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Note

A new synthesis of 2-deoxy-D-*arabino*-hexose

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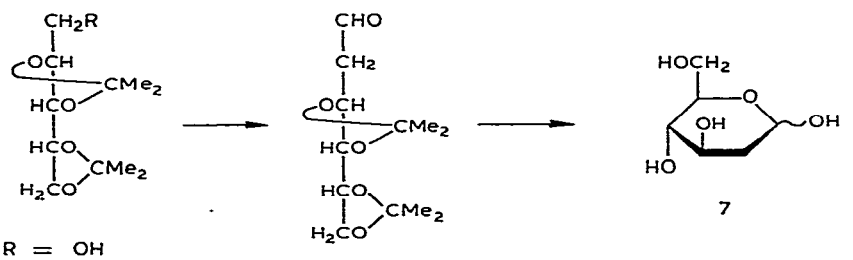
2-Deoxy-D-*arabino*-hexose (**7**) has been widely used as a D-glucose analog in the study of various aspects of carbohydrate transport and metabolism. During the course of developing labeled tracers to serve as probes for the measurement of local D-glucose metabolism in man[1,2], we required a synthesis that could conveniently be adapted for the preparation of **7** labeled at C-1 with an isotopic carbon atom (^{11}C, ^{13}C, or ^{14}C). Although a number of syntheses of **7** have been published[3–5], none appeared suitable for our purpose. We therefore investigated a new route to synthesize 2-deoxy-D-*arabino*-hexose.



1 R = OH
2 R = OSO_2CF_3
3 R = OTs
4 R = I
5 R = CN

6

7

The present synthesis is similar to that used by Bayly and Turner[6] for the preparation of 2-deoxy-D-(1-^{14}C)ribose with some modifications. D-Arabinose was converted into 2,3:4,5-di-*O*-isopropylidene-D-arabinitol (**1**) in an overall yield of 39% by the method of Zinner and Kristen[7]. Treatment of **1** with trifluoromethanesulfonic anhydride and *p*-toluenesulfonyl chloride gave 2,3:4,5-di-*O*-isopropylidene-1-*O*-trifluoromethylsulfonyl-D-arabinitol (**2**) and 2,3:4,5-di-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-D-arabinitol (**3**), respectively. Reaction of either **2** or **3** with sodium iodide gave 1-deoxy-1-iodo-2,3:4,5-di-*O*-isopropylidene-D-arabinitol (**4**). The reaction of **3** with sodium iodide was, however, much slower than that of **2**; it took one week to complete the reaction. Reaction of **2**, **3**, or **4** with sodium cyanide gave

2,3:4,5-di-*O*-isopropylidene-D-arabinononitrile (**5**). Of these three intermediates, **2** was preferred for cyanide displacement reaction as it reacts much faster than **3** or **4**, and the product is easier to purify. The iodide **4**, however, is more stable and easily stored.

The conversion of **5** to **7** was accomplished by two methods: (a) it was converted directly into **7** by reduction–hydrolysis with Raney alloy[8] in hot, aqueous formic acid solution; and (b) an alternative, stepwise sequence, involving reduction of the nitrile **5** with di-isobutylaluminum hydride and partial hydrolysis to give the protected aldehyde **6**. Hydrolysis of **6** in an ethanolic formic acid solution gave **7**.

The use of isotopic cyanide (^{11}CN or ^{13}CN) and an excess of triflate **2** resulted in the production of 2-deoxy-D-(1-^{11}C or ^{13}C)*arabino*-hexose in a yield of 30 to 50% calculated on the basis of isotopic cyanide used[9]. This procedure provides an alternative method for the synthesis of 2-deoxy-D-*arabino*-hexose and is especially suited for the synthesis of the C-1-labeled compounds.

EXPERIMENTAL

General methods. — Melting points were determined with a Fisher–Johns melting point apparatus and are uncorrected. N.m.r. spectra were recorded with a JEOL MH-100 spectrophotometer on solutions in chloroform-*d*, with tetramethylsilane as an internal standard. I.r. spectra were recorded with a Perkin–Elmer Model 337 spectrophotometer. G.l.c. analyses were carried out with a Hewlett–Packard 5830A gas chromatograph equipped with a thermal conductivity-detector. Mass spectra were recorded with a Hitachi–Perkin–Elmer RMU-7 mass spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, New York 11377.

*1-Deoxy-1-iodo-2,3:4,5-di-*O*-isopropylidene-*D*-arabinitol* (**4**). — A solution of trifluoromethanesulfonic anhydride (6.5 mL, 38.6 mmol) in pentane (50 mL) was added dropwise to a solution of 2,3:4,5-di-*O*-isopropylidene-D-arabinitol[7] (**1**) (6.8 g, 29.3 mmol) and pyridine (3.0 mL, 37.1 mmol) in pentane (50 mL) in an ice-bath over a period of 30 min. The mixture was then stirred at room temperature for an additional 90 min. The precipitate was filtered off, washed with pentane, and the combined filtrates were evaporated to give 2,3:4,5-di-*O*-isopropylidene-1-*O*-trifluoromethylsulfonyl-D-arabinitol (**2**) (7.9 g, 74%), which was used in the next step without further purification; ^{1}H-n.m.r.: δ 4.80 (m, 2 H), 4.20 (m, 4 H), 3.80 (m, 1 H), and 1.44 (s, 12 H).

A solution of **2** (7.9 g, 21.7 mmol) and sodium iodide (6.0 g, 40 mmol) in acetone (150 mL) was stirred overnight at room temperature. The solution was then evaporated to dryness and the residue was dissolved in water (30 mL).The solution was decolorized with sodium hydrogensulfite and extracted with ether (4×50 mL). The ethereal solution was dried (sodium sulfate), and evaporated to dryness to give 6.37 g (85.8%) of **4**; g.l.c. (10% SE-30 on Chromosorb 80/100 mesh, 1.8 m × 3 mm column, 160°, 40 mL of He/min): R_T 8.58 min; ^{1}H-n.m.r.: δ 4.20 (m, 4 H); 3.80 (m, 1 H), 3.50 (m, 2 H), 1.48 (s, 3 H), 1.44 (s, 3 H), 1.40 (s, 3 H), and 1.36 (s, 3 H).

Anal. Calc. for $C_{11}H_{19}IO_4$: C, 38.61; H, 5.60. Found: C, 38.97; H, 5.40.

2,3:4,5-Di-O-isopropylidene-D-arabinononitrile (**5**). — A mixture of **2** (7.9 g) and sodium cyanide (2.0 g, 41 mmol) in *N,N*-dimethylformamide (60 mL) was stirred overnight at room temperature (or for 1 h at 60°), and then evaporated *in vacuo* to dryness. The residue was suspended in water (20 mL) and extracted with pentane (3×40 mL). G.l.c. analysis of the pentane solution showed peaks at R_T 4.18, 5.69, and 6.06 min in the area ratio of 15.83:1:17.82. The peaks at 4.18 and 6.06 min correspond to 2,3:4,5-di-*O*-isopropylidene-D-arabinitol and **5**, respectively. Compound **5** was purified by washing the reaction mixture with water and M potassium hydroxide until the peaks at R_T 4.18 and 5.69 (g.l.c.) disappeared. The pentane solution was dried (sodium sulfate), evaporated, and distilled to give 1.47 g (21%) of **5**, b.p.$_{0.4\ mm}$ 122°; t.l.c. (1:10 ether–pentane; silica gel): single spot at R_F 0.72; ν_{max}^{film} 2250 cm^{-1} (C≡N); ^{1}H-n.m.r.: δ 4.12 (m, 4 H), 3.80 (m, 1 H), 2.88 (m, 2 H), 1.50 (s, 3 H), 1.48 (s, 3 H), 1.44 (s, 3 H), and 1.40 (s, 3 H).

Anal. Calc. for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.83; H, 8.11; N, 5.72.

*2-Deoxy-*arabino*-hexose* (**7**). — *From* **6**. To a stirred solution of **5** (95.2 mg, 0.395 mmol) in anhydrous ether (9 mL) was added dropwise 1.25 mL of a 20% solution of diisobutylaluminum hydride in hexane (1.13 mmol, 2.85 equiv.), while under a blanket of argon. The reaction mixture was stirred for 10 min at ambient temperature. A 1:1 (v/v) methanolic solution of 1% sulfuric acid (9 mL) was cautiously added, and the resulting two-phase reaction mixture was stirred for 10 min at ambient temperature. A 3-μl aliquot of the ether phase was analyzed by g.l.c. for 2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-*arabino*-hexose (**6**); the average yield of **6** was 79%, with the flame-ionization detector response standardized with samples of authentic material. The two-phase mixture was diluted with water (20 mL), and the aqueous layer was separated and extracted with ether (4×10 mL). The combined ethereal layers were washed with water (2×10 mL), 5% sodium hydrogencarbonate solution, water (10 mL), and saturated sodium chloride solution (10 mL). The dried (magnesium sulfate) ethereal layer was evaporated *in vacuo* to give 63.7 mg (66%) of **6** as a colorless oil; the g.l.c. analysis indicated less than 6% of impurities; ν_{max}^{film} 1725 (C = 0), 1380, and 1370 cm^{-1} (*gem*-dimethyl); n.m.r.: δ 9.92 (t, 1 H, J 2.5 Hz), 4.38 (m, 1 H, H-4), 4.03 (m, 3 H), 3.57 (m, 1 H, H-3), 2.67 (m, 2 H), 1.40–1.28 (2s, 12 H); m.s. (major ions, 40 eV): *m/e* (rel. abund.) 244 (M^+ – 1), 229 (M^+ – 15, 69), 171 (M^+ – 73, 15), 143 (M^+ – 101, 54), 101 (M^+ – 143, 67), 85 (M^+ – 159, base, 100), 83 (M^+ – 161, 64), 59 (M^+ – 185, 51), 55 (M^+ – 189, 69), and 43 (M^+ – 201, 72).

A solution of 0.116 g (0.477 mmol) of **6** in 1 : 1 (v/v) 31% formic acid–ethanol (6 mL) was heated to 90° for 9 min in a medium-sized test tube. The reaction mixture was cooled to ambient temperature, and the solvents were evaporated *in vacuo* to give 0.078 g (100%) of **7** as a colorless oil; the spectral data indicated a mixture of α and β anomers. This oil was homogeneous in t.l.c. (silica gel; 39:9:1, v/v, chloroform–methanol–water), as detected with the orcinol reagent spray[10]. The oil was crystallized by diluting it with hot acetone (1 mL) and cooling the resulting solution to 5°. After

48 h, the crystals were collected, washed with ice-cold acetone (0.5 mL), and dried *in vacuo* to give a first crop (42 mg, 54%) of **7**, m.p. 140–143 °. The mother liquor yielded a second crop (26 mg, 33%), m.p. 137–141°; lit.[5] m.p. 142–144°.

From **5**. A mixture of **5** (300 mg, 1.243 mmol) and Raney alloy (420 mg) in 35% formic acid (30 mL) was stirred for 1 h at 100–110°. The mixture was then cooled to room temperature and passed through Celite, and the green solution was evaporated *in vacuo* to dryness. The residue was dissolved in water, passed through a column (2×13 cm) of Dowex AG 50-X8 (H^+) ion-excharge resin and eluted with water. The eluate was evaporated to dryness to give 183 mg (89.7%) of a residue that was identified as **7** by t.l.c., n.m.r. spectrometry, g.l.c. (silyl derivative), and formation of the 2,4-dinitrophenylhydrazone derivative[11].

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