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Note

A convenient synthesis of apiose

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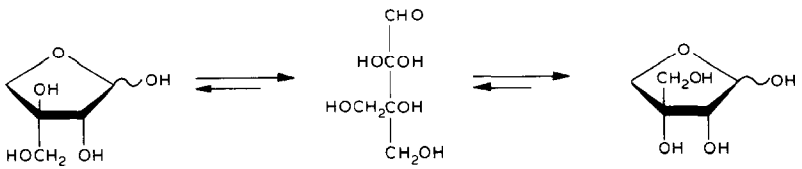
The occurrence, reactions, stereochemistry, and synthesis of apiose (**1**) and its derivatives[1], and that of other branched-chain sugars[2], have been reviewed. The hydroxymethyl branch in terminal, branched-chain sugars has been most commonly introduced by the condensation of formaldehyde with a protected *aldehydo* sugar[3–5]. This scheme was used by Schaffer[3] for the synthesis of L-apiose and by Williams and Jones[4] for D-apiose. The protected *aldehydo*-aldose was obtained from a precursor dithioacetal[6]. More recently Ho[7] has published a procedure in-



Tautomeric forms of D-apiose (1)

volving base-catalyzed condensation (48 h, 80°) of an excess of formaldehyde with the readily available 2,3:5,6-di-*O*-isopropylidene-D-mannose. We have experienced difficulties in scaling up these procedures, and have sought an alternative route that retains the same basic approach for introducing the hydroxymethyl branch.

The route used is essentially that of Williams and Jones[4], who started with an L-arabinose derivative, but we started with 2,3:4,5-di-*O*-isopropylidene-D-xylose, as shown in Scheme I. In this approach the C-1 aldehyde group of the starting pentose derivative **2** becomes one of the hydroxymethyl groups, and C-4 of the starting pentose becomes the C-1 aldehyde group of the final apiose derivative **5**; that is, the head and tail of the starting pentose chain become reversed. As the chirality at C-2 in the original pentose derivative **2** is lost by the symmetrical substitution of two hydroxymethyl groups in **3**, and that at C-4 is lost by conversion into

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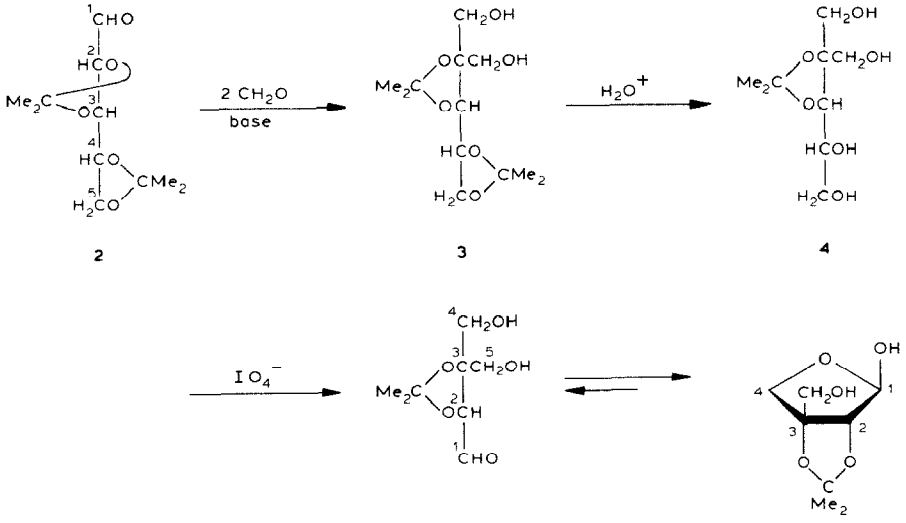
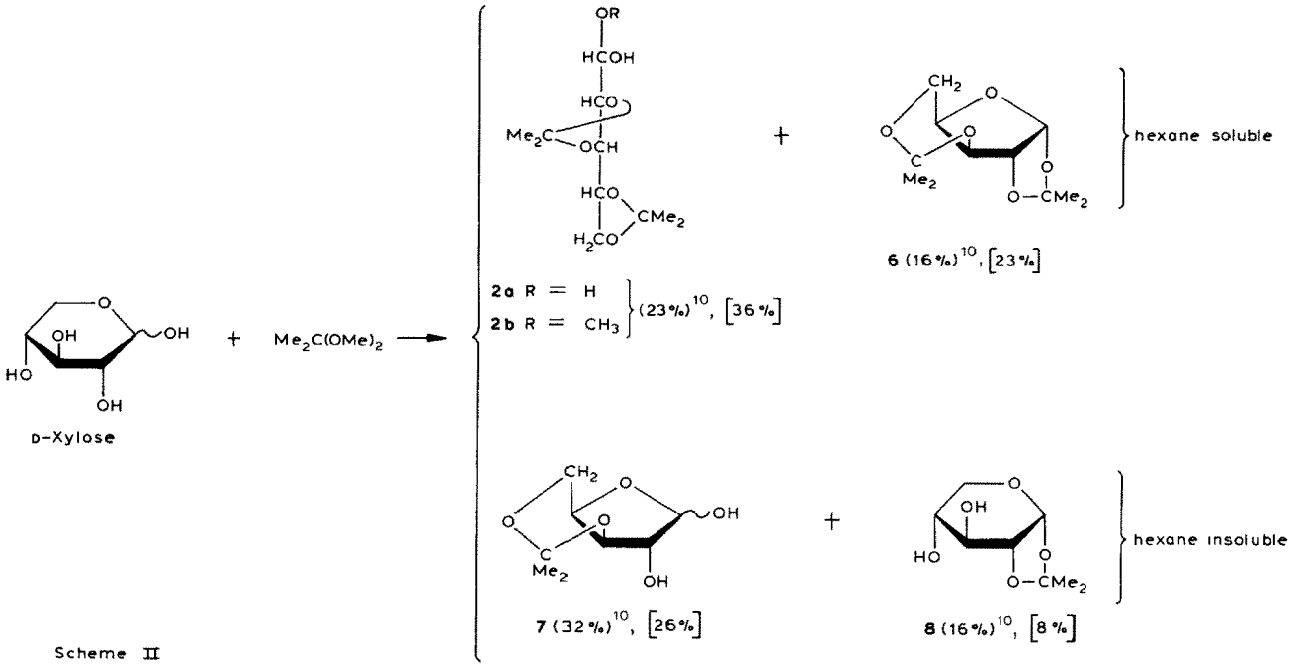


Scheme I

the aldehyde group in **5**, only the stereochemistry at C-3 in the starting pentose determines whether D- or L-apiose will be formed. Thus, the choice of starting pentose is a matter of availability of the suitable protected *aldehyde*-pentose and whether the target is D- or L-apiose.

RESULTS AND DISCUSSION

The key step is the kinetically controlled isopropylidenation of D-xylose. Cyclic acetal formation of aldoses has been reviewed[8,9]. Kiso and Hasegawa[10] described the treatment of D-xylose with 2,2-dimethoxypropane (*N,N*-dimethylformamide as solvent, 40°, *p*-toluenesulfonic acid, 2–3 h) to give a mixture of five isopropylidene acetals, which were separated by chromatography and shown to have the structures given in Scheme II (yields in parentheses). We have reinvestigated this reaction under the conditions reported[10] and have confirmed these products, but in slightly different yields [shown in brackets in Scheme II]. The desired *aldehydo* product **2**, its hydrate **2a**, and its methyl hemiacetal **2b**, are formed in a combined isolated yield of 36%. For preparative purposes, chromatographic separation of these was unnecessary. The diisopropylidene acetals **2a, 2b,** and **6**, were removed from the mixture by extracting with hexane, leaving two insoluble monoisopropylidene acetals **7** and **8**. Treatment of the hexane-soluble fraction (**2a, 2b,** and **6**) with a slight excess of formaldehyde caused only **2a** and **2b** to react, giving the aldol-Cannizzaro dihydrodroxymethyl product **3**, mixed with unreacted **6**. Extraction with cold hexane removed **6** from the mixture, and the remaining syrup crystallized to give **3** in 30% yield from xylose. Selective hydrolysis of **3** gave the glycol **4** as an oil which was cleaved by periodate to give the desired, crystalline 2,3-*O*-isopropylidene-β-D-apiofuranose (**5**) as a single anomer (H-1 and


D-Xylose
Me2C(OMe)2
2a R = H
2b R = CH3
(23%)10, [36%]
6 (16%)10, [23%]
hexane soluble
7 (32%)10, [26%]
8 (16%)10, [8%]
hexane insoluble

Scheme II

H-2 signals, singlets δ 5.54 and 4.29 p.p.m.)[7] in 24% overall yield from D-xylose in four steps. This product was hydrolyzed to (non-crystalline) D-apiose (**1**), which was converted into its known, crystalline *N*-benzylphenylhydrazone[4,7].

Gelas and Horton[11,12] have studied kinetically controlled isopropylidenation with 2-methoxypropene rather than 2,2-dimethoxypropane, but details of the reaction with xylose have not been published to our knowledge*. Based on the foregoing studies, we re-investigated the isopropylidenation of xylose with 2-methoxypropene and now find that the initial diisopropylidenation product is the free aldehyde **2**, which hydrates on standing to **2a** (51–53% yield). This compound was separated from monoisopropylidenation products and other water-soluble impurities by extraction with hexane. Isopropylidenation of D-xylose by 2-methoxypropene followed by direct treatment of the hexane-soluble extract with formaldehyde by the same procedure outlined in Scheme II converted D-xylose into the crystalline apiose derivative **5** in overall 36–38% yield. L-Xylose by this identical procedure was converted into 2,3-*O*-isopropylidene-L-apiose.

EXPERIMENTAL

General methods. — Melting points determined in capillaries on an aluminum block are uncorrected. Nuclear magnetic resonance (n.m.r.) spectra were determined at 100 MHz with a Varian XL-100 Fourier-transform instrument with $CDCl_3$ as solvent and tetramethylsilane as the internal standard and lock signal. Chemical shifts (δ) are given in p.p.m. downfield from Me_4Si, and coupling constants in Hz; d, doublet; m, multiplet; s, singlet; and t, triplet. Optical rotations were determined with an Autopol III (Rudolph Research Company) automatic polarimeter with a reproducibility of $\pm 0.002°$. Reactions were monitored by t.l.c. on 10 × 2.5 cm silica gel GF Uniplates (Analtech Company). Detection was by spraying with 20% H_2SO_4 and heating to 150°. Column chromatography was with silica gel (Davison, Davisil 62) with either solvent system *A*, 3:2 (v/v) ethyl acetate–hexane; or *B*, 9:1 (v/v) chloroform–methanol.

Isopropylidenation of D-*xylose with 2,2-dimethoxypropane.* — The procedure of Kiso and Hasegawa[10] was carried out under similar conditions (DMF as solvent, *p*-toluenesulfonic acid catalyst, 2–3 h, 40–45°). The crude mixture was separated on a column (40 × 4 cm) of silica gel with solvent *A* to give the following products from 4 g of xylose: 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**6**, 1.4 g, 23%, R_F 0.69); a mixture of 2,3:4,5-di-*O*-isopropylidene-D-xylose hydrate, **2a**, and the methyl hemiacetal, **2b**, 2.3 g (33%, both having R_F 0.49); 1,2-*O*-isopropylidene-α-D-xylopyranose (**8**, 0.4 g, 8%, R_F 0.35), and 3,5-*O*-isopropylidene-D-xylofuranose (**7**, 1.3 g, 26%, R_F 0.24). This procedure was repeated several times on the 4-, 8-,

*It is stated in a review[12] that "Xylose . . . does not give any single stable cyclic acetal in high yield". In a personal communication, Gelas and Horton report that this is with 1.8–2.0 eq. of 2-methoxypropene; with 3 eq. the aldehydo derivative is isolated (J. Barbat, J. Gelas and D. Horton, to be published; J. Barbat, Thesis, Clermont-Ferrand, France, 1985).

and 20-g scale, with essentially the same results. In the larger runs, the mixture was stirred for 17–24 h at room temperature instead of for 2–3 h at 40–45°. It was determined that the diisopropylidene acetals (**2** and **6**) could be extracted from the monoacetals (**7** and **8**) by cold hexane. This procedure was used in the overall preparative scheme (see later).

For further synthesis, chromatographic purification of **2a** and **2b** was unnecessary; the mixture of products from the reaction of 2,2-dimethoxypropane with xylose (4.0 g) was extracted with cold hexane. The hexane extracts were evaporated to give 3.5 g of a mixture of **2a, 2b,** and **6**, which was dissolved in ethanol and stirred with formaldehyde (3.5 mL of 37% aqueous solution) and sodium hydroxide (1.65 g of NaOH in 25 mL of H_2O) for 6 h at room temperature. The solution was made neutral (96% formic acid, 1.5 mL) and processed as already indicated to give a crude mixture of **3** and unreacted **6**. Extraction of this mixture with cold hexane removed the unreacted **6** (1.5 g), leaving a gummy product that crystallized from chloroform–hexane to give **3** (2.1 g, 30% yield in two steps from xylose).

N,N-*Dimethylhydrazone of 2,3:4,5-di-*O*-isopropylidene-*D*-xylose.* — The acyclic structures of **2a** and **2b**, equivalent to the free aldehydo form, were shown by their quantitative conversion into a single *N,N*-dimethylhydrazone. A mixture of **2a** and **2b** obtained by chromatography (R_F 0.61, 500 mg in 15 mL of CH_3OH) was boiled for 30 min under reflux with 1,1-dimethylhydrazine (132 mg). Evaporation of the solvent and the excess of reagent gave a single hydrazone (pale-yellow oil, 522 mg, 96%); n.m.r. δ 6.34 (d, 1 H, $J_{1,2}$ 6.3 Hz, H-1), 4.44–5.58 (m, 5 H, H-2,3,4, 2 H-5), 2.84 (s, 6 H, NMe), 1.45 (s, 3 H), 1.43 (s, 6 H), and 1.38 (s, 6 H).

Anal. Calc. for $C_{13}H_{24}N_2O_4$: C, 57.37; H, 8.82; N, 10.29. Found: C, 57.11; H, 8.91; N, 10.19.

This n.m.r. spectrum clearly indicates a single compound, and the $J_{1,2}$ coupling strongly supports the *syn* arrangement of H-1 and the NMe_2 group of the hydrazone[13,14].

Isopropylidenation of D*-xylose with 2-methoxypropene.* — *p*-Toluenesulfonic acid hydrate (40 mg) was added with stirring to a solution of D-xylose (10 g, 0.067 mol) and 2-methoxypropene (14.4 g, 0.2 mol) in DMF (130 mL) at 0°. After 8 h at 0–5°, the xylose had reacted (t.l.c., solvent *A*) and three spots were evident by t.l.c. (R_F 0.61, 0.30, and 0.28). The acid was neutralized by stirring with dried Amberlite IRA-400 resin (OH^- form). The resin was removed, washed with CH_3OH, and the extracts and reaction mixture were evaporated under vacuum (1 mm, <40°) to give a syrup (14.4 g) that was thoroughly extracted with dry hexane. The insoluble residue (5.9 g, t.l.c., solvent *A*, R_F 0.28, major; 0.30, minor; 0.61, trace) has inappreciable amounts of **7** and/or **8** and may have been made up of acyclic monoisopropylidenation products. Vacuum evaporation of the hexane-soluble fraction gave 8.5 g (51% yield, R_F 0.61) of the free aldehyde **2** (n.m.r., δ 9.8 p.p.m., relative area 1). On being kept outside a desiccator, compound **2** forms the hydrate **2a** (signal at δ 9.8 p.p.m.) disappears and an OH signal, area 2, at $\delta \sim 5$ p.p.m., broad, appears). This material, without further purification, was treated with formal-

dehyde in the aldol-Cannizzaro reaction as described next, to give 7.3 g of crystalline **3** (76% yield from **2**, 42% from xylose). Hydrolysis and oxidation of this sample as described next gave crystalline 2,3-*O*-isopropylidene-β-D-apiofuranose (**5**), 4.59 g, m.p. 71–72° (85% yield from **2**, 36% from xylose).

In a slightly different procedure, 2-methoxypropene (8.6 g, 0.12 mol) was added over the course of 1 h at 10–15° to a stirred solution of D-xylose (7.5 g, 0.05 mol) in DMF (100 mL) and *p*-toluenesulfonic acid (25 mg, anhydrous). The mixture was stirred at 10–15° for an additional 5–6 h until t.l.c. showed that the xylose had reacted. Treatment as before gave aldehyde **2** (6.6 g, 57%, R_F 0.61) upon vacuum evaporation of the hexane-soluble fraction. The same procedure was performed starting with L-xylose, with comparable results.

*2-C-(Hydroxymethyl)-2,3:4,5-di-O-isopropylidene-*D-threo-*pentitol* (**3**). — Formaldehyde (0.5 mL of 37% aqueous solution, 5.6 mmol) was added to a stirred solution of the mixture of **2a** and **2b** (500 mg, 2 mmol from the 2,2-dimethoxypropane isopropylidenation) in ethanol (5 mL), followed by sodium hydroxide (235 mg in 3.5 mL of water). After stirring for 3 h at 20°, all of the starting material (R_F 0.49, solvent *A*) had been converted into product (R_F 0.24). On a larger scale, the mixture was stirred overnight with the same result. The mixture was made neutral with formic acid (0.2 mL, 96%), the ethanol was evaporated off, and the residual water layer was extracted thoroughly with $CHCl_3$. The extracts were dried ($MgSO_4$) and the solvent evaporated to give crystalline **3**, which was recrystallized from hexane–chloroform to give **3** as needles (424 mg, ~75%), m.p. 103–104°, $[\alpha]_D^{20}$ +4.2° (*c* 1.0, methanol): n.m.r. ($CDCl_3$): δ 1.41, 1.48, (2 s, 12 H, 2 CMe_2), 2.12 (t, 1 H, *J* 6.6 Hz, D_2O exchangeable), 2.90 (t, 1 H, *J* 6.6 Hz, D_2O exchangeable), 3.42–3.88 (m, 4 H), and 3.96–4.50 (m, 4 H).

Anal. Calc. for $C_{12}H_{22}O_6$: C, 54.98; H, 8.39. Found: C, 54.98; H, 8.45.

*2,3-O-Isopropylidene-β-*D-*apiofuranose* (**5**). — Compound **3** (100 mg) was hydrolyzed with 65% acetic acid (15 mL) for 20 h at room temperature until the starting material (R_F 0.52, solvent *A*) had been converted into the product (R_F 0.10). Acetic acid and water were removed under vacuum below 40° to give a syrup (**4**) which, without purification, was dissolved in water (10 mL) and treated for 1.5 h at room temperature with $NaIO_4$ (150 mg in 10 mL of H_2O). The pH was adjusted to 7–8 with HOAc, and ethylene glycol (0.3 mL) was added to the mixture (1 h) to decompose unreacted periodate. Water (10 mL) was added and the mixture extracted with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and the solvent evaporated to give crude, crystalline product, which was chromatographed with solvent *B* and a short column of silica gel to give **5** as white crystals (62 mg, 86% from **3**), m.p. 71–72°; n.m.r. and analytical data were identical to those reported[7]. This procedure was repeated several times on a 5–10 g scale with 82–86% yields. In the preparative experiments, **3** was hydrolyzed with 0.01M H_2SO_4 (20 mL/g of **3**) for 18–24 h at room temperature until hydrolysis was complete (t.l.c. solvent *B*). The acid was neutralized at 0–5° with solid Na_2CO_3. This aqueous solution was treated with $NaIO_4$ solution at 0–5° for 45–60 min; for each mol of **4**, 1.1 mol of

$NaIO_4$ was used (20 g H_2O per g $NaIO_4$). The pH was adjusted* to 6 and the reaction allowed to proceed for 2 h at room temperature. The excess of IO_4^- was decomposed by a few drops of ethylene glycol, the mixture was evaporated to dryness under vacuum, and the product isolated by extraction as already indicated.

D-*Apiose* (**1**), *and its* N-*benzylphenylhydrazone*. — A solution of **5** (630 mg) in water (25 mL) was treated with Dowex 50W resin (H^+ form, 1 g) for 5 h at 70°. The resin was removed, washed with water, and the aqueous extracts and filtrate evaporated under vacuum to give **1** as a syrup, yield 473 mg, $[\alpha]_D^{25}$ +5.1° (*c* 1.1, H_2O), lit.[7] $[\alpha]_D^{15}$ +5.6° (H_2O). This syrup (460 mg) in ethanol (30 mL) was treated with *N*-benzyl-*N*-phenylhydrazone (714 mg) for 18 h at 20°. The solvent was evaporated and the hydrazone crystallized by dissolving it in $CHCl_3$–CH_3OH and adding pentane to incipient precipitation; white needles, m.p. 139°, $[\alpha]_D^{20}$ −29.5° (*c* 1.1, CH_3OH); lit.[7] m.p. 138–139°, $[\alpha]_D$ −29° (*c* 1.1, CH_3OH).

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*Careful control of the pH is important; if too acidic, **5** is hydrolyzed to the diol, which undergoes further periodate oxidation.