SYNTHESIS OF 3-*C*-HYDROXYMETHYL-1,2-*O*-ISOPROPYLIDENE-α-D-ERYTHROFURANOSE AND D-APIOSE

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ABSTRACT

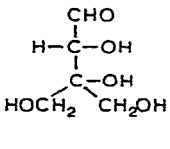
A synthesis of 3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-erythrofuranose (an essential intermediate in a preparation of 4′-*O*-methylapiin), based on L-threose, is described. The procedure involves sequential acetonation, oxidation, epoxidation, and basic cleavage of the epoxide. The configurations of the epoxide and its cleavage products have been established.

INTRODUCTION

A peculiar feature of the chemistry of the naturally occurring, branched-chain sugar apiose (**1**) is that two furanose forms are possible, depending on which hydroxymethyl group at C-3 becomes involved in ring formation. As part of a project directed towards the synthesis of the 4′-*O*-methyl derivative of apiin, to be described elsewhere[1], we required as an intermediate 3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-erythrofuranose (**2**)* (1,2-*O*-isopropylidene-α-D-apio-D-furanose) in which the oxygen groups on C-2 and C-3 have the D-*erythro* configuration, since this has been shown to be the stereochemistry of the apiofuranose ring in apiin[2]. The acetonation of apiose affords a mixture of di-*O*-isopropylidene derivatives, from which 3-*C*-hydroxymethyl-1,2:1′,3-di-*O*-isopropylidene-β-L-threo- and -α-D-erythro-furanose have been isolated as major and minor components, respectively, and these may be partially hydrolysed to give the corresponding 3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-β-L-threo- and -α-D-erythro-furanose compounds[3,4] (**3** and **2**). The required isomer **2** is obtained in poor yield by this method, and we have developed, therefore, a convenient synthesis of **2** starting from L-threose. This method utilises the readily accessible 1,2-*O*-iso-

*In the absence of a recommended system of nomenclature for branched-chain sugars, we propose to name these furanose compounds as alkylated derivatives of the corresponding straight-chain sugars. Thus, the isomeric forms of apiofuranose can be considered as being derived from erythrose or threose, depending on whether the relationship of hydroxyl groups at C-2 and C-3 is *cis* or *trans*, respectively. This is a direct extension of the procedure generally adopted for other branched-chain sugars. Although the use of two parent names for the ring forms of the same sugar may be considered by some to be a disadvantage, the translation of names to structures and *vice versa* is straightforward and the use of a special nomenclature system to cover this particular situation is avoided. This procedure has already been adopted by Ball *et al.*[4].

propylidene-α-D-*glycero*-tetros-3-ulose (**4**) as an intermediate, and branching is introduced through reaction with diazomethane. A preliminary report of this work was published in 1969[5], and a synthesis of the L-isomer of compound **2** has been described in which the enantiomer of the ketone **4** is treated with vinylmagnesium bromide[6]. Both these procedures were developed in our laboratory for syntheses of hamamelose and epihamamelose[7].



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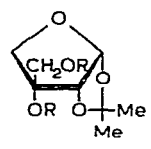

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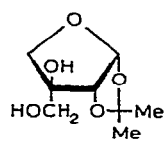
11 R = Ac



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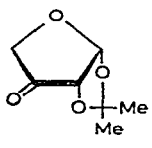

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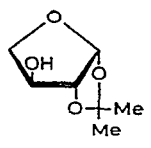

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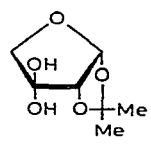

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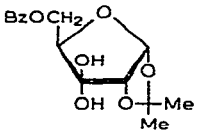
DISCUSSION

L-Threose, prepared by standard procedures from L-arabinitol[8], was acetonated to yield 1,2-*O*-isopropylidene-β-L-threofuranose (**5**), and this was oxidised with ruthenium tetraoxide in carbon tetrachloride[9] to give a product in 45% yield, which showed both hydroxyl (3400 cm^{-1}) and carbonyl (1780 cm^{-1}) absorption in its infrared spectrum and which was a mixture of the glycosulose **4** and its hydrate **6**. When a solution of the product in chloroform was treated with molecular sieve 4A, the absorption at 3400 cm^{-1} disappeared with a concurrent increase in carbonyl absorption. Although neither Parikh and Jones[10] nor Carey, Ball, and Long[3] reported the formation of any *gem*-diol in their samples of the glycosulose **4**, a similar *gem*-diol has been isolated from the synthesis of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[9], and recently we have obtained the corresponding *gem*-diol (**7**) from 5-*O*-benzoyl-1,2 *O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose by crystallisation of this oxo sugar from aqueous tetrahydrofuran (work in our laboratory by A. E. Dann). These compounds exhibit no absorption in the carbonyl region of the infrared spectrum, but conversely they have a strong hydroxyl-absorption near 3400 cm^{-1}, and their n.m.r. spectra in either deuteriated methyl sulphoxide or deuteriochloroform show resonances for two hydroxyl protons which disappear when the solution is shaken with deuterium oxide. Although satisfactory spectra for the free glycosulose **4** were obtained in anhydrous solution, a crystalline sample could not be prepared free of hydrate. The hydrate was obtained as analytically pure crystals from wet ether, but with a diffuse m.p. (65–80°) attributed to concomitant dehydration on heating. A sample of compound **4** prepared by periodate oxidation of compound **3**, according to the procedure of Carey

et al.[3], also furnished a ketone–*gem*-diol mixture similar to that obtained by ruthenium tetraoxide oxidation of compound **5**.



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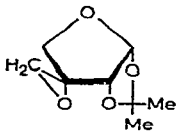

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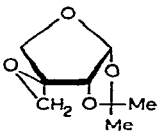

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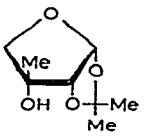

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Treatment of the glycosulose **4** with diazomethane in methanol–ethyl ether yielded a mixture of epoxides which was fractionated on silica gel to give crystalline 1′,3-anhydro-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-erythrofuranose (**8**) in 46% yield. The minor component, presumed to be the L-*threo* epoxide **9** isomeric with epoxide **8** at C-3, was not obtained pure. Similar results were obtained with the pure *gem*-diol derivative of **4**. Sequential alkaline and acid hydrolysis of the epoxide mixture yielded only apiose as shown by paper chromatography. There was no evidence for the formation (by methylene insertion) of deoxypentose derivatives in the reaction of **4** with diazomethane, as was found in the analogous reaction of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose[11]. The preferential formation of the *erythro* epoxide conforms to the expectation that diazomethane would attack the less-hindered side of the carbonyl group in **4** on the opposite side to the isopropylidene ring. The same stereochemistry of addition was observed by Tronchet and Tronchet[6], who obtained only the *erythro* isomer in the addition of vinylmagnesium bromide to the L enantiomer of **4**. Similarly, reduction of the ketone **4** with lithium aluminium hydride yielded only 1,2-*O*-isopropylidene-α-D-erythrofuranose.

Treatment of the ketone **4** with dimethyloxosulphonium methylide, as an alternative route to the spiro-epoxide[12], afforded a mixture of the spiro-epoxides in very poor yield (~10%), and the method was not further pursued. Ball *et al.*[4] have recently reported that this reaction mixture contains (g.l.c.) predominantly the *threo* isomer but they did not state the yield obtained. They did obtain compound **8** in crystalline form by the reaction of **4** with dimethylsulphonium methylide, but only in 17% yield.

The *erythro* configuration assigned to the epoxide **8** was based on the following evidence. Reduction with lithium aluminium hydride afforded 1,2-*O*-isopropylidene-3-*C*-methyl-α-D-erythrofuranose (**10**). That the anticipated cleavage of the epoxide oxygen–primary carbon bond had occurred was shown by the n.m.r. spectrum of compound **10** [3 methyl singlets, and a singlet at τ 7.36 in Me_2SO-d_6 (disappearing on addition of D_2O) assigned to a tertiary hydroxyl proton] and also by the resistance of the compound to tritylation, characteristic of a tertiary hydroxyl group. A 5mM solution of **10** in carbon tetrachloride showed an infrared absorption band at 3570 cm^{-1}, as expected for a hydroxyl group that is hydrogen-bonded to an adjacent

cis oxygen atom. A similar band was shown by 1,2-*O*-isopropylidene-α-D-erythrofuranose, whereas no hydrogen bonding would be expected with an adjacent *trans* oxygen atom as in the *threo* isomer; the resulting hydroxyl-group absorption would then be[13] near 3630 cm^{-1}.

Thus, whereas 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose shows absorption at 3545 cm^{-1} under these conditions (C-2 oxygen/C-3 hydroxyl, *cis*), the isomeric xylofuranose derivative gave[14] a band at 3628 cm^{-1}. Further, methanolysis of compound **10** with methanolic hydrogen chloride afforded an αβ-mixture of methyl furanosides which consumed 1.02 mol. of sodium periodate in 1 h, whereas a similar anomeric mixture of methyl L-threofuranosides required 30 h to consume 1.04 mol. of the oxidant. Tetrofuranosides having a *cis-erythro* configuration for the C-2, C-3 diol function are oxidised much more rapidly than the corresponding *trans-threo* isomer[15,16]. Thus, an anomeric mixture of methyl 3-*C*-methyl-D-ribofuranosides consumed 1.04 mol. of periodate in 30 min at room temperature, but a mixture of the isomeric xylofuranosides required 42 h at 35° for similar oxidation[11,14].

Alkaline hydrolysis of the epoxide **8** afforded he branched-chain derivative **2** in 55% yield after recrystallisation; **2** was clearly distinguished from its isomer **3** by its physical constants. As expected, cleavage of the primary carbon–oxygen bond occurs, leading to a product with retained configuration at C-3. Compound **8** was also characterised by formation of a crystalline 1′,3-diacetate (**11**) and by its conversion into 3-*C*-hydroxymethyl-1,2:1′,3-di-*O*-isopropylidene-α-D-erythrofuranose[4], both obtained via compound **2**.

EXPERIMENTAL

All liquid ratios are volume/volume. Melting points are uncorrected. Infrared spectra were obtained on a Perkin–Elmer Infracord spectrophotometer, Model 137; syrups were examined as liquid films on potassium bromide discs. High-resolution infrared spectra in the 3500 cm^{-1} region were measured on a Unicam SP 700 recording spectrophotometer, using solutions in 1-cm silica cells. P.m.r. spectra were recorded on a Varian A-60 or HA-100 spectrometer, using deuteriochloroform as solvent unless otherwise stated, with tetramethylsilane as the internal reference. Paper chromatography was performed on Whatman No. 1 paper with butyl alcohol–acetic acid–water (4:1:5, organic phase), spots being located with 5% ammoniacal silver nitrate spray. Thin-layer chromatography (t.l.c.) was performed with Kieselgel G (Stahl) activated for 12 h at 50°. Solvents used for t.l.c. and silica gel columns were (*a*) light petroleum (b.p. 40–60°)–ethyl ether (1:3) and (*b*) ethyl ether–acetone (3:1). Spots were detected by using either anisaldehyde–sulphuric acid–ethanol (1:1:20) or sulphuric acid–ethanol (1:10) at 150°. Periodate consumption was estimated by the spectrophotometric method[17]. Diazomethane was prepared from *N*-methyl-*N*-nitroso-toluene-*p*-sulphonamide[18]. All solutions were concentrated under reduced pressure.

1,2-O-Isopropylidene-β-L-threofuranose (**5**). — Syrupy L-threose[8] (85 g) was aceton-

ated in acetone (4.5 l) containing anhydrous cupric sulphate (340 g) and conc. sulphuric acid (2 ml), according to the method of Levene and Raymond[19], to give **5** as colourless needles (80 g, 69%), m.p. 79–81° (from ethyl ether–pentane), $[\alpha]_D$ +14.1° (*c* 1.0, carbon tetrachloride); lit.[20] m.p. 84°, $[\alpha]_D$ −15.1° (acetone) for the D enantiomer). P.m.r. data: τ 4.07 (d, $J_{1,2}$ 3.5 Hz, H-1), 5.53 (d, H-2), 5.71–5.83 (m, H-3), 6.04 (q, $J_{4a,4b}$ 10.0 Hz, CH_2), 7.24 (s, absent on addition of D_2O, OH), 8.58 (s), 8.74 (s) (CMe_2).

*1,2-O-Isopropylidene-α-*D-glycero-*tetros-3-ulose* (**4**). — A solution of **5** (20 g) in carbon tetrachloride (500 ml), cooled in an ice-bath, was treated with a solution of ruthenium tetraoxide [prepared from ruthenium dioxide (20 g)] in carbon tetrachloride[9]. Oxidation was complete in 1 h, as indicated by t.l.c. After filtration, the solution was concentrated to yield a crystalline residue which was recrystallised from hexane to give colourless plates and needles (8.0 g, 45%), m.p. 50–60°, $[\alpha]_D$ +151° (*c* 1.9, chloroform); lit.[3] m.p. 60–61.5°, $[\alpha]_D$ +140°; ν_{max} (carbon tetrachloride) 3400 (OH), 1780 cm^{-1} (C=O), (in carbon tetrachloride containing molecular sieve 4A) 1780 cm^{-1} (C=O), no band at 3400 cm^{-1}. P.m.r. data (deuteriochloroform containing molecular sieve 4A): τ 3.90 (d, $J_{1,2}$ 4.2 Hz, H-1), 5.63 (d, H-2), 5.70 (q, $J_{4a,4b}$ 17.5 Hz, CH_2), 8.47 (s), 8.57 (s) (CMe_2). A crystalline sample of **4** could not be obtained free of its hydrate **6**.

*1,2-O-Isopropylidene-α-*D-glycero-*tetros-3-ulose hydrate* (**6**). — Crystals (1.0 g) of **4** obtained from hexane were dissolved in wet ether (100 ml), and the solution was left to evaporate at room temperature and pressure. The crystalline residue was triturated with ether–light petroleum (b.p. 40–60°), and the mixture was filtered to give **6** as colourless needles (0.92 g, 82%), m.p. 65–80°, $[\alpha]_D$ +79.5° (*c* 1.0, chloroform); lit.[6] m.p. 60–73° for L enantiomer; ν_{max} 3400 cm^{-1} (OH), no band at 1780 cm^{-1}. Mass spectrum, 158 $(M-H_2O)^+$. P.m.r. data (methyl sulphoxide-d_6): τ 3.90 (s, absent on addition of D_2O; 2 OH), 4.27 (d, $J_{1,2}$ 3.8 Hz, H-1), 5.93 (d, H-2), 6.39 (q, $J_{4a,4b}$ 8.5 Hz, CH_2), 8.57 (s), 8.75 (s) (CMe_2).

Anal. Calc. for $C_7H_{12}O_5$: C, 47.7; H, 6.9. Found: C, 47.7; H, 6.95%.

*1',3-Anhydro-3-C-hydroxymethyl-1,2-O-isopropylidene-α-*D-*erythrofuranose* (**8**). — (*a*) Compound **4** (20 g) in methanol (240 ml) was treated with diazomethane (6.0 g) in ethyl ether (250 ml). After 15 min at room temperature, the solution was concentrated to a syrup that was fractionated on a column of silica gel [solvent (*a*)] to yield **8** as colourless crystals (10.0 g, 46%), m.p. 69–70°, $[\alpha]_D$ +90° (*c* 1.0, ethyl ether); Ball *et al.*[4] reported m.p. 66–67° for this compound. P.m.r. data: τ 4.05 (d, $J_{1,2}$ 4.0 Hz, H-1), 5.66 (d, H-2), 5.69 (d, $J_{4a,4b}$ 9.5 Hz, H-4a), 6.29 (d, H-4b), 6.89 (q, $J_{1'a,1'b}$ 5.5, $J_{1'a,4a}$ 1.2 Hz, H-1'a), 7.02 (d, H-1'b), 8.30 (s), 8.62 (s) (CMe_2).

Anal. Calc. for $C_8H_{12}O_4$: C, 55.8; H, 7.0. Found: C, 55.9; H, 6.9%.

Both the syrup and the crystals give a positive test for epoxide[21]. Hydrolysis of the syrup, first with sodium hydroxide and then with hydrochloric acid[7b], yielded a syrup showing a single spot (R_F 0.21, identical with apiose) on paper chromatography.

(*b*) A solution of **4** (1.58 g) in methyl sulphoxide (10 ml) containing molecular sieve 4A was added to a solution of dimethyloxosulphonium methylide prepared[12]

from a mixture of trimethyloxosulphonium iodide (2.64 g) and sodium hydride (0.30 g) in methyl sulphoxide (20 ml). The reaction mixture was quenched with ice–water after 90 sec. The resulting solution was repeatedly extracted with ethyl ether, and the combined extracts were concentrated to yield a syrup, which was fractionated on silica gel as before to give **8** (0.17 g, 10%), m.p. 69–70°. A repeat experiment using trimethyloxosulphonium chloride instead of the iodide, dissolving the sugar in tetrahydrofuran containing molecular sieve, and stirring for 6 min before quenching with ice-cold water, failed to raise the yield.

1,2-O-Isopropylidene-3-C-methyl-α-D-erythrofuranose (**10**). — A solution of compound **8** (0.5 g) in dry ethyl ether (100 ml) was treated with lithium aluminium hydride (0.8 g) and the mixture was heated under reflux for 2 h. The crystalline solid obtained after the usual work-up was recrystallised from ethyl ether–pentane to furnish **10** as colourless plates (0.25 g, 50%), m.p. 108–109°, $[\alpha]_D$ +28° (*c* 0.8, chloroform); ν_{max} (5mM carbon tetrachloride) 3570 cm^{-1} (bonded OH). P.m.r. data: τ 4.26 (d, $J_{1,2}$ 4.0 Hz, H-1), 6.0 (d, H-2), 6.43 (q, $J_{4a,4b}$ 8.0 Hz, CH_2), 7.40 (s, absent on addition of D_2O, OH), 8.49 (s), 8.60 (s), 8.62 (s) (C–Me, CMe_2).

Anal. Calc. for $C_8H_{14}O_4$: C, 55.2, H, 8.1. Found: C, 55.2, H, 8.1%.

3-C-Hydroxymethyl-1,2-O-isopropylidene-α-D-erythrofuranose (**2**). — Compound **8** (10.0 g) in aqueous ethanol (250 ml, 2:3) was treated with M sodium hydroxide (8 ml), and the mixture was stored at room temperature for 24 h. The solution was neutralised with dilute hydrochloric acid and then concentrated in the presence of barium carbonate. The resulting syrup was fractionated on a column of silica gel [solvent (*b*)] to afford **2**, recrystallised from ethyl ether–hexane as colourless needles (6.0 g, 55%), m.p. 118–120°, $[\alpha]_D$ +54.5° (*c* 1.3, ethanol); Ball *et al.*[4] reported m.p. 116–118°, $[\alpha]_D$ +44.0° for this compound; Tronchet and Tronchet[6] reported m.p. 112–115°, $[\alpha]_D$ −39.5° for the L enantiomer. P.m.r. data: τ 4.15 d, $J_{1,2}$ 4.0 Hz, H-1), 5.58 (d, H-2), 6.25 (s, side-chain CH_2), 6.40 (m, ring CH_2), 7.03 (s, absent after addition of D_2O, tertiary OH), 7.60 (m, absent after addition of D_2O, primary OH), 8.42 (s), 8.62 (s) (CMe_2).

Anal. Calc. for $C_8H_{14}O_5$: C, 50.5; H, 7.4. Found: C, 50.65; H, 7.4%.

A sample of the *β-L-threo* isomer **3**, prepared by partial, acidic hydrolysis of 3-*C*-hydroxymethyl-1,2:1′,3-di-*O*-isopropylidene-β-L-threofuranose (kindly provided by Dr. J. A. Mills) by the method of Carey *et al.*[3], had m.p. 124–125°, $[\alpha]_D$ +45° (*c* 1.0, ethanol); lit.[3] m.p. 124–125°, $[\alpha]_D$ +46°. It was shown to be different from **2** by mixed m.p. (95–105°), and comparison of p.m.r. spectra in deuterium oxide.

1′,3-Di-O-acetyl-3-C-hydroxymethyl-1,2-O-isopropylidene-α-D-erythrofuranose (**11**). — Compound **2** (0.50 g) was treated with acetic anhydride (6 ml) in pyridine (24 ml), and the mixture was heated under reflux for 2.5 h. The solution was then concentrated and the residue treated with ice–water. The crystals obtained were recrystallised from hexane to give **11** as colourless needles (0.40 g, 56%), m.p. 110–110.5°, $[\alpha]_D$ +64° (*c* 1.4, chloroform). P.m.r. data: τ 4.27 (d, $J_{1,2}$ 4.0 Hz, H-1), 5.36 (d, H-2), 5.60 (q, *J* 12.0 Hz, CH_2), 5.96 (q, *J* 9.0 Hz, CH_2), 7.82 (s), 7.86 (s) (2 COMe), 8.46 (s), 8.64 (s) (CMe_2).

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.6. Found: C, 52.8; H, 6.6%.

3-C-Hydroxymethyl-1,2:1',3-di-O-isopropylidene-α-D-erythrofuranose. — Compound **2** (0.44 g) was treated[19] with acetone (60 ml) containing anhydrous cupric sulphate (5 g) and one drop of conc. sulphuric acid to give the title compound, purified by sublimation, as a crystalline solid (0.22 g, 42%), m.p. 46–49°, $[\alpha]_D$ +62.4° (*c* 1.0, chloroform); Ball *et al.*[4] reported m.p. 52.5–54°, $[\alpha]_D$ +76.5° (ethanol) for this derivative. P.m.r. data (carbon tetrachloride): τ 4.42 (d, $J_{1,2}$ 3.8 Hz, H-1), 5.90 (d, H-2), 6.24 (s, CH_2), 6.32 (q, *J* 8.5 Hz, CH_2), 8.50 (s), 8.62 (s), 8.68 (s), 8.72 (s) (2-CMe_2)

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9. Found: C, 57.5; H, 7.95%.

3-*C*-Hydroxymethyl-1,2:1',3-di-*O*-isopropylidene-β-L-threofuranose has m.p. 80–82°, $[\alpha]_D$ +58° (ethanol)[3,22], and the α-D-*erythro* and β-L-*threo* isomers may be further distinguished by p.m.r.[3,4] and t.l.c. [light petroleum (b.p. 40–60°)–ethyl ether (2:1)].

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