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Note

Reaction of benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside with diazomethane: synthesis of 2-*O*-methyl-D-galactose and some derivatives

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Samples of 2-*O*-methyl-D-galactose (**1**) were required for renal cell-transport studies[1].

An improved synthesis of **1** has been described recently[2]. Treatment of benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside[3,4] (**2**) with excess of diazomethane in the presence of boron trifluoride etherate gave compound **3**, which was debenzoylated to give benzyl 4,6-*O*-benzylidene-2-*O*-methyl-β-D-galactopyranoside (**4**). Exhaustive hydrogenation of **4** over a palladium catalyst gave **1** in good yield.

As part of further studies of selective acylation[3,4] and alkylation, benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**5**) has been treated with diazomethane in the presence of various catalysts. A simplified synthesis of **1**, and some derivatives, from **5** is now described.

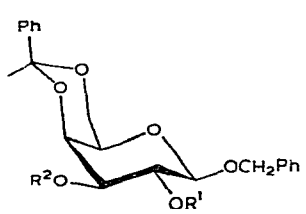
Treatment of **5** in methanol–dichloromethane with excess of diazomethane, in the presence of a catalytic amount of stannous chloride dihydrate[5], gave a crystalline, mono-*O*-methylated derivative in high yield. The melting point (152–154°) did not correspond with that of either of the previously synthesised[2] mono-methylated derivatives of **5**, namely, the 2-ether **4** (m.p. 106–110°) and the 3-ether **6** (m.p. 182–183°). Thin-layer chromatography showed that the new product had the same mobility as compound **4**. Catalytic hydrogenation of the product over palladium oxide gave crystalline 2-*O*-methyl-β-D-galactose (**1**), characterised as 1,3,4,6-tetra-*O*-acetyl-2-*O*-methyl-α-D-galactopyranose (**7**).

Previously[2], compound **4** had been recrystallized from propan-2-ol but tended to form gels in this solvent. However, when a sample of **4** prepared earlier[2] was recrystallised from propan-2-ol with addition of seed crystals of the new, higher-melting product, it yielded this form exclusively. Acetylation of **4** and the new product gave the same crystalline acetate **8**. Mild, acid hydrolysis of the two forms yielded benzyl 2-*O*-methyl-β-D-galactopyranoside (**9**), thus confirming the dimorphic nature of the products.

Little reaction of **5** occurred with excess of diazomethane in the presence of

catalytic amounts of cobaltous chloride, cuprous chloride, magnesium chloride, mercuric chloride, or nickel chloride; only traces (t.l.c.) of the ether **4** were obtained. The catalytic action of stannous chloride is not understood.

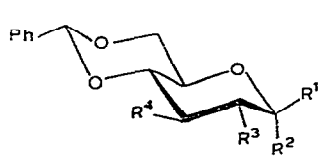
Reaction of **5** with diazomethane in the presence of boron trifluoride etherate or boron trifluoride methanolate gave benzyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-galactopyranoside (**10**) in yields of 84 and 79%, respectively. No reaction was observed between the diol **5** and diazomethane in the absence of a catalyst. Hydrogenation of **10** over a palladium catalyst yielded syrupy 2,3-di-*O*-methyl-D-galactose (**11**), which was characterised as 2,3-di-*O*-methyl-*N*-phenyl-D-galactopyranosylamine.



2 $R^1 = H; R^2 = Bz$
3 $R^1 = Me; R^2 = Bz$
4 $R^1 = Me; R^2 = H$
5 $R^1 = R^2 = H$
6 $R^1 = H; R^2 = Me$
8 $R^1 = Me; R^2 = Ac$
10 $R^1 = R^2 = Me$

Depending on the catalyst used, intramolecular hydrogen-bonding is probably the main influence responsible for the different reactivities of the hydroxyl groups in the diol **5**. It is known[3,4] that HO-3 in **5** is much more reactive than HO-2 towards benzoylating agents. This has been ascribed[3] to strong hydrogen-bonding of the equatorial HO-3 to the axial O-4. In the presence of the boron trifluoride etherate or methanolate, the hydrogen bonding is precluded during complex formation[6], and both hydroxyl groups are methylated. With stannous chloride as a catalyst, the hydrogen-bonding pattern presumably remains unaffected. The 2-hydroxyl group, being non-bonded or less strongly bonded than HO-3, and relatively more acidic, reacts readily to give compound **4** in high yield. Intramolecular hydrogen-bonding is possible between an equatorial hydroxyl group and a neighbouring, equatorial oxygen atom[7]. There are examples of compounds that contain a hydroxyl group adjacent to another polar substituent and are not methylated by diazomethane, due to chelation or bonding effects[8–10].

An earlier study[5] on the partial methylation of *C*- and *O*-glucosides, with diazomethane and stannous chloride as a catalyst, showed O-3 methylation to be a favoured process. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**12**), for example, gave the 3-*O*-methyl derivative **13** (93%) plus a trace of dimethyl ether **14**, whereas the β-D anomer **15** afforded a mixture of the 2-ether **16** (34%), 3-ether **17** (52%), and the diether (trace). In **12**, the formation of an intramolecular hydrogen-bond between



12 $R^1 = H; R^2 = OMe; R^3 = R^4 = OH$
13 $R^1 = H; R^2 = R^4 = OMe; R^3 = OH$
14 $R^1 = H; R^2 = R^3 = R^4 = OMe$
15 $R^1 = OMe; R^2 = H; R^3 = R^4 = OH$
16 $R^1 = R^3 = OMe; R^2 = H; R^4 = OH$
17 $R^1 = R^4 = OMe; R^2 = H; R^3 = OH$

HO-2 and the axial MeO-1 could account for the high yield of **13**. The lower proportion of **16** in the mixture of products from the β-D-glucoside **15** may be due to steric reasons. Here, hydrogen bonding is less favoured and HO-2, being more acidic than HO-3, would be expected to react more readily with diazomethane.

It is interesting that the order of reactivity of the hydroxyl groups in the diols **5** and **12** during methylation by this procedure is the reverse of that for selective acylation[3,4,11–13].

EXPERIMENTAL

I.r. spectra were determined for Nujol mulls. Descending paper chromatography was performed as described previously[14]. Silica gel G (Merck) was used for t.l.c., with benzene–dichloromethane–ether (4:2:1, v/v); compounds were detected by charring with sulphuric acid. Dichloromethane was redistilled from phosphorus pentaoxide before use. Evaporations were carried out at 40° *in vacuo*. All melting points are uncorrected.

Treatment of benzyl 4,6-O-benzylidene-β-D-galactopyranoside (**5**) *with diazomethane.* — (*a*) *With stannous chloride dihydrate as catalyst.* A solution of compound **5** (4.0 g) in methanol (200 ml) and dichloromethane (100 ml), containing stannous chloride dihydrate (10 mg), was cooled to 0° and treated with a solution of diazomethane [from *N*-nitrosomethylurea[15] (14.0 g)]. The mixture was stirred at room temperature for 4–6 h; t.l.c. then indicated complete reaction. The solvent was evaporated, and a solution of the residue in dichloromethane (100 ml) was washed with water (2 × 25 ml), dried (Na_2SO_4), and evaporated. The crystalline residue (4.15 g) was recrystallized from propan-2-ol to give benzyl 4,6-*O*-benzylidene-2-*O*-methyl-β-D-galactopyranoside (**4**; 3.78 g, 91%), m.p. 152–154°, $[\alpha]_D^{22}$ −45° (*c* 2.0, dichloromethane); lit.[2] m.p. 106–110°, $[\alpha]_D$ −41.2° (Found: C, 67.4; H, 6.8. $C_{21}H_{24}O_6$ calc.: C, 67.7; H, 6.5%).

(*b*) *With boron trifluoride etherate as catalyst.* A solution of compound **5** (1.0 g) in dichloromethane (70 ml) at −10° was treated with boron trifluoride etherate (0.05 ml) and, at the same temperature, a solution of diazomethane in dichloromethane[15] was then added until a faint-yellow colour persisted for 10–15 sec. After 3 h at 0°, polymethylene was filtered off and washed with dichloromethane (50 ml), and the combined filtrate and washings were washed successively with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated. The crystalline residue (1.05 g) was recrystallized from ether–hexane to yield benzyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-galactopyranoside (**10**; 0.905 g, 84%), m.p. 141°, $[\alpha]_D^{22}$ −22.5° (*c* 1.6, chloroform) (Found: C, 68.3; H, 6.8. $C_{22}H_{26}O_6$ calc.: C, 68.4; H, 6.8%).

(*c*) *With boron trifluoride methanolate as catalyst.* A solution of compound **5** (1.0 g) in dichloromethane (70 ml) was treated with boron trifluoride methanolate (0.06 ml) and then with diazomethane, as described in (*b*), to yield, after recrystallization, **10** (0.85 g, 79%), m.p. 139–140°, $[\alpha]_D^{23}$ −21.6° (*c* 1.1, chloroform).

Benzyl 3-O-acetyl-4,6-O-benzylidene-2-O-methyl-β-D-galactopyranoside (**8**). — A solution of **4** (0.5 g) in dry pyridine (4 ml) was treated with acetic anhydride (2.5 ml) and kept at room temperature for 9 days. The usual work-up procedure gave, after recrystallization from ethanol–light petroleum (60–80°), **8** (0.38 g, 68%), m.p. 99–100°, $[\alpha]_D^{23}$ +53° (*c* 1.3, chloroform) (Found: C, 66.85; H, 6.3. $C_{26}H_{26}O_7$ calc.: C, 66.7; H, 6.3%).

Acetylation of the dimorphic form[2] of compound **4** (m.p. 106–110°) in the same manner also gave **8**, which was identical in all respects to the above product.

Benzyl 2-O-methyl-β-D-galactopyranoside (**10**). — A solution of **4** (or the dimorphic form[2]) (1.0 g) in glacial acetic acid (30 ml) was heated on a boiling-water bath. Water (20 ml) was added in portions during 5 min, and heating was continued for a further 2 h. Evaporation of the solvent, followed by re-evaporation with water (4 × 10 ml) and several portions of dry toluene, gave a white residue which, on recrystallization from ethanol–ether, gave compound **10** (558 mg, 73.5%), m.p. 118–120°, $[\alpha]_D^{24}$ −36° (*c* 1.4, chloroform) (Found: C, 59.0; H, 7.2. $C_{14}H_{20}O_6$ calc.: C, 59.1; H, 7.1%).

2-O-Methyl-β-D-galactose (**1**). — A solution of compound **4** (1.09 g) in methanol (100 ml) was hydrogenated exhaustively in the presence of palladium (from 1.25 g of the oxide). The filtered mixture was concentrated and the residue recrystallized from ethanol–ether to yield **1** (0.4 g, 77%), m.p. 145–148°, $[\alpha]_D^{23}$ +81.6° (equil., *c* 1.4, water); lit.[16] m.p. 147–149°, $[\alpha]_D$ +82.6° (equil.).

A portion of the product (0.2 g) in glacial acetic acid (4 ml) and acetic anhydride (2 ml) was cooled to −5° and treated with perchloric acid (70%, 0.12 ml). The mixture was stirred for 48 h at 0°, then poured into ice–water (100 ml), and extracted with chloroform (50 ml). The chloroform solution was washed successively with water, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated. The residue was crystallized and recrystallized from 95% ethanol to give 1,3,4,6-tetra-*O*-acetyl-2-*O*-methyl-α-D-galactopyranose (190 mg, 51%), m.p. 98–101°, $[\alpha]_D^{22}$ +95.5° (*c* 1.5, chloroform); lit.[16] m.p. 101–102°, $[\alpha]_D$ +98° (chloroform).

2,3-Di-O-methyl-D-galactose (**11**). — Exhaustive hydrogenation of **10** (1.0 g), as described above for **4**, gave syrupy **11** (520 mg), $[\alpha]_D^{23}$ +89° (equil., *c* 2.8, water); lit.[17] $[\alpha]_D$ +94°.

A portion of the product in methanol was treated with one equivalent of redistilled aniline and the mixture was heated under reflux for 4 h. Evaporation of the solvent and crystallization of the residue from acetone–hexane at 0° gave 2,3-di-*O*-methyl-*N*-phenyl-D-galactopyranosylamine, m.p. 150–153°; lit.[17] m.p. 151–153°.

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