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Note

Partial benzylation of methyl α-L-fucopyranoside

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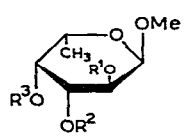
The relative reactivity of hydroxyl groups in glycopyranosides depends upon both steric and electronic influences[1]. In acylation reactions, generally performed in mildly basic media, steric effects apparently predominate, and prediction of regioselectivity is usually possible on the basis of conformational factors. Alkylation reactions, however, often involve more basic conditions with possible carbohydrate *O*-anion intermediates. Under limiting conditions of base and/or alkylating agents, the rate of formation and reaction of competing charged species may then determine the product(s) of reaction. Thus, in distinction to the lower reactivity of the axial HO-4 than the equatorial HO-3 in galactopyranosides towards acylation, the former is more rapidly benzylated in methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside by benzyl bromide and sodium hydride[2]. Benzylation of methyl α-L-fucopyranoside with benzyl chloride and potassium hydroxide in 1,4-dioxane–toluene also favored substitution at HO-4 over that at HO-3, but the total yield of dibenzyl ethers isolated was low and a possible monobenzyl ether fraction was not investigated[3]. A similar pattern of substitution was obtained in allyl α-L-fucopyranoside[4].

Alkylations with sodium hydride in *N*,*N*-dimethylformamide usually proceed very efficiently and with high yields[2]. The selective benzylation of methyl α-L-fucopyranoside (**1**) with these reagents was therefore investigated and an attempt made



1 $R^1 = R^2 = R^3 = H$	**8** $R^1 = R^2 = Bzl, R^3 = Ac$
2 $R^1 = Bzl, R^2 = R^3 = H$	**9** $R^1 = R^3 = Bzl, R^2 = Ac$
3 $R^1 = R^3 = H, R^2 = Bzl$	**10** $R^1 = R^3 = Ac, R^2 = Bzl$
4 $R^1 = R^2 = Bzl, R^3 = H$	**11** $R^1 = Bzl, R^2 = R^3 = Ac$
5 $R^1 = R^3 = Bzl, R^2 = H$	**12** $R^1 = R^2 = R^3 = Bzl$
6 $R^1 = R^2 = H, R^3 = Bzl$	**13** $R^1 = R^2 = R^3 = Ac$
7 $R^1 = H, R^2 = R^3 = Bzl$	**14** $R^1 = Ac, R^2 = R^3 = Bzl$

TABLE I

MONOMOLAR BENZYLATION OF **1**

Compound[a]	*Yield (%)*	*M.p. (degrees)*	$[\alpha]_D$ *(CHCl₃) (degrees)*	*Chemical shifts (p.m.r., δ)*			
				H-1	*H-2*	*H-3*	*H-4*
2		79–81	−119	4.69	3.88	5.26–5.40	
3[b]			−133.5	4.74	3.58	3.79–3.88	
4		78–80	−60				
5[c]			−66				
8	4.7		−61				5.37
9	14.0		−91			5.24	3.77
10[d]	16.5	122–124	−159	4.91	5.10	3.92	5.39
11	32.0		−75	4.69	3.82	5.26–5.40	
13				4.13	4.92	5.18–5.30	
14					5.33		

[a]Lit.[3] m.p.: **2**, 79–81°; **4**, 78–80°; lit.[3] $[\alpha]_D$: **2**, −118°; **4**, −57.8°; **5**, −61.7°; **8**, −46°; **9**, −96°; **11**, −77°. [b]Found: C, 62.80; H, 7.66. Calc. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. [c]Acid hydrolysis of **5** gave 2,4-di-*O*-benzyl-L-fucose, m.p. 135–137°, $[\alpha]_D$ −74.5° (*c* 0.87, chloroform); lit.[3] m.p. 133–135°, $[\alpha]_D$ −75.5°. [d]Found: C, 61.40; H, 6.96. Calc. for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86.

to isolate optimal yields of monobenzylated products in order to elucidate the relative reactivities of the three hydroxyl groups in **1**.

Selective benzylation of **1** with equimolar proportions of sodium hydride and benzyl bromide in *N,N*-dimethylformamide gave a good yield (70%) of mono- and di-benzyl ethers; unchanged **1** was recovered and could be recycled. P.m.r. spectroscopy indicated that the separated mono- and di-benzyl ether fractions (2.5:1 ratio) were mixtures. After acetylation of these fractions, t.l.c. showed the presence of several components in each. Column chromatography led to the isolation of three separate components from each fraction which were characterised by n.m.r. spectroscopy and comparison of physical constants with those of authentic specimens (Table I). Catalytic deacetylation afforded benzyl ethers of **1** which were also characterised.

Employment of two molar proportions of sodium hydride and benzyl bromide converted **1**, in high yield, into mono- and di-benzyl ethers in the ratio 1:4. The components present in each fraction and their relative proportions were very similar to those obtained previously.

The products obtained were identified as methyl 2-*O*-benzyl- (**2**), 3-*O*-benzyl- (**3**), 2,3-di-*O*-benzyl- (**4**), and 2,4-di-*O*-benzyl-α-L-fucopyranoside (**5**). The ratio **2**:**3** was ~2:1, and that of **4**:**5** was ~1:3. Traces of methyl 4-*O*-benzyl- (**6**) and 3,4-di-*O*-benzyl-α-L-fucopyranoside (**7**) were also obtained.

Benzylation of **2** with sodium hydride–benzyl bromide resulted in only slight regioselectivity, the ratio of **4**:**5** in the product being ~2:3.

In the early stages of benzylation of **1**, HO-2 and HO-3 were apparently the most reactive, since only traces of 4-benzyl ether (**6**) could be detected in the mono-

benzyl ether fraction. It seems that HO-4 is thus by far the least reactive group to benzylation under the conditions employed. However, although monobenzylation of **1** gave only traces of **6**, the accompanying dibenzyl ether fraction was relatively enriched in **5** and the composition of this fraction remained similar whether formed in relatively small amounts (under conditions of unimolar benzylation) or in high proportions (dimolar benzylation). Furthermore, benzylation of **2** again leads to considerable reaction at HO-4. Thus, the paucity of 4-benzyl ether (**6**) is not necessarily due to lack of reactivity of HO-4 in **1**, but may well be caused by enhanced reactivity at HO-2 of the transient **6** formed, leading to its rapid conversion into **5**. In fact, dimolar benzylation affords a convenient way to prepare **5** directly from **1**. The preferential production of **5** from **2** may indicate either an activation of the 1,3-diol system after monobenzylation or depression of the reactivity of HO-3 by a vicinal benzyl group at O-2. The negligible proportion of **7** formed from **1** on dimolar benzylation, in contrast to the considerable formation of **5**, is again consonant with a lack of tendency for formation of vicinal dibenzyl ethers. The regioselectivity in benzylation of methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside[2] strongly favoring 4-substitution is also in agreement with this tendency to avoid substitution at O-3 which is vicinal to the benzyl group at O-2.

However, under other reaction conditions, the results may be different. Thus, the reaction of benzyl chloride–KOH in 1,4-dioxane–toluene[3] with **1** gave mainly **5**, accompanied by a considerable proportion of **7**, whereas **4** was absent.

The use of a phase-transfer catalyst[5] for monobenzylation of **1** gave **2** and **3** in a very different product ratio (1 : 3) and favored substitution at O-3. However, yields were rather poor. The best method for direct production of **3** from **1** was by means of the stannylidene procedure, leading to a total yield of 70% (from **1**) of acetylated monobenzyl ethers that consisted of **10** and **11** in the ratio of 6 : 1.

Benzylation of **2** *via* the dibutyltin complex[6] led to an apparently regiospecific

TABLE II

CHEMICAL SHIFTS (δ) OF CMe AND OAc IN ACETYLATED α-L-FUCOPYRANOSIDES

Compound	*CMe*	*OAc*		
		C-2	*C-3*	*C-4*
2	1.26	—	—	—
3	1.29	—	—	—
4	1.22	—	—	—
5	1.25	—	—	—
8	1.13	—	—	2.14
9	1.12	—	1.96	—
10	1.17	2.09	—	2.16
11	1.11	—	1.97	2.12
13	1.18	2.08	1.98	2.17
14	1.17	2.08	—	—

reaction and isolation of **8** in good yield as the sole product. Similar results have been recently reported in the absence of a catalyst[7]. Regioselectivity in this reaction can be explained as due to preliminary formation of a cyclic ester involving O-3(*eq*) and O-4(*ax*), leading to activation of the 3-position. However, it is not clear, how the bis(tributyltin) oxide reagent[8] used with **1** leads to regioselectivity and activation at O-3, with stereoselective formation of **3**. From the different results obtained in reactions performed with sodium hydride and KOH, it is clear that conformational factors alone do not determine the products formed and the relatively low reactivity of HO-3, but that such other factors as the relative acidities of hydroxyl groups in the media employed and the effect of neighboring groups play an important role.

Examination of the p.m.r. spectra of the substituted fucopyranosides showed that the chemical shifts of the CMe and OAc protons are affected by neighboring substituents in a predictable fashion (Table II). Thus, the strongest shielding of CMe occurred when HO-2 was benzylated but there did not seem to be any correlation between substituents at C-3 or C-4 and δ for CMe. All of the OAc protons could be defined with a high degree of accuracy and were little affected by neighboring substituents.

EXPERIMENTAL

General methods. — See ref. 9. P.m.r. spectra ($CDCl_3$) were recorded on a Bruker HFX-10 (90 MHz) spectrometer.

Monomolar benzylation. — Sodium hydride (55% dispersion in oil; 0.95 g, 0.02 mol) was added to a stirred solution of **1** (3.65 g, 0.02 mol) in *N*,*N*-dimethylformamide (50 ml). After stirring for 90 min, benzyl bromide (2.36 ml, 0.02 mol) was added dropwise during 15 min and stirring was continued for an additional 60 min. Methanol (1 ml) was then added, the solution evaporated, and the residue extracted with 14:14:1 benzene–ether–methanol. The extract was passed through a column of silica gel, and elution with the above solvent mixture gave **12** (0.15 g, 2.6%), and dibenzyl (1.0 g, 18.7%) and monobenzyl (2.1 g, 47%) ethers. Finally, **1** (1.14 g, 32%) was eluted with 4:1 chloroform–methanol. The monobenzyl and dibenzyl ether fractions (as indicated by their p.m.r. spectra) were acetylated (pyridine–acetic anhydride) and the products were fractionated on silica gel by elution with 9:1 benzene–ether, and characterised (see Table I). Catalytic deacetylation of the separated products afforded the pure mono- and di-benzyl ethers in quantitative yields. For known compounds, identification utilised comparisons of melting points (when crystalline), optical rotations, and p.m.r. spectra.

Dimolar benzylation. — The foregoing conditions were employed, except that 2 mol. proportions of sodium hydride and benzyl bromide were used; **1** (1.78 g, 0.01 mol) gave **12** (0.4 g, 9%), and dibenzyl (1.8 g, 50%) and monobenzyl (0.46 g, 18%) ethers.

Phase-transfer catalysis. — A vigorously stirred mixture of **1** (3.56 g, 0.02 mol), tetrabutylammonium iodide (1.85 g, 0.005 mol), and benzyl bromide (2.95 ml,

0.025 mol) in 5% aqueous NaOH (20 ml) and dichloromethane (150 ml) was kept for 45 h at 40°. After cooling, the organic layer was washed with water and evaporated, and the residue was subjected to chromatography on silica gel. A dibenzyl ether fraction (0.5 g, 9%) was not examined further. A monobenzyl ether fraction (1.30 g, 29%) was fractionated, after acetylation, into **10** and **11** in the ratio 3:1.

Benzylations using stannylidene complexes. — The general approach was that described in refs. 5, 7, and 8, using catalytic amounts of tetrabutylammonium bromide. For the reaction of **2**, 2 mol. equiv. of benzyl bromide were added to the mixture obtained by boiling **2** under reflux for 3 h with 1.1 equiv. of dibutyltin oxide. For the benzylation of **1**, 2 equiv. of (bistributyltin) oxide were used. After reaction, the solvent was evaporated, water was added, the mixture was re-evaporated, and the residue was dried by azeotropic distillation of toluene and then acetylated with acetic anhydride–pyridine. After removal of reagents by distillation in high vacuum, a solution of the residue in benzene was washed with aqueous sodium hydrogencarbonate and water, and concentrated to a syrup that was dissolved in the appropriate solvent and applied to a column of silica gel. Compound **8** (61% yield) was the sole product isolated from **2**, whereas **1** (1.0 g, 0.057 mol) gave **10** (1.2 g, 60%) and **11** (0.2 g, 10%).

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