Carbohydrate Research, 212 (1991) C5–C7
Elsevier Science Publishers B.V., Amsterdam

Preliminary communication

Synthesis of 2,6-anhydro-3-deoxy-L-*threo*-hex-2-enitol ("L-sorbal") and of L-tagatose from D-galactose

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(Received November 29th, 1990; accepted for publication, February 14th, 1991)

Whereas glycals derived from aldopyranoses have been investigated widely, little is known of the corresponding derivatives of ketopyranoses. The only examples appear to be derivatives of D-fructal[1,2].

We have described[3] a high-yielding conversion of 3,4-*O*-isopropylidene-β-D-galactopyranosides into 4-deoxy-α-L-*threo*-hex-4-enopyranosides by treatment with potassium *tert*-butoxide in *N*,*N*-dimethylformamide or methyl sulphoxide. We now report that application of this reaction to 1,5-anhydro-3,4-*O*-isopropylidene-D-galactitol derivatives provides an easy access to 2,6-anhydro-3-deoxy-L-*threo*-hex-2-enitol ("L-sorbal", **5**) and L-tagatose (**13**).

As found for D-galactopyranosides[4], when a 0.1M solution of 1,5-anhydro-D-galactitol[5] (**1**) in 2,2-dimethoxypropane that contained a small amount of camphorsulphonic acid was stored at room temperature for 48 h, 1,5-anhydro-3,4-*O*-isopropylidene-2,6-di-*O*-(1-methoxy-1-methylethyl)-D-galactitol (**2**, 40%), m.p. 50–51° (from hexane), $[\alpha]_D$ +36°, and 1,5-anhydro-3,4-*O*-isopropylidene-6-*O*-(1-methoxyl-1-methylethyl)-D-galactitol (**3**, 50%), m.p. 138–140° (from ethyl acetate–hexane), $[\alpha]_D$ +39.5°, were obtained and isolated by flash chromatography*. Reaction of **2** with potassium *tert*-butoxide in methyl sulphoxide[3] (4 h at 80°) yielded 2,6-anhydro-3-deoxy-1,5-di-*O*-(1-methoxy-1-methylethyl)-L-*threo*-hex-2-enitol (**4**, 70%), $[\alpha]_D$ +54°, which was deprotected with methanolic 1% acetic acid (10 min, room temperature) to produce 2,6-anhydro-3-deoxy-L-*threo*-hex-2-enitol (**5**, 90%), m.p. 93–95° (from acetone), $[\alpha]_D$ +153° (methanol).

Reaction of **4** with 3-chloroperoxybenzoic acid (1.8 molar equiv.) in methanol gave methyl 1,5-di-*O*-(1-methoxy-1-methylethyl)-α-L-tagatopyranoside (**6**, 70%), $[\alpha]_D$ −20°. The high diastereo- and regio-selectivity of this reaction, which involves formation of a 2,3-epoxide followed by methanolysis, can be explained by the *syn* orienting effect of HO-4 in the epoxidation step, and preferred *anti* attack by the alcohol at the more electrophilic C-2.

Compound **6** was deprotected as above, to produce methyl α-L-tagatopyranoside

* All $[\alpha]_D$ values were determined at 20° on solutions in chloroform (*c* 1), except where stated otherwise.

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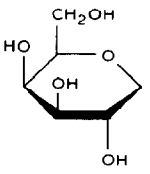

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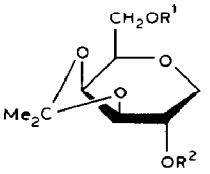
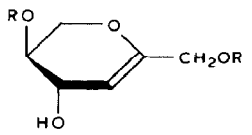
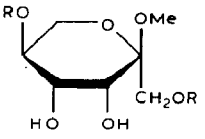


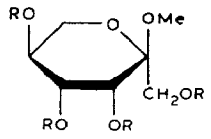
2 $R^1 = R^2 = C(OMe)Me_2$
3 $R^1 = C(OMe)Me_2, R^2 = H$
9 $R^1 = R^2 = H$
10 $R^1 = R^2 = Bn$



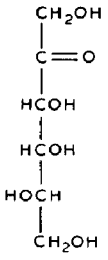
4 R = $C(OMe)Me_2$
5 R = H
11 R = Bn



6 R = $C(OMe)Me_2$
12 R = Bn



7 R = H
8 R = Ac



13

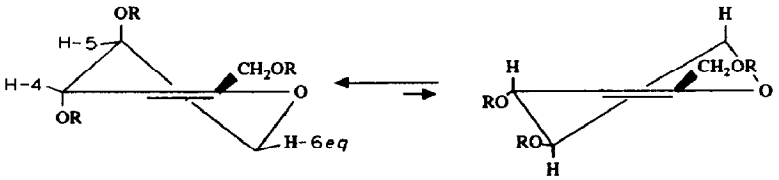
(**7**, 96%), m.p. 126–128° (from acetone), $[\alpha]_D$ −43° (methanol); lit.[6] for the D enantiomer, m.p. 128°, $[\alpha]_D$ +56.8° (methanol). The tetra-acetate (**8**) of **7** had m.p. 121–123° (from ether–light petroleum), $[\alpha]_D$ −24°; lit.[6] for the D enantiomer, m.p. 125°, $[\alpha]_D$ +23.8°.

As an alternative approach to **7**, the crude mixture of **2** and **3** was deprotected with methanolic 1% acetic acid to give 1,5-anhydro-3,4-*O*-isopropylidene-D-galactitol (**9**, 90% from **1**), m.p. 92–93° (from ethyl acetate–hexane), $[\alpha]_D$ +73°, which was converted, with sodium hydride and benzyl bromide in *N,N*-dimethylformamide, into 1,5-anhydro-2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-D-galactitol (**10**, 86%), m.p. 83–85° (from hexane), $[\alpha]_D$ +7.5°. Treatment of **10** with potassium *tert*-butoxide in methyl sulphoxide gave 2,6-anhydro-1,5-di-*O*-benzyl-3-deoxy-L-*threo*-hex-2-enitol (**11**, 70%), $[\alpha]_D$ +79°, which, with 3-chloroperoxybenzoic acid in methanol, gave methyl 1,5-di-*O*-benzyl-α-L-tagatopyranoside (**12**, 75%), m.p. 115–117°(from ethyl acetate–hexane), $[\alpha]_D$ −15.5°. Hydrogenolysis of **12** (10% Pd/C, MeOH) then yielded **7** (94%).

The glycoside **7** was converted (91–95%) into free L-tagatose (**13**), $[\alpha]_D$ −0.4° → +2.2° (water) {lit.[7] $[\alpha]_D$ +1° (water)} by acid-catalysed hydrolysis [Amberlyst 15 (H^+) resin or aqueous 20% CF_3CO_2H]. The ^{13}C-n.m.r. spectra of **7** and **13** corresponded closely with those reported[8] for the corresponding D enantiomers.

All of the above new compounds gave satisfactory elemental analyses, and their structures were substantiated by their ^1H- and ^{13}C-n.m.r. spectra. The 2,6-anhydro-3-deoxy-L-*threo*-hex-2-enitols, such as **4**, **5**, and **11**, exhibit a marked preference for the $^5H_6$ (**14**) over the $^6H_5$ (**15**) conformation, as indicated by the low values (2.85–3.00 Hz) of $J_{4,5}$ and the long-range couplings ($J_{4,6eq}$ 1.5 Hz), which are possible only if H-4 is equatorial. 4-Deoxy-α-L-*threo*-hex-4-enopyranosides, the 6-alkoxy analogues of the compounds under discussion, exist in the triaxial conformation, which has been attributed to the anomeric effect[3]. The present results show that, even in the absence of an anomeric

substituent, the conformer with 4,5-diaxial groups is strongly favoured, possibly because of the allylic effect[9] (pseudo-axial preference for an allylic electronegative substituent).



14 ($^5H_6$) 15 ($^6H_5$)

The present results facilitate access to L-tagatose, its endocyclic glycal, and a range of derivatives. L-Tagatose has been prepared hitherto in low yield by isomerisation of L-galactose[7] or by synthesis from L-threose[10].

ACKNOWLEDGMENT

This work was supported by a grant from CNR (Progetto Finalizzato Chimica Fine II).

REFERENCES

1 R. K. Ness and H. G. Fletcher, Jr., *J. Org. Chem.*, 33 (1968) 181–184.
2 S. Hahn, W. Doleschal, and F. W. Lichtenthaler, *Eur. Carbohydr. Symp., 4th, Darmstadt, 1987*, Abstr. A-124.
3 P. L. Barili, G. Berti, G. Catelani, F. Colonna, and F. D'Andrea, *Carbohydr. Res.*, 190 (1989) 13–21.
4 P. L. Barili, G. Berti, G. Catelani, F. Colonna, and A. Marra, *Tetrahedron Lett.*, 27 (1986) 2307–2310.
5 P. Kocienski and C. Pant, *Carbohydr. Res.*, 110 (1982) 330–332.
6 Y. Khouvine, G. Arragon, and Y. Tomoda, *Bull. Soc. Chim. Fr.*, 6 (1939) 354–359.
7 L. Glatthaar and T. Reichstein, *Helv. Chim. Acta*, 20 (1937) 1537–1541.
8 S. J. Angyal and G. S. Bethell, *Aust. J. Chem.*, 29 (1976) 1249–1265.
9 R. J. Ferrier and G. H. Sankey, *J. Chem. Soc., C*, (1966) 2345–2349.
10 T. Mukayama, Y. Yuchi, and K. Suzuki, *Chem. Lett.*, (1982) 1169–1170.