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Note

Convenient synthesis of 3-deoxy-D-*ribo*-hexose and 3-deoxy-D-*arabino*-hexose

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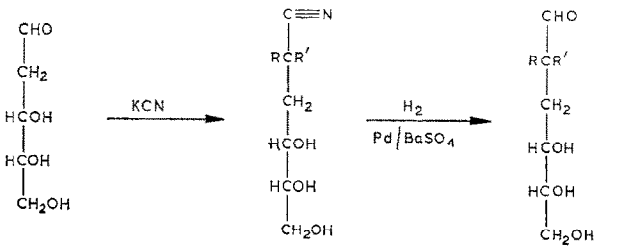
As part of a study of the effects of sugar analogs on glycoprotein biosynthesis[1,2], it was necessary to prepare 3-deoxy-D-*ribo*-hexose (**4**) and 3-deoxy-D-*arabino*-hexose (**5**). Several satisfactory syntheses of these deoxy sugars have been reported[3–7]. For example, 3-deoxy-D-*ribo*-hexose may be obtained by reduction of an appropriate thiocarbonyl derivative of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose by tributylstannane[4–6]. Reduction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside by lithium aluminum hydride leads to 3-deoxy-D-*arabino*-hexose[7]. Wood and Fletcher prepared compounds **4** and **5** by a Kiliani–Fischer synthesis that involved addition of cyanide to 2-deoxy-D-*erythro*-pentose (2-deoxy-D-ribose) followed by successive separation of the calcium salts of the epimeric aldonic acids, lactonization, and reduction by sodium amalgam[8].

Improvements have been made by several investigators in the original Kiliani–Fischer procedure. Kuhn and co-workers were able to isolate the initial cyanohydrin intermediates by treating an aldose with anhydrous hydrogen cyanide in nonaqueous solvents. The cyanohydrins were catalytically reduced directly to the chain-extended products in aqueous solution at low pH[9–11]. Although this procedure was employed primarily for the synthesis of amino sugars[9], several neutral sugars also were prepared in this manner[10,11]. Recently, Barker and co-workers have further simplified the method for chain-extending an aldose by one carbon atom[12,13]. In their procedure, a pair of epimeric cyanohydrins is formed from the parent sugar by the addition of



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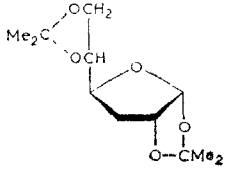
2 R = H, R' = OH
3 R = OH, R' = H

4 R = H, R' = OH
5 R = OH, R' = H

cyanide in aqueous solution and converted without isolation into the chain-extended aldose by catalytic hydrogenation. In this report we describe the use of this modified reaction to produce 3-deoxy-D-*ribo*-hexose (**4**) and 3-deoxy-D-*arabino*-hexose (**5**) directly from 2-deoxy-D-*erythro*-pentose (**1**) in 38 and 41 % isolated yields, respectively.

The addition of 2-deoxy-D-*erythro*-pentose (**1**) to an aqueous solution of potassium cyanide (≥ 3 molar equivalents) at pH 7.8 resulted in rapid formation of the epimeric aldononitriles **2** and **3**. As the reaction proceeded, the pH was maintained at 7.8 (± 0.1) by the addition of 20 % acetic acid. No pH change was observed after 15 min, and analysis of a per(trimethylsilylated) aliquot of the mixture confirmed >95 % conversion of the 2-deoxypentose into aldononitriles. The pH of the mixture was lowered to 4.2 by 50 % aqueous acetic acid and the excess of hydrogen cyanide was purged by vigorous aeration with nitrogen. The resulting solution was hydrogenated directly over palladium on barium sulfate at one atmosphere to yield a mixture of 3-deoxy-D-*ribo*-hexose and 3-deoxy-D-*arabino*-hexose contaminated with 1-amino-1-deoxyalditols. After treatment of the mixture with Dowex 50W X8 (H^+ form) resin to remove the amines, the epimeric sugars **4** and **5** were separated by passage through a column of Dowex 50W X8 (Ba^{+2} form) resin[14].

The purified 3-deoxy-D-*ribo*-hexose (**4**) was obtained as a thick syrup having $[\alpha]_D^{22}$ +29.4° (*c* 2.6, water), in agreement with literature values[3,15]. Compound **4** was also prepared by a two-step graded hydrolysis[3] of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexopyranose[6] (**6**). The independently prepared samples of **4** gave essentially identical ^{13}C-n.m.r. spectra. The purified 3-deoxy-D-*arabino*-hexose (**5**) crystallized from methanol as a product having physical constants in good



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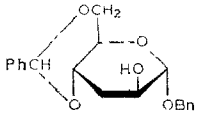

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agreement with literature values[7]. This compound was identical to an independently synthesized sample of **5** prepared by hydrogenolysis of benzyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside[16] (**7**), as judged by ^{13}C-n.m.r. spectral data and by mixed m.p. In contrast to the analogous reaction in which D-glucose and D-mannose are obtained in 3:7 ratio[12], the D-*ribo* and D-*arabino* products **4** and **5** are produced in ~1:1 ratio. Apparently, under the conditions of the modified cyanohydrin synthesis, there is no significant asymmetric induction[17] when C-2 is achiral.

In addition to providing a simple and convenient synthesis of the deoxy sugars, this reaction may be used to prepared products isotopically enriched at C-1. Fig. 1 shows the ^{13}C-n.m.r. spectra of compounds **4** and **5** enriched with carbon-13 at C-1. Peak assignments for the C-1 atoms of the pyranose anomers (Table I) were based on the studies of Bock and Pedersen, who observed that $J_{C\text{-}1,H\text{-}1}$ is ~10 Hz larger

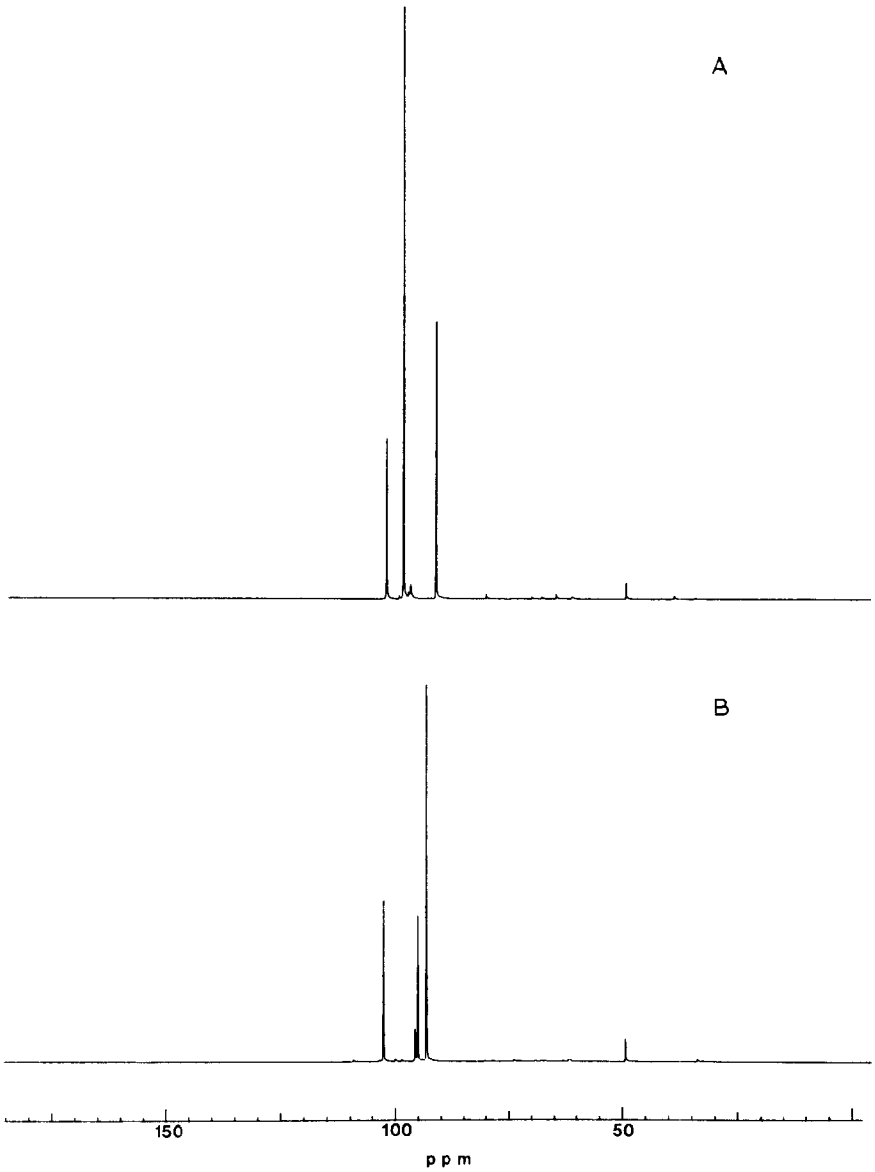

Fig. 1. ^{13}C-N.m.r. spectra of [1-^{13}C]-enriched (*a*) 3-deoxy-D-*ribo*-hexose (**4**) and (*b*) 3-deoxy-D-*arabino*-hexose (**5**).

for pyranoses having the hydroxyl group axial[18]. Peak assignments for the C-1 atoms of the furanose anomers (Table I) assume that C-1 of the *trans*-1,2-diol resonates at lower field than that of the corresponding *cis*-1,2-diol[10,19]. It is evident that, in contrast to D-glucose and D-mannose, aqueous solutions of the 3-deoxy sugars **4** and **5** contain a significant amount of the furanose forms. The relative

TABLE I

^{13}C-N.M.R. PARAMETERS FOR C-1 OF [1-^{13}C]-ENRICHED COMPOUNDS **4** AND **5**

Peak assignment	*Compound* **4**		*Compound* **5**	
	δ (p.p.m.)	$J_{C-1,H-1}$ *(Hz)*	*δ (p.p.m.)*	$J_{C-1,H-1}$ *(Hz)*
α-Pyranose	91.0	168	92.8	168
β-Pyranose	98.1	161	94.8	161
α-Furanose	96.6	174	102.2	172
β-Furanose	101.9	174	95.4	172

proportions of α- and β-furanose and pyranose forms of 3-deoxy-D-*ribo*-hexose are in qualitative agreement with reported values[20].

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover capillary apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. ^{13}C-N.m.r. measurements were made in D_2O with a JEOL FX90Q or Bruker WM-3000 spectrometer. Chemical shifts are expressed in p.p.m. downfield from tetramethylsilane with methanol as the internal standard (δ = 49.0). G.l.c. analyses were performed on a column (1.8 m × 2 mm) of OV-17 (3%) on High Performance Chromosorb W-AW (Applied Sciences) with a temperature program of 100–230° at 6°/min. Palladium on barium sulfate (5%) was obtained from Sigma Chemical Co.

Synthesis of 3-deoxy-D-ribo-*hexose* (**4**) *and 3-deoxy*-D-arabino-*hexose* (**5**) *from 2-deoxy*-D-erythro-*pentose* (**1**). — An aqueous solution (3 mL) of potassium cyanide (52 mg, 8 mmol) was placed in a test-tube stoppered with a no-air septum containing an exact opening for a pH electrode. The pH was adjusted to 7.8 by the addition of 50% aqueous acetic acid and a solution of 2-deoxy-D-*erythro*-pentose (268 mg, 2 mmol) was added in a single portion by syringe. The pH of the mixture was maintained at 7.8 until no further change was observed (10–15 min), and then the pH was lowered to 4.2 by addition of 50% acetic acid. If desired, g.l.c. analysis of a trimethylsilylated aliquot of the mixture could be performed at this point. The excess of hydrogen cyanide was purged from the solution by vigorous aeration with nitrogen introduced via a gas-dispersion tube. Ethanolic potassium hydroxide was used to trap the hydrogen cyanide.

The degassed solution of aldononitriles was readjusted to pH 4.2 if necessary and hydrogenated at 1 atm and room temperature over 5% palladium on barium sulfate (180 mg) that had been pre-reduced in 10 mL of water. Hydrogenation was generally complete in 3–4 h. After removal of the catalyst and concentration of the

solution under diminished pressure, the solution was diluted with 30 mL of water and treated with 20 mL of Dowex 50W (H^+ form) resin to remove 1-deoxyalditol-1-amines resulting from over-reduction (generally 15–20% of the product). The ion-exchange resin was removed by filtration and the filtrate concentrated under diminished pressure.

The aldoses **4** and **5** were purified by passage through a column (3.4 × 100 cm) of Dowex 50W X8 (200–400 mesh, Ba^{+2} form) resin[14]. Fractions (6 mL) were collected at a flow rate of 0.4 mL/min. Hexose-containing fractions were detected with phenol–sulfuric acid reagent[21]. Fractions 81–88 and 95–105, which contained 3-deoxy-D-*ribo*-hexose and 3-deoxy-D-*arabino*-hexose, respectively, were pooled and evaporated (bath ≤40°).

After drying *in vacuo* over phosphorus pentaoxide, 3-deoxy-D-*ribo*-hexose was obtained as a thick syrup (126 mg, 38%); $[\alpha]_D^{22}$ +29.4° (*c* 1, water, equil.) {lit. $[\alpha]_D^{22}$ +29.0° (*c* 1, water) for the α anomer[3] and $[\alpha]_D^{22}$ +30.4° (*c* 3.55, water) for the β anomer[22]}.

3-Deoxy-D-*arabino*-hexose crystallized from a small amount of methanol to give small prisms (133 mg, 41%); m.p. 141–142° (lit.[7] m.p. 141–142°), $[\alpha]_D^{19}$ +46.3° (*c* 2.4, water, equil.) {lit.[7] $[\alpha]_D$ +53.1° (*c* 2.8, water, 10 min)}.

Hydrogenolysis of benzyl 4,6-O-benzylidene-3-deoxy-α-D-arabino-hexopyranoside (**7**). — Benzyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside[14] (300 mg, 0.87 mmol) in 35 mL of abs. ethanol was reduced at one atm in the presence of 10% palladium on carbon (250 mg) at room temperature. When the uptake of hydrogen ceased, the mixture was filtered and the filtrate evaporated under diminished pressure to a syrup that crystallized from methanol (130 mg, 90%, m.p. 136–138°). Recrystallization from methanol gave **5**; m.p. 140.5–141.5°, $[\alpha]_D^{22}$ +53.0° (*c* 2.2, water).

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