Carbohydrate Research, 114 (1983) 335–337
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

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

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(Received October 25th, 1982; accepted for publication, November 16th, 1982)

The selective sulfonylation of 1,5-anhydroalditols[1–3] having the *gluco* and *xylo* configurations has previously been investigated, and the effects of the aglycon on the relative reactivity of the hydroxyl groups have been reported. The selective tosylation of 1,5-anhydro-D-galactitol (**1**) is now described.

Reaction of **1** with three molar equivalents of *p*-toluenesulfonyl chloride in pyridine at 0° gave a mixture that was fractionated on silica gel to afford the 2,3,4,6-tetrasulfonate **2** (6%), the 2,3,6-trisulfonate **3** (76%), the 3,6-disulfonate **4** (15%), and the 6-sulfonate **5** (2%).

Dimolar tosylation of **1** gave a product mixture from which **3** (12%), **4** (47%), and **5** (6%) were isolated, after column chromatography.

The structure of **3** was established by comparison of the p.m.r. spectra of **3** and its benzoate **6**. The signal of H-4 in the spectrum of **3** appeared at higher field than those of H-2 and H-3, whereas a doublet characteristic of the H-4 signal of **6** occurred to low field of all other ring-proton resonances. This finding indicates that C-4 of **3** and **6** is substituted with a hydroxyl and a benzoyl group, respectively.

The structure of **4** was confirmed by preparing the dibenzoate, which was shown to be 1,5-anhydro-2,4-di-*O*-benzoyl-3,6-di-*O*-*p*-tolylsulfonyl-D-galactitol (**7**) by p.m.r. spectroscopy. The signals of H-2 and H-4 of **7** appeared to the lowest field of the ring-proton resonances, because of the deshielding effect of benzoyloxy groups on the same methine protons at C-2 and C-4.

The structure of **5** was demonstrated by benzoylation of **5** to give the known 1,5-anhydro-2,3,4-tri-*O*-benzoyl-6-*O*-*p*-tolylsulfonyl-D-galactitol[4] (**8**).

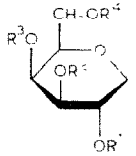
The respective isolation of **3** and **4** as the major product from trimolar and dimolar tosylation of **1** shows that the order of the relative reactivity of the hydroxyl groups of **1** is OH-6 > OH-3 > OH-2 > OH-4. The finding that the OH-3 group is the most reactive among the ring-hydroxyl groups is in agreement with the results[5] of selective sulfonylation of galactopyranosides, as explained by an effect of the *cis* OH-3–OH-4 hydrogen-bonding. The lowest reactivity of the OH-4 group in **1** is consistent with the results[5] of selective benzoylation and sulfonylation of galacto-

pyranosides, and could be rationalized as the result of steric hindrance by the tosyloxymethyl group on C-5. Interestingly, the 2,6-disulfonate could not be isolated, because depression of the steric hindrance at C-2 derived from the methylene group at C-1 enhances[1-3] the reactivity of the 2-hydroxyl group. This result supports the previous prediction[1,6] that intramolecular hydrogen-bonding is more important than stereochemical factors (depression of gauche interactions).

EXPERIMENTAL

For general methods, see refs. 2 and 3.

p-Toluenesulfonylation of 1,5-anhydro-D-galactitol (**1**). — (*a*) *With three molar equivalents.* *p*-Toluenesulfonyl chloride (3.832 g, 3.3 mol. equiv.) was added portionwise to a stirred solution of **1** (1 g) in dry pyridine (20 mL) at 0 °. The mixture was kept for 24 h at 0 °, stirred for 48 h at 5 °, and then extracted with chloroform. The extract was washed successively with dilute hydrochloric acid, saturated sodium hydrogen-carbonate, and water, dried (sodium sulfate), and evaporated to a syrup that was fractionated on silica gel (250 g). Elution with 9 : 1 benzene–acetone gave the 2,3,4,6-tetrasulfonate **2** (304 mg, 6%) as a syrup that could not be crystallized; $[\alpha]_D^{25}$ +35.0° (*c* 2.3, chloroform).



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

Elution with 4 : 1 benzene–acetone gave the 2,3,6-trisulfonate **3** (2.882 g, 76%), which crystallized from benzene; m.p. 170–171 °, $[\alpha]_D^{24}$ +28.5° (*c* 1.9, chloroform); p.m.r.: δ 4.72 (sextet, 1 H, $J_{1a,2}$ 10, $J_{2,3}$ 9 Hz, H-2), 4.37 (q, 1 H, $J_{3,4}$ 2 Hz, H-3), 4.2–4.0 (m, 4 H, H-4,5,6,6'), 3.77 (q, 1 H, $J_{1a,1e}$ 12 Hz, H-1*e*), 3.18 (q, 1 H, H-1*a*), 2.52 (d, 1 H, $J_{4,OH}$ 4 Hz, OH-4; exchanges on addition of D_2O), and 2.40 (s, 9 H, 3 $C_6H_4CH_3$).

Anal. Calc. for $C_{27}H_{30}O_{11}S_3$: C, 51.74; H, 4.83; S, 15.35. Found: C, 51.49; H, 4.71; S, 15.19.

Elution with 2:1 benzene-acetone gave the 3,6-disulfonate **4** (439 mg, 15%) as a foam that could not be crystallized: $[\alpha]_D^{26}$ +42.6° (*c* 2.8, chloroform).

Elution with 1:1 benzene–acetone gave the 6-sulfonate **5** (38 mg, 2%), which crystallized from acetone; m.p. 139–140°, $[\alpha]_D^{26}$ +35.0° (*c* 1.1, acetone).

Anal. Calc. for $C_{13}H_{18}O_7S$: C, 49.04; H, 5.71; S, 10.07. Found: C, 49.02; H, 5.60; S, 10.22.

(*b*) *With two molar equivalents.* Treatment of **1** (1 g) with *p*-toluenesulfonyl chloride (2.555 g, 2.2 mol. equiv.) in pyridine (20 mL), followed by chromatographic fractionation of the product on silica gel as described in (*a*), afforded three fractions: **3** (378 mg, 10%), **4** (1.337 g, 46%), and **5** (106 mg, 6%).

*1,5-Anhydro-4-*O*-benzoyl-2,3,6-tri-*O*-p-tolylsulfonyl-*D*-galactitol* (**6**). — The sulfonate **3** (200 mg) was treated with benzoyl chloride (0.1 mL) in pyridine (2 mL) at 0°. The mixture was stirred overnight at room temperature, and extracted with chloroform. The extract was evaporated, and the resulting, crystalline residue recrystallized from dichloromethane–ethanol, to give **6** (202 mg, 87%); m.p. 166–167°, $[\alpha]_D^{24}$ +83.1° (*c* 4.4, chloroform); p.m.r.: δ 5.53 (d, $J_{3,4}$ 1, $J_{4,5}$ ~0 Hz, H-4), 4.8–4.5 (m, 2 H, H-2,3), 4.20 (q, 1 H, $J_{1a,1e}$ 11, $J_{1e,2}$ 5 Hz, H-1*e*), 4.0–3.6 (m, 3 H, H-5,6,6′), 3.33 (q, 1 H, $J_{1a,2}$ 9 Hz, H-1*a*), and 2.33 (s, 12 H, 4 $C_6H_4CH_3$).

Anal. Calc. for $C_{34}H_{34}O_{12}S_3$: C, 55.88; H, 4.69; S, 13.16. Found: C, 55.82; H, 4.52; S, 13.27.

*1,5-Anhydro-2,4-di-*O*-benzoyl-3,6-di-*O*-p-tolylsulfonyl-*D*-galactitol* (**7**). — Benzoylation of **4** (678 mg) with benzoyl chloride (0.4 mL) in pyridine (3 mL) at 0° gave a crystalline product which, on recrystallization from chloroform–ethanol, afforded **7** (746 mg, 84%); m.p. 194–195°, $[\alpha]_D^{21}$ +134.0° (*c* 1.1, chloroform); p.m.r.: δ 5.72 (d, 1 H, $J_{3,4}$ 4, $J_{4,5}$ ~0 Hz, H-4), 5.45 (sextet, 1 H, $J_{1a,2}$ 11, $J_{1e,2}$ 6, $J_{2,3}$ 10 Hz, H-2), 4.95 (q, 1 H, H-3), 4.28 (q, 1 H, $J_{1a,1e}$ 12 Hz, H-1*e*), 4.03 (s, 3 H, H-5,6,6′), 3.35 (q, 1 H, H-1*a*), and 2.32 and 2.25 (2 s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{34}H_{32}O_{11}S_2$: C, 59.99; H, 4.74; S, 9.42. Found: C, 59.80; H, 4.66; S, 9.68.

*1,5-Anhydro-2,3,4-tri-*O*-benzoyl-6-*O*-p-tolylsulfonyl-*D*-galactitol* (**8**). — The sulfonate **5** (20 mg) was benzoylated with benzoyl chloride (0.1 mL) in pyridine (2 mL), to give **8** (35 mg, 88%); m.p. 188–189°, $[\alpha]_D^{22}$ +166.3° (*c* 1.6, chloroform) {lit.[4] m.p. 187°, $[\alpha]_D^{20}$ +165° (*c* 1.293, chloroform}; p.m.r.: δ 5.83 (d, $J_{3,4}$ 2, $J_{4,5}$ ~0 Hz, H-4), 5.8–5.5 (m, 2 H, H-2,3), 4.40 (q, 1 H, $J_{1a,1e}$ 12, $J_{1e,2}$ 5 Hz, H-1*e*), 4.2–3.9 (m, 3 H, H-5,6,6′), 3.57 (q, 1 H, $J_{1a,2}$ 10 Hz, H-1*a*), and 2.28 (s, 3 H, $C_6H_4CH_3$).

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