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Note

Partial tosylation of methyl α-D-mannopyranoside

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Selective esterification provides a facile synthetic route for the preparation of important intermediates in carbohydrate chemistry, and the order of relative reactivity of the hydroxyl groups in sugars is closely correlated to their stereochemistry[1,2]. This communication describes partial tosylation of methyl α-D-mannopyranoside (**1**).

Treatment of **1** with 2 molar equivalents of *p*-toluenesulfonyl chloride in pyridine gave a mixture which was fractionated by column chromatography on silica gel to afford the 2,3,6-trisulfonate **2** (3%), the 3,4,6-trisulfonate **3** (1%), the 3,6-disulfonate **4** (35%), a mixture of the 4,6- (**5**) and 2,6- (**6**) disulfonate (14%), and the 6-sulfonate **7** (35%).

The structure of **2** was demonstrated by preparing the monobenzoate, which was shown to be the 4-benzoate **8** by ^{1}H-n.m.r. spectroscopy. The signal of H-4 of **8** appeared to the lowest field of the ring-proton resonances, because of the deshielding effect of benzoyloxy groups on the same methine proton at C-4. The structure of **3** was also confirmed by comparison of the ^{1}H-n.m.r. spectra of **3** and its benzoate **9**. The signal of H-2 in the spectrum of **9** appeared in lower field than that of H-2 in the spectrum of **3**. This finding indicates that C-2 of **3** and **9** is substituted with a hydroxyl and a benzoyloxy group, respectively.

The structure of **4** was established by preparing the dibenzoate **10**. The signal of H-3 in the ^{1}H-n.m.r. spectrum of **4** appeared at lower field than those of H-2 and H-4, whereas the signals of H-2 and H-4 in the ^{1}H-n.m.r. spectrum of **10** appeared at the lowest field of the ring-proton resonances. Compounds **5** and **6** showed the same R_F value on t.l.c., and could not be crystallized. Therefore, in order to determine the molar ratio of the disulfonates **5** and **6**, a mixture of the two was benzoylated and the product analyzed by ^{1}H-n.m.r. spectroscopy. An authentic specimen of **11** was prepared by acetalation of **7**, followed by tosylation, deacetalation, and benzoylation. The remaining disulfonate **12** was isolated by fractional crystallization from the benzoylated mixture of **11** and **12**. The ^{1}H-n.m.r. spectrum of the resulting benzoylated mixture indicated the ratio of **11** and **12** in the mixture to be 3:7, based on the relative proton-intensities of the tosyloxy methyl group in the spectrum.

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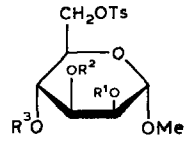
The structure of **7** was confirmed by ^{1}H-n.m.r. spectroscopy. The signals of H-2, H-3, and H-4 in the spectrum of its benzoylated derivative **13** appeared at the lowest field of the ring-proton resonances. This finding indicates that C-6 of **7** is substituted with a tosyloxy group.

Trimolar tosylation of **1** gave a product mixture from which **2** (5%), **3** (2%), **4** (40%), a mixture of **5** and **6** (15%), and **7** (25%) were isolated, after column chromatography. The mixture of **5** and **6** was converted into the corresponding benzoyl derivatives **11** and **12** in the ratio of 1:3 (shown by ^{1}H-n.m.r. spectroscopy as described for dimolar tosylation).

In di- and tri-tosylation of **1**, the highest yield of **4** in the disulfonates and the preponderance of **6** over **5** showed that the realtive reactivity of the hydroxyl groups in **1** towards *p*-toluenesulfonyl chloride is OH-6 > OH-3 > OH-2 > OH-4.

The highest reactivity among the secondary hydroxyl groups in **1**, that of O-3, may be explained by intramolecular hydrogen-bonding between OH-3 and the (axial) OH-2 group. Interestingly, OH-2, which is axial, is more reactive than the equatorial OH-4 group. This finding is in good agreement with the foregoing observations[3–5] that the hydroxyl groups participating in intramolecular hydrogen-bonding activate each other. The lowest reactivity that of the OH-4 group, is consistent with the results[6] of trimolar methanesulfonylation of **1**, which affords the 2,3,6-trimethanesulfonate as the major product in 41% yield.

Partial tosylation of the 3,6-disulfonate **4** gave further information on the relative reactivity of the hydroxyl groups in **1**. No reaction occurred when **4** was subjected to mono- and di-tosylation; however, addition of a large excess of *p*-toluenesulfonyl chloride resulted in formation of the 2,3,4,6-tetrasulfonate, the 2,3,6-trisulfonate, the 3,4,6-trisulfonate, and the starting material in the molar ratios of 3:5:2:1. This result indicates that the low yields of the trisulfonates (7%) in tritosylation of **1** may be due to the retardation effect as described[4,7] previously in tosylation. However, it seems that isolated hydroxyl groups in the trisulfonates are not so sterically hindered, judging from the yield of the tetrasulfonate in tosylation of **4**.



	R^1	R^2	R^3
2	Ts	Ts	H
3	H	Ts	Ts
4	H	Ts	H
5	H	H	Ts
6	Ts	H	H
7	H	H	H
8	Ts	Ts	Bz
9	Bz	Ts	Ts
10	Bz	Ts	Bz
11	Bz	Bz	Ts
12	Ts	Bz	Bz
13	Bz	Bz	Bz

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 for solutions in chloroform, 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. T.l.c. was performed on TLC silica gel 60 G (Merck), and column chromatography on silica gel 60 (70–230 mesh, Merck).

*Partial tosylation of methyl α-*D*-mannopyranoside* (**1**). — (*a*) *With two molar equivalents.* *p*-Toluenesulfonyl chloride (2.16 g, 2.2 mol, equiv.) was added portionwise to a stirred solution of **1** (1 g) in dry pyridine (40 mL) at 0°. The mixture was kept for 24 h at 0°, stirred for 40 h at 5°, and then for 48 h at room temperature. The mixture was extracted with dichloromethane, and 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–acetone gave the syrupy 2,3,6-trisulfonate **2** (90 mg, 3%); $[\alpha]_D^{24}$ +4.6° (*c* 1.7) and the syrupy 3,4,6-trisulfonate **3** (38 mg, 1%); $[\alpha]_D^{22}$ +59.2° (*c* 2.6); ^{1}H-n.m.r.: δ 4.82 (t, 1 H, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 4.60 (q, 1 H, $J_{2,3}$ 3 Hz, H-3), 3.25 (s, 3 H, CH_3O), and 2.40 (s, 9 H, 3 $C_6H_4CH_3$).

Elution with 4:1 benzene–acetone afforded the syrupy 3,6-disulfonate **4** (893 mg, 35%); $[\alpha]_D^{21}$ +37.0° (*c* 0.7); ^{1}H-n.m.r.: δ 4.57 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.53 (q, 1 H, $J_{2,3}$ 4, $J_{3,4}$ 9 Hz, H-3), 3.22 (s, 3 H, CH_3O), and 2.38 (s, 6 H, 2 $C_6H_4CH_3$). Further elution with 4:1 benzene–acetone gave a mixture of the 4,6- (**5**) and 2,6- (**6**) disulfonate (349 mg, 14%) as a syrup.

Final elution with 2:1 benzene–acetone gave the foamy 6-*p*-toluenesulfonate **7** (626 mg, 35%); $[\alpha]_D^{24}$ +37.4° (*c* 1.1); ^{1}H-n.m.r.: δ 4.60 (s, 1 H, $J_{1,2}$ 0 Hz, H-1), 3.23 (s, 3 H, CH_3O), and 2.38 (s, 3 H, $C_6H_4CH_3$).

(*b*) *With three molar equivalents.* Treatment of **1** (1 g) with *p*-toluenesulfonyl chloride (2.945 g, 3.0 mol. equiv.) in pyridine (40 mL), followed by chromatographic fractionation of the product on silica gel as described in (*a*), afforded five fractions: **2** (176 mg, 5%), **3** (76 mg, 2%), **4** (1.032 g, 40%), **5** + **6** (388 mg, 15%), and **7** (449 mg, 25%).

*Methyl 4-*O*-benzoyl-2,3,6-tri-*O*-*p*-tolylsulfonyl-α-*D*-mannopyranoside* (**8**). — Benzoylation of the trisulfonate **2** (90 mg) with benzoyl chloride (0.1 mL) in pyridine (2 mL) at 0° gave a crystalline solid (95 mg, 91%) which, on recrystallization from ethanol, yielded the title compound **8**; m.p. 150–151°, $[\alpha]_D^{24}$ +8.4° (*c* 0.9); ^{1}H-n.m.r.: δ 5.10 (t, 1 H, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 3.38 (s, 3 H, CH_3O), and 2.42, 2.33, and 2.18 (3 s, 9 H, 3 $C_6H_4CH_3$).

Anal. Calc. for $C_{35}H_{36}O_{13}S_3$: C, 55.25; H, 4.77; S, 12.64. Found: C, 55.11; H, 4.70; S, 12.44.

*Methyl 2-*O*-benzoyl-3,4,6-tri-*O*-*p*-tolylsulfonyl-α-*D*-mannopyranoside* (**9**). —

The trisulfonate **3** (77 mg) was treated with benzoyl chloride (0.1 mL) in pyridine (2 mL) to afford the title compound **9** (88 mg, 99%). Attempts to crystallize it failed; $[\alpha]_D^{24}$ −14.8° (*c* 0.2); ^{1}H-n.m.r.: δ 5.03 (q, 1 H, $J_{2,3}$ 2, $J_{3,4}$ 8 Hz, H-3), 4.92 (broad s, 1 H, H-2), 4.62 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 3.27 (s, 3 H, CH_3O), and 2.40, 2.37, and 2.32 (3 s, 9 H, 3 $C_6H_4CH_3$).

*Methyl 2,4-di-*O*-benzoyl-3,6-di-*O*-*p*-tolylsulfonyl-α-*D*-mannopyranoside* (**10**). — Treatment of the disulfonate **4** (183 mg) with benzoyl chloride followed by crystallization from ethanol gave the title compound **10** (154 mg, 60%); m.p. 85°, $[\alpha]_D^{26}$ −31.5° (*c* 0.9); ^{1}H-n.m.r.: δ 5.58 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9 Hz, H-4), 5.37 (q, 1 H, $J_{1,2}$ 2, $J_{2,3}$ 4 Hz, H-2), 5.17 (q, 1 H, H-3), 4.80 (d, 1 H, H-1), 6.38 (s, 3 H, CH_3O), and 5.28, and 5.18 (2 s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{35}H_{34}O_{12}S_2$: C, 59.15; H, 4.82; S, 9.02. Found: C, 58.98; H, 4.74; S, 9.16.

*Methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-*p*-tolylsulfonyl-α-*D*-mannopyranoside* (**11**). — A solution of the 6-sulfonate **7** (100 mg) in *N,N*-dimethylformamide (1 mL) containing *p*-toluenesulfonic acid (4 mg) was heated for 1.5 h at 70° with 2,2-dimethoxypropane (1 mL). The mixture was extracted with dichloromethane and the extract was evaporated to a syrup. *O*-Deacetonation in 70% acetic acid (10 mL), followed by column-chromatographic purification of the product afforded the syrupy 4,6-disulfonate **5** (73 mg, 51%); $[\alpha]_D^{22}$ +53.3° (*c* 2.1). Benzoylation of **5** (62 mg) with benzoyl chloride in pyridine yielded the title compound **11** (100 mg, 97%), which could not be crystallized; $[\alpha]_D^{25}$ −79.7° (*c* 2.4); ^{1}H-n.m.r.: δ 5.73 (q, 1 H, $J_{2,3}$ 3, $J_{3,4}$ 9 Hz, H-3), 5.53 (q, 1 H, $J_{1,2}$ 1 Hz, H-2), 5.23 (t, $J_{4,5}$ 9 Hz, H-4), 4.80 (d, 1 H, H-1), 3.42 (s, 3 H, CH_3O), and 2.42 ad 2.15 (2 s, 6 H, $C_6H_4CH_3$).

*Methyl 3,4-di-*O*-benzoyl-2,6-di-*O*-*p*-tolylsulfonyl-α-*D*-mannopyranoside* (**12**). — A mixture of **5** and **6** (87 mg) in pyridine was treated with benzoyl chloride. Conventional processing, followed by two recrystallizations from chloroform–ethanol, gave the title compound **12** (27 mg, 22%); m.p. 186–187°, $[\alpha]_D^{25}$ +21.3° (*c* 0.9); ^{1}H-n.m.r.: δ 3.40 (s, 3 H, CH_3O), and 2.35 and 2.08 (2 s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{35}H_{34}O_{12}S_2$: C, 59.15; H, 4.82; S, 9.02. Found: C, 59.03; H, 4.68; S, 9.17.

*Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-*p*-tolylsulfonyl-α-*D*-mannopyranoside* (**13**). — Treatment of the 6-sulfonate **7** (100 mg) with benzoyl chloride in pyridine yielded a solid which was recrystallized from ethanol to give the title compound **13** (163 mg, 86%); m.p. 205–206°, $[\alpha]_D^{18}$ −105.8° (*c* 2.8); ^{1}H-n.m.r.: δ 6.0–5.5 (m, 2 H, H-3,4), 5.57 (broad q, 1 H, H-2), 4.83 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), 3.43 (s, 3 H, CH_3O), and 2.28 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{35}H_{32}O_{12}S$: C, 63.63; H, 4.88; S, 4.85. Found: C, 63.42; H, 4.86; S, 5.03.

*Partial tosylation of methyl 3,6-di-*O*-p-tolylsulfonyl-α-*D*-mannopyranoside* (**4**). — Compound **4** (103 mg) was tosylated for 4 days at room temperature by daily addition of 48 mg (1.2 mol. equiv.) of *p*-toluenesulfonyl chloride. After conventional processing, column-chromatographic fractionation gave the syrupy

2,3,4,6-tetrasulfonate (37 mg, 23%); $[\alpha]_D^{28}$ +20.5° (*c* 1.9), the 2,3,6-trisulfonate **2** (50 mg, 37%), the 3,4,6-trisulfonate **3** (19 mg, 14%), and the starting material **4** (8 mg, 8%).

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