APIOSE. III.* A SYNTHESIS OF METHYL 2,3-*O*-ISOPROPYLIDENE-β-D-APIO-D-FURANOSIDE INVOLVING INTRAMOLECULAR ACETAL MIGRATION, AND STEREOSPECIFIC SYNTHESES OF APIOSE METHYL ETHERS

D. H. BALL, F. H. BISSETT, I. L. KLUNDT**, AND L. LONG, JR.

Pioneering Research Laboratory, U.S. Army Natick Laboratories, Natick, Massachusetts 01760 (U. S. A.)

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ABSTRACT

Under anhydrous methanolysis conditions, methyl 2,3-*O*-isopropylidene-β-D-apio-D-furanoside (methyl 3-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-D-erythrofuranoside, **4**) can be prepared in high yield from 1,2-*O*-isopropylidene-α-D-apio L-furanose (**1**). The acetal migration was shown to be intramolecular; and the furanose ring opened and re-formed at the other primary hydroxyl during the reaction, thus inverting the configuration at C-3. Pfitzner–Moffatt oxidation of **4** gave an aldehyde, the stable oxime of which was shown to have the *syn* configuration. Starting from **1** and **4**, the four possible methyl tri-*O*-methyl-D-apiosides were synthesized, and it was confirmed that apiose occurs with the D-furano configuration in apiin.

INTRODUCTION

In Part I of this series[1], the thermodynamically stable isomer of di-*O*-isopropylidene-D-apiose was shown to have the α-D-apio-L-furano configuration. Partial acid hydrolysis gave a crystalline 1,2-*O*-isopropylidene derivative **1** in high yield, and **1** is therefore a convenient starting compound for apiose derivatives with this configuration. The isomeric diisopropylidene acetal of apiose with the α-D-apio-D-furano configuration[2], can also be partially hydrolyzed to a crystalline 1,2-*O*-isopropylidene derivative, but the diisopropylidene acetal cannot be obtained in good yield and does not represent a good starting point for apiose derivatives in this series.

This paper describes the preparation, in high yield from **1**, of methyl 2,3-*O*-isopropylidene-β-D-apio-D-furanoside, that is, methyl 3-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-D-erythrofuranoside (**4**). This compound, formed by a novel rearrangement involving an acetal migration and a change in ring configuration,

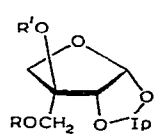
*For Part II, see Ref. 2.

**Present address: Aldrich Chemical Co., Inc., 940 W. St. Paul Avenue, Milwaukee, Wisconsin 53233 (U. S. A.).

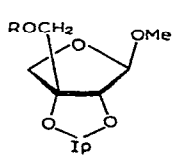
affords a convenient entry to apiose derivatives having the D-furano configuration at C-3. Syntheses of the four possible fully methylated D-apiofuranose derivatives (**10**, **11**, **13**, and **15**) are also described.

DISCUSSION

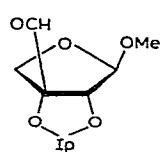
Preliminary experiments indicated that the methanolysis of 1,2-*O*-isopropylidene-α-D-apio-L-furanose (**1**) catalyzed by Dowex 50W-X8 (H^+) resin, gave, in addition to a mixture of methyl D-apiosides, a methyl apioside which retained an isopropylidene group. Under strictly anhydrous conditions, t.l.c. indicated this to be the major product, and it was obtained after distillation, as a colorless, chromatographically homogeneous oil in 84% yield. The p.m.r. spectrum showed sharp singlets for H-1 and H-2, indicating these protons to be *trans* on the furanose ring, and that the compound was a methyl β-D-apiofuranoside. That the free hydroxyl group was primary was also indicated (and later confirmed by Pfitzner–Moffatt oxidation to the aldehyde **7**). The product was therefore assigned the structure methyl 2,3-*O*-isopropylidene-β-D-apio-D-furanoside (**4**). No evidence for the α-D anomer could be detected by t.l.c. or p.m.r. The unlikely possibility that the isopropylidene group was *trans*-fused to the furanose ring (*i.e.* that the product had retained the L-furano configuration of **1**) was later eliminated when **1** and **4** gave rise to different pairs of anomeric methyl tri-*O*-methyl-D-apiosides. The rearrangement product **4** could not be induced to crystallize, but treatment with *p*-toluenesulfonyl chloride in pyridine gave crystalline methyl 2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-D-apio-D-furanoside (**5**).



1 R = R' = H
2 R = Ts, R' = H
3 R = R' = Me



4 R = H
5 R = Ts
6 R = Me



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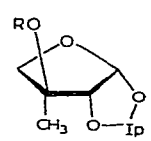
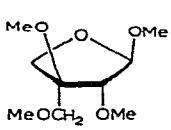


8 R = H
9 R = *p*-nitrobenzoyl



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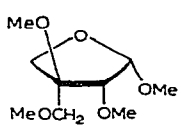

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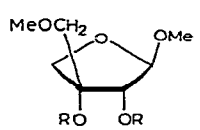
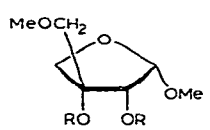


12 R = 3,5-dinitrobenzoyl

13 R = Me



14 R = *p*-nitrobenzoyl

15 R = Me

When the rearrangement **1**→**4** was carried out in the presence of two molar equivalents of acetone-d_6, the integrated p.m.r. spectrum of the product was indistinguishable from that of **4**, indicating that no more than *ca.* 10% incorporation of acetone-d_6 could have occurred. (A completely intermolecular reaction would have

resulted in a decrease in the integrated intensities of the C–Me resonances to 33% of the original values.) The mass spectra of both rearrangement products were also similar, but two minor fragments in the spectrum of the second rearrangement product (absent in the spectrum of **4**) at *m/e* 192 and 46 were attributed to M-d_6–CD_3 and $CD_3 \cdot CO$ ions respectively. The intensities of these ions, relative to those of the M–CH_3 and $CH_3 \cdot CO$ ions, indicated 1.8 and 1.9% incorporation of acetone-d_6 during the rearrangement.

Pfitzner–Moffatt oxidation[3] of **4** gave methyl 3-*C*-formyl-2,3-*O*-isopropylidene-β-D-erythrofuranoside (**1**) as a low-melting solid. Oximation of **1**, and fractionation of the products by silica gel chromatography, gave a crystalline oxime. A small amount of a second oxime was also obtained from the column, and this slowly isomerized to the major product at 0°. In the p.m.r. spectrum of the preponderant isomer, the C-5 proton resonance occurred at a field that was 0.68 p.p.m. lower than that of the minor isomer, and the major and thermodynamically stable isomer therefore has the *syn* configuration[4].

Reduction of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-apio-L-furanose[2] (**2**) with lithium aluminum hydride in ether–benzene gave crystalline 5-deoxy-1,2-*O*-isopropylidene-α-D-apio-L-furanose (**8**). A feature of the p.m.r. spectrum of **8** was a long-range coupling of *ca.* 1 Hz between H-2 and H-4A (the proton at C-4 "above" the plane of the ring), also evident in the spectrum of the derived *p*-nitrobenzoate **9**.

Methanolysis of **8** under the same conditions used for the rearrangement **1**→**4** gave only methyl deoxyapiosides and no indication of a product retaining the isopropylidene group. The possibility that the rearrangement occurred via a C-3 carbonium ion therefore appears unlikely. The rearrangement thus involves: (*a*) opening of the furanose ring and re-closing on the other primary hydroxyl group; (*b*) intramolecular migration of the isopropylidene group; and (*c*) methyl glycoside formation, although the sequence of these events has not been determined.

Migration of an isopropylidene group was also observed during the hydrolysis (with 80% acetic acid) of 1,6-anhydro-3,4-*O*-isopropylidene-β-L-talopyranose[5]. Rearrangement to 1,6-anhydro-2,3-*O*-isopropylidene-β-L-talopyranose was shown to be competing with hydrolysis. A migration more closely related to **1**→**4** was observed when methyl 5-*O*-benzoyl-2,3-*O*-isopropylidene-3-*C*-methyl-β-D-ribofuranoside was isolated after acidic methanolysis of 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose. Addition of water to the methanolysis solution prevented the acetal migration[6].

No evidence could be found by t.l.c. for the formation of **4** in methanolysis solutions of **1** containing 5% of water and it is perhaps not surprising that acetal migrations were not observed in hydrolyses carried out in 3:1 methanol–water[7]. We have found analogous rearrangements to be useful in syntheses of apiose derivatives containing sulfur[8] or nitrogen[9] as the ring heteroatom.

Methylation of **1** by the procedure of Kuhn *et al.*[10] gave 1,2-*O*-isopropylidene-3,5-di-*O*-methyl-α-D-apio-L-furanose (**3**) as a colorless oil. Methanolysis of **3** and Purdie methylation of the products afforded a mixture of two fully methylated

methyl apiosides. Fractionation on silica gel afforded methyl 2,3,5-tri-*O*-methyl-β-D-apio-L-furanoside (**10**) and methyl 2,3,5-tri-*O*-methyl-α-D-apio-L-furanoside (**11**) as liquids (see Table I).

TABLE I

PHYSICAL CONSTANTS OF METHYL TRI-*O*-METHYL-D-APIOFURANOSIDES

Compound	$[\alpha]_D^{26}$ (*CHCl₃*) (*degrees*)	R^a_{TMG}	*Anomeric proton*	
			τ	$J_{1,2}$ (*Hz*)
β-D-Apio-L-furanoside (**10**)	−110	0.36	5.20	2.3
α-D-Apio-L-furanoside (**11**)	+135	0.43	4.96	4.5
β-D-Apio-D-furanoside (**13**)	−79	0.40	5.05	2.6
α-D-Apio-D-furanoside (**15**)	+116	0.52	5.05	2.5

[a]Retention time relative to methyl tetra-*O*-methyl-α-D-glucopyranoside on Column B at 150°.

Purdie methylation of **4** was a surprisingly slow reaction, but the 5-*O*-methyl derivative (**6**) was obtained as a liquid in good yield. Removal of the isopropylidene group from **6** was effected by methanolysis. A little water was added and the mixture was twice concentrated at intermediate stages to remove liberated acetone. The two products were isolated by chromatography on silica gel. The faster moving and major component was a syrup, the p.m.r. spectrum of which showed an anomeric proton at τ 5.13 with $J_{1,2}$ ~2 Hz, indicative of *trans* protons at C-1 and C-2 and the β-D-glycosidic configuration. Treatment with 3,5-dinitrobenzoyl chloride in pyridine gave the crystalline bis(3,5-dinitrobenzoate) **12**. In the p.m.r. spectrum of the slower moving minor product, a syrup, the anomeric proton at τ 5.12 had $J_{1,2}$ ~5 Hz, indicative of *cis* protons at C-1 and C-2 and an α-D-glycosidic configuration. Treatment with *p*-nitrobenzoyl chloride in pyridine gave a crystalline di-*p*-nitrobenzoate **14**. Purdie methylation of each fraction gave the corresponding fully methylated derivatives **13** and **15**. Table I lists, for each of the isomers, values for the specific rotations, chemical shifts, and coupling constants for the anomeric protons from the p.m.r. spectra, and g.l.c. retention times relative to methyl tetra-*O*-methyl-α-D-glucopyranoside. The retention times cannot be correlated with values obtained under similar conditions by Jones and co-workers[11] and by Lindberg and co-workers[12] for presumed mixtures of the four isomers. Reported peaks at 0.582 and 0.905 (Ref. 11), and 0.63 and 0.95 (Ref. 12) cannot be due, as implied, to isomers **10** and **11**. A tri-*O*-methyl-D-apiose obtained from methylated apiin* was treated with methanol and Dowex 50-W (H^+) resin and the major product was identical (t.l.c., g.l.c., n.m.r., and specific rotation) with isomer **13**, confirming the configuration previously assigned[11] to the apiose moiety in apiin.

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The p.m.r. spectra of the apiose compounds described here (and in previous publications) are noteworthy in that they are generally amenable to first-order analysis. This is due primarily to the absence of a proton at C-3 which considerably simplifies the spectrum usually obtained from furanose sugars. Long-range couplings between H-2 and H-4A were also readily observed in compounds **8** and **9**. Reduction of the aldehyde **7** with lithium aluminum deuteride gave **4** labelled with deuterium at C-5 and compounds **6**, **12**, and **14** (similarly labelled) were then prepared from **4**-5*d*. From the p.m.r. spectra of these derivatives, assignments of the *endo* and *exo* cyclic methylene protons were readily made. Most assignments were as predicted, except that in **14** the C-4 protons were equivalent and appeared as a singlet at τ 5.62; the C-5 protons gave an AB quartet. The introduction of deuterium at the exocyclic methylene group has also been utilized for p.m.r. assignments in an L-apiose derivative[13].

EXPERIMENTAL

General. — Solutions were concentrated under diminished pressure. Melting points were determined in glass capillaries with a Thomas–Hoover apparatus. T.l.c. was performed on silica gel G and detection was effected with α-naphthol–sulfuric acid. Column chromatography was performed on 70–325 mesh ASTM silica gel (E. Merck AG, Darmstadt, Germany; distributed by Brinkmann Instruments, Inc.) and on aluminum oxide (Woelm, neutral, activity grade 1; distributed by Waters Associates Inc., Framingham, Mass.). I.r. spectra were recorded with a Perkin–Elmer Model 137 "Infracord" spectrophotometer and were calibrated against the 1600 cm^{-1} band of polystyrene. Optical rotations were measured with a Bendix–Ericcson ETL-NPL Automatic Polarimeter, and p.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer operating in the "frequency-sweep" mode, with tetramethylsilane (τ = 10.00) as the internal reference. Mass spectra were recorded with an A.E.I. MS-9 mass spectrometer, source temp. 240°, ionizing potential 70 eV. Gas–liquid chromatographic analyses were performed on a Wilkens Aerograph Model A-700 (Autoprep), equipped with a flame-ionization detector, at flow rates of 80–100 ml nitrogen/min with the following 6 ft × 1/4 in. columns: A, neopentyl glycol sebacate; B, carbowax 6000 (both 10% w/w on 80–100 mesh Chromosorb W, DMCS-AW).

The acid-catalyzed reaction of 1,2-O-isopropylidene-α-D-apio-L-furanose (**1**) *with methanol.* — To a stirred solution of **1** (9.50 g, 0.05 mole) in a mixture of anhydrous methanol (400 ml) and anhydrous acetone (100 ml) was added Dowex 50 (W-X8, H^+) ion-exchange resin (200–400 mesh, 5 g, previously extracted with boiling methanol and dried over phosphoric anhydride). The mixture was maintained at *ca.* 55°, and the reaction was monitored by t.l.c. (ethyl acetate). After 20 h, no starting material remained and the major product appeared on t.l.c. as a faster moving spot. Resin was removed by filtration and the solution was concentrated to a mobile syrup. Kugelrohr distillation (90°/1 torr) gave a chromatographically homogeneous oil (8.55 g, 84%),

$[\alpha]_D^{25}$ −108° (*c* 3.9, chloroform); p.m.r. data (chloroform-*d*): τ 5.06 (singlet, H-1), 5.71 (singlet, H-2), 6.05, 6.18 (AB quartet with J_{AB} ~10 Hz, H-4,4'), 6.25 (2-proton singlet, H-5,5'), 6.68 (3-proton singlet, OMe), 7.78 (broad peak, OH), 8.49, 8.58 (3-proton singlets, CMe_2). The five most-abundant ions in the mass spectrum were at *m/e* 43, 59, 68, 85, and 86, and a peak at *m/e* 189 corresponded to the M–CH_3 ion.

The acid-catalyzed reaction of **1** *with methanol in the presence of acetone*-d_6. — A solution of **1** (1.90 g, 0.01 mole) in methanol (100 ml) containing acetone-d_6 (1.28 g, 0.02 mole) was stirred at 55° with dry Dowex 50 (W-X8, H^+) ion-exchange resin (200–400 mesh, 2 g). When t.l.c. (ethyl acetate) indicated the absence of **1**, the product (1.32 g, 65%) was isolated as just described. The p.m.r. spectrum was identical with that just described, and no difference could be detected in the integrated intensities of the peaks. The five most-abundant ions in the mass spectrum were identical with those just described, and the M–CH_3 ion was found at *m/e* 189.

*Methyl 2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-*D*-apio-*D*-furanoside* (**5**). — To a solution of the rearrangement product **4** (2.04 g, 10 mmoles) in anhydrous pyridine (15 ml) was added *p*-toluenesulfonyl chloride (2.10 g, 11 mmoles). The solution was kept overnight at room temperature, after which t.l.c. (ether) indicated complete reaction. Pyridine hydrochloride was removed by filtration, and the filtrate was concentrated to a syrup which was purified by chromatography on a column made of alumina (50 g) superposed to silica gel (100 g) with ether as eluant. The product crystallized and was recrystallized from ether–hexane, 3.23 g (90%), m.p. 90–91°, $[\alpha]_D^{28}$ −82.1° (*c* 4.0, chloroform); p.m.r. data (chloroform-*d*): τ 2.12–2.80 (4-proton multiplet, aromatic protons), 5.10 (singlet H-1), 5.74 (singlet, H-2) 5.79, 5.84 (incompletely resolved AB quartet with J_{AB} ~10 Hz, H-5,5'), 6.09, 6.26 (AB quartet, J_{AB} ~10 Hz, H-4,4'), 6.73 (3-proton singlet, OMe), 7.55 (3-proton singlet, Ar-Me), 8.56, 8.71 (3-proton singlets, CMe_2).

Anal. Calc. for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19; S, 8.95. Found: C, 53.60; H, 6.24; S, 9.08.

Oxidation of **4**. — To a solution of **4** (2.04 g, 10 mmoles) in dimethyl sulfoxide (20 ml) and benzene (20 ml) was added dicyclohexylcarbodiimide (6.2 g, 30 mmoles), pyridine (0.80 ml, 10 mmoles), and trifluoroacetic acid (0.40 ml, 5 mmoles). After 16 h at room temp., t.l.c. (ether–hexane, 1:1) indicated incomplete reaction, additional portions (half of the previous amounts) of dicyclohexylcarbodiimide, pyridine, and trifluoroacetic acid were added. After a further 24 h, t.l.c. indicated almost complete reaction. Addition of ether (250 ml) was followed by a solution of oxalic acid (7.5 g) in methanol (30 ml). After 1 h, 1,3-dicyclohexylurea was removed by filtration, and the solution was concentrated to an oil which was fractionated on silica gel (200 g) with 1:1 ether–hexane as eluant. Fractions containing the aldehyde were combined and concentrated, and the product was distilled at 70–75°/1.5 torr. Methyl 3-*C*-formyl-2,3-*O*-isopropylidene-β-*D*-erythrofuranoside (**7**) was obtained as a colorless syrup (1.40 g, 70%) which solidified in the freezer and melted at *ca.* 18°, $[\alpha]_D^{26}$ −127° (*c* 0.52, chloroform); ν_{max}^{film} 1730 cm^{-1} (C=O); p.m.r. data (chloroform-*d*): τ 0.19 (singlet, aldehydic proton at C-5), 5.01 (singlet, H-1), 5.48 (singlet, H-2), 5.82,

6.02 (AB quartet, J_{AB} ~10 Hz, H-4,4'), 6.62 (3-proton singlet, OMe), 8.41, 8.58 (3-proton singlets, CMe_2).

Preparation of the oxime of 7. — To a solution of 7 (0.202 g, 1 mmole) in ethanol (1 ml) was added a solution of hydroxylamine hydrochloride (0.087 g, 1.25 mmoles) in water (0.5 ml), followed by a solution of sodium carbonate (0.078 g, 0.63 mmole) in water (0.5 ml). T.l.c. (1:1 ether–hexane) indicated complete reaction in less than 30 min at room temp. The solution was concentrated and the oxime was isolated by chromatography on silica gel (100 g) with 1:1 ether–hexane as eluent. The product crystallized, and recrystallization from ether–hexane gave fine needles (0.17 g, 77%), m.p. 45–46°, $[\alpha]_D^{24}$ −122° (*c* 0.41, chloroform); p.m.r. data (chloroform-*d*): τ 1.86 (singlet, N–OH), 2.37 (singlet, CH=N), 5.02 (singlet, H-1), 5.39 (singlet, H-2), 5.94 (2-proton singlet, H-4,4'), 6.63 (3-proton singlet, OMe), 8.46, 8.60 (3-proton singlets, CMe_2).

Anal. Calc for $C_9H_{15}O_5N$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.96; H, 6.99; N, 6.55.

A small amount (10 mg) of a second product was obtained from the column and its p.m.r. spectrum was indicative of the *anti*-oxime. It slowly isomerized to the *syn*-oxime at 0°. P.m.r. data (chloroform-*d*): τ 1.31 (broad peak, N–OH), 3.05 (singlet, CH=N), 5.03 (singlet, H-1), 5.07 (singlet, H-2), 5.77, 5.87 (AB quartet J_{AB} ~10 Hz, H-4,4'), 6.59 (3-proton singlet, OMe), 8.46, 8.59 (3-proton singlets, CMe_2).

5-Deoxy-1,2-O-isopropylidene-α-D-apio-L-furanose (**8**). — To a stirred solution of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-apio-L-furanose (**2**) (1.72 g, 5 mmoles) in dry ether (40 ml) and dry benzene (20 ml) was added lithium aluminum hydride (*ca.* 300 mg), and the suspension was boiled under reflux. After 20 h, t.l.c. (ether) indicated one product and the absence of **2**. Excess hydride was destroyed by addition of ethyl acetate and then water, and the white gelatinous mixture was filtered through Celite. Concentration of the colorless filtrate gave an oil which crystallized from hexane, 0.75 g (86%), m.p. 57–60°, after two recrystallizations from hexane, $[\alpha]_D^{29}$ +29.8° (*c* 1.5, chloroform); p.m.r. data (chloroform-*d*): τ 4.06 (doublet, $J_{1,2}$ ~3.5 Hz, H-1), 5.76 (broad doublet, $J_{2,4A}$ ~1 Hz, H-2), 6.13, 6.29 (AB quartet, J_{AB} ~9.5 Hz, H-4B, 4A), 7.78 (singlet, OH), 8.46, 8.61, 8.64 (3-proton singlets, 3C–Me).

Anal. Calc. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.25; H, 8.18.

Treatment of **8** with *p*-nitrobenzoyl chloride in pyridine at room temperature, followed by evaporation of pyridine and isolation by chromatography on silica gel with ether as eluant, afforded the crystalline *p*-nitrobenzoate **9**, m.p. 124–125° after recrystallization from hexane, $[\alpha]_D^{30}$ +69° (*c* 1.7, chloroform); p.m.r. data (chloroform-*d*): τ 1.64–1.94 (4-proton multiplet, aromatic protons), 4.02 (doublet, $J_{1,2}$ ~3.5 Hz, H-1), 5.24 (broad doublet, $J_{2,4A}$ ~1 Hz, H-2), 5.49, 6.05 (AB quartet, J_{AB} ~10.5 Hz, H-4A, 4B), 8.22, 8.42, 8.59 (3-proton singlets, 3C–Me).

Anal. Calc. for $C_{15}H_{17}NO_7$: C, 55.72; H, 5.30; N, 4.33. Found: C, 55.55; H, 5.33; N, 4.24.

1,2-O-Isopropylidene-3,5-di-O-methyl-α-D-apio-L-furanose (**3**). — To a cooled (0°), stirred solution of **1** (1.90 g, 10 mmoles) in *N*,*N*-dimethylformamide (50 ml)

were added methyl iodide (5 ml) and silver oxide (5 g). After 2 days at room temperature, t.l.c. (ether) indicated complete reaction. The mixture was filtered, and the filtrate was concentrated to a yellow residue which was chromatographed on silica gel (150 g) with ether as eluant. The product, purified by Kugelrohr distillation (*ca.* 60°/0.1 torr), was a mobile oil, homogeneous by t.l.c. and g.l.c. (column A at 140°), 1.55 g (71%); p.m.r. data (chloroform-*d*): τ 4.07 (doublet $J_{1,2}$ ~3.7 Hz, H-1), 5.62 (broad doublet, $J_{2,4A}$ ~0.8 Hz, H-2), 5.90, 6.19 (AB quartet, J_{AB} ~10.5 Hz, H-4A, 4B), 6.27, 6.32 (incompletely resolved AB quartet, J_{AB} ~11 Hz, H-5,5'), 6.55, 6.59 (3-proton singlets, 2 OMe), 8.42, 8.61 (3-proton singlets, CMe_2).

*Methyl 2,3,5-tri-*O*-methyl-α- and -β-*D*-apio-*L*-furanosides.* — A solution of **3** (1.09 g, 5 mmoles) in methanol (100 ml) was boiled under reflux with methanol-washed Dowex 50 (W-X8, H^+) ion-exchange resin (200–400 mesh, 2 g). After 6 h, t.l.c. (ether) indicated the absence of **3** and the formation of two compounds. P.m.r. indicated that these were the expected methyl di-*O*-methylapiosides in an α:β ratio of 2:3.

A portion (0.40 g) of the methyl apioside mixture was methylated with boiling methyl iodide–silver oxide, and the products were fractionated by chromatography on a column of silica gel (60 g) with ether as eluent.

Fraction A (0.15 g) was homogeneous by t.l.c. and g.l.c., and its p.m.r. and specific rotation were consistent with its formulation as methyl 2,3,5-tri-*O*-methyl-β-D-apio-L-furanoside (**10**) (see Table I).

Fraction B (0.09 g) was a mixture of the two anomers.

Fraction C (0.12 g) was homogeneous by t.l.c. and g.l.c., and its p.m.r. and specific rotation were indicative of the α-glycoside **11** (see Table I).

*Methyl 2,3-*O*-isopropylidene-5-*O*-methyl-β-*D*-apio-*D*-furanoside* (**6**). — Methylation of **4** (1.0 g) with silver oxide–boiling methyl iodide was followed by g.l.c. (Column B at 160°). Slow methylation occurred and several additions of reagents were made during 1 week. The mixture was then filtered, the silver residues were extracted with chloroform, and the combined filtrates were concentrated to an oil which was purified by Kugelrohr distillation at 70°/2 torr. The product (**6**) (1.0 g) was homogeneous by t.l.c. and g.l.c. and had $[\alpha]_D^{25}$ −106° (*c* 2.4, chloroform); p.m.r. data (chloroform-*d*): τ 5.07 (singlet, H-1), 5.73 (singlet, H-2), 5.97, 6.18 (AB quartet, J_{AB} ~10 Hz, H-4,4'), 6.40 (2-proton singlet, H-5,5'), 6.58, 6.67 (3-proton singlets, 2 OMe), 8.50, 8.57 (3-proton singlets, CMe_2).

Methanolysis of **6**. — To a solution of **6** (0.60 g) in dry methanol (25 ml) was added water (0.1 ml) and dry Dowex 50 (W-X8, H^+) ion-exchange resin (200–400 mesh, 0.5 g). The mixture was stirred and boiled under reflux, and the reaction was monitored by t.l.c. (ethyl acetate). After 16 h, starting material remained and the mixture was concentrated (to remove acetone), the residue was taken up in dry methanol (25 ml) containing water (0.1 ml) and stirred and boiled under reflux as just described. After 16 h, this procedure was repeated and, after a further 6 h, the resin was removed by filtration and the brown solution was concentrated to a syrup which was fractionated on silica gel (40 g) with ethyl acetate as eluant.

Fraction A (0.020 g) was mainly starting material **6**.

Fraction B (0.240 g), the faster moving major product, was a chromatographically homogeneous syrup. In the p.m.r. spectrum (chloroform-*d*), the anomeric proton at τ 5.13 had $J_{1,2}$ ~2 Hz, indicative of the β-furanoside configuration. Treatment of the syrup with 2.5 equiv. of 3,5-dinitrobenzoyl chloride in pyridine, and isolation of the product by silica gel chromatography, afforded a crystalline bis(3,5-dinitrobenzoate) **12**. Recrystallization from ethanol gave a pure material, m.p. 129–130.5°, $[\alpha]_D^{25}$ −40.5° (*c* 1.0, chloroform); p.m.r. data (chloroform-*d*): τ 0.78–1.04 (6-proton multiplet, aromatic protons), 4.31 (singlet, H-1), 4.81 (singlet H-2), 5.46, 5.60 (AB quartet, J_{AB} ~11 Hz, H-4,4′), 5.85 (2-proton singlet, H-5,5′), 6.52, 6.60 (3-proton singlets, 2 OMe).

Anal. Calc. for $C_{21}H_{18}N_4O_{15}$: C, 44.53; H, 3.20; N, 9.89. Found: C, 44.47; H, 3.18; N, 9.91.

Fraction C (0.084 g), the slower moving product, was a chromatographically homogeneous syrup. In the p.m.r. spectrum (chloroform-*d*), the anomeric proton at τ 5.12 had $J_{1,2}$ ~5 Hz, indicative of the α-furanoside configuration. Treatment of the syrup with 2.5 equiv. of *p*-nitrobenzoyl chloride in pyridine, and isolation of the product by silica gel chromatography, afforded a crystalline di-*p*-nitrobenzoate (**14**). Recrystallization from ethanol gave pure material, m.p. 112.5–113.5°, $[\alpha]_D^{25}$ +29.3° (*c* 0.7, chloroform); p.m.r. data (chloroform-*d*): τ 1.58–1.96 (8-proton multiplet, aromatic protons), 4.56 (doublet, $J_{1,2}$ ~5 Hz, H-1), 4.72 (doublet, H-2), 5.62 (2-proton singlet, H-4,4′), 5.94, 6.04 (AB quartet, J_{AB} ~9.5 Hz, H-5,5′), 6.60 (6-proton singlet, 2 OMe).

Anal. Calc. for $C_{21}H_{20}N_2O_{11}$: C, 52.94; H, 4.23; N, 5.88. Found: C, 52.78; H, 4.35; N, 5.97.

*Methyl 2,3,5-tri-*O*-methyl-α- and -β-*D*-apio-*D*-furanosides.* — The β anomer of methyl 5-*O*-methyl-D-apio-D-furanoside (Fraction B from **6**) was methylated with silver oxide–boiling methyl iodide. G.l.c. (column B at 150°) indicated fairly rapid methylation, complete within 1 day. The product, methyl 2,3,5-tri-*O*-methyl-β-D-apio-D-furanoside (**13**), was homogeneous by t.l.c. and g.l.c. (see Table I) and identical with a sample obtained by methyl glycosidation of a tri-*O*-methyl-D-apiose prepared *via* methylation of apiin.

The α-anomer (Fraction C from **6**) was also readily methylated with Purdie's reagents giving methyl 2,3,5-tri-*O*-methyl-α-D-apio-D-furanoside (**15**) as a chromatographically homogeneous oil (see Table I).

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