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Note

Partial tosylation of 1,5-anhydro-L-arabinitol

YÔTARO KONDO
Department of Agricultural Chemistry, Tottori University, Tottori 680 (Japan)
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In previous publications on the selective tosylation[1] and benzoylation[2] of 1,5-anhydro-D-galactitol, the effects of intramolecular hydrogen-bonding on the relative reactivity of the hydroxyl groups have been investigated. In connection with these studies, the partial tosylation of 1,5-anhydro-L-arabinitol (**1**) is now described.

Selective tosylation of **1** with 2 molar equivalents of *p*-toluenesulfonyl chloride in pyridine at 0° gave a mixture of products which was shown by quantitative, t.l.c. analysis to consist of the 2,3,4-tritosylate **2** (17.0%), the 2,4-ditosylate **3** (31.5%), a mixture of the 2,3-ditosylate **4** and the 3,4-ditosylate **5** (38.8%), the 2-tosylate **6** (0.2%), the 3-tosylate **7** (5.0%), and the 4-tosylate **8** (7.5%). Chromatographic fractionation of the mixture on silica gel afforded five fractions, with a trace of **6**, as just described.

The position of the sulfonate group in **3** was assigned from the ^{1}H-n.m.r. spectrum. The signals of H-2 and H-4 appeared, respectively, as a one-proton sextet and a one-proton quintet at lower field than the other ring-proton resonances, because of the deshielding effect of sulfonate groups on the same methine protons attached to C-2 and C-4. Compounds **4** and **5** showed the same R_F value in t.l.c., and could not be separated by chromatography, but were separated by fractional recrystallization, in yields of 9.8% and 20.7%, respectively. In the ^{1}H-n.m.r. spectra of **4** and **5**, the ring protons geminal to the deshielding tosyl groups (H-2 and H-3 in **4**; H-3 and H-4 in **5**) appeared at the lowest field, indicating that a hydroxyl group is attached to C-4 of **4** and C-2 of **5**. The structures of **4** and **5** were further confirmed by preparing *O*-benzoyl derivatives **10** and **11**. In the ^{1}H-n.m.r. spectra of **10** and **11**, the signal of H-4 in **10** and that of H-2 in **11** appeared to low field of all other ring-proton resonances. This finding indicates that a benzoyloxy group is present on C-4 of **10** and on C-2 of **11**. The physical and spectral properties of **10** and **11** were different for each other and for the remaining benzoate **9** prepared from **3**.

The position of the sulfonate group in the monotosylates **6**, **7**, and **8** was also established by ^{1}H-n.m.r. spectroscopy. In the ^{1}H-n.m.r. spectra of **6**, **7**, and **8**, the respective lowest-field ring-proton resonance was assigned to H-2, H-3, and H-4,

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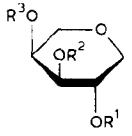
and appeared as a sextet, a quartet, and a quintet. This finding suggests that a tosyl group is attached to O-2 in **6**, O-3 in **7**, and O-4 in **8**. Further structural elucidation of **6**, **7**, and **8** was obtained from the ^{1}H-n.m.r. spectra of their benzoates **12**, **13**, and **14**. The signals of H-3 and H-4 of **12**, H-2 and H-4 of **13**, and H-2 and H-3 of **14** occurred as the most downfield of the ring-proton resonances, showing that these protons must be geminal to deshielding benzoyl groups.

Treatment of **1** with 1 molar equivalent of *p*-toluenesulfonyl chloride at 0° gave **3** (16.0%), a mixture of **4** and **5** (15.5%), **6** (12.7%), **7** (23.0%), and **8** (32.8%), which were quantitatively determined by t.l.c.

In order to determine the molar ratio of the mixture of **4** and **5**, this mixture was acetylated, and the product was analyzed by ^{1}H-n.m.r. spectroscopy. In the ^{1}H-n.m.r. spectrum of the resulting acetylated mixture, the signals of the methyl proton of the respective acetoxyl groups appeared at δ 1.89 and 1.87, with relative proton intensities of 4:3. The ^{1}H-n.m.r. spectra of authentic specimens of **15** and **16** showed the signals of the methyl proton of the acetoxyl group at δ 1.87 and 1.89, respectively; this indicated that the ratio **4** to **5** in the mixture was 3:4.



	R^1	R^2	R^3
1	H	H	H
2	Ts	Ts	Ts
3	Ts	H	Ts
4	Ts	Ts	H
5	H	Ts	Ts
6	Ts	H	H
7	H	Ts	H
8	H	H	Ts
9	Ts	Bz	Ts
10	Ts	Ts	Bz
11	Bz	Ts	Ts
12	Ts	Bz	Bz
13	Bz	Ts	Bz
14	Bz	Bz	Ts
15	Ts	Ts	Ac
16	Ac	Ts	Ts
17	Ts	Ac	Ts

In dimolar tosylation of **1**, the isolation of **3** and **5** as the major products, and the preponderance of (**3** + **4**) over (**4** + **5**), showed that the order of the relative reactivity of the hydroxyl groups in **1** is OH-4 > OH-2 > OH-3. On the other hand,

the order of the reactivity of the hydroxyl groups in monomolar tosylation of **1** is OH-4 > OH-3 > OH-2, judging from the molar ratios of the monotosylated products.

Interestingly, the axial OH-4 group is more reactive than the equatorial hydroxyl groups in **1**. The difference in the orders of reactivity of the hydroxyl groups toward monomolar and dimolar proportions of *p*-toluenesulfonyl chloride suggests that dimolar tosylation of **1** proceeds in two or three stages. However, it is probable that, in both tosylations of **1**, the axial OH-4 group is indeed more reactive than the equatorial hydroxyl groups. This highest reactivity of the OH-4 group may be explained by depression of the steric hindrance derived from the methylene group at C-5, in addition to the activating effect of intramolecular hydrogen-bonding between the OH-3 and OH-4 groups.

For the purpose of confirming the difference in reactivity in the second stage of dimolar tosylation of **1**, the monotosylates of **1** were further tosylated with 1 molar equivalent of *p*-toluenesulfonyl chloride. Selective tosylation of the 2-tosylate **6** gave the 2,4-ditosylate **3** and the 2,3-ditosylate **4**, with unreacted starting-material **6**, in the molar ratios of 17:5:28, respectively. This result indicates that the OH-4 group is much more reactive than the OH-3 group, and is contrary to the result obtained by Reist *et al.*[3] for selective tosylation of methyl 2-*O*-benzoyl-β-L-arabinopyranoside. This higher reactivity of the OH-4 group may be due to the competitive depression of the reactivity of the OH-3 group caused by steric hindrance with the vicinal tosyl group.

In monotosylation of the 4-tosylate **8**, the 2,3,4-tritosylate **2**, the 2,4-ditosylate **3**, the 3,4-ditosylate **5**, and the starting material **8** were respectively obtained in the molar ratios of 6:14:17:63. In this case, the difference in reactivity of the hydroxyl groups is small; however, it seems probable that the OH-3 group is slightly more reactive than the OH-2 group. This finding is understandable on the assumption that the reactivity of the OH-3 group is accelerated by intramolecular hydrogen-bonding, but decelerated by steric hindrance of a tosyl group.

On the other hand, surprisingly, no reaction occurred when the 3-tosylate **7** was subjected to monomolar tosylation, even at higher temperatures; however, prolonged treatment with a large excess of *p*-toluenesulfonyl chloride resulted in formation of the 2,3-ditosylate **4**, the 3,4-ditosylate **5**, and the starting material **7** in the molar ratios of 7:9:84. Quantitative analysis of the tosylated mixtures was conducted by ^{1}H-n.m.r. spectroscopy, in which the signal of the acetyl methyl protons in the acetylated products **15** and **16** appeared at δ 1.89 and 1.73, respectively. This result suggests that the retarding effect of a tosyl group on the reactivity of the neighboring hydroxyl groups is stronger at O-3, compared with O-2 or O-4 in **1**. A similar retardation effect in tosylation was reported by Staněk *et al.*[4] for methyl 6-deoxy-β-D-glucopyranoside, but not so strong as in the present case.

In order to investigate the reactivity of the hydroxyl groups of **1** in the third stage of tosylation, an equimolar mixture of the ditosylates **3**, **4**, and **5** was treated with 2 molar equivalents of *p*-toluenesulfonyl chloride. After acetylation of the to-

sylated products, the remaining ditosylates were quantitatively analyzed by ^{1}H-n.m.r. spectroscopy. It was found that the resulting mixture was composed of the 2-acetate **16** (11%), the 3-acetate **17** (12%), the 4-acetate **15** (11%), and the 2,3,4-tritosylate **2** (66%). This result indicates that the reactivity of each hydroxyl group of the ditosylates is almost the same toward further tosylation. It seems that the isolated hydroxyl group in the ditosylates is not so sterically hindered, particularly as tosylation becomes slow, judging from the yields.

From the foregoing observations, it was found that hydroxyl groups participating in intramolecular hydrogen-bonding activate each other. The difference in the order of the reactivity between mono- and di-tosylation was ascribable to a *gauche* interaction derived from a bulky, vicinal tosyloxy group, and therefore, it seems that the influence of a *gauche* interaction of a tosyloxy group should be taken into account as an inactivating factor in the second stage of sulfonylation, as described[5] previously.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro hot-stage apparatus and are uncorrected. ^{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 standard, unless stated otherwise. Quantitative, thin-layer chromatography was performed on quartz rods sintered with 1:2 silica gel H (Merck)–glass powder, as described previously. Column chromatography was performed on silica gel 60 (70–230 mesh, Merck).

p-*Toluenesulfonylation of 1,5-anhydro*-L-*arabinitol* (**1**). — *(a) With two molar equivalents.* *p*-Toluenesulfonyl chloride (1.564 g, 2.2 mol. equiv.) was added portionwise to a stirred solution of **1** (500 mg) in dry pyridine (20 mL) at 0°. The mixture was allowed to stand for 24 h at 0°, stirred for 48 h at 5°, and then extracted with chloroform. The extract was successively washed with dilute hydrochloric acid, saturated sodium hydrogencarbonate, and water, dried (sodium sulfate), and evaporated to a syrup which was chromatographed on silica gel (250 g). Elution with 9:1 benzene–ethyl acetate gave the 2,3,6-tritosylate **2** (283 mg, 13.5%), which crystallized from ethanol; m.p. 138–139°, $[\alpha]_D^{14}$ −46.8° (*c* 1.0, chloroform).

Anal. Calc. for $C_{26}H_{28}O_{10}S_3$: C, 52.33; H, 4.74; S, 16.12. Found: C, 52.26; H, 4.60; S, 16.01.

Elution with 4:1 benzene–ethyl acetate gave the 2,4-ditosylate **3** (424 mg, 25.7%), which crystallized from ethanol; m.p. 132°, $[\alpha]_D^{19}$ +40.1° (*c* 1.7, chloroform); ^{1}H-n.m.r.: δ 4.73 (quintet, 1 H, $J_{3,4} = J_{4,5a} = 2.9$, $J_{4,5e}$ 5.9 Hz, H-4), 4.52 (sextet, 1 H, $J_{1e,2}$ 2.9, $J_{1a,2} = J_{2,3} = 5.8$ Hz, H-2), 2.75 (d, 1 H, $J_{3,OH}$ 5.2 Hz, OH-3), and 2.43 (s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{19}H_{22}O_8S_2$: C, 51.57; H, 5.01; S, 14.49. Found: C, 51.38; H, 4.93; S, 14.40.

Elution with 2:1 benzene–ethyl acetate afforded a mixture of the 2,3-ditosyl-

ate **4** and the 3,4-ditosylate **5**. Compound **5** could be isolated as a homogeneous syrup (341 mg, 20.8%), as shown by ^{1}H-n.m.r. spectroscopy, after removal of crystalline **4** (161 mg, 9.8%) from the mother liquor by repeated fractional recrystallization from ethanol or 2-propanol–petroleum ether.

Compound **4** was recrystallized from ethanol to give fine needles; m.p. 179–180°, $[\alpha]_D^{18}$ +7.0° (*c* 3.6, pyridine); ^{1}H-n.m.r. (in 10:1 chloroform-*d*–dimethyl sulfoxide-d_6): δ 4.72 (sextet, 1 H, $J_{1a,2}$ 8.1, $J_{1e,2}$ 4.2, $J_{2,3}$ 7.3 Hz, H-2), 4.43 (q, $J_{3,4}$ 2.5 Hz, H-3), and 2.43 (s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{19}H_{22}O_8S_2$: C, 51.57; H, 5.01; S, 14.49. Found: C, 51.66; H, 5.10; S, 14.47.

Compound **5** could not be crystallized; $[\alpha]_D^{16}$ +25.5° (*c* 0.8, chloroform); ^{1}H-n.m.r.: δ 4.82 (quintet, 1 H, $J_{3,4} = J_{4,5a} = 3$, $J_{4,5e}$ 5.2 Hz, H-4), 4.50 (q, 1 H, $J_{2,3}$ 7.1 Hz, H-3), and 2.38 (s, 6 H, 2 $C_6H_4CH_3$).

Elution with 1:1 benzene–ethyl acetate afforded the 3-tosylate **7** (111 mg, 10.3%), which crystallized from benzene; m.p. 115°, $[\alpha]_D^{20}$ +55.2° (*c* 1.5, acetone); ^{1}H-n.m.r.: δ 4.47 (q, 1 H, $J_{2,3}$ 7.8, $J_{3,4}$ 2.9 Hz, H-3) and 2.43 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59; S, 11.12. Found: C, 50.07; H, 5.52; S, 10.97.

Further elution with 1:1 benzene–ethyl acetate gave the 4-tosylate **8** (137 mg, 12.7%), which crystallized from chloroform–petroleum ether; m.p. 143–144°, $[\alpha]_D^{14}$ +53.0° (*c* 1.0, chloroform); ^{1}H-n.m.r. (in acetone-d_6): δ 4.77 (quintet, 1 H, $J_{3,4} = J_{4,5a} = 2.3$, $J_{4,5e}$ 5.1 Hz, H-4), 4.32 and 4.18 (2 broad s, 2 H, OH-2,3), and 2.45 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59; S, 11.12. Found: C, 50.03; H, 5.59; S, 11.05.

(b) With one molar equivalent. Treatment of **1** (500 mg) with *p*-toluenesulfonyl chloride (746 mg, 1.1 mol. equiv.) in pyridine (20 mL), followed by column chromatography on silica gel as described in (*a*), yielded five fractions: **3** (124 mg, 7.5%), **4** and **5** (106 mg, 6.4%), the 2-tosylate **6** (93 mg, 8.7%), **7** (139 mg, 12.9%), and **8** (272 mg, 25.3%).

The 2-tosylate **6** was obtained as a syrup; $[\alpha]_D^{17}$ +10.0° (*c* 2.0, chloroform); ^{1}H-n.m.r.: δ 4.63 (sextet, 1 H, $J_{1a,2} = J_{2,3} = 7.1$, $J_{1e,2}$ 4.4 Hz, H-2), and 2.43 (s, 3 H, $C_6H_4CH_3$).

1,5-Anhydro-3-O-*benzoyl-2,4-di*-O-p-*tolylsulfonyl*-L-*arabinitol* (**9**). — Benzoyl chloride (0.13 mL) was added to a solution of **3** (165 mg) in pyridine (3 mL) at 0°, and the mixture was stirred overnight at room temperature. Water was added, and the mixture was extracted with chloroform. The extract was evaporated, and the resulting, crystalline residue was recrystallized from chloroform–petroleum ether, to give **9** (150 mg, 81%); m.p. 170–171°, $[\alpha]_D^{24}$ +71.7° (*c* 1.7, chloroform); ^{1}H-n.m.r.: δ 5.3–4.6 (m, 3 H, H-2,3,4), and 2.33 and 2.18 (2 s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{26}H_{26}O_9S_2$: C, 57.13; H, 4.78; S, 11.73. Found: C, 57.16; H, 4.68; S, 11.86.

*1,5-Anhydro-4-*O*-benzoyl-2,3-di-*O*-*p*-tolylsulfonyl-*L*-arabinitol* (**10**). — Benzoylation of **4** (71 mg) with benzoyl chloride in pyridine gave a crystalline product, which was recrystallized from ethanol to afford **10** (77 mg, 88%); m.p. 169–170°, $[\alpha]_D^{24}$ +40.8° (*c* 2.4, chloroform); ^{1}H-n.m.r.: δ 5.27 (broad quintet, 1 H, H-4), 4.9–4.5 (m, 2 H, H-2,3), and 2.45 and 2.27 (2 s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{26}H_{26}O_9S_2$: C, 57.13; H, 4.78; S, 11.73. Found: C, 57.12; H, 4.75; S, 11.55.

*1,5-Anhydro-2-*O*-benzoyl-3,4-di-*O*-*p*-tolylsulfonyl-*L*-arabinitol* (**11**). — The sulfonate **5** (99 mg) was benzoylated with benzoyl chloride in pyridine to give **11** (97 mg, 83%); m.p. 151–154°, $[\alpha]_D^{26}$ +80.4° (*c* 1.5, chloroform); ^{1}H-n.m.r.: δ 5.30 (sextet, 1 H, $J_{1a,2} = J_{2,3} = 6$, $J_{1e,2}$ 4.1 Hz, H-2), 4.85 (quintet, 1 H, $J_{3,4} = J_{4,5a} = 2.7$, $J_{4,5e}$ 6 Hz, H-4), 4.80 (q, 1 H, H-3), and 2.37 (s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{26}H_{26}O_9S_2$: C, 57.13; H, 4.78; S, 11.73. Found: C, 57.07; H, 4.91; S, 11.70.

*1,5-Anhydro-3,4-di-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-*L*-arabinitol* (**12**). — Benzoylation of **6** (32 mg) with benzoyl chloride yielded **12** (34 mg, 62%); m.p. 137–139°, $[\alpha]_D^{16}$ +216.9° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 5.65 (m, 1 H, H-4), 5.50 (q, 1 H, $J_{3,4}$ 3.4 Hz, H-3), 5.03 (sextet, 1 H, $J_{1a,2} = J_{2,3} = 8.6$, $J_{1e,2}$ 5.1 Hz, H-2), and 2.23 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{26}H_{24}O_8S$: C, 62.89; H, 4.87; S, 6.46. Found: C, 62.63; H, 4.86; S, 6.44.

*1,5-Anhydro-2,4-di-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl-*L*-arabinitol* (**13**). — Benzoylation of **7** (84 mg) gave **13** (139 mg, 96%); m.p. 152–153°, $[\alpha]_D^{22}$ +154.8° (*c* 0.95, chloroform); ^{1}H-n.m.r.: δ 5.6-5.2 (m, 2 H, H-2,4), 5.04 (q, 1 H, $J_{2,3}$ 6.6, $J_{3,4}$ 3.1 Hz, H-3), and 2.23 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{26}H_{24}O_8S$: C, 62.89; H, 4.87; S, 6.46. Found: C, 62.96; H, 4.84; S, 6.47.

*1,5-Anhydro-2,3-di-*O*-benzoyl-4-*O*-*p*-tolylsulfonyl-*L*-arabinitol* (**14**). — Compound **8** (50 mg) was benzoylated to yield **14** (67 mg, 78%); m.p. 155–156°, $[\alpha]_D^{22}$ +115.3° (*c* 2.0, chloroform); ^{1}H-n.m.r.: δ 5.55 (sextet, 1 H, $J_{1a,2} = J_{2,3} = 7.2$, $J_{1e,2}$ 3.8 Hz, H-2), 5.62 (q, 1 H, $J_{3,4}$ 4.1 Hz, H-3), 5.07 (m, 1 H, H-4), and 2.20 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{26}H_{24}O_8S$: C, 62.89; H, 4.87; S, 6.46. Found: C, 62.98; H, 4.80; S, 6.29.

Partial p-*toluenesulfonylation of monotosylates of 1,5-anhydro-*L*-arabinitol* (**1**). — *(a) 1,5-Anhydro-2-*O*-p-tolylsulfonyl-*L*-arabinitol* (**6**). A mixture of **6** (10 mg) and *p*-toluenesulfonyl chloride (10 mg, 1.5 mol. equiv.) in pyridine (0.5 mL) was stirred overnight at 5° and then for 2 days at room temperature. The mixture was poured into ice–water, and extracted with chloroform. Evaporation of the extract gave a syrupy residue which consisted of the 2,4-ditosylate **3** (34%), the 2,3-ditosylate **4** (10%), and **6** (56%), as shown by t.l.c. analysis.

*(b) 1,5-Anhydro-3-*O*-p-tolylsulfonyl-*L*-arabinitol* (**7**). Compound **7** (10 mg) was tosylated for 2 weeks at room temperature by daily addition of 10 mg of *p*-

toluenesulfonyl chloride. Direct acetylation of the mixture with acetic anhydride (0.5 mL), followed by the usual work-up as already described, then afforded a mixture of the 2,3-ditosylate **4** (7%), the 3,4-ditosylate **5** (9%), and **7** (84%) as the corresponding acetates (proportions estimated by ^{1}H-n.m.r. spectroscopy).

*(c) 1,5-Anhydro-4-*O-p-*tolylsulfonyl-*L-*arabinitol* (**8**). A solution of **8** (10 mg) in pyridine (2 mL) was stirred with *p*-toluenesulfonyl chloride (10 mg, 1.5 mol. equiv.) for 24 h at 0°, for 48 h at 5°, and then overnight at room temperature. After the usual work-up, quantitative t.l.c. examination indicated that the resultant reaction product was composed of the 2,3,4-tritosylate **2** (6%), the 2,4-ditosylate **3** (14%), the 3,4-ditosylate **5** (17%), and **8** (63%).

Partial p-*toluenesulfonylation of ditosylates of 1,5-anhydro-*L-*arabinitol* (**1**). —*p*-Toluenesulfonyl chloride (26 mg, 2 mol. equiv.) was added to a solution of the 2,4-ditosylate **3** (10 mg), the 2,3-ditosylate **4** (10 mg), and the 3,4-ditosylate **5** (10 mg) in pyridine (1 mL). The mixture was stirred for 2 days at room temperature. The mixture was treated with acetic anhydride (0.5 mL) and processed as usual, to give the corresponding mixture of acetates of **3** (12%), **4** (11%), and **5** (11%), along with the tritosylate **2** (66%) (proportions estimated by ^{1}H-n.m.r. spectroscopy).

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