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Note

Selective esterification of 1,5-anhydro-4,6-*O*-benzylidene-D-galactitol

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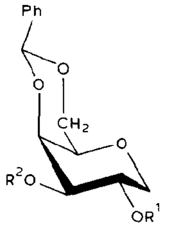
In previous papers[1–3], we reported partial esterification of 1,5-anhydro-4,6-*O*-benzylidene-D-glucitol with benzoyl chloride and *p*-toluenesulfonyl chloride, and investigated the influence of the aglycon on the relative reactivity of the hydroxyl groups. As an extension of this study, this report describes the selective benzoylation and tosylation of 1,5-anhydro-4,6-*O*-benzylidene-D-galactitol (**1**).

Partial benzoylation of **1** with 1 molar equivalent of benzoyl chloride in pyridine at −15° gave the dibenzoate **2** (0.9%), the 2-benzoate **3** (0.8%), the 3-benzoate **4** (96.1%), and the starting material **1** (0.2%), as detected by quantitative t.l.c. Partial tosylation of **1** with 1 molar equivalent of *p*-toluenesulfonyl chloride in pyridine at 0° gave a mixture of products which was shown by quantitative t.l.c. to consist of the ditosylate **5** (8.7%), the 2-tosylate **6** (5.7%), the 3-tosylate **7** (80.3%), and the starting material **1** (5.3%).

The position of the benzoyloxy group in **3** and **4** was established by ^{1}H-n.m.r. spectroscopy. The signal of H-2 of **3** and of H-3 of **4** respectively appeared at lowest field of the ring-proton resonances, because of the deshielding effect of benzoyloxy groups. The structure of **7** was demonstrated by preparing the monotosylate, which was shown to be the 3-tosylate **8** by comparing the physical constants with those of the position isomer **9** obtained by tosylation of the 3-benzoate **4**. The structure of **6** could not be further investigated because of its low yield.



	R^1	R^2
1	H	H
2	Bz	Bz
3	Bz	H
4	H	Bz
5	Ts	Ts
6	Ts	H
7	H	Ts
8	Bz	Ts
9	Ts	Bz

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The preponderant isolation of 3-*O*-substituted product over the 2-*O*-substituted one in both selective benzoylation and tosylation of **1** shows that the relative reactivity of the hydroxyl groups in **1** towards benzoyl chloride and *p*-toluenesulfonyl chloride is HO-3 > HO-2. This order is in accord with data reported for partial benzoylation and tosylation of 1,5-anhydro-D-galactitol[4,5], and methyl 4,6-*O*-benzylidene-α- and β-D-galactopyranosides[6–8], and partial tosylation of 1,5-anhydro-4,6-*O*-benzylidene-D-glucitol[3], methyl L-arabinopyranoside[9], and methyl β-D-galactopyranoside[10]. The high reactivity of HO-3 of **1** in both esterifications may be explained by the presence of an activating factor (intramolecular hydrogen-bonding), which enhances the reactivity of the 3-hydroxyl group. This result supports the previous prediction[4,5,9] that intramolecular hydrogen-bonding is more important than the stereochemical effect caused by deoxygenation at C-1. In contrast, partial tosylation of methyl β-L-arabinopyranoside[9] and methyl α-D-galactopyranoside[10] showed the reactivity of the secondary hydroxyl groups to be in the order HO-2 > HO-3. These observations suggest that the activating effect attributable to intramolecular hydrogen-bonding on the reactivity of the adjacent hydroxyl groups is greater in the *cis*-OH–OR orientation than in the *cis*-OH–OH orientation, in accordance with previous results[9]. It also appears that the reactivity of the adjacent hydroxyl group in galactopyranosides is more progressively affected by *cis*-OH–OR hydrogen-bonding at C-3 than by that at C-1. The high selectivity in acylation reactions of **1** may be due to the absence of the anomeric substituent.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were recorded at 60 MHz with a Hitachi R-24 spectrometer for solutions in chloroform-*d*, with tetramethylsilane as the internal standard, unless otherwise stated. T.l.c. was conducted on TLC-Silica gel 60 G (Merck) and column chromatography on silica gel 60 (70–230 mesh, Merck). Quantitative t.l.c. was performed on quartz rods sintered with silica gel H (Merck) and glass powder (1:2). Toluene–acetone (9:1) completely resolved the benzoylation products and the bands were detected with an Iatron TH-10 chromatoscanner equipped with a hydrogen flame-ionization detector. The solvent system used for chromatography was a graded mixture of benzene–acetone.

*1,5-Anhydro-4,6-O-benzylidene-*D*-galactitol* (**1**). — 1,5-Anhydro-D-galactitol (2 g) was benzylidenated with α,α′-dimethoxytoluene (3 mL) in *N,N*-dimethylformamide (8 mL) in the presence of *p*-toluenesulfonic acid monohydrate (5 mg) at 60° for 1 h as described by Evans[11] to give **1** (1.4 g, 45%), m.p. 181–183° (from EtOH), $[\alpha]_D^{25}$ +61.2° (*c* 0.9, CHCl$_3$); ^{1}H-n.m.r. (in acetone-d_6): δ 7.6–7.2 (m, 5 H, C_6H_5CH) and 5.50 (s, 1 H, C_6H_5CH).

Anal. Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.49; H, 6.49.

*Partial benzoylation of 1,5-anhydro-4,6-O-benzylidene-*D*-galactitol* (**1**). — A solution of **1** (300 mg) in dry pyridine (12 mL) was cooled to −15° and then BzCl (0.16 mL, 1.2 mol. equiv.) was added in portions with stirring during 15 min. The mixture was kept for 24 h at 0° and then extracted with $CHCl_3$. The extract was washed successively with dilute HCl, aq. $NaHCO_3$, and water, dried (Na_2SO_4), and then evaporated to dryness. The residue was subjected to quantitative analysis and then to column-chromatographic fractionation to give three fractions accompanied by the starting material.

1,5-Anhydro-2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-D-galactitol (**2**) was obtained as fine needles (13 mg, 3%), m.p. 182–185° (from EtOH), $[\alpha]_D^{28}$ +160° (*c* 0.9, $CHCl_3$); R_F 0.82 (4:1); ^{1}H-n.m.r.: δ 5.80 (sex, 1 H, $J_{1a,1e}$ 10, $J_{1a,2}$ 10, $J_{1e,2}$ 3 Hz, H-2), 5.50 (s, 1 H, C_6H_5CH), and 5.38 (q, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3 Hz, H-3).

Anal. Calc. for $C_{27}H_{24}O_7$: C, 70.42; H, 5.25. Found: C, 70.18; H, 5.37.

1,5-Anhydro-2-*O*-benzoyl-4,6-*O*-benzylidene-D-galactitol (**3**) was obtained as crystals (20 mg, 5%), m.p. 184–186° (from EtOH), $[\alpha]_D^{26}$ +31.5° (*c* 0.6, $CHCl_3$); R_F 0.60 (4:1); ^{1}H-n.m.r.: δ 5.60 (sex, 1 H, $J_{1a,1e}$ 10, $J_{1a,2}$ 10, $J_{1e,2}$ 3 Hz, H-2) and 5.49 (s, 1 H, C_6H_5CH).

Anal. Calc. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.29; H, 5.66.

1,5-Anhydro-3-*O*-benzoyl-4,6-*O*-benzylidene-D-galactitol (**4**) was crystallized from EtOH (280 mg, 67%), m.p. 195–197°, $[\alpha]_D^{25}$ +184° (*c* 1.5, pyridine); R_F 0.50 (4:1); ^{1}H-n.m.r. (in 2:1 $CDCl_3$–Me_2SO-d_6): δ 5.45 (s, 1 H, C_6H_5CH), 4.97 (q, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 4 Hz, H-3), and 4.45 (d, 1 H, $J_{4,5}$ 0 Hz, H-4).

Anal. Calc. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.17; H, 6.13.

*Partial tosylation of 1,5-anhydro-4,6-O-benzylidene-*D*-galactitol* (**1**). — To a chilled solution of **1** (300 mg) in pyridine (12 mL) at 0° *p*-toluenesulfonyl chloride (272 mg, 1.2 mol. equiv.) was added portionwise. The mixture was kept for 24 h at 0° and then processed as already described to give a crystalline residue, which was chromatographed on silica gel (250 g) after quantitative t.l.c. analysis.

1,5-Anhydro-4,6-*O*-benzylidene-2,3-di-*O*-*p*-tolylsulfonyl-D-galacitol (**5**) was obtained as a syrup (49 mg, 7%), $[\alpha]_D^{25}$ +78.9° (*c* 0.9, $CHCl_3$); R_F 0.60 (9:1); ^{1}H-n.m.r.: δ 5.27 (s, 1 H, C_6H_5CH) and 2.37 (s, 6 H, $2C_6H_4CH_3$).

Anal. Calc. for $C_{27}H_{28}O_9S_2$: C, 57.84; H, 5.03; S, 11.44. Found: C, 58.11; H, 5.43; S, 11.10.

1,5-Anhydro-4,6-*O*-benzylidene-3-*O*-*p*-tolylsulfonyl-D-galactitol (**7**) was obtained as a syrup (244 mg, 50%), $[\alpha]_D^{22}$ +32.1° (*c* 2.6, $CHCl_3$); R_F 0.25 (9:1); ^{1}H-n.m.r.: δ 5.27 (s, 1 H, C_6H_5CH), and 2.37 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{20}H_{22}O_7S$: C, 59.10; H, 5.46; S, 7.89. Found: C, 58.87; H, 5.77; S, 7.74.

*1,5-Anhydro-2-O-benzoyl-4,6-O-benzylidene-3-O-p-tolylsulfonyl-*D*-galactitol* (**8**). — Benzoylation of **7** (120 mg) with BzCl (0.06 mL) in pyridine (2 mL) yielded **8** which was crystallized from $CHCl_3$–EtOH to give crystals (108 mg, 73%), m.p. 186° (dec.), $[\alpha]_D^{24}$ +194° (*c* 0.7, pyridine). The ^{1}H-n.m.r. spectrum of **8** could not measured because of the low solubility of **8** in the common deuterated solvents such as benzene, chloroform, dimethyl sulfoxide, and pyridine.

Anal. Calc. for $C_{27}H_{26}O_8S$: C, 63.51; H, 5.13; S, 6.28. Found: C, 63.13; H, 5.01; S, 6.10.

*1,5-Anhydro-3-*O*-benzoyl-4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-*D*-galactitol* (**9**). — The 2-benzoate **3** (140 mg) was treated with *p*-toluenesulfonyl chloride (224 mg) in pyridine (2 mL) for 2 days at room temperature to yield **9** which was crystallized from $CHCl_3$–EtOH to give crystals (168 mg, 84%), m.p. 131–132°, $[\alpha]_D^{20}$ +176° (*c* 0.8, $CHCl_3$); ^{1}H-n.m.r.: δ 5.48 (s, 1 H, C_6H_5CH), 5.22 (q, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3 Hz, H-3), 5.14 (sec, 1 H, $J_{1a,1e}$ 10, $J_{1a,2}$ 10, $J_{1e,2}$ 3 Hz, H-2), 4.52 (d, 1 H, $J_{4,5}$ 0 Hz, H-4), and 2.35 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{27}H_{26}O_8S$: C, 63.51; H, 5.13; S, 6.28. Found: C, 63.48; H, 5.35; S, 6.12.

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