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APIOSE. II.* 1,2:3,5-Di-*O*-ISOPROPYLIDENE-α-D-APIO-D-FURANOSE AND STEREOSELECTIVE SYNTHESES OF 3-DEOXY-1,2-*O*-ISOPROPYLIDENE-α-D-APIO-L-FURANOSE AND 3,5-ANHYDRO-1,2-*O*-ISOPROPYLIDENE-α-D-APIO-L-FURANOSE

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ABSTRACT

Isolation of the second isomer of di-*O*-isopropylidene-D-apiose, namely, 1,2:3,3[1]-di-*O*-isopropylidene-[3-*C*-(hydroxymethyl)-α-D-erythrofuranose] (**2**), has been achieved. Graded, acid hydrolysis gave the corresponding 1,2-*O*-isopropylidene derivative (**3**). High stereoselectivity was observed in the hydroboration of 3-deoxy-1,2-*O*-isopropylidene-3-*C*-methylene-D-*glycero*-tetrose (**4**), and acid hydrolysis of the product afforded 3-deoxy-D-apiose, which may be differentiated from 3-deoxy-D-*erythro*-pentose by its color reaction with *p*-anisidine hydrochloride. Epoxidation of **4** with *m*-chloroperoxybenzoic acid was also highly stereoselective, and gave a *spiro*-epoxide. A synthesis of the same epoxide (**8**) from 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-apio-L-furanose (**7**) established that epoxidation occurred *trans* to the isopropylidene ring, as anticipated. The minor product (4%) of the epoxidation reaction was shown to be identical chromatographically with 3,5-anhydro-1,2-*O*-isopropylidene-α-D-apio-D-furanose (**9**), which was prepared by the reaction of 1,2-*O*-isopropylidene-D-*glycero*-tetros-3-ulose (**10**) with dimethylsulfonium methylide.

INTRODUCTION

In Part I of this series[1], the structure of the known diisopropylidene acetal of D-apiose was established as 1,2:3,5-di-*O*-isopropylidene-α-D-apio-L-furanose, that is, 1,2:3,3[1]-di-*O*-isopropylidene-[3-*C*-(hydroxymethyl)-β-L-threofuranose] (**1**). Graded, acid hydrolysis of **1** gave the 1,2-isopropylidene acetal **6**, which was also synthesized by hydroxylation of 3-deoxy-1,2-*O*-isopropylidene-3-*C*-methylene-D-*glycero*-tetrose (**4**) with osmium tetraoxide. This reaction was highly stereoselective, in that crystalline **6** was formed to the apparent exclusion of its epimer, 1,2-*O*-isopropylidene-α-D-

*For Part I, see ref. 1.

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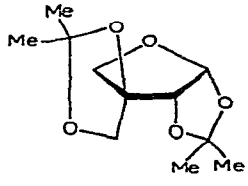
apio-D-furanose (**3**), which would arise by addition of osmium tetraoxide from the more-hindered side of the double bond, namely, *cis* to the isopropylidene ring. Similar steric control was observed in the borohydride reduction of 1,2-*O*-isopropylidene-D-*glycero*-tetros-3-ulose (**10**), which afforded 1,2-*O*-isopropylidene-D-erythrose exclusively.



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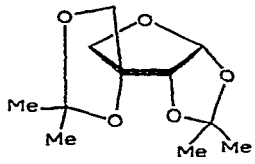

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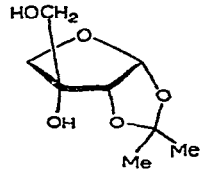

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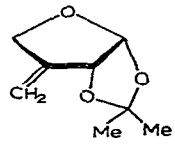

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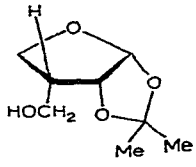

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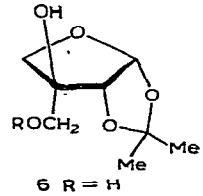

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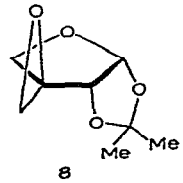

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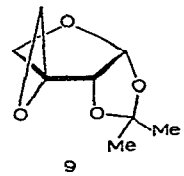

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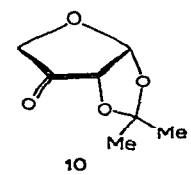

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This paper describes the preparation of the second isomer of di-*O*-isopropylidene-D-apiose, namely, 1,2:3,5-di-*O*-isopropylidene-α-D-apio-D-furanose, that is, 1,2:3,3[1]-di-*O*-isopropylidene-[3-*C*-(hydroxymethyl)-α-D-erythrofuranose] (**2**), the corresponding 1,2-isopropylidene acetal (**3**), and stereoselective syntheses of 3,5-anhydro- and 3-deoxy-D-apiose derivatives.

DISCUSSION

Pure D-apiose was conveniently prepared from the 1,2-isopropylidene acetal **6** by stirring an aqueous solution, heated to 50°, with washed, cation-exchange resin in the acid form, followed by filtration, and lyophilization of the filtrate. The chromatographically homogeneous product was condensed with acetone containing sulfuric acid, and the course of the reaction was followed by g.l.c. and by t.l.c. In addition to the known diisopropylidene acetal (**1**), a second component of the reaction mixture, having similar chromatographic mobilities, was observed. If the condensation was allowed to reach equilibrium, this component was no longer present, but, by neutralizing the mixture after about 90 min, followed by fractionation

on silica gel, a complete separation of the two major products was achieved. The faster-moving and preponderant component was found to be the isomer **1** previously characterized. The other component, which also crystallized, had physical properties consistent with its formulation as the alternative isomer, 1,2:3,5-di-*O*-isopropylidene-α-D-apio-D-furanose (**2**).

Graded hydrolysis with acid, under the conditions used[1] for the preparation of **6** from **1**, also gave a crystalline 1,2-isopropylidene acetal (**3**), which was different, by p.m.r. spectroscopy and mixture m.p., from **6**.

The antibiotic cordycepin was originally thought to be the adenine nucleoside of 3-deoxy-D-apiose[2,3], but subsequent work has clearly established that its structure is 9-(3-deoxy-β-D-*erythro*-pentofuranosyl)adenine[4]. It would, however, be of interest to devise a simple test to differentiate 3-deoxy-D-apiose and 3-deoxy-D-*erythro*-pentose, in order to avoid possible future confusion. The olefinic sugar **4**, described previously[1], appeared to be a likely intermediate for the preparation of 3-deoxy-D-apiose derivatives*, since anti-Markownikov hydration would generate the desired skeleton. Hydroboration has been successfully applied to carbohydrates for effecting such transformations[5], and it offers the advantage that, where necessary, hindered boranes may be used for increasing the stereoselectivity of the addition.

Treatment of **4** with diborane in tetrahydrofuran, followed by oxidative, alkaline hydrolysis, afforded 3-deoxy-3-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-erythrofuranose (3-deoxy-1,2-*O*-isopropylidene-α-D-apio-L-furanose, **5**) as a colorless syrup (in 68% yield), which was characterized as its crystalline *p*-phenylazobenzoate. Analysis (g.l.c.) of the reaction mixture indicated a stereoselectivity of hydroboration (even with this unhindered borane) of at least 95%. The p.m.r. spectrum of **5** clearly showed that, as anticipated, the addition of diborane to the double bond had occurred *trans* to the isopropylidene ring. The H-2 signal appeared as a triplet having a spacing of 4 Hz. For H-2 to be coupled equally with H-1 and H-3, it must be *cis* to both, since the coupling constant between H-2 and H-3 is quite small (<0.5 Hz) when they are *trans* in similar systems[7]. We have found that, for the structurally analogous 1,2-*O*-isopropylidene-D-erythrose, H-2 also gives a triplet ($J_{1,2} \approx J_{2,3} \approx 4$ Hz), whereas, for 1,2-*O*-isopropylidene-D-threose, H-2 gives a doublet ($J_{1,2} \approx 4$ Hz, $J_{2,3} < 0.5$ Hz).

Hydrolysis of **5** with aqueous acetic acid gave 3-deoxy-D-apiose as a pale-yellow syrup which, although not readily separable from 3-deoxy-D-*erythro*-pentose** by paper chromatography, gave a different color-reaction (yellow-brown, compared with dark pink) with the *p*-anisidine hydrochloride spray.

Mono-*p*-toluenesulfonylation of **6** readily gave a high yield of crystalline 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-apio-L-furanose (**7**), and treatment of **7** with sodium methoxide in methanol at room temperature gave 3,5-anhydro-1,2-*O*-

*Racemic 3-deoxyapiose has been synthesized[6].

**Obtained by hydrolysis of synthetic cordycepin, kindly provided by Drs. E. Walton and F. W. Holly of Merck and Company, Rahway, New Jersey.

isopropylidene-α-D-apio-L-furanose (**8**) as a colorless syrup in 78% yield. The p.m.r. spectrum of **8** was consistent with the *spiro*-epoxide structure and the oxirane-ring protons gave a well-resolved AB system (J = 4.4 Hz) at relatively high field. The same epoxide (**8**) was obtained by treatment of olefin **4** with *m*-chloroperoxybenzoic acid in chloroform. G.l.c. of the reaction mixture indicated that **8** was the major component (96%), and also showed the presence of a minor component (4%). The *spiro*-epoxide **8** was isolated in 52% yield, and was found to be identical with the epoxide prepared from **7**. This result substantiates the previous stereochemical assignments[1], because the sensitivity of peroxy acid oxidations to steric factors is even more well-documented than that of osmium tetraoxide[9].

The minor component from the epoxidation was shown (by g.l.c.) to be 3,5-anhydro-1,2-*O*-isopropylidene-α-D-apio-D-furanose (**9**). The latter was readily synthesized, although in low yield, by transfer of methylene to 1,2-*O*-isopropylidene-D-*glycero*-tetros-3-ulose (**10**). Treatment of **10** with dimethylsulfonium methylide[10] in methyl sulfoxide–tetrahydrofuran gave **9** as a crystalline solid, m.p. 66–67°. The p.m.r. spectrum of **9** was similar to that of the isomeric epoxide **8**, except that the oxirane protons gave rise to a poorly resolved AB system, with little separation of the signals. The mass spectra of the two epoxides were also quite similar; each exhibited virtually no parent ion, and gave intense fragments corresponding to the loss of methyl from the isopropylidene group. This mode of fragmentation is well established for isopropylidene acetals of carbohydrates[13]. The exact, measured mass of the M − 15 peak corresponded closely, in each case, to the value calculated.

It is significant that, whereas dimethylsulfonium methylide reacts with **10** to give **9**, dimethyloxosulfonium methylide produces mainly **8** (86%), together with a minor proportion (14%) of **9**; this result is consistent with those from studies, reported in other contexts[10,11], in which it appears that kinetic control obtains with the sulfonium ylide, and thermodynamic control with the oxosulfonium ylide. In a brief report of the reaction of a glycofuranosulose derivative with the oxosulfonium ylide, no details were given[12].

EXPERIMENTAL*

General. — Solutions were concentrated under diminished pressure. Melting points were determined in glass capillaries with a Thomas–Hoover apparatus, and are corrected. T.l.c. was performed on Kieselgel G, and detection was effected with sulfuric acid. 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–Ericsson ETL–NPL Automatic Polarimeter, and n.m.r. spectra were recorded with a Varian A-60 spectrometer. Peak positions are given in τ units relative to internal tetramethylsilane (τ = 10.00).

*In experimental procedure *A* for the preparation of 1,2-*O*-isopropylidene-α-D-apio-L-furanose 3,5-thionocarbonate, described[1] in Part I, the following should be inserted after the second sentence: "Methyl iodide (0.25 ml, 3.8 mmoles) was added, and the solution was stirred for 30 min at 25° and then boiled for 30 min under reflux."

Gas–liquid chromatographic analyses were performed on a Pye Argon instrument at flow rates of *ca.* 50 ml of argon/min with the following columns: *A*, neopentyl glycol sebacate (10% w/w on 80–100 mesh Chromosorb W, DMCS-AW); *B*, 1:1 mixture of (*a*) Apiezon M and (*b*) diethylene glycol adipate — both 20% w/w on 80–100 mesh Chromosorb W (DMCS-AW).

Preparation of D-*apiose.* — A solution of 1,2-*O*-isopropylidene-α-D-apio-L-furanose[1] (5 g) in water (250 ml) was stirred for 24 h at ~50° with Dowex-50W x8 (H^+) ion-exchange resin (200–400 mesh, 2.5 g) that had been washed with hot methanol and dried. T.l.c. (ethyl acetate) indicated complete hydrolysis. The resin was removed by filtration, and the filtrate was lyophilized to give a clear glass. Paper chromatography (4:1:5 butyl alcohol–acetic acid–water) indicated a homogeneous product.

*Preparation of 1,2:3,5-di-*O*-isopropylidene-α-*D*-apio-*D*-furanose* (**2**). — The product from the hydrolysis of 5 g of mono-*O*-isopropylidene-D-apiose was stirred vigorously with acetone (900 ml), and concentrated sulfuric acid (4.5 ml) was added. After 90 min, anhydrous sodium carbonate (20–30 g) was added, and the suspension was stirred until neutral (~30 min). T.l.c. (ether) indicated two di-*O*-isopropylidene derivatives, together with slower-moving compounds. G.l.c. (column *A* at 160°) indicated that the first two were present in a ratio of *ca.* 4:1, the α-D-apio-L-furanose isomer (**1**) preponderating. The suspension was filtered, the filtrate was concentrated, and the mixture was fractionated by chromatography on a column of Brinkmann silica gel (300 g) with 1:1 ether–hexane as eluant. The two isomers were separated completely. The faster-moving isomer (2.4 g) was identical (by m.p., mixture m.p., and i.r. spectrum) with the previously characterized[1] **1**. The slower-moving isomer (0.50 g), which crystallized from ether–hexane, had m.p. 52.5–54° and $[\alpha]_D^{28}$ +76.5° (*c* 3.0, ethanol); n.m.r. data (chloroform-*d*): τ 4.29 (doublet, $J_{1,2}$ ~3.5 Hz, H-1), 5.69 (doublet, H-2), 5.98 and 6.35 (AB quartet, $J_{4,4'}$ ~8 Hz, H-4,4'); 6.10 (center of a poorly resolved AB quartet, H-5,5'); 8.42, 8.54, 8.61, and 8.65 (3-proton singlets, CMe_2).

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.00; H, 7.98.

Partial hydrolysis of **2**. — A solution of **2** (0.46 g, 2 mmoles) in acetic acid (5 ml) and water (2.5 ml) was kept at room temperature (~28°). The hydrolysis was monitored by t.l.c. (ethyl acetate) and, after 50 h, the major component appeared to be a mono-*O*-isopropylideneapiose (together with **2** and apiose). The solution was concentrated, and the residue was fractionated by chromatography on a column of Brinkmann silica gel (50 g) with ethyl acetate as eluant. Fractions containing the major product were combined, and evaporated to a crystalline residue (0.16 g, 42%) which, after recrystallization from ethyl acetate–hexane, had m.p. 116–118°, depressed to 95–115° by admixture with **6**; $[\alpha]_D^{29}$ +44.0° (*c* 1.0, ethanol); n.m.r. data (pyridine): τ 3.96 (doublet, $J_{1,2}$ ~3.7 Hz, H-1), 5.35 (doublet, H-2), 5.86 and 6.04 (2-proton singlets, C-4 and C-5 protons), 8.44 and 8.64 (3-proton singlets, CMe_2).

Anal. Calc. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.50, H, 7.48.

*Hydroboration of 3-deoxy-1,2-*O*-isopropylidene-3-*C*-methylene-*D*-glycero-tetrose*

(4). — A solution of **4** (0.80 g, 5.1 mmoles) in anhydrous tetrahydrofuran (15 ml) was stirred at 25° under an atmosphere of dry nitrogen, and a M solution of diborane in tetrahydrofuran* (6 ml) was added. After 1 h, M sodium hydroxide solution (10 ml) was added, followed by 30% hydrogen peroxide (2 ml). The solution was stirred overnight, tetrahydrofuran was removed by evaporation at 25°, and the residual, aqueous solution was extracted with dichloromethane (3 × 10 ml). The extracts were dried over magnesium sulfate, and evaporation gave 3-deoxy-3-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-erythrofuranose (3-deoxy-1,2-*O*-isopropylidene-α-D-apio-L-furanose, **5**) as a clear syrup (0.61 g, 68%). G.l.c. (column *A* at 160°) indicated the product to be at least 95% pure, and, at most, only trace amounts of material isomeric at C-3 could be present. After "Kugelrohr" distillation at 100°/1 torr, the syrup had $[\alpha]_D^{30}$ +38.2° (*c* 2.0, chloroform); n.m.r. data (chloroform-*d*): τ 4.14 (doublet, $J_{1,2}$ ~4 Hz, H-1), 5.29 (triplet, $J_{2,3}$ ~4 Hz, H-2), 5.85–6.40 (poorly resolved multiplet, H-3, 4, and 5), 8.50 and 8.68 (3-proton singlets, CMe_2).

Treatment of **5** (85 mg, 0.5 mmole) in pyridine (1.5 ml) with *p*-phenylazobenzoyl chloride (172 mg, 0.7 mmole) followed by chromatography on Woelm silica gel (30 g) gave crystalline 3-deoxy-1,2-*O*-isopropylidene-5-*O*-*p*-phenylazobenzoyl-α-D-apio-L-furanose (75 mg, 39%). Three recrystallizations from ethanol gave red plates having m.p. 130.5–131.5°, $[\alpha]_D^{30}$ +48.8° (*c* 0.5, chloroform).

Anal. Calc. for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.32. Found: C, 66.18; H, 5.90; N, 7.25.

Hydrolysis of **5**. — A solution of **5** (124 mg, 0.71 mmole) in water (3 ml) and acetic acid (1 ml) was heated for 90 min at 100° and then lyophilized to give 3-deoxy-D-apiose (91 mg) as a light-yellow syrup having $[\alpha]_D^{31}$ +8.2° (*c* 1.6, ethanol). Descending paper-chromatography on Whatman No. 1 filter paper in 3:1:1 butyl alcohol–ethanol–water gave the following *R* values relative to rhamnose: apiose, 0.95; 3-deoxyapiose, 1.2; 3-deoxy-*erythro*-pentose, 1.2. Detection with *p*-anisidine hydrochloride[8] gave yellow-brown spots for apiose and 3-deoxyapiose, whereas 3-deoxy-D-*erythro*-pentose (obtained by hydrolysis of cordycepin) gave a dark-pink color, similar to that given by D-ribose.

Preparation of 1,2-O-isopropylidene-5-O-p-tolylsulfonyl-α-D-apio-L-furanose (**7**). — To a solution of **6** (2.5 g, 13 mmoles) in anhydrous pyridine (25 ml) was added *p*-toluenesulfonyl chloride (3.0 g, 16 mmoles), and the solution was kept overnight at ~25°. Most of the pyridine was removed by evaporation, and the residue was chromatographed on Davison silica gel (grade 950, 60–200 mesh, 150 g) with ethyl acetate as eluant. Fractions containing the product were combined, and evaporated to a crystalline solid. Recrystallization from ether gave the mono-*p*-toluenesulfonate **7** (3.52 g, 78%), having m.p. 137–138°, $[\alpha]_D$ +43.2° (*c* 4.4, chloroform).

Anal. Calc. for $C_{15}H_{20}O_7S$: C, 52.31; H, 5.85; S, 9.31. Found: C, 52.23; H, 5.80; S, 9.33.

*Alfa Inorganics Inc., Beverly, Massachusetts, U. S. A.

Synthesis of 3,5-anhydro-1,2-O-isopropylidene-α-D-apio-L-furanose (**8**). — *A. From* **7**. To a solution of **7** (0.86 g, 2.5 mmoles) in methanol (25 ml) was added sodium methoxide (2.5 mmoles) in methanol (5 ml). After a few h, t.l.c. (ether) indicated complete conversion of the ester into the epoxide. The solution was evaporated, and the residue was extracted with boiling ether. Evaporation of the extracts afforded the epoxide (**8**) as a syrup (0.34 g, 79%). An analytical sample, prepared by "Kugelrohr" distillation at 110°/15 torr, had $[\alpha]_D^{31}$ +67.3° (*c* 1.9, chloroform); n.m.r. data (carbon tetrachloride): τ 4.06 (doublet, $J_{1,2}$ ~4 Hz, H-1), 5.81 (doublet, H-2), 5.70 and 6.44 (AB quartet, $J_{4,4'}$ ~10 Hz, H-4,4'), 6.95 and 7.12 (AB quartet, $J_{5,5'}$ ~4.4 Hz, oxirane-ring protons), 8.53, 8.71 (3-proton singlets, CMe_2).

Anal. Calc. for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 55.85; H, 6.87.

The i.r. spectrum was devoid of absorption in the hydroxyl region, and had bands at 925 and 940 cm^{-1} (epoxide). The exact measured mass of the $M-CH_3$ fragment, measured by high-resolution mass spectrometry, was 157.0508. Calc. for $C_7H_9O_4$: 157.0501.

B. By epoxidation of **4**. To a solution of **4** (0.16 g, 1.0 mmole) in chloroform (10 ml) was added *m*-chloroperoxybenzoic acid (0.32 g, 85% pure ≡1.6 mmoles). The solution was kept for 1 week at ~25° and then extracted with saturated sodium hydrogen carbonate solution and dried (magnesium sulfate). Analysis by g.l.c. (column *B* at 175°) indicated that epoxide **8** was the major product (96%), and that a small proportion (4%) of the isomeric 3,5-anhydro-1,2-*O*-isopropylidene-α-D-apio-D-furanose (**9**) was formed (see later). Evaporation of the chloroform solution, followed by distillation of the residue at 110°/15 torr, afforded the epoxide **8**, identical (by g.l.c., t.l.c., and by i.r. and p.m.r. spectroscopy) with that prepared from **7**.

Reaction of 1,2-O-isopropylidene-D-glycero-tetros-3-ulose (**10**) *with dimethylsulfonium methylide.* — Sodium hydride (0.96 g of a 55% dispersion in mineral oil, ≡20 mmoles) was washed with hexane to remove the oil, methyl sulfoxide (7 ml) was added, and the mixture was heated at 60° under nitrogen until evolution of hydrogen ceased. The resulting solution of sodium methylsulfinyl carbanion was diluted with dry tetrahydrofuran (7 ml), and cooled to 0°. A solution of trimethylsulfonium iodide (4.08 g, 20 mmoles) in methyl sulfoxide (14 ml) was added, and the solution was stirred for 1 min. A solution of 1,2-*O*-isopropylidene-D-*glycero*-tetros-3-ulose[1,14] (**10**, 0.63 g, 4 mmoles) in tetrahydrofuran (2 ml) was then added. The bright-red solution that resulted was stirred for 30 min at 0–10° and for 1 h at 25°, and then poured into water (75 ml). The aqueous solution was extracted with ether (5 × 10 ml), and the extracts were combined, washed with water (7 ml), and dried (magnesium sulfate). Evaporation afforded a syrup (0.12 g, 17%) which, after "Kugelrohr" distillation at 140°/15 torr, gave a crystalline product. Recrystallization from hexane gave needles having m.p. 66–67°; n.m.r. data (carbon tetrachloride): τ 4.24 (doublet, $J_{1,2}$ ~4 Hz, H-1), 5.78 (doublet, H-2), 5.92 and 6.44 (AB quartet, $J_{4,4'}$ ~9 Hz, H-4,4'), 7.10 and 7.15 (oxirane ring protons), 8.47 and 8.70 (3-proton singlets, CMe_2).

Anal. Calc. for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 56.15; H, 7.12.

The i.r. spectrum of the product was similar to that of **8** and consistent with its formulation as 3,5-anhydro-1,2-*O*-isopropylidene-α-D-apio-D-furanose (**9**). The exact measured mass of the $M \div CH_3$ fragment was 157.0506. Calc. for $C_7H_9O_4$: 157.0501.

Reaction of **10** *with dimethyloxosulfonium methylide.* — To a stirred solution of trimethyloxosulfonium iodide (0.24 g, 1.1 mmoles) in methyl sulfoxide (10 ml) was added sodium hydride (54 mg of a 55% dispersion in mineral oil ≡1.1 mmoles). The solution was stirred under nitrogen for 30 min, a solution of **10** (0.16 g, 1 mmole) in methyl sulfoxide (1 ml) was added, and the solution was stirred for a further 60 min. The solution was then poured into water (50 ml), and the mixture was extracted with ether (3 × 10 ml). The extracts were combined, dried (magnesium sulfate), and evaporated to a syrup. G.l.c. (column *B*) indicated that the epoxide mixture contained 86% of **8** and 14% of **9**.

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