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Note

A new route for the synthesis of D-tagatose

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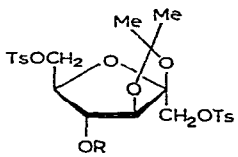
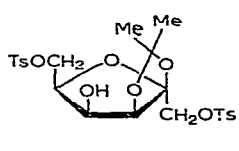
In recent years, many new routes to rare sugars have been developed by the technique of oxidation of a suitable, blocked compound, followed by reduction to the epimer of the starting alcohol[1]. We now describe its application to the synthesis of the rare ketose D-tagatose and several derivatives of D-tagatofuranose.

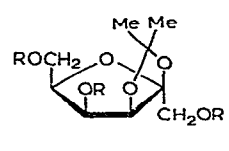
2,3-*O*-Isopropylidene-1,6-di-*O*-tosyl-β-D-fructofuranose[2] (**1**) has been prepared in an improved yield and characterised as its 4-*O*-acetyl derivative (**2**). Oxidation of **1** with methyl sulphoxide–acetic anhydride, followed by reduction with sodium borohydride, gave 2,3-*O*-isopropylidene-1,6-di-*O*-tosyl-β-D-tagatofuranose (**3**). Attempts to isolate the intermediate ketone were unsuccessful.



1 R=H
2 R=Ac



3



4 R=H
5 R=Ac

In the mass spectrum of **3**, the ion of highest *m/e* value was that at 513 (M − 15) formed from the molecular ion by elimination of one of the methyl groups from the isopropylidene group. This behaviour is typical of such acetals[3]. Reduction of the ketone would be expected on steric grounds to occur predominantly from the α-face to give the *tagato* configuration.

Treatment of compound **3** in aqueous methanol with sodium amalgam removed the sulphonic ester groups to give 2,3-*O*-isopropylidene-β-D-tagatofuranose (**4**) characterised as its tri-*O*-acetyl derivative (**5**).

Hydrolysis of compound **4** with aqueous acetic acid gave D-tagatose in 63% yield, identical with an authentic sample; the overall yield from D-fructose was 21%. The ketose has been prepared from D-galactose in 6.5% yield[4], but a recent improvement[5] in the method raised the yield to 16%.

EXPERIMENTAL

2,3-O-Isopropylidene-1,6-di-O-tosyl-β-D-fructofuranose (**1**). — This compound was prepared by the literature method[2], except that ethanol-free chloroform was

used, which gave an improved yield. The product (32%) had m.p. 131–133°, $[\alpha]_D^{18}$ +14.9° (*c* 2, ethanol) {lit.[2], m.p. 132–133°, $[\alpha]_D^{20}$ +14.5 ±0.8° (*c* 1.24, ethanol)}.

Compound **1** was acetylated in the usual way with acetic anhydride–pyridine to give the 4-acetate **2**, m.p. 80–82° (from ethanol–light petroleum), $[\alpha]_D^{20}$ +15.8° (*c* 2, ethanol) (Found: C, 53.0; H, 5.5; $C_{25}H_{30}O_{11}S_2$ calc.: C, 52.6; H, 5.3%). N.m.r. data ($CDCl_3$): τ 2.0–2.75 (8-proton multiplet, aromatic); 4.98 (1-proton singlet, H-4); 5.4, 5.78, 5.89 (6 protons, H-1,3,5,6); 7.55 (6-proton singlet, OTs); 7.92 (3-proton singlet, Ac); 8.63, 8.72 (3-proton singlets, CMe_2).

2,3-O-Isopropylidene-1,6-di-O-tosyl-β-D-tagatofuranose (**3**). — 2,3-*O*-Isopropylidene-1,6-di-*O*-tosyl-β-D-fructofuranose (**1**) (10 g) was stirred with methyl sulphoxide (150 ml) and acetic anhydride (100 ml) for 30 h at room temperature. Iced water (500 ml) was added, and the mixture was extracted with chloroform (3 × 200 ml). The combined extracts were washed with aqueous sodium hydrogen carbonate and water, and then dried and evaporated to dryness. The yellow syrup (which was not homogeneous by t.l.c.) was used directly for the next step.

The product was dissolved in methanol (150 ml) and anhydrous *N,N*-dimethylformamide (20 ml), and sodium borohydride (10 g) was added in portions with stirring over 30 min. The mixture was then stirred for a further hour at room temperature. Water was added, and the mixture was extracted with chloroform (3 × 200 ml). The combined extracts were washed with water, dried, and evaporated to a syrup which contained three components, one of which appeared to be starting material (t.l.c.).

The crude product (10 g) was chromatographed on silica gel (3 × 60-cm column, 400 g), and eluted with benzene–ether (85:15). The initial eluent contained a substance (0.2 g) which decomposed on isolation and which was not compound **2** (t.l.c.). Starting material (0.9 g) was eluted next, followed by compound **3** (8.8 g, 88%); $[\alpha]_D^{20}$ +7.8° (*c* 1.0, ethanol). N.m.r. data ($CDCl_3$): τ 2.15–2.75 (8-proton multiplet, aromatic); 5.5–5.9 (7 protons, H-1–H-6); 7.1 (1-proton, broad singlet, O-H); 7.6 (6-proton singlet, OTs); 8.63 and 8.72 (3-proton singlets, CMe_2). Mass spectrum ($C_{23}H_{28}O_{10}S_2$ requires *m/e* 528): *m/e* 513 ($M-CH_3$).

2,3-O-Isopropylidene-β-D-tagatose (**4**). — Compound **3** (6 g) in aqueous methanol (96 ml, 80%) was shaken in an open flask with 4% sodium amalgam (60 g) (t.l.c. monitoring). After 24 h, only traces of starting material were present together with two new compounds, the slower of which preponderated. The filtered mixture was saturated with carbon dioxide and evaporated to dryness. Work-up via chloroform extraction gave **4** as a colourless syrup (2.4 g, 80%), $[\alpha]_D^{25}$ +15.4° (*c* 2, chloroform), which was characterised as the 1,4,6-triacetate **5**, $[\alpha]_D^{20}$ −3.9° (*c* 2, chloroform) (Found: C, 52.4; H, 6.7; $C_{15}H_{22}O_9$ calc.: C, 52.0; H, 6.4%). N.m.r. data ($CDCl_3$): τ 5.25–5.75 (7 protons H-1–H-6); 7.83, 7.88, 8.02 (3-proton singlets, acetyls); 8.35 and 8.60 (3-proton singlets, CMe_2).

D-*Tagatose*. — 2,3-*O*-Isopropylidene-β-D-tagatose (**4**) (2 g) was heated under reflux with M aqueous acetic acid (100 ml) for 1 h. Evaporation of the solvent gave a clear syrup, which was twice co-distilled with ethanol (20 ml) and dried. Trituration

with absolute ethanol gave white crystals, m.p. 124–126°, which were recrystallised from aqueous ethanol to give the ketose (1.8 g, 63%), m.p. 130–131°, $[\alpha]_D^{20}$ +1° (*c* 1, water), undepressed on admixture with an authentic sample which had m.p. 130–131°.

The product gave a *p*-bromophenylhydrazone, m.p. 181–182°, undepressed on admixture with an authentic sample which had m.p. 180–182°.

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