Carbohydrate Research, 39 (1975) 245–251

SELECTIVE BENZYLATION OF SOME D-GALACTOPYRANOSIDES. UNUSUAL RELATIVE REACTIVITY OF THE HYDROXYL GROUP AT C-4

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(Received July 22nd, 1974; accepted October 8th, 1974)

ABSTRACT

Partial benzylation of methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside gave methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside as the major product, whereas the isomeric 2,6-di-*O*-benzyl ether gave a mixture of products in which the ratio of methyl 2,4,6- to methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside was ~4:1. The proportion of unreacted starting-material was low in both cases, whereas after a similar reaction of methyl 2,6-di-*O*-benzyl-β-D-galactopyranoside more than 50% of the dibenzyl ether was recovered unchanged. In this case also, considerably higher reactivity was exhibited by the hydroxyl group at C-4 than that at C-3. Acid hydrolysis of the methyl glycosides of the tribenzyl ethers afforded crystalline 2,4,6-tri-*O*-benzyl-α-D-galactose and syrupy 2,3,6-tri-*O*-benzyl-D-galactose. Structures of intermediates were established by acetylation, examination of their n.m.r. spectra, and conversion into the known 3-*O* and 4-*O*-methyl-D-galactose.

INTRODUCTION

A number of conclusions have been drawn on the relative reactivities of the different hydroxyl groups in hexopyranosides toward electrophilic reagents[1,2]. The axial hydroxyl group at C-4 in methyl α-D-galactopyranoside was shown to be the one least readily benzoylated[3], while partial methylation of methyl 6-deoxy-α-L-galactopyranoside again showed that the hydroxyl group at C-4 had the lowest reactivity[4]. However, this same hydroxyl group at C-4 was recently shown to be more reactive than that at C-3_{eq} under conditions of benzylation[5].

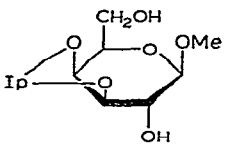
The potential value of partially benzylated ethers of D-galactose in synthetic work and the theoretical interest of the reaction encouraged us to investigate the partial benzylation of some derivatives of methyl α-D-galactopyranoside and to demonstrate the effect of the configuration of the aglycon (α or β) on the reaction.

RESULTS AND DISCUSSION

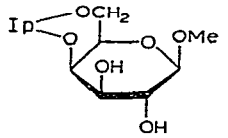
Treatment of methyl β-D-galactopyranoside[6] with acetone in the presence of sulfuric acid afforded the 3,4-acetal[7] (**1**), together with a small amount of its 4,6-

isomer, which was isolated and characterized. The 3,4-acetal (**1**) was benzylated and removal of the acetal group afforded methyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (**6**), which was isolated as a crystalline solid.

Selective benzylations of **6**, methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**7**), and methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside[8] (**8**) were performed with a slight molar excess of sodium hydride and benzyl bromide in *N*,*N*-dimethylformamide. The resulting mixture was separated chromatographically into its components, which were identified on the basis of: (a) Their n.m.r. spectra and those of their acetates; (b) methylation of the tribenzyl ethers obtained from **7** and **8** by Hakomori's method[9], followed by catalytic hydrogenolysis and periodate oxidation of the resultant methyl 4-*O*- and 3-*O*-methyl-α-D-galactopyranosides (**15** and **16**, respectively); (c) the n.m.r. spectra of the triacetates of **15** and **16**; (d) acid hydrolysis of **15** and **16** and isolation of the known 4-*O*- and 3-*O*-methyl-D-galactose (**4** and **5**); (e) examination of the n.m.r. spectra of the products from **6**; and (f) examination of the product of hydrolysis of the methyl tri-*O*-benzyl-β-D-galactopyranosides resulting from the benzylation of **6**.



1



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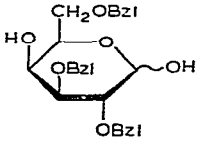

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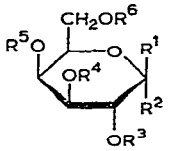

4 R^1 = OH, R^2=R^3=R^4 = R^6 = H, R^5 = Me
5 R^1 = R^3=R^5=R^6=H, R^2 = OH, R^4 = Me
6 R^1 = OMe, R^2=R^4=R^5=H, R^3=R^6= Bzl
7 R^1 = R^4 = R^5 = H, R^2 = OMe, R^3=R^6= Bzl
8 R^1 = R^5=R^6=H, R^2=OMe, R^3=R^4= Bzl
9 R^1 = R^5=H, R^2=OMe, R^3=R^4=R^6= Bzl
10 R^1 = R^4=H, R^2=OMe, R^3=R^5=R^6= Bzl
11 R^1 = OMe, R^2=R^4=H, R^3= R^5=R^6= Bzl
12 R^1 = OMe, R^2=R^5=H, R^3=R^4=R^6= Bzl
13 R^1 = H, R^2=OMe, R^3=R^4=R^6=Bzl, R^5=Me
14 R^1 = H, R^2=OMe, R^3=R^5=R^6=Bzl, R^4=Me
15 R^1 = R^3=R^4=R^6= H, R^2= OMe, R^5= Me
16 R^1 = R^3=R^5=R^6=H, R^2=OMe, R^4= Me
17 R^1=R^4=H, R^2=OH, R^3=R^5=R^6= Bzl
18 R^1 = H, R^2=OMe, R^3=R^4=R^5=R^6= Bzl
19 R^1 = OMe, R^2=H, R^3=R^4=R^5=R^6= Bzl

Selective benzylation of **8** gave, in a high yield (73%), methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**9**); no 2,3,4-tri-*O*-benzyl ether could be detected in the reaction mixture; thus, the hydroxyl group at C-6 was much more reactive than that at C-4. A medium yield of tribenzyl ether (50%) was isolated from the product of benzylation of **7**, with a ratio of methyl 2,3,6- (**9**) to methyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**10**) of ~1:4; here, the greater relative reactivity of the hydroxyl group at C-4 over that at C-3 was clearly apparent. Only small amounts of unreacted **7** and **8** were recovered, whereas, in the reaction of the β-D-glycoside (**6**), much less

material was alkylated (50% of **6** was recovered unchanged). Although the ratios of 3- and 4-substituted products were rather different, substitution had again favored the 4_{ax} position: methyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**11**) and methyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**12**) were isolated in a ratio of 2:1. The rates of migration of the α- and β-glycosides on silica gel showed an interesting phenomenon. Although **9** emerged from the column before **10**, the β-D-glycoside of the 2,4,6-benzyl ether (**11**) preceded the 2,3,6-isomer (**12**) on chromatography.

The n.m.r. chemical shifts of the acetyl protons of acetylated **9** and **10** were clearly consonant with axial and equatorial conformations, respectively. In the acetate of **10**, H-3 was identified as a pair of doublets shifted downfield due to the effect of the acetoxy group on C-3. The acetates of **11** and **12** were also distinguished on the basis of the chemical shifts of the acetyl protons. In addition, there was a clear difference between the chemical shift of OMe_{ax} at C-1 in **9**, **10** and their acetates (τ 6.68), and OMe_{eq} at C-1 in **11**, **12**, and their acetates (τ 6.50).

Acid hydrolysis of **10** afforded, in a good yield, 2,4,6-tri-*O*-benzyl-α-D-galactose (**17**) which crystallized from absolute ethanol. The compound mutarotated downwards, at a slow rate, in chloroform solution and was thus designated α-D; the value observed for the optical rotation after 68 h may not represent the final equilibrium, as the total mutarotation was small. An identical compound was obtained by hydrolysis of **11**, thus confirming the structure assigned to **11**. Acid hydrolysis of **9** gave 2,3,6-tri-*O*-benzyl-D-galactose (**3**), isolated as a syrup that could not be crystallized.

The differential reactivity of the substituted methyl β- and α-D-galactopyranosides (**6** and **7**) with benzyl bromide and sodium hydride is intriguing and represents a relative inactivation of both free hydroxyl groups in **6** that cannot readily be explained. However, selective methylation of methyl α- and β-D-galactopyranosides proceeds at different speeds for both compounds. In both compounds **6** and **7**, the hydroxyl group at C-4 is more reactive than that at C-3. The n.m.r. spectra of **6** and **7** and their derivatives are in apparent agreement with the $^4C_1$ conformation, and it would appear that the axial or equatorial disposition of the group is not the only factor determining its reactivity. Furthermore, the proximity of the substituent at C-6 to the axial hydroxyl group at C-4, which depresses its reactivity in some acylations[1–3], does not seem to cause any hindrance to benzylation. The effect of the substituent at C-6 may be electronic rather than steric and may be manifested more by an acyl than by an alkyl group, although methyl α-L-fucopyranoside shows selective deactivation of the hydroxyl group at C-4 to methylation[4] and benzoylation[11]. It should be emphasised that the present study entails treatment of a carbohydrate with sodium hydride to generate the oxygen anion that is the species benzylated*. Presumably, a similar species is formed when powdered potassium hydroxide is used in organic

*The author's attention was drawn by a referee to the selective benzylation of methyl α-D-glucopyranoside by benzyl chloride and sodium hydride, which gave methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside in a 62% yield [S. Koto, Y. Takebe, and S. Zen, *Bull. Chem. Soc. Jap.*, 45 (1972) 291–293].

solvents[5]. In a study of the partial methylation of methyl α-D-mannopyranoside[12], it was concluded that there was a slight preference for the hydroxyl group at C-4 over that at C-3 under the conditions of Hakomori's procedure. However, analysis of the trimethyl ethers produced led the authors to conclude that the presence of a methoxyl group at C-2 and C-6 *enhanced* the activity at C-3 relative to that at C-4. In their case, there were no conformational effects involved since both hydroxyl groups at C-3 and C-4 are in equatorial position in methyl α-D-mannopyranoside.

In conclusion, it can be predicted, on the basis of this study and the previous one in the L-fucose series[5], that the reactivity of the hydroxyl group at C-4 in strongly alkaline media will be considerable and sufficient to enable selective substitution at C-4, thus opening the way to the facile preparation of a number of valuable derivatives of hexoses, which had been previously considered difficult to obtain.

EXPERIMENTAL

General methods. — See Ref. 13.

Methyl 3,4- (**1**) *and 4,6-O-isopropylidene-β-D-galactopyranoside* (**2**). — Treatment of methyl β-D-galactopyranoside[6] (15.0 g) with acetone–sulfuric acid, followed by neutralization of the acid and evaporation of the solvent[7], gave a syrup that, on crystallization from benzene, afforded methyl 3,4-*O*-isopropylidene-β-D-galactopyranoside [**1**, 7.5 g, 41%, m.p. 130–132°, $[\alpha]_D^{24}$ +21.7° (*c* 1.18, water); lit.[7]: m.p. 134°, $[\alpha]_D$ +21° (water)]; n.m.r. data: τ 6.46 (3 H, OMe), 8.46, 8.60 (6 H, CMe_2). The mother liquors were evaporated to a syrup that was dissolved in 4:1 (v/v) ethyl acetate–acetone and chromatographed on a silica gel column. The 3,4-acetal (**1**) emerged first from the column (2.5 g), followed by a slower-migrating fraction that crystallized on removal of the solvent. Recrystallization of this second fraction from ethanol gave **2** (1.0 g, 5.5%), m.p. 160–162°; $[\alpha]_D^{25}$ −31.2° (*c* 0.90, chloroform); n.m.r. data: τ 6.46 (3 H, OMe), and 8.52 (6 H, CMe_2).

Anal. Calc. for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.47; H, 7.88.

Methyl 2,6-di-O-benzyl-β-D-galactopyranoside (**6**). — To a solution of **1** (8.7 g) in *N*,*N*-dimethylformamide (100 ml) was added, portionwise, sodium hydride (7 g, 50% dispersion in oil, Fluka, Buchs, Switzerland), and the mixture was stirred for 90 min at ambient temperature. Benzyl chloride (50 ml) was added cautiously and, after completion of the reaction (less than 1 h required as shown by t.l.c.), the mixture was cooled and diluted with benzene, and water was added cautiously. The organic layer was separated, washed thoroughly with water, concentrated, and the excess of benzyl chloride removed by several additions of water and of toluene, followed by evaporation. The residual, pale-orange syrup was treated with aqueous acetic acid (60%, v/v, 100 ml) for 30 min at 100°. After removal of the acid by evaporation, followed by addition and evaporation of water and toluene, the residual syrup was dissolved in 14:14:1 (v/v) benzene–ether–methanol and purified by silica gel chromatography. A homogeneous eluate (11.4 g, 82%) crystallized in needles from diisopropyl ether containing a little ethanol, yield 8.5 g; m.p. 83–85°; $[\alpha]_D^{25}$ +8.6° (*c* 1.08, chloro-

form); n.m.r. data: τ 2.74 (10 H, 2 Ph), 5.28 (d, J 8 Hz, H-1), and 6.48 (3 H, OMe).

Anal. Calc. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.54; H, 6.97.

General method of selective benzylations. — To a stirred solution of the requisite dibenzyl ether in *N*,*N*-dimethylformamide (10 ml/g) was added sodium hydride (50% in oil) in 10% excess (calculated on the basis of complete reaction with a single free hydroxyl group). The solution was stirred for 2 h at ambient temperature, benzyl bromide (1.1 mole) was added dropwise, and stirring was continued for an additional 3 h.

The solution was cooled, processed as described previously, and the residual syrup dissolved in 4:1 (v/v) benzene–ether for chromatographic separation on silica gel. A number of components were separated from the mixture as homogeneous fractions (t.l.c.) and are reported in subsequent paragraphs in the order of their emergence from the column.

(*a*). Methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside[8] (**7**, 2.5 g) gave four separate fractions: methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside (**18**, 0.52 g, 13.5%); methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**9**, 0.33 g, 10.6%); methyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**10**, 1.24 g, 40.0%); and unreacted **7** (0.48 g, 19.2%). Repetition of the reaction on a separate sample of **7** gave the same components in the yields of 15, 12, 40, and 12.5%, respectively.

The structure of the first component was established as that of **18** on the basis of n.m.r. spectroscopy and lack of reaction with acetic anhydride–pyridine, and it was not investigated further. Compound **9** was a syrup, $[\alpha]_D^{25}$ +39.5° (*c* 2.38, chloroform); n.m.r. data: τ 2.72 (15 H, 3 Ph) and 6.66 (3 H, OMe); it was identical (t.l.c., n.m.r.) with the major product of the selective benzylation of **8** (see *b*).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.74. Found: C, 72.50; H, 6.88.

Acetylation of **9** gave a syrupy acetate, $[\alpha]_D^{24}$ +50.6° (*c* 1.77, chloroform); n.m.r. data: τ 2.72 (15 H, 3 Ph), 4.49 (d, J 3 Hz, H-1), 6.68 (3 H, OMe), and 7.96 (3 H, axial OAc).

Compound **10** was a syrup, $[\alpha]_D^{25}$ +46.6° (*c* 1.04, chloroform); n.m.r. data: τ 2.72 (15 H, 3 Ph) and 6.38 (3 H, OMe).

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

Acetylation of **10** gave a syrup, $[\alpha]_D^{24}$ +63.6° (*c* 2.12, chloroform); n.m.r. data: τ 2.72 (15 H, Ph), 4.78 (2 d, $J_{3,2}$ 10 Hz, $J_{3,4}$ 3 Hz, H-3), 6.68 (3 H, OMe), and 8.10 (3 H, equatorial OAc).

(*b*). Methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside (**8**, 2.0 g) gave three major fractions: **18** (0.30 g, 9.7%); **9** (1.80 g, 72.6%); and unchanged **8** (0.30 g, 15.0%).

(*c*). Two separate benzylations of methyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (**6**) gave the following fractions (yields of two separate experiments): methyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (**19**, 7.2%, 7.2%), **11** (25.4%, 21.2%), **12** (14.4%, 11.0%), and unchanged **6** (50.0%, 55.0%).

Compound **11**: $[\alpha]_D^{24}$ +1.0° (*c* 1.90, chloroform); n.m.r. data, τ 2.76 (15 H, 3 Ph) and 6.50 (3 H, OMe).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.09; H, 7.15.

Acetate of **11**: τ 2.76 (15 H, 3 Ph), 6.50 (3 H, OMe), and 8.16 (3 H, equatorial OAc).

Compound **12**: $[\alpha]_D^{24}$ +3.1° (*c* 2.58, chloroform); n.m.r. data: τ 2.72 (15 H, 3 Ph) and 6.50 (3 H, OMe).

Anal. Calc. for $C_{28}H_{32}O_6$, C, 72.39; H, 6.94. Found: C, 72.48; H, 6.85.

Acetate of **12**: τ 2.75 (15 H, 3 Ph), 6.50 (3 H, OMe), and 7.96 (3 H, axial OAc).

General method of methylation of dibenzyl ethers. — Nitrogen was passed through a stirred solution of the requisite compound in dimethyl sulfoxide (20 ml/g), sodium hydride (3-fold excess) was added and, after 2 h under nitrogen, methyl iodide (10 ml/g) and the mixture was stirred for an additional 1 h at ambient temperature. After the cooled mixture was diluted with chloroform, the excess of sodium hydride was decomposed by cautious addition of cold water, and the organic layer was separated, decolorized with a solution of sodium thiosulfate, washed with water, dried, and evaporated. A solution of the residue in 9:1 (v/v) benzene–ether was passed through a column of silica gel to give, after evaporation a colorless syrup. Compound **9** gave methyl 2,3,6-tri-*O*-benzyl-4-*O*-methyl-α-D-galactopyranoside (**13**) (95% yield), $[\alpha]_D^{24}$ +20.3° (*c* 1.00, chloroform); n.m.r. data: τ 2.70 (15 H, 3 Ph), 6.48 (3 H, OMe ether), and 6.68 (3 H, OMe, α-glycoside). Compound **10** gave methyl 2,4,6-tri-*O*-benzyl-3-*O*-methyl-α-D-galactopyranoside (**14**) (98% yield), $[\alpha]_D^{24}$ +14.5° (*c* 2.00, chloroform); n.m.r. data: τ 2.70 (15 H, 3 Ph), 6.48 (3 H, OMe, ether), and 6.64 (3 H, OMe, α-glycoside).

Methyl 4-O-methyl-α-D-galactopyranoside (**15**) *and methyl 3-O-methyl-α-D-galactopyranoside* (**16**). — Debenzylation of **13** and **14** by catalytic hydrogenolysis (10% palladium-on-charcoal, 3 atm, 24 h) afforded **15** and **16**, respectively, in quantitative yield. Compound **15** crystallized from abs. ethanol, m.p. 125–127°, $[\alpha]_D^{25}$ +169.9° (*c* 1.02, chloroform); it consumed 0.94 mole periodate/mole during 48 h at room temperature in the dark[14].

Anal. Calc. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.28; H, 7.78.

Compound **16** was a syrup, $[\alpha]_D^{25}$ +163.5° (*c* 1.81, chloroform); it consumed <0.1 mole periodate/mole during 48 h.

Anal. Calc. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.04; H, 7.81.

Acetylation of **15** gave a syrup, $[\alpha]_D^{24}$ +123.0° (*c* 1.35, chloroform); n.m.r. data: τ 6.42, 6.66 (6 H, 2 OMe), and 7.90 (s, 9 H, 3 OAc). Acetylation of **16** gave a syrup, $[\alpha]_D^{24}$ +136.4° (*c* 1.70, chloroform); n.m.r. data: τ 6.62, 6.66 (6 H, 2 OMe), and 7.85–7.95 (t, 9 H, 3 OAc).

4-O-Methyl-D-galactose (**4**). — A solution of **15** (100 mg) in M sulfuric acid (5 ml) was kept for 2 h at 100°. T.l.c. (9:1, v/v acetone–methanol) showed complete hydrolysis of the glycoside. The solution was diluted with water, neutralized with barium carbonate, and evaporated to a syrup that was dissolved in methanol. Filtration removed a little residual barium salts. The solution was concentrated to a small volume, and addition of acetone to turbidity led to slow crystallization (yield, 50 mg), m.p. 217–220°; $[\alpha]_D^{24}$ +60.0° → +85.6° (*c* 1.20, water); [lit.[15]: m.p. 218–221°; $[\alpha]_D^{22-24}$ +61° → +83° (*c* 2.17, water)].

3-O-Methyl-D-galactose (**5**). — Similar treatment of **16** (100 mg) gave **5** (60 mg), m.p. 144–146°; $[\alpha]_D^{24}$ +168° → +113.2° (*c* 1.23, water) [lit.[16]: m.p. 144–147°; $[\alpha]_D^{24}$ +150.6° → +108.6°].

On paper chromatography, in 3:1:1 (v/v) 1-butanol–pyridine–water, **4** and **5** had R_{Gal} 1.45 and 1.68, respectively, and in 4:4:1 (v/v) 1-butanol–acetic acid–water, the R_{Gal} was 1.46 and 1.60, respectively.

2,4,6-Tri-O-benzyl-α-D-galactose (**17**). — (*a*). A stirred solution of **10** (1.35 g) in *p*-dioxane (25 ml) and 6M hydrochloric acid (5 ml) was kept for 20 h at 95–100°. The resulting orange-red solution was diluted with chloroform, and the organic layer was washed with a sodium hydrogencarbonate solution (which removed all the colored impurities), then with water, dried, and evaporated. The resulting syrup, which contained (in addition to a major fraction) a small amount of nonmigrating material on t.l.c. in 1:1 (v/v) benzene–ether, was dissolved in 4:1 (v/v) benzene–ether and purified by silica gel chromatography. A homogeneous product, eluted from the column (0.96 g, 73.5%), gave a white, crystalline solid on removal of the solvent. It was recrystallized from abs. ethanol to yield 0.75 g, m.p. 125–127°; $[\alpha]_D^{24}$ +41.7° (5 min) → 40.0° (20 h) → +39.4° (68 h, *c* 1.10, chloroform).

Anal. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 72.03; H, 6.86.

(*b*). Hydrolysis of **11** (0.50 g) afforded a product identical with **17** (0.30 g), m.p. 125–127°.

2,3,6-Tri-O-benzyl-D-galactose (**3**). — A similar hydrolysis of **9** (1.0 g), followed by silica gel chromatography, afforded a syrup (0.70 g, 71.5%); $[\alpha]_D^{25}$ +13.5° (*c* 2.70, chloroform).

Anal. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.85; H, 6.59.

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