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Note

A new synthesis of DL-apiose

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This report describes a new synthesis of DL-apiose from 2-methoxy-4-(methoxycarbonyl)tetrahydrofuran (**1**) which has been prepared in our laboratory via the Birch reduction of 3-furoic acid[1]. The only reported synthesis of DL-apiose is that of Raphael *et al.*[2], although several groups[3] have reported the synthesis of D- or L-apiose.

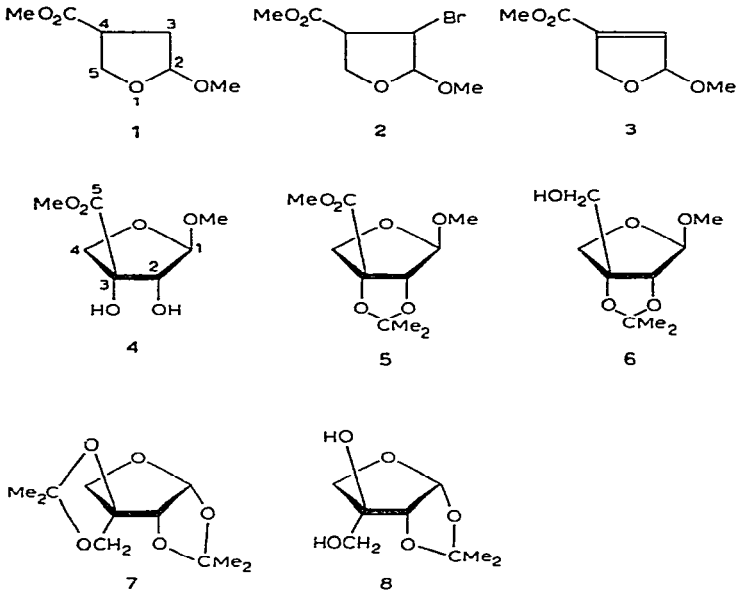
Bromination of **1** by pyridinium hydrobromide perbromide in tetrahydrofuran gave 3-bromo-2-methoxy-4-(methoxycarbonyl)tetrahydrofuran (**2**), which was a mixture of diastereoisomers with respect to each functional group. An analytical sample was separated as the main peak by g.l.c.; the latter indicated three peaks (bromo derivatives) in the ratio 1:4:2. This compound showed a positive Beilstein test and its elemental analysis agreed with structure **2**. The mass spectrum showed M^+ at *m/e* 240 and 238 because of the isotope peaks of the halogen atom. No n.m.r. coupling was observed between H-2 and H-3, indicating that the methoxyl group is *trans*-disposed to the bromine atom.

On treatment of the isomeric mixture **2** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene, 2-methoxy-4-methoxycarbonyl-2,5-dihydrofuran (**3**) was obtained. Compound **3** was stable for a week below 20°, but decomposed immediately above 100° to afford methyl 3-furoate and methanol.

Methyl 3-*C*-methoxycarbonyl-β-DL-erythrofuranoside (**4**) was obtained in 91% yield from **3** on treatment with osmium tetraoxide. Sharp singlets for H-1 and H-2 in the n.m.r. spectrum indicate these protons to be *trans* on the furanoid ring[4].

Methyl 3-*C*-methoxycarbonyl-2,3-*O*-isopropylidene-β-DL-erythrofuranoside (**5**) was obtained quantitatively from **4**. As g.l.c. of **5** under various conditions showed only one peak, anomers seemed not to be present. These results suggest that only the *trans*-form resulted in this reaction, although the hydroxylation of unsaturated ring-compounds with osmium tetraoxide usually gives a *cis-trans* mixture with respect to the methoxyl group[5].

Reduction of **5** with lithium aluminum hydride gave methyl 3-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-DL-erythrofuranoside (**6**) in good yield. Compound **6** was identified by comparing its physical constants with those of a sample prepared by Ball's method[4] from 1,2-*O*-isopropylidene-α-D-apio-L-furanose (**8**) and also directly in 95% yield from 1,2:3,5-di-*O*-isopropylidene-α-D-apio-L-furanose (**7**) under the



same conditions as the foregoing. Compound **7** was prepared from D-apiose that had been obtained from *Posidonia australis* Hook. f[6].

The present synthesis is unique in that the furan ring is maintained throughout the course of the synthesis. The presence of the ring restricts the hydroxylation of **3** with osmium tetraoxide to a *cis*-glycol group, which is formed *trans* to the anomeric methoxyl group. Compound **5** is suitable for production of tritium- or deuterium-labeled DL-apiose by the reaction **5**→**6** employing a tritiated, or a deuterated reducing agent.

EXPERIMENTAL

General. — T.l.c. was performed on Kieselgel G, 0.2-mm layers on glass plates, by using 6:4 benzene–ether as solvent. Detection was effected with sulfuric acid. G.l.c. was performed on a Shimadzu GC-4BM instrument and a Varian Aerograph Model 90-P instrument equipped with a 3 mm × 1 m column and a 4 mm × 2 m column, respectively, of Carbowax 20M (20% on Chromosorb W-AW, DMCS). The column temperature was 150 or 170°, and the flow rate was 50 ml of helium/min. I.r. spectra were taken neat on a JASCO Model IR-E i.r. spectrophotometer and were calibrated against the 1600 cm^{-1} band of polystyrene. N.m.r. spectra were recorded in chloroform-*d* solution at 100 MHz with a Jeolco PS-100 spectrometer and tetramethylsilane (τ 10.00) as an internal reference. Mass spectra were recorded with a Hitachi RMU-6 mass spectrometer.

2-Methoxy-4-(methoxycarbonyl)tetrahydrofuran (**1**). — This compound was readily prepared in 85% yield by the Birch reduction of 3-furoic acid[1]; it was a stable colorless liquid, b.p. 90–92° at 10 mmHg, n_D^{25} 1.4327. The *trans-cis* ratio was 2:1.

3-Bromo-2-methoxy-4-(methoxycarbonyl)tetrahydrofuran (**2**). — To a stirred solution of **1** (2.40 g, 15 mmoles) in anhydrous tetrahydrofuran (25 ml) was added crystalline pyridinium hydrobromide perbromide (4.59 g, 15 mmoles). The reddish solution was stirred at room temperature. After 12 h, a white precipitate appeared and the color disappeared. The precipitate was filtered off and the filtrate was concentrated to a light-brown oil, which was purified by chromatography on a column of silica gel (100 g) with benzene as the eluant. The product was a colorless liquid; yield 2.54 g (71%). An analytical sample was separated as a main peak by g.l.c. The chromatogram indicated three peaks (bromo compounds) in the ratio 1:4:2. The product showed ν_{max} 2830 (OMe)[8] and 1735 cm^{-1} (C=O); n.m.r.: τ 6.76 (3 H, s, OMe), 6.58–6.77 (1 H, m, $J_{4,5}$ 2 Hz, $J_{3,4}$ 4 Hz, H-4), 6.35 (3 H, s, CO_2Me), 5.80 (1 H, s, H-5), 5.72 (1 H, d, H-5), 5.51 (1 H, H-3), 4.96 (1 H, s, H-2); mass spectrum: *m/e* 240, 238 (M^+), 209, 207, 180, 178, 149, 147, 127, 99.

Anal. Calc. for $C_7H_{11}BrO_4$: C, 35.14; H, 4.60. Found: C, 35.02; H, 4.72.

2-Methoxy-4-methoxycarbonyl-2,5-dihydrofuran (**3**). — To a vigorously stirred solution of **2** (1.7 g, 7.1 mmoles) in anhydrous benzene (30 ml) was added DBU (2.0 g, 13.1 mmoles) at room temperature. Immediately there appeared a white precipitate of DBU hydrobromide. Water (20 ml) was added to the reaction mixture and the organic layer was separated, washed with water (10 ml × 2), dried over sodium sulfate, and evaporated, to give the 2,5-dihydrofuran derivative **3** as a colorless liquid (710 mg, 64%); ν_{max} 3075 (C=C–H), 2830 (OMe), 1723 (C=O), 1625 cm^{-1} (C=C); n.m.r.: τ 6.63 (3 H, s, OMe), 6.30 (3 H, s, CO_2Me), 5.20–5.30 (2 H, m, H-5), 4.20 (1 H, m, H-2), 3.48 (1 H, m, H-3).

Methyl 3-C-methoxycarbonyl-β-DL-erythrofuranoside (**4**). — Osmium tetraoxide (500 mg, 2 mmoles) in dry ether (10 ml) was added at room temperature to a stirred solution of the dihydro derivative **3** (316 mg, 2 mmoles) in dry ether (10 ml). The color of the solution changed immediately. To this solution was added one drop of pyridine and the reaction was monitored by t.l.c. After stirring for 6 h at room temperature, a black precipitate gradually appeared on the surface of the flask. No starting material (R_F 0.60) remained, and a slower-moving spot (R_F 0.11) appeared on t.l.c. After replacing the ether solvent with chloroform, the solution of osmate complex was reductively decomposed by passing hydrogen sulfide through it. The black precipitate produced again during the reduction was removed by filtration through Celite and the colorless solution was concentrated under diminished pressure to a syrup; yield 350 mg, (91%); ν_{max} 3540 (OH), 2830 (OMe), 1750 cm^{-1} (C=O); n.m.r.: τ 6.65 (3 H, s, OMe), 6.24 (3 H, s, CO_2Me), 6.10 (1 H, s, H-2), 5.75 (2 H, d, *J* 10 Hz, H-4), 5.22 (1 H, s, H-1).

Methyl 3-C-methoxycarbonyl-2,3-O-isopropylidene-β-DL-erythrofuranoside (**5**). — A mixture of the diol **4** (140 mg, 0.73 mmole) and anhydrous copper(II) sulfate (320 mg) in dry acetone (10 ml) was stirred on a magnetic stirrer for 3 days at room temperature. No starting material (R_F 0.11) remained, and a product appeared as a faster-moving spot (R_F 0.57) by t.l.c. Inorganic material was filtered off and the filtrate was evaporated to a syrup under diminished pressure. The resulting yellowish

syrup was distilled to afford a colorless syrup; yield 159 mg (94%), b.p. 76–79° (bath temp.) at 0.05 mmHg; ν_{max} 2830 (OMe), 1735 cm^{-1} (C=O); n.m.r.: τ 8.52 (3 H, s, C–Me), 8.65 (3 H, s, C–Me), 6.68 (3 H, s, OMe), 6.23 (3 H, s, CO_2Me), 6.01, 5.88 (2 H, AB quartet, J 10 Hz, H-4), 5.27 (1 H, s, H-2), 5.08 (1 H, s, H-1); mass spectrum: *m/e* 217 ($M^+ - CH_3$), 172, 157, 143, 114, 85, 73, 59, 43.

Anal. Calc. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.45; H, 6.98.

*Methyl 3-C-hydroxymethyl-2,3-O-isopropylidene-β-*DL*-erythrofuranoside* (**6**). — The ester **5** (120 mg, 0.52 mmole), on reduction with lithium aluminum hydride (50 mg) in boiling dry ether (10 ml) for 2.5 h, gave the alcohol **6** as a colorless liquid; yield 93 mg (81%); b.p. 78–83° (bath temp.) at 0.02 mmHg; t.l.c.: R_F 0.3; g.l.c.: T 14.2 min; ν_{max} 3450 (OH), 2830 (OMe), 1100 cm^{-1} (COC); n.m.r.: 8.62 (3 H, s, C–Me), 8.55 (3 H, s, C–Me), 7.32 (1 H, s, OH), 6.71 (3 H, s, OMe), 6.30 (2 H, s, H-5), 6.22, 6.08 (2 H, AB quartet, J 10 Hz, H-4), 5.74 (1 H, s, H-2), 5.10 (1 H, s, H-1); mass spectrum: *m/e* 189, 86, 85, 69, 68, 59, 43.

Anal. Calc. for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.58; H, 8.01.

*Preparation of 1,2;3,5-di-*O*-isopropylidene-α-*D*-apio-*L*-furanose* (**7**) *and 1,2-*O*-isopropylidene-α-*D*-apio-*L*-furanose* (**8**). — Extraction of apiose and preparation of **7** and **8** were performed in accordance with Carey's method[7] from air-dried *Posidonia australis* Hook. f. (140 g). Compound **7** was obtained as tan crystals (200 mg, 0.14%), m.p. 79–80°, and **8** gave colorless needles (90%) from **7**; m.p. 123–124°.

Direct preparation of compound **6** *by the acid-catalyzed solvolysis of compound* **7**. — Compound **6** was also obtained directly from **7**, in 95% yield by the conditions described by D. H. Ball *et al.*[4], and also from compound **8** in 92% yield. It had R_F 0.3; g.l.c.: T 14.2 min; ν_{max} 3450 (OH), 2830 (OMe), 1100 cm^{-1} (COC); n.m.r.: τ 8.60 (3 H, s, C–Me), 8.53 (3 H, s, C–Me), 8.10 (1 H, s, OH), 6.69 (3 H, s, OMe), 6.28 (2 H, s, H-5), 6.20, 6.06 (2 H, AB quartet, J 10 Hz, H-4), 5.72 (1 H, s, H-2), 5.08 (1 H, s, H-1); mass spectrum: *m/e* 189, 86, 85, 69, 68, 59, 43.

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