subsequent hydrolysis. The use of the *O*-allyl group is of particular value in the preparation of partially methylated[3] or benzylated[2] monosaccharides.



1 R = H
2 R = Ac
3 R = Bzl



4 R = R' = H
5 R = Tr, R' = H
6 R = H, R' = CH_2—CH=CH_2
7 R = Bzl, R' = H



8 R = R' = H
9 R = Tr, R' = H
10 R = Tr, R' = CH_2—CH=CH_2
11 R = H, R' = CH_2—CH=CH_2
12 R = H, R' = CH=CH—CH_3
13 R = CH_2—CH=CH_2, R' = H

In an extension of our work[4] on the cycloaddition of butyl glyoxylate to a protected dienyl ether of a monosaccharide, a derivative of D-glucose having a free hydroxyl group at C-4 was required. We describe here the synthesis of benzyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**7**). Our starting material was benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**), previously described by Inch and Lewis[5]. Following their procedure, we obtained **1** in an overall yield of 14% from D-glucose;

*Studies in oligosaccharide chemistry. Part V. For Part IV, see Ref. 1.

but neither the melting point nor the optical rotation observed by us were in agreement with the values given by Inch and Lewis, although the n.m.r. spectrum and the higher optical rotation seemed indicative of a pure α anomer. Treatment of **1** with benzyl bromide and sodium hydride in boiling tetrahydrofuran gave the crystalline 2,3-di-*O*-benzyl ether **3** in 67% yield. Acid hydrolysis of **3** afforded benzyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**4**) in nearly quantitative yield. Tritylation, followed by allylation and acid hydrolysis gave benzyl 4-*O*-allyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (**6**), which was isolated in crystalline form after purification on silica gel, with an overall yield of 63% from **4**. After benzylation of the free hydroxyl group at C-6, the *O*-allyl group was removed by isomerisation in dimethyl sulfoxide in the presence of potassium *tert*-butoxide, followed by hydrolysis with mercuric chloride. These three last steps afforded benzyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**7**) in 70% yield as a syrup purified by chromatography and distillation.

Benzyl 2,4-di-*O*-benzyl-β-D-galactopyranoside[6] (**8**) has been used for the preparation of a branched trisaccharide[1] by simultaneous condensation at positions 3 and 6. The preparation of a more complex pentasaccharide related to blood-group substances requires a two-step condensation; as a possible starting material, we synthesized benzyl 6-*O*-allyl-2,4-di-*O*-benzyl-β-D-galactopyranoside (**13**), in which the *O*-allyl group should be useful as a "temporary" blocking group. Tritylation of **8**, followed by allylation and acid hydrolysis afforded crystalline benzyl 3-*O*-allyl-2,4-di-*O*-benzyl-β-D-galactopyranoside (**11**) in 37% yield. Isomerisation with potassium *tert*-butoxide in dimethyl sulfoxide gave the crystalline 1-propenyl ether **12** in 73% yield. Allylation at C-6, followed by acid hydrolysis of the 1-propenyl group at C-4 gave **13** isolated as a syrup in 56% yield after chromatography and distillation.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured with a Roussel–Jouan electronic, digital, micropolarimeter. I.r. spectra were recorded with a Perkin–Elmer model 257 spectrometer. N.m.r. spectra were recorded with a Jeol-C-60-H n.m.r. spectrometer at 60 MHz, with chloroform-*d* as solvent and tetramethylsilane as internal standard. T.l.c. was performed on plates of silica gel (with fluorescence indicator; layer thickness 0.25 mm; E. Merck, Darmstadt, Germany). The compounds were detected by spraying the plates with 1:19 (v/v) conc. sulfuric acid-ethanol. Silica gel Merck (70–325 mesh; E. Merck) was used for column chromatography. Microanalyses were performed by the Laboratoire Central de Micro-Analyse du C.N.R.S.

Benzyl 4,6-O-benzylidene-α-D-glucopyranoside (**1**). — This compound was prepared as described in Ref. 5, except that approximately three times the quantities of water and light petroleum described were used for precipitation; m.p. 161–162°, $[\alpha]_D^{20}$ +107° (*c* 1.04, chloroform); n.m.r. data: δ 5.5 (s, 1 H, PhCH), 4.95 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.8 (d, 1 H, $J_{a,b}$ 12 Hz, $PhCH_aH_bO$), and 4.5 (d, 1 H, $J_{a,b}$ 12 Hz, $PhCH_aCH_bO$); lit.[5]: m.p. 152°, $[\alpha]_D^{20}$ +51° (*c* 3, chloroform).

Anal. Calc. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19; O, 26.79. Found: C, 66.55; H, 6.31; O, 27.37.

After acetylation with 1:1 (v/v) acetic anhydride–pyridine, **1** afforded a crystalline diacetate **2**, m.p. 107–108°, $[\alpha]_D^{20}$ +114° (*c* 1.45, dichloromethane; lit.[5]: m.p. 103–105°, $[\alpha]_D^{20}$ +52.6° (*c* 3, chloroform).

Anal. Calc. for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92; O, 28.93. Found: C, 65.06; H, 5.92; O, 28.67.

*Benzyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**3**). — To a solution of **1** (10 g, 28 mmol) in dry tetrahydrofuran (100 ml) and benzyl bromide (10 ml), sodium hydride (2.02 g, 84 mmol) was added portionwise, and the mixture was heated under reflux. T.l.c. in 9:1 (v/v) chloroform–methanol showed complete conversion after 24 h. The reaction mixture was cooled and methanol–water was added cautiously to decompose the excess of hydride. The solvent was evaporated and the residue was extracted with chloroform; the extract was dried (sodium sulfate) and evaporated. The residue crystallized from ethyl acetate–light petroleum to give **3** (9.92 g, 67%), m.p. 137.5–138°, $[\alpha]_D^{20}$ +25° (*c* 1.02, chloroform); n.m.r. data: δ 7.6–7.2 (m, 20 H, 4 Ph) and 5.58 (s, 1 H, PhCH).

Anal. Calc. for $C_{34}H_{34}O_6$: C, 75.81; H, 6.36; O, 17.82. Found: C, 75.90; H, 6.32; O, 18.18.

*Benzyl 2,3-di-*O*-benzyl-α-*D*-glucopyranoside* (**4**). — A suspension of **3** (8.9 g) in 0.5M hydrochloric acid (45 ml) and methanol (135 ml) was heated under reflux. After 30 min, all the starting material was dissolved and t.l.c. in 5:1 (v/v) toluene–acetone showed complete hydrolysis. An excess of sodium hydrogencarbonate was added to the cooled solution. The solvents were evaporated and the residue was extracted with chloroform. The extract was dried (sodium sulfate) and evaporated. The residue crystallized from ethyl acetate–light petroleum to give **4** (6.6 g, 90%), m.p. 111–111.5°, $[\alpha]_D^{20}$ +65° (*c* 1.01, chloroform).

Anal. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71; O, 21.31. Found: C, 72.02; H, 6.79; O, 21.57.

*Benzyl 2,3-di-*O*-benzyl-6-*O*-trityl-α-*D*-glucopyranoside* (**5**). — A solution of **4** (5.6 g, 12.5 mmol) in dry pyridine (30 ml) was treated with chlorotriphenylmethane (4.1 g, 14.7 mmol) for 6 h at 100–105°. Toluene was added to the cooled solution until no further precipitation of pyridinium hydrochloride occurred. The solid was filtered off and the filtrate was poured with stirring into 0.03M sodium hydrogencarbonate (1500 ml). The layers were separated; the aqueous layer was washed once with toluene, and the combined toluene solutions were washed twice with 0.03M sodium hydrogencarbonate, and evaporated. The residue (8.5 g, 97%) was a brown, viscous syrup, $[\alpha]_D^{20}$ +45° (*c* 1.03, chloroform).

Anal. Calc. for $C_{46}H_{44}O_6$: C, 79.74; H, 6.40; O, 13.86. Found: C, 79.72; H, 6.21; O, 13.56.

*Benzyl 4-*O*-allyl-2,3-di-*O*-benzyl-α-*D*-glucopyranoside* (**6**). — A solution of **5** (10 g, 14 mmol) in dry benzene (20 ml) was added dropwise at room temperature to a suspension of sodium hydride (4.7 g) in dry benzene (20 ml) and allyl bromide

(4.9 ml). The mixture was heated under reflux for 16 h. The excess of hydride was cautiously decomposed by the addition of methanol–water. The upper layer was washed with water, dried (sodium sulfate), and evaporated. The residue was treated with 80% acetic acid (150 ml) at 95–100°. After 2 h, t.l.c. in 2:1 (v/v) ether–light petroleum showed complete hydrolysis. An excess of sodium hydrogencarbonate was added to the cooled solution. The mixture was extracted twice with ether; the extract was dried (sodium sulfate) and evaporated. The resulting material was chromatographed on silica gel with 2:1 (v/v) ether–light petroleum to give **6** (4.6 g, 65%) which crystallized from light petroleum, m.p. 77–78°, $[\alpha]_D^{20}$ +89.4° (*c* 1.3, chloroform); i.r. data: ν_{max}^{KBr} 3480 (OH), 1640, and 930 cm^{-1} (–O–CH_2–CH=CH_2); n.m.r. data: δ 5.9 (m, 1 H, –O–CH_2–C*H*=CH_2) and 5.4–5.0 (m, 2 H, –O–CH_2–CH=CH_2).

Anal. Calc. for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99; O, 19.57. Found: C, 73.45; H, 6.87; O, 19.64.

*Benzyl 2,3,6-tri-*O*-benzyl-α-*D*-glucopyranoside* (**7**). — Sodium hydride (0.294 g, 12.8 mmol) was added portionwise to a solution of **6** (4 g, 8 mmol) in dry tetrahydrofuran (50 ml) and benzyl bromide (1.4 ml, 12 mmol). The mixture was heated under reflux for 6 h. The excess of hydride was decomposed by the addition of methanol–water. The solvents were evaporated and the residue was extracted with chloroform. The extract was washed with water, dried (sodium sulfate), and evaporated. The resulting material (4.4 g) was dissolved in dry dimethyl sulfoxide (8 ml) and treated with potassium *tert*-butoxide (0.421 g, 3.75 mmol) at 100° under dry nitrogen. After 30 min, t.l.c. in 1:3 (v/v) ether–light petroleum showed complete isomerisation. The mixture was cooled, diluted with water, and extracted with ether. The extract was dried (sodium sulfate) and evaporated. The resulting brown syrup (3.5 g) was dissolved in 10:1 (v/v) acetone–water (20 ml). To the solution were added yellow mercuric oxide (1.65 g), and then dropwise during 5 min a solution of mercuric chloride (1.65 g) in 10:1 (v/v) acetone–water (20 ml). When the addition was complete, the solid was removed by filtration through Celite, the acetone evaporated, and ether added. The ether layer was washed with a saturated aqueous solution of potassium iodide and then with water, dried (sodium sulfate), and evaporated. The resulting material was chromatographed on silica gel with 1:1 (v/v) ether–light petroleum to give a syrup (3 g, 70%) that was distilled, b.p.$_{0.01mm}$ 280°, $[\alpha]_D^{20}$ +43° (*c* 1.16, chloroform).

Anal. Calc. for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71; O, 17.76. Found: C, 75.36; H, 6.75; O, 17.70.

*Benzyl 2,4-di-*O*-benzyl-6-*O*-trityl-β-*D*-galactopyranoside* (**9**). — A solution of benzyl 2,4-di-*O*-benzyl-β-D-galactopyranoside[6] (**8**) (4.5 g, 10 mmol) in dry pyridine (50 ml) was treated with chlorotriphenylmethane (3.1 g, 11 mmol) for 24 h at room temperature. The mixture was poured into iced water (400 ml). The gum that was precipitated was dissolved in chloroform. The extract was washed successively with ice-cold M hydrochloric acid and water, then dried (magnesium sulfate) and evaporated. The residue was chromatographed on silica gel with 1:1 (v/v) ether–light petroleum to give a material that precipitated as a white, amorphous solid from

ethanol solution by addition of iced water (4.3 g, 62%), $[\alpha]_D^{20}$ −19° (*c* 1.00, chloroform).

Anal. Calc. for $C_{46}H_{44}O_6$: C, 79.74; H, 6.40; O, 13.86. Found: C, 79.45; H, 6.45; O, 13.73.

Benzyl 3-O-allyl-2,4-di-O-benzyl-6-O-trityl-β-D-galactopyranoside (**10**). — A solution of **9** (4.2 g, 6 mmol) in dry tetrahydrofuran (10 ml) was treated with sodium hydride (0.66 g) and allyl bromide (4.5 ml) for 1 h at room temperature, and then under reflux for 5 h. The excess of hydride was decomposed by the addition of methanol to the cooled mixture. The solvents were evaporated and the residue was extracted with ether; the extract was washed with water, dried (magnesium sulfate), and evaporated. The residue was chromatographed on silica gel with 1:3 (v/v) ether–light petroleum to give a syrup (4.0 g, 90%), $[\alpha]_D^{20}$ −29° (*c* 1.20, chloroform); i.r. data: ν_{max}^{film} 1645 and 925 cm^{-1} (–O–CH_2–CH=CH_2); n.m.r. data: δ 5.92 (m, 1 H, –O–CH_2–C*H*=CH_2) and 5.55–5.00 (m, 2 H, –O–CH_2–CH=CH_2).

Anal. Calc. for $C_{49}H_{48}O_6$: C, 80.30; H, 6.60; O, 13.10. Found: C,80.43; H, 6.44; O, 12.86.

Benzyl 3-O-allyl-2,4-di-O-benzyl-β-D-galactopyranoside (**11**). — To a solution of **10** (4.1 g, 5.6 mmol) in glacial acetic acid (10 ml) at 100°, hot water (5 ml) was added slowly. The mixture was kept at 100° for 1 h, and then cooled and evaporated. The remaining water and acid were codistilled with 1:1 (v/v) toluene–ethanol. The residue was chromatographed on silica gel with 1:1 (v/v) ether–ligth petroleum, and then with pure ether to give a material that crystallized from ethyl acetate–ether (1.8 g, 66%), m.p. 101°, $[\alpha]_D^{20}$ −58° (*c* 1.15, chloroform); i.r. data: ν_{max}^{KBr} 3520 (OH), 1645, and 930 cm^{-1} (–O–CH_2–CH=CH_2); n.m.r. data: δ 6.05 (m, 1 H, –O–CH_2–C*H*=CH_2) and 5.60–5.00 (m, 2 H, –O–CH_2–CH=CH_2).

Anal. Calc. for $C_{30}H_{34}O_6$: C, 73.44; H, 6.99; O, 19.57. Found: C, 73.62; H, 6.94; O, 19.50.

Benzyl 2,4-di-O-benzyl-3-O-(1-propenyl)-β-D-galactopyranoside (**12**). — A solution of **11** (4.9 g, 10 mmol) in dry dimethyl sulfoxide (20 ml) was treated with potassium *tert*-butoxide (2.2 g, 20 mmol) under dry nitrogen for 1 h at 100°. Examination by t.l.c. in various solvents did not permit to distinguish between **11** and **12**. Hydrolysis of a portion of the reaction mixture with dilute hydrochloric acid indicated complete conversion after 1 h. The mixture was cooled, diluted with water, and extracted with ether. The extract was dried (magnesium sulfate) and evaporated. The residue was crystallized from ethyl acetate–light petroleum to give **12** (3.6 g, 73%), m.p. 116°, $[\alpha]_D^{20}$ −25° (*c* 1.19, chloroform); i.r. data: ν_{max}^{KBr} 3520 (OH) and 1665 cm^{-1} (–O–CH=CH–CH_3); n.m.r. data: δ 6.15 (d, 1 H, –O–C*H*=CH–CH_3, $J_{1',2'}$ 7 Hz) and 1.64 (d, 3 H, –O–CH=CH–CH_3, $J_{2',3'}$ 7.5 Hz).

Anal. Calc. for $C_{30}H_{34}O_6$: C, 73.44; H, 6.99; O, 19.57. Found: C, 73.43; H, 6.97; O, 19.56.

Benzyl 6-O-allyl-2,4-di-O-benzyl-β-D-galactopyranoside (**13**). — A solution of **12** (4.9 g, 10 mmol) in dry tetrahydrofuran (10 ml) was treated with sodium hydride (1.1 g) and allyl bromide (7.5 ml) for 1 h at room temperature, and then for 5 h under

reflux. The mixture was processed as described for **10**. The residue (4.2 g, 80%) was dissolved in acetone (36 ml) and M hydrochloric acid (4 ml), and the mixture was boiled for 15 min under reflux. An excess of potassium hydrogen carbonate was added and the solvents were evaporated. The residue was extracted with ether; the extract was washed with water, dried (magnesium sulfate), and evaporated. The resulting material was chromatographed on silica gel with 1:1 (v/v) ether–light petroleum to give a syrup (2.5 g, 70%) that was distilled, b.p.$_{0.01\,mm}$ 230–240°, $[\alpha]_D^{20}$ −19° (*c* 0.905, chloroform); i.r. data: ν_{max}^{film} 3560 (OH), 1640, and 920 cm^{-1} (–O–CH_2–CH=CH_2); n.m.r. data: δ 5.80 (m, 1 H, –O–CH_2–C*H*=CH_2) and 5.40–4.95 (m, 2 H, –O–CH_2–CH=CH_2).

Anal. Calc. for $C_{30}H_{34}O_6$: C, 73.44; H, 6.99; O, 19.57. Found: C, 73.44; H, 6.80; O, 19.35.

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