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D-FRUCTOSE DERIVATIVES MODIFIED AT C-4 BY DIRECT DISPLACEMENT AND BY OXIRANE OPENING

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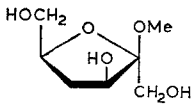
ABSTRACT

The epoxide ring of methyl 3,4-anhydro-β-D-tagatofuranoside is opened by attack of nucleophiles at C-4 to yield derivatives of D-fructose. Treatment of 2,3-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-β-D-fructofuranose with sulfuryl chloride resulted in attack at C-6, not C-4. 2,3-*O*-Isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-β-D-tagatofuranose behaved normally with this reagent. Methyl 4-deoxy-β-D-*threo*-hexulofuranoside was not hydrolysed by invertase.

DISCUSSION

Target molecules in our study[1] of the structure–activity relationship of invertase (β-D-fructofuranosidase) are those modified at C-4, particularly methyl 4-deoxy-β-D-*threo*-hexulofuranoside (**1**).

We have described[2] a facile, single-step synthesis of methyl 3,4-anhydro-β-D-tagatofuranoside (**2**) from methyl β-D-fructofuranoside and have now characterised **2** as the 1,6-dibenzoate (**3**). It would be predicted that the epoxide ring-opening of **2** and **3** would proceed selectively (if not exclusively) at C-4. The analogous methyl 2,3-anhydro-β-D-pentofuranosides react almost exclusively[3] at C-3 (the analogous position to C-4 in **2** and **3**). In **2** and **3**, there are additional factors that would be expected to drive the opening towards C-4, namely the presence of a substituent (C-1) on the α-face at C-2 and also the neopentyl nature of C-3. Electronic arguments also favour opening at C-4, which yields products having the required D-fructose configuration[4].



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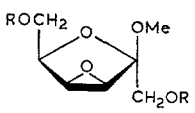

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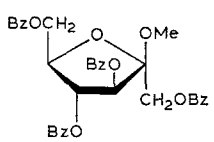
3 R = Bz



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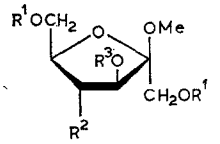
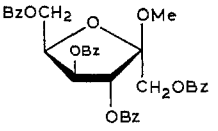
The reaction of **2** with boiling M sodium hydroxide for 24 h and subsequent benzoylation gave methyl 1,3,4,6-tetra-*O*-benzoyl-β-D-fructofuranoside (**4**) identical to the compound prepared by benzoylation of methyl β-D-fructofuranoside. Compound **4** was also prepared by treatment of the dibenzoate **3** with sodium benzoate in hexamethylphosphoramide at 110°, to give methyl 1,3,6-tri-*O*-benzoyl-β-D-fructofuranoside (**5**, 73%), and then conventional benzoylation.



5 R^1 = Bz, R^2 = OBz, R^3 = H
7 R^1 = Ac, R^2 = I, R^3 = Ac



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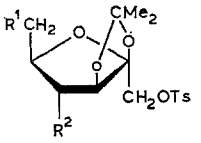
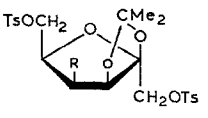


8 R^1 = OTs, R^2 = OH
9 R^1 = Cl, R^2 = OH
10 R^1 = OTs, R^2 = Cl
11 R^1 = H, R^2 = OH

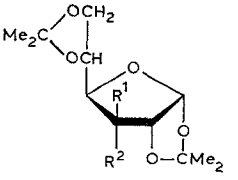
The above reactions clearly demonstrated that the oxirane ring in **2** and **3** is opened at C-4, since opening at C-3 would have led eventually to methyl 1,3,4,6-tetra-*O*-benzoyl-β-D-sorbofuranoside (**6**).

Treatment of **2** with hydrogen iodide in pyridine at 90° for 19 h and then acetylation gave syrupy methyl 1,3,6-tri-*O*-acetyl-4-deoxy-4-iodo-β-D-fructofuranoside (**7**, 66%), $[\alpha]_D^{25}$ −52° (chloroform), which was de-iodinated by Raney nickel, hydrazine hydrate, and barium carbonate in methanol, to give **1** (83%), which was characterised as the 1,3,6-triacetate. That the deoxy group was at C-4 and not C-3 was clearly demonstrated by the ^{1}H-n.m.r. spectrum.

An alternative route to **1** appeared possible *via* 2,3-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-β-D-fructofuranose[5] (**8**) and the reaction of HO-4 with sulfuryl chloride[6], or carbon tetrachloride–triphenyl phosphine[7], to yield the 4-chloro-4-deoxytagatose derivative **12**. However, with either reagent, the product was not **12**, but 6-chloro-6-deoxy-2,3-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-β-D-fructofuranose (**9**), which was also synthesised from **8** by reaction with lithium chloride in *N*,*N*-dimethylformamide. It is well known in ketose chemistry[8] that 6-sulfonates are more readily displaced than 1-sulfonates. In order to substantiate the structure of **9**, it was converted into the known[5] 6-deoxy derivative **11**, which showed a doublet in its ^{1}H-n.m.r. spectrum for the newly introduced methyl group.



12 R = Cl
13 R = OH



14 R^1 = H, R^2 = OTs
15 R^1 = OTs, R^2 = H

TABLE I

^{13}C-N.M.R. DATA[a–c] (90 MHz, $CDCl_3$)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Other signals*
1[d]	61.2	104.8	73.5	35.2	78.4	66.3	49.1 (OMe)
3	63.0	104.1	56.7[a]	54.4[a]	74.9	66.2	52.5 (OMe)
5	61.9	103.1	79.1[a]	76.6[a]	80.1	65.0	
7	62.2	102.0	80.3	17.9	81.9	62.5	49.7 (OMe)
8	68.0[a]	113.7[b]	85.8[c]	75.1	86.0[c]	68.9[a]	112.6[b] (*C*Me$_2$), 21.6 (ArCH$_3$), 25.8, 26.8 (C*Me*)$_2$
9	68.2	113.8[a]	86.3	75.9	88.8	43.4	112.8[a] (*C*Me$_2$), 21.3 (ArCH$_3$), 25.7, 27.1 (C*Me*)$_2$
10	67.8[a]	114.5[b]	86.0	58.3	87.0	68.1[a]	112.8[b] (*C*Me$_2$), 21.6 (ArCH$_3$), 26.2, 26.9 (C*Me*)$_2$
11	64.6	113.9[a]	86.0	76.3	87.4	19.7	113.6[a] (*C*Me$_2$), 21.5 (ArCH$_3$), 26.3, 27.5 (C*Me*)$_2$

[a–c]Numbers with the same letter in a horizontal row may be interchanged. Acyl carbons are not given.
[d]As the 1,3,6-triacetate.

Each of the above reagents can displace secondary hydroxyl groups with inversion. A molecular model of **8** showed that the approach to the back of C-4 is extremely hindered because of the V-shape of the two fused five-membered rings.

In contrast, the C-4 epimer of **8**, namely, the tagatose derivative **13**[9], reacted with sulfuryl chloride, to produce a chloro product that still contained two sulfonate groups and to which, from the known S_N2 nature of the reaction and from ^{1}H- and ^{13}C-n.m.r. data, is assigned the structure 4-chloro-4-deoxy-2,3-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-β-D-fructofuranose (**10**). The approach to the back of C-4 in **13** is not hindered and also there is steric relief in changing from the tagatose to the fructose configuration. The displacement of TsO-6 in **13** occurs *less* readily than that of the secondary chlorosulfonate group formed at C-4 as an intermediate in the production of **12**. The difference in the ease of displacement at C-4 of these epimeric ketofuranoses is reminiscent of the behaviour of the C-3 epimeric allo- and gluco-furanose derivatives **14** and **15**, respectively[8].

Methyl 4-deoxy-β-D-*threo*-hexulofuranoside (**1**) was not hydrolysed by invertase under conditions in which sucrose was readily cleaved. This demonstrates that, in addition to HO-1 and HO-6 in the fructofuranosyl moiety[1], HO-4 is also necessary for binding to the enzyme.

The ^{13}C-n.m.r. data in Table I show the expected features, including the large downfield-shift for C-2 in **8–11** (*cf.* ref. 10). The ^{1}H-n.m.r. data[11] will be discussed elsewhere.

EXPERIMENTAL

Optical rotations were measured for solutions in $CHCl_3$ with a Perkin–Elmer 241 polarimeter. ^{13}C-N.m.r. spectra were recorded with a Bruker HX-90 spectrometer. All organic extracts were washed with dilute hydrochloric acid, dilute, aqueous

sodium carbonate, and water, dried ($MgSO_4$), and concentrated *in vacuo* at $<50°$ (bath).

*Methyl 1,3,4,6-tetra-*O*-benzoyl-β-*D*-fructofuranoside* (**4**). — (*a*) To a solution of methyl β-D-fructofuranoside (0.5 g) in dry pyridine (5.0 mL) at 0° was slowly added benzoyl chloride (1.7 mL, 2.0 g). The mixture was stored at room temperature overnight and then poured into ice–water (200 mL). The resulting gum was extracted into chloroform, and the resulting, colourless syrup was chromatographed on silica gel (toluene–chloroform, 9:1), to give **4** (0.9 g, 70%) as a colourless syrup, $[\alpha]_D$ −44° (*c* 1).

Anal. Calc. for $C_{35}H_{30}O_{10}$: C, 68.8; H, 4.95. Found: C, 69.1; H, 5.05.

(*b*) Methyl 3,4-anhydro-β-D-tagatofuranoside (**2**, 250 mg) was treated with M sodium hydroxide under reflux for 25 h. T.l.c. (ethyl acetate–methanol, 4:1) then showed only a slow-moving product. After neutralisation, the mixture was concentrated, dried, and then treated with benzoyl chloride and pyridine. Work-up gave a syrup which was purified by flash chromatography[12] (ethyl acetate–hexane, 1:2), to give **4** (425 mg, 49%).

*Methyl 3,4-anhydro-1,6-di-*O*-benzoyl-β-*D*-tagatofuranoside* (**3**). — Treatment of **2** with benzoyl chloride and pyridine as described above, with crystallisation of the product from methanol, gave **3** (1.7 g, 78%), m.p. 81–82°, $[\alpha]_D^{21}$ −58.5° (*c* 2).

Anal. Calc. for $C_{21}H_{20}O_7$: C, 65.6; H, 5.2. Found: C, 65.4; H, 5.3.

*Methyl 1,4,6-Tri-*O*-benzoyl-β-*D*-fructofuranoside* (**5**). — A mixture of **3** (450 mg, 1.17 mmol), sodium benzoate (845 mg, 5 equiv.), and hexamethylphosphoramide (15 mL) was kept at 110° overnight. T.l.c. then revealed one major and one minor product of polarity higher than that of **3**. Extraction with ethyl acetate gave a syrup which was purified by flash chromatography (ethyl acetate–hexane, 1:4), to give **5** as a syrup (430 mg, 73%), $[\alpha]_D^{21}$ −5° (*c* 1).

Anal. Calc. for $C_{28}H_{26}O_9$: C, 66.4; H, 5.2. Found: C, 66.5; H, 5.4.

*Methyl 1,3,6-tri-*O*-acetyl-4-deoxy-4-iodo-β-*D*-fructofuranoside* (**7**). — Aqueous 30% hydrogen iodide (5 mL) was added dropwise to a solution of **2** (1 g) in dry pyridine (20 mL), and the dark solution was stirred at 90° for 18 h. T.l.c. (acetone–dichloromethane, 1:1) then revealed a slow-moving product together with a small proportion of **2**. The mixture was diluted with chloroform (50 mL), washed with aqueous sodium thiosulphate, aqueous sodium hydrogencarbonate, and water, and concentrated, and the syrup was dried and then acetylated. Flash chromatography (acetone–hexane, 1:3) gave **7** as a syrup (1.61 g, 66%), $[\alpha]_D$ −52° (*c* 1).

Anal. Calc. for $C_{13}H_{19}IO_8$: C, 36.3; H, 4.5. Found: C, 36.5; H, 4.7.

*Methyl 4-deoxy-β-*D*-threo-hexulofuranoside* (**1**). — Compound **7** (1.4 g) was treated with hydrazine hydrate (10 mL), barium carbonate (2.0 g), and Raney nickel (~1 g) in methanol (50 mL) at 60° for 2 h. Work-up gave a syrup which was purified by flash chromatography (ethyl acetate–methanol, 18:1), to give **1** as a syrup (480 mg, 83%), $[\alpha]_D$ −45° (*c* 1, methanol). Microanalytical data were unsatisfactory due to the hygroscopic nature of **1**. The 1,3,6-triacetate was a syrup, $[\alpha]_D$ −30°.

Anal. Calc. for $C_{13}H_{20}O_8$: C, 53.1; H, 6.6. Found: C, 53.1; H, 6.8.

*6-Chloro-6-deoxy-2,3-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-β-*D*-fructofuranose* (**9**). — (*a*) A mixture of 2,3-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-β-D-fructofuranose[2,5] (**8**, 200 mg), *N*,*N*-dimethylformamide (10 mL), and lithium chloride (400 mg) was stirred at 90–100° for 20 h, cooled, poured into water, and extracted with ether. Column chromatography of the syrupy product on silica gel gave **9** (120 mg, 80%), m.p. 76° (from methanol), $[\alpha]_D$ +17° (*c* 1). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.30 (s, 3 H, CMe), 1.50 (s, 3 H, CMe), 2.43 (s, 3 H, Ts-Me), 2.77 (s, 1 H, OH), 2.63 (d, 2 H, $J_{5,6}$ 6.3 Hz, H-5), 4.17 (d, 2 H, $J_{1,1}$ 2 Hz, H-1), 3.8–4.4 (m, 2 H, H-4,5), 4.52 (s, 1 H, H-3), and 7.46 (dd, 4 H, aromatic). Mass spectrum: *m*/*z* 377.0462 $(M - Me)^+$. Calc. for $C_{16}H_{21}ClO_7S$: *m*/*z* 377.0461.

(*b*) A solution of 2,3-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-β-D-fructofuranose (**8**, 320 mg) in dry carbon tetrachloride (50 mL) containing triphenylphosphine (180 mg) was boiled under reflux for 24 h. Chromatography on silica gel gave **9** (30%) identical to the product in (*a*).

*6-Deoxy-2,3-*O*-isopropylidene-1-*O*-p-*tolylsulphonyl-β-D-fructofuranose* (**11**). — (*a*) To a solution of **9** (100 mg) in methanol (20 mL) were added barium carbonate (1 g), hydrazine hydrate (10 mL), and freshly prepared Raney nickel W-4 (1 g). After boiling under reflux for 8 h, the mixture was cooled, filtered through Celite, and concentrated, and the residue was extracted with ether. On addition of hexane to the extract, **11** slowly formed (70%); m.p. 112°, $[\alpha]_D$ +10° (*c* 1, methanol); lit.[5] m.p. 112–114°, $[\alpha]_D^{21}$ +11 ±2° (*c* 1, ethanol).

(*b*) A solution of **8** (550 mg) in pyridine (4 mL) and chloroform (10 mL) was cooled to ~−70° and sulfuryl chloride (0.5 mL) was added with stirring. After 2 h, the mixture was warmed to room temperature and then boiled under reflux for 48 h. The mixture was diluted with chloroform and, after the usual work-up, the product was purified by p.l.c. (ethyl acetate–hexane, 1:1), to give **11** identical to the product in (*a*).

*4-Chloro-4-deoxy-2,3-*O*-isopropylidene-1,6-di-*O*-p-*tolylsulfonyl-D-fructofuranose* (**10**). — 2,3-*O*-Isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-β-D-tagatofuranose[9] (**13**, 3.9 g) was treated with sulfuryl chloride (3 mL) as described above. Chromatography (ethyl acetate–hexane, 1:3) of the product gave **10** (2.9 g, 71%), m.p. 99–99.5°, $[\alpha]_D$ +20° (*c* 1).

Anal. Calc. for $C_{23}H_{27}ClO_9S_2$: C, 50.5; H, 5.0. Found: C, 50.4; H, 5.1.

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REFERENCES

1 R. D. Guthrie, I. D. Jenkins, P. J. Rogers, W. F. Sum, J. J. Watters, and R. Yamasaki, *Carbohydr. Res.*, 75 (1979) c1–c4.
2 R. D. Guthrie, I. D. Jenkins, and R. Yamasaki, *Chem. Commun.*, (1980) 784–785; *J. Chem. Soc., Perkin 1*, (1981) 2328–2334.

3 N. R. WILLIAMS, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 109–179.
4 R. KHAN, in G. G. BIRCH AND K. J. PARKER (Eds.), *Sugar: Science and Technology*, Applied Science Publishers, London, 1979, p. 181.
5 W. T. J. MORGAN AND T. REICHSTEIN, *Helv. Chim. Acta*, 21 (1938) 1023–1031.
6 W. A. SZAREK, *Adv. Carbohydr. Chem. Biochem.*, 28 (1973) 225–306.
7 R. G. WEISS AND E. I. SNYDER, *Chem. Commun.*, (1968) 1358–1359.
8 R. S. TIPSON, *Adv. Carbohydr. Chem.*, 8 (1953) 107–216; D. H. BALL AND F. W. PARRISH, *Adv. Carbohydr. Chem. Biochem.*, 24 (1969) 139–198.
9 A. A. H. AL-JOBORE, R. D. GUTHRIE, AND R. D. WELLS, *Carbohydr. Res.*, 16 (1971) 474–476.
10 D. M. VYAS, H. C. JARRELL, AND W. A. SZAREK, *Can. J. Chem.*, 53 (1975) 2748–2754.
11 R. D. GUTHRIE, I. D. JENKINS, AND R. YAMASAKI, in press.
12 W. C. STILL, M. KHAN, AND A. MITRA, *J. Org. Chem.*, 43 (1978) 2923–2925.