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Note

Selective benzylation of some D-galactopyranosides

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The differential reactivity of hydroxyl groups in glycopyranosides towards acylating and alkylating reagents has been described[1,2] and the effects of neighboring substituent groups on benzylation of 6-deoxy-L-galactopyranosides have been reported[3].

Selective benzylation of glycopyranosides can afford a convenient method for preparing intermediates, *e.g.*, for the synthesis of oligosaccharides[4], although lower yields of desired benzyl ethers may result from this approach compared with those resulting from reactions involving a protection–benzylation–deprotection sequence. The site of benzylation can be controlled by choice of starting carbohydrate and selection of reaction conditions. The partial benzylation of methyl α- (**1**) and β-D-galactopyranosides (**2**) and some of their isopropylidene derivatives is now reported.

TABLE I

ACETYLATED DERIVATIVES OF METHYL α- AND β-D-GALACTOPYRANOSIDE

Compound	*M.p. (degrees)*	$[\alpha]_D$ *(CHCl₃) (degrees)*	*P.m.r. data[a] (CDCl₃, δ scale)*									
			H-1	$J_{1,2}$	*H-2*	*H-3*	*H-4*	$J_{3,4}$	*AcO-2*	*AcO-3*	*AcO-4*	*AcO-6*
3[b]	87–89	+130	4.40	3.6	5.15	5.06	5.38	3.6	2.06	1.98	2.15	2.05
4[c]	92–94	−14	4.99	8.1	5.25	5.03	5.43	3.6	2.09	1.98	2.15	2.05
12[d]	—	+75	4.73	4.0	3.84	5.26	5.40	4.0	—	1.97	2.10	2.03
13	—	+91.5				3.92	5.56	3.6	2.08	—	2.13	2.07
14	—	+100				5.30	4.85	3.6	2.08	2.01	—	2.03
15	—	+87	4.99	3.6	5.23	(5.43–5.47)			2.05	1.97	2.07	—
18	—	+8	4.38	8.1	4.15	4.96	5.34	3.6	—	1.96	2.10	2.04
19	121–123	+48	4.31	8.0	5.14	3.69	5.49	3.6	2.06	—	2.12	2.02
20	—	−31	4.37	8.1	5.14	5.08	5.45	3.5	2.05	1.97	2.05	—

[a]All separated H-1 peaks were doublets, H-2 and H-3 peaks were double doublets, and H-4 peaks were multiplets. [b]Lit.[15] m.p. 86–87°, $[\alpha]_D$ +132.5°. [c]Lit.[16] m.p. 94°, $[\alpha]_D$ −14.05°. [d]*Anal.* Calc. for $C_{20}H_{26}O_9$: C, 58.53; H, 6.39. Found for **12**: C, 58.85; H, 6.24. **13**: C, 58.76; H, 6.51. **14**: C, 58.75; H, 6.48. **15**: C, 58.82; H, 6.56. **18**: C, 58.75; H, 6.60. **19**: C, 58.72; H, 6.52. **20**: C, 58.59; H, 6.15.

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TABLE II

BENZYL ETHERS OF METHYL α- AND β-D-GALACTOPYRANOSIDE

Compound benzylated	*Product*[a]	*Yield (%)*	*M.p. (degrees)*	$[\alpha]_D$ *(CHCl₃) (degrees)*
1	**5**	8	121–123	+114.5
	6	4	—	+95
	7	15	83–85	+91
	8[b]	23.5	143–145	+117.5
2	**9**	6	145–147	+13
	10	15	135–137	0 ($[\alpha]_{365}$ +5.9)
	11	25	100–102	−33
24	**26**	43	—	+83.5
	27	4	—	—
25	**28**	37.5	—	+4
	29	15	—	+8
30	**18**[c]	6		
	19[c]	40		

[a] *Anal.* Calc. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found for **5**: C, 59.26; H, 7.14. **7**: C, 59.25; H, 7.21. **9**: C, 59.01; H, 7.25. **10**: C, 58.98; H, 6.99. **11**: C, 59.22; H, 7.07. Calc. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found for **26**: C, 62.78; H, 7.57. **28**: C, 63.06; H, 7.58. [b] Lit.[8] m.p. 143–145°, $[\alpha]_D$ + 113.2°. [c] See Table I.

TABLE III

BENZYL ETHERS OF D-GALACTOSE

Compound	*M.p. (degrees)*	$[\alpha]_D$ *(H_2O) (degrees)*
2-*O*-Benzyl[a]	145–147	50 → 67.5
3-*O*-Benzyl (**30**)[b]	—	73.4
4-*O*-Benzyl (**31**)	135–137	49.7 → 59.3
6-*O*-Benzyl[c]	96–98	67.4 → 39.4

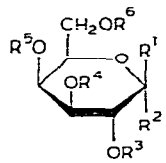
[a] Lit.[17] m.p. 143–144°, $[\alpha]_D$ 47.1→64.4°. [b] *Anal.* Calc. for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found for **30**: C, 57.60; H, 6.99. **31**: C, 57.70; H, 6.75. [c] Lit.[9] m.p. 96–98°.

Monomolar benzylation of **1** and **2** with sodium hydride and benzyl bromide in *N,N*-dimethylformamide gave 50% of a monobenzyl ether fraction, the components of which could be isolated by column chromatography of the tetra-acetates. Deacetylation of these products (Table I) gave the corresponding benzylated glycosides in quantitative yield (Table II). The structures of the various products were established on the basis of elemental analyses, comparison with authentic specimens, p.m.r. data, and hydrolysis to the *O*-benzyl-D-galactose stage (Table III).

3-*O*-Benzyl-D-galactose was prepared by acid hydrolysis, and methyl 3-*O*-

benzyl-α-D-galactopyranoside (**6**) by methanolysis of 3-*O*-benzyl-4,6-*O*-ethylidene-1,2-*O*-isopropylidene-α-D-galactopyranose[5]. Methyl 4-*O*-benzyl-α-D-galactopyranoside (**7**) was prepared by treatment of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[6] (**16**) with benzyl bromide, silver trifluoromethanesulfonate, and 2,4,6-trimethylpyridine[7], followed by debenzoylation. Acid hydrolysis of **7** gave crystalline 4-*O*-benzyl-D-galactose. Crystalline methyl 6-*O*-benzyl-α-D-galactopyranoside[8] (**8**) and 6-*O*-benzyl-D-galactose[9] were prepared by benzylation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose followed by methanolysis and acid hydrolysis, respectively.

The yields of the products of partial benzylation (Table II) showed regioselectivity at HO-6 for both **1** and **2**, and differences in the reactivities of the secondary hydroxyl groups, of which HO-4 was the most reactive in **1** (30% of **7** in the monobenzyl ether fraction) and HO-3 in **2** (33% of **10** in the monobenzyl ether fraction). The reactivity of HO-2 was similar in **1** and **2** (16% of **5** and 13% of **9** in the respective monobenzyl ether fractions). The greater reactivity of HO-6 probably reflects its relatively exposed position and greater acidity. If selectivity in the benzylation of **1** and **2** depends upon the relative acidities of hydroxyl groups and the rate of formation and reactivity of carbohydrate *O*-anions[3], it is difficult to explain the different proportions of 3- and 4-benzyl ethers formed (Table II). A low reactivity of HO-3 in methyl α-D-glucopyranoside towards alkylation has been reported[10], and HO-3 in methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside is less reactive than HO-4 towards benzylation[2].



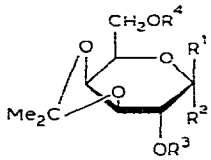
1 $R^1 = R^3 = R^4 = R^5 = R^6 = H, R^2 = OMe$
2 $R^1 = OMe, R^2 = R^3 = R^4 = R^5 = R^6 = H$
3 $R^1 = H, R^2 = OMe, R^3 = R^4 = R^5 = R^6 = Ac$
4 $R^1 = OMe, R^2 = H, R^3 = R^4 = R^5 = R^6 = Ac$
5 $R^1 = R^4 = R^5 = R^6 = H, R^2 = OMe, R^3 = Bzl$
6 $R^1 = R^3 = R^5 = R^6 = H, R^2 = OMe, R^4 = Bzl$
7 $R^1 = R^3 = R^4 = R^6 = H, R^2 = OMe, R^5 = Bzl$
8 $R^1 = R^3 = R^4 = R^5 = H, R^2 = OMe, R^6 = Bzl$
9 $R^1 = OMe, R^2 = R^4 = R^5 = R^6 = H, R^3 = Bzl$
10 $R^1 = OMe, R^2 = R^3 = R^5 = R^6 = H, R^4 = Bzl$
11 $R^1 = OMe, R^2 = R^3 = R^4 = R^5 = H, R^6 = Bzl$
12 $R^1 = H, R^2 = OMe, R^3 = Bzl, R^4 = R^5 = R^6 = Ac$
13 $R^1 = H, R^2 = OMe, R^3 = R^5 = R^6 = Ac, R^4 = Bzl$
14 $R^1 = H, R^2 = OMe, R^3 = R^4 = R^6 = Ac, R^5 = Bzl$
15 $R^1 = H, R^2 = OMe, R^3 = R^4 = R^5 = Ac, R^6 = Bzl$
16 $R^1 = R^5 = H, R^2 = OMe, R^3 = R^4 = R^6 = Bz$
17 $R^1 = H, R^2 = OMe, R^3 = R^4 = R^6 = Bz, R^5 = Bzl$
18 $R^1 = OMe, R^2 = H, R^3 = Bzl, R^4 = R^5 = R^6 = Ac$
19 $R^1 = OMe, R^2 = H, R^3 = R^5 = R^6 = Ac, R^4 = Bzl$
20 $R^1 = OMe, R^2 = H, R^3 = R^4 = R^5 = Ac, R^6 = Bzl$
21 $R^1 = OH, R^2 = R^4 = R^5 = R^6 = H, R^3 = Bzl$
22 $R^1 = OH, R^2 = R^3 = R^4 = R^6 = H, R^5 = Bzl$
23 $R^1 = R^3 = R^4 = R^5 = H, R^2 = OH, R^6 = Bzl$

For methyl α-D-xylopyranoside, HO-2 is the most reactive towards mesylation[11], but least reactive in the β anomer. In the methylation of aromatic glucosides with diazomethane, HO-3 was more reactive than HO-2, especially in the α anomers[12]. Benzylation of methyl 4,6-*O*-benzylidene-D-glucopyranosides in *N*,*N*-dimethyl-

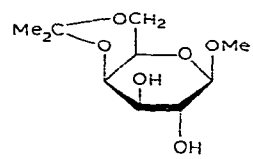
formamide gave preferential 2-*O*-substitution in the α anomer, but 3-*O*-substitution in the β anomer[13]. Little difference was found in the present work in the reactivity of HO-2 towards benzylation in **1** and **2**, but, with methyl 3,4-*O*-isopropylidene-α- (**24**) and -β-D-galactopyranosides (**25**), HO-2 was more reactive in the former.

For **1** and **2**, HO-2 had considerably lower reactivity than HO-6. However, selective benzylation of **24** and **25** produced little substitution at O-6, and the bulk of the monobenzyl ether fractions were the 2-benzyl ethers (**26** and **28**). The mixtures **26** + **27** and **28** + **29** could be fractionated directly. There was enhanced reactivity of HO-2 in the α anomer **24**: the ratio of 6- (**27**) and 2-benzyl (**26**) ethers formed from **24** was 1:11, whereas that for **29** and **28** from **25** was 1:2.5. The relatively high reactivity of HO-2 in **24** and **25** is not shown in methyl 4,6-*O*-isopropylidene-β-D-galactopyranoside (**30**), which gave the 2- (**18**) and the 3-benzyl ethers (**19**) in the ratio 1:6.

The interaction of HO-2 with O-3 in **24** and **25** probably contributes to the enhanced reactivity of HO-2. Likewise, for the 4,6-acetal (**30**), the interaction of HO-3 with O-4 contributes to the enhanced reactivity of O-4. Additional activation of HO-2 in **24** may result from interaction with MeO-1, which is more suitably placed than in the β anomer **25**.



24 R^1 = H, R^2 = OMe, R^3 = R^4 = H
25 R^1 = OMe, R^2 = R^3 = R^4 = H
26 R^1 = R^4 = H, R^2 = OMe, R^3 = Bzl
27 R^1 = R^3 = H, R^2 = OMe, R^4 = Bzl
28 R^1 = OMe, R^2 = R^4 = H, R^3 = Bzl
29 R^1 = OMe, R^2 = R^3 = H, R^4 = Bzl



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The p.m.r. data for the tetra-acetates in Table I showed certain correlations between chemical shifts and positions of substitution. For example, the lowest-field chemical shift was always exhibited by AcO-3 (1.96–2 p.p.m.) and the highest by AcO-4*ax*, although, for **15** and **20**, a considerable displacement of the signal for AcO-4 occurred, presumably due to interaction with BzlO-6. On the other hand, there was little effect of BzlO-4 on the chemical shift of AcO-6 in **14**. The chemical shift of AcO-2 was also hardly changed by BzlO-3, and it remained at 2.05–2.09 p.p.m. The effect of acetylation on the signal for the proton attached to the corresponding carbon was in agreement with previous observations[14]. Thus, for BzlO-2, the signal for H-2 was at 4 p.p.m. (**12**, **18**), whereas, for AcO-2, the signal for H-2 was at >5 p.p.m. The signal for H-3 was similarly shifted from <4 to 5 p.p.m., and there was also a lesser shift of the signal for H-4 from 4.85 to 5.4 p.p.m. in **14**, or greater in derivatives with AcO-4 (**3**, **12**, **13**, **15**).

EXPERIMENTAL

For general methods, see refs. 2 and 3.

Selective benzylation. — Sodium hydride (55% dispersion in oil; 0.48 g, 0.011 mol) was added to a stirred solution of the compound (0.01 mol) in *N,N*-dimethylformamide (25 ml), and stirring was continued for 150 min with the addition of benzyl bromide (1.30 ml, 0.011 mol) after 90 min. Methanol (1 ml) was then added, followed by water (5 ml), and the mixture was concentrated *in vacuo* to a syrup.

For the products from **1** and **2**, the residue was extracted with 14:14:1 benzene–ether–methanol; an insoluble residue that was non-carbohydrate in nature was removed by filtration and the filtrate was loaded onto a column (1.8 × 50 cm) of silica gel. Benzene–ether (1:1) eluted a dibenzyl ether fraction (15–20%, identified by p.m.r. spectroscopy), benzene–ether–methanol (14:14:1) eluted a monobenzyl ether fraction (50%), and chloroform–methanol (4:1) eluted **1** or **2** (20–30%).

For **24**, **25**, and **30**, the material extracted from the crude product mixture with 1:1 benzene–ether was subjected to chromatography. Benzene–ether (1:1) first eluted a dibenzyl ether fraction (10–15%), followed by monobenzyl ethers (50–55%). Unchanged acetal (20–30%) was eluted with 14:14:1 benzene–ether–methanol. Deacetalation was achieved by treating the acetal with 60% acetic acid for 30 min at 95–100°, followed by evaporation of the reagent.

T.l.c. of the monobenzyl ether fractions revealed several components which could not be isolated by column chromatography on silica gel. The fractions were therefore acetylated (acetic anhydride–pyridine) and the products were eluted from silica gel with 4:1 benzene–ether. The order of elution was as follows: from **1**: **15**, **13**, **14**, **12**; from **2**: **20**, **18**, **19**.

Benzylated methyl galactopyranosides were hydrolysed with 1:1 1,4-dioxane–M sulfuric acid at 100° for 2 h. Each hydrolysate was diluted with water, neutralised with barium carbonate, and concentrated. The residue, which was contaminated with a little inorganic material, was dissolved in 4:1 chloroform–methanol and chromatographed on silica gel. 3-*O*-Benzyl-D-galactose was a syrup, but the 2- and 6-*O*-benzyl isomers crystallised from ethanol, and 4-*O*-benzyl-D-galactose from methanol–ethyl acetate.

Methyl 3-O-benzyl-α-D-galactopyranoside (**6**). — Treatment of 3-*O*-benzyl-4,6-*O*-ethylidene-1,2-*O*-isopropylidene-α-D-galactopyranose[5] with boiling, methanolic 1% HCl for 18 h, followed by neutralisation with Amberlite IR-45(HO^-) resin, concentration, and elution of the residue from silica gel with 4:1 ethyl acetate–acetone, gave **6**.

Methyl 4-O-benzyl-α-D-galactopyranoside (**7**). — A solution of benzyl bromide (0.8 ml, 6 mmol) in cyclohexane (5 ml) was added to a mixture of silver trifluoromethanesulfonate (1.6 g, 6 mmol) and cyclohexane (40 ml) stirred at −70°. A solution of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[6] (**16**; 1.57 g, 3 mmol) and 2,4,6-trimethylpyridine (1.06 ml, 8 mmol) in dichloromethane (10 ml) was added and the stirred solution was allowed to attain room temperature and then kept

thereat for 18 h. After the addition of pyridine (1 ml) and excess of dichloromethane, the solution was washed with water, and the organic layer was dried and concentrated. A solution of the residue in 9:1 benzene–ether was chromatographed on silica gel. Syrupy methyl 2,3,6-tri-*O*-benzoyl-4-*O*-benzyl-α-D-galactopyranoside (**17**; 1.30 g, 70%) was eluted by this solvent, followed by recovered **16** (0.38 g, 26%). Catalytic debenzoylation of **17** afforded **7**, which crystallised from ethyl acetate.

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