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Note

Selective benzoylation of 1,5-anhydro-D-galactitol

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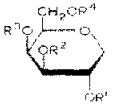
Selective acylation[1] provides much information on the relative reactivities of hydroxyl groups in carbohydrates. The selective benzoylation of 1,5-anhydro-D-glucitol[2] and 1,5-anhydroxylitol[3] has recently been reported, and the influence of electronic and steric factors on the reactivity of hydroxyl groups has been investigated. The selective benzoylation of 1,5-anhydro-D-galactitol (**1**) is now described.

Treatment of **1** with 2 molar equivalents of benzoyl chloride in pyridine at −40° gave the 2,3,6-tribenzoate **2** (15.3%), the 3,4,6-tribenzoate **3** (3.0%), the 3,6-dibenzoate **4** (75.1%), the 4,6-dibenzoate **5** (4.7%), and the 2,6-dibenzoate **6** (1.8%), as detected, and determined, by quantitative t.l.c.



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

Bz = PhCO
Ts = $(HO)C_6H_4Me$-*p*

After chromatographic separation, the position of the benzoyl groups in **2** was assigned from the ^{1}H-n.m.r. spectrum. The signals of H-2 and H-3 appeared to lower field than the other ring-proton resonances, showing that these protons

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must be geminal to the deshielding benzoyloxy groups. The structure of **3** was demonstrated by comparison of the ^{1}H-n.m.r. spectra of **3** and its tosylate (**7**). The signals of H-3 and H-4 in the spectrum of **3** appeared at the lowest field, whereas the H-2 signal of **7** occurred to higher field than those of H-3 and H-4, indicating that C-2 of **3** and **7** is substituted with a hydroxyl and a benzoyloxy group, respectively. In the ^{1}H-n.m.r. spectra of **4** and **5**, the signal of H-3 in **4** and that of H-4 in **5** appeared, respectively, as a one-proton quartet and a one-proton doublet at low field of all other ring-proton resonances. This finding supported the conclusion that a benzoyl group is attached to O-3 in **4** and O-4 in **5**. The ^{1}H-n.m.r. spectrum of **6** was unresolved, although it suggested that **6** was a dibenzoate. Therefore, **6** must be the remaining 2,6-dibenzoate.

In the dibenzoylation of **1**, the respective isolation of the 2,3,6-tribenzoate and the 3,6-dibenzoate, as the major products among the tribenzoates and dibenzoates, shows that the relative reactivity of the hydroxyl groups in **1** is in the order: OH-6 > OH-3 > OH-2 > OH-4, consistent with the results[2] of dibenzoylation of 1,5-anhydro-D-glucitol, which gives the 2,3,6-tribenzoate (8%), the 3,4,6-tribenzoate (1%), the 3,6-dibenzoate (34%), and the 2,6-dibenzoate (5%).

The total yield of the reaction products of **1** (80%) is higher than that of 1,5-anhydro-D-glucitol (48%), indicating that the former is more rapidly benzoylated than the latter. The higher yield of the 3,6-dibenzoate of **1** (57%), compared with that of the 3,6-dibenzoate of 1,5-anhydro-D-glucitol (34%), shows that the OH-3 group in **1** is more reactive towards benzoyl chloride than that in 1,5-anhydro-D-glucitol. This observation could be rationalized from the activating effect of intramolecular hydrogen-bonding between OH-3 and OH-4 in **1**, a bonding that is absent in 1,5-anhydro-D-glucitol. Interestingly, in the dibenzoylation of **1**, the 4,6- was isolated in higher yield than the 2,6-dibenzoate, whereas, in the dibenzoylation of 1,5-anhydro-D-glucitol, the 4,6-dibenzoate could not be found among the dibenzoates, other than the 3,6- and 2,6-dibenzoate. Of the secondary hydroxyl groups in **1**, the OH-4 group is the least reactive to benzoylation, in agreement with the results obtained in the benzoylation of methyl α-D-glycopyranosides[4,5]. It seems that the axial OH-4 group in **1** is more sterically hindered than that of 1,5-anhydro-D-glucitol, because of steric hindrance derived from the large 5-benzoyloxymethyl group, thus causing isolation of a preponderance of the 2,6- over the 4,6-dibenzoate. However, the reverse is true for the benzoylation of **1**. Therefore, this finding suggests that intramolecular hydrogen-bonding has an accelerating effect on the axial OH group also; this effect is probably masked by competitive interaction involving the steric hindrance of the 5-benzoyloxymethyl group.

EXPERIMENTAL

General methods. — Melting points were determined on a Yanagimoto hot-stage microscope and are uncorrected. Optical rotations were measured with a Jasco DIP-181 digital polarimeter, and ^{1}H-n.m.r. spectra were recorded with a

Hitachi R-24 60 MHz instrument for solutions in chloroform-*d* with tetramethylsilane as the internal reference, unless stated otherwise. Quantitative, thin-layer chromatography was performed on quartz rods sintered with 1:2 silica gel H (Merck)–glass powder, with 9:1 benzene–acetone, and the spots were detected with an Iatoron chromatoscanner TH-10 equipped with a hydrogen-flame ionization detector. Percentages are expressed on a relative molar basis. Preparative, column chromatography was conducted on silica gel 60 (Merck; 70–230 mesh).

*Selective benzoylation of 1,5-anhydro-*D*-galactitol* (**1**). — The anhydrogalactitol **1** (1 g) was dissolved in dry pyridine (40 mL), and benzoyl chloride (1.56 mL, 2.2 mol. equiv.) was added at −40°. The solution was stirred for 3 h at −20°, kept for 48 h at 0°, and then stirred for 48 h at room temperature. Water was added, the mixture extracted with chloroform, and the extract washed successively with dilute sulfuric acid, saturated sodium hydrogencarbonate, and water, and dried (sodium sulfate). The chloroform solution was directly used for quantitative, t.l.c. analysis of the components in the mixture.

The extract was evaporated, and the residue was chromatographed on silica gel (250 g). Elution with 9:1 benzene–acetone gave 1,5-anhydro-2,3,6-tri-*O*-benzoyl-D-galactitol (**2**) (402 mg, 14%), which crystallized from ethanol; m.p. 138–139°, $[\alpha]_D^{22}$ +73.3° (*c* 1.5, chloroform); ^{1}H-n.m.r.: δ 5.72 (sextet, 1 H, $J_{1a,2}$ 10, $J_{1e,2}$ 7, $J_{2,3}$ 11 Hz, H-2), 5.38 (q, 1 H, $J_{3,4}$ 3 Hz, H-3), 4.7–4.1 (m, 4 H, H-4,5,6,6'), 3.95 (q, 1 H, $J_{1a,1e}$ 11 Hz, H-1*e*), 3.43 (t, 1 H, H-1*a*), and 2.80 (d, 1 H, $J_{OH,4}$ 5 Hz, OH-4; exchanges on addition of D_2O).

Anal. Calc. for $C_{27}H_{24}O_5$: C, 68.06; H, 5.08. Found: C, 68.12; H, 5.05.

Elution with 4:1 benzene–acetone afforded 1,5-anhydro-3,4,6-tri-*O*-benzoyl-D-galactitol (**3**) (77 mg, 3%) as a syrup; $[\alpha]_D^{18}$ +24.7° (*c* 3.9, chloroform); ^{1}H-n.m.r.: δ 6.30 (d, 1 H, $J_{3,4}$ 4, $J_{4,5}$ 0 Hz, H-4), 5.30 (q, 1 H, $J_{2,3}$ 9 Hz, H-3), 3.17 (broad s, 1 H, OH-2; exchanges on addition of D_2O). The tribenzoate **3** (77 mg) was treated with *p*-toluenesulfonyl chloride (118 mg) in pyridine (2 mL) for 5 days, to give 1,5-anhydro-3,4,6-tri-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-D-galactitol (**7**) (98 mg, 96%), $[\alpha]_D^{24}$ +80.6° (*c* 1.7, chloroform); ^{1}H-n.m.r.: δ 5.90 (d, 1 H, $J_{3,4}$ 3, $J_{4,5}$ 0 Hz, H-4), 5.53 (q, 1 H, $J_{2,3}$ 9 Hz, H-3), 5.02 (sextet, 1 H, $J_{1a,2}$ 10, $J_{1e,2}$ 7 Hz, H-2), 4.6–4.0 (m, 3 H, H-5,6,6'), 3.63 (q, 1 H, $J_{1a,1e}$ 12 Hz, H-1*e*), 3.63 (q, 1 H, H-1*a*), and 2.15 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{34}H_{30}O_{10}S \cdot 2\ H_2O$: C, 61.25; H, 5.14; S, 4.80. Found: C, 61.09; H, 4.62; S, 4.57.

Elution with 4:1 benzene–acetone gave 1,5-anhydro-3,6-di-*O*-benzoyl-D-galactitol (**4**) (1.284 g, 57%), which crystallized from ethanol; m.p. 150–152°, $[\alpha]_D^{15}$ +6.0° (*c* 2.4, chloroform); ^{1}H-n.m.r. (in acetone-d_6), δ 5.03 (q, 1 H, $J_{3,4}$ 9, $J_{3,4}$ 3 Hz, H-3).

Anal. Calc. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.75; H, 5.32.

Elution with 2:1 benzene–acetone afforded 1,5-anhydro-4,6-di-*O*-benzoyl-D-galactitol (**5**) (114 mg, 5%), which crystallized from ethanol; m.p. 165–167°, $[\alpha]_D^{22}$ +4.0° (*c* 2.0, acetone); ^{1}H-n.m.r. (in 5:2 dimethyl sulfoxide-d_6–acetone-d_6): δ 5.48

(d, 1 H, $J_{3,4}$ 3, $J_{4,5}$ 0 Hz, H-4), and 4.92 and 4.75 (2 d, 2 H, $J_{OH,2} = J_{OH,3} = 4$ Hz, OH-2,3; exchanged on addition of D_2O).

Anal. Calc. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.57; H, 5.45.

Final elution, with 1:1 benzene–acetone, yielded a syrupy dibenzoate (27 mg, 1%); $[\alpha]_D^{20}$ +33.0° (*c* 1.0, chloroform), which was probably 1,5-anhydro-2,6-di-*O*-benzoyl-D-galactitol (**6**).

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