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SYNTHESIS OF 3-DEOXY-3-FLUORO-D-MANNOSE AND 4-DEOXY-4-FLUORO-D-MANNOSE

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ABSTRACT

Addition of potassium cyanide to 2-deoxy-2-fluoro-D-arabinose (**1**) at pH 7.8 followed by catalytic hydrogenation over palladium–barium sulfate (5%) produced 3-deoxy-3-fluoro-D-glucose (**4**) and 3-deoxy-3-fluoro-D-mannose (**5**) in 25 and 40% isolated yields, respectively. The epimeric sugars were purified by passage through a column of Dowex-50W × 8 (Ca^{2+}). In a similar manner, 3-deoxy-3-fluoro-D-arabinose (**6**) was converted into 4-deoxy-4-fluoro-D-glucose (**9**) and 4-deoxy-4-fluoro-D-mannose (**10**) in 27 and 45% isolated yields, respectively. Deoxyfluorohexoses **4, 5, 9** and **10** enriched with carbon-13 and carbon-14 at C-1 have been prepared by this procedure.

INTRODUCTION

Compounds that modify or inhibit protein glycosylation are valuable tools for examining the biosynthesis and function of the oligosaccharide chains of glycoproteins[1,2]. The D-mannose analogs 2-deoxy-D-*arabino*-hexose (2-deoxyglucose) and 2-deoxy-2-fluoro-D-mannose have been particularly useful for studies of the *N*-asparagine-linked oligosaccharide units of complex and high-mannose type glycoproteins. These C-2 modified mannose derivatives disrupt the normal assembly of the dolichol oligosaccharide diphosphate that is the precursor of asparagine-linked carbohydrates[2,3]. When cultured mammalian cells are incubated in medium containing either analog, underglycosylated proteins are synthesized. These compounds have also been shown to inhibit virus multiplication in virus-infected cells[4].

Little information is available about the biological activity of mannose derivatives modified at C-3 or C-4. Kučár and coworkers have synthesized analogs of guanosine 5′-(α-D-mannosyl diphosphate) in which the 3-hydroxyl or the 4-hydroxyl group of the mannosyl group is replaced by hydrogen[5]. The 3-deoxygenated mannose derivative was utilized as a sugar donor by a mannosyltransferase from *Salmonella anatum*[6]. We have been interested in preparing C-3 and C-4 substituted mannose analogs in order to examine their effects on glycoprotein biosynthesis. It is possible that such compounds might affect the biosynthesis of glycoproteins by unique mechanisms. For example, a 3-substituted analog might lead to

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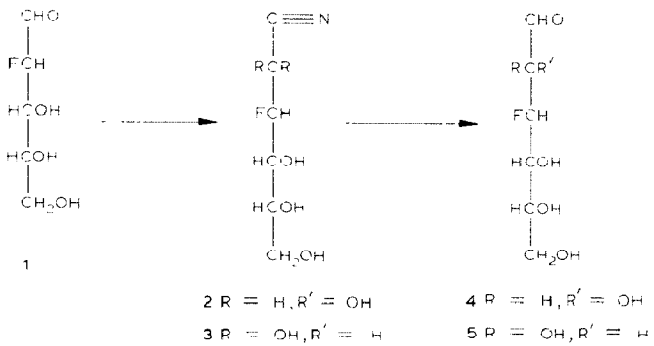
lipid-linked oligosaccharides lacking (1→3)-linked branches or to high-mannose glycoproteins that resist normal processing to complex glycoproteins.

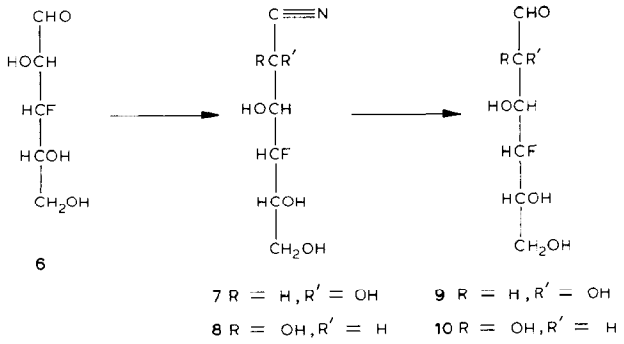
Practical syntheses of 3-deoxy-D-*arabino*-hexose (3-deoxy-D-mannose) and 4-deoxy-D-*lyxo*-hexose (4-deoxy-D-mannose) have been described[7,8]. The former was prepared by a one-carbon chain extension of 2-deoxy-D-*erythro*-pentose, using a cyanohydrin synthesis developed by Barker and coworkers[9]. In this report the syntheses of 3-deoxy-3-fluoro-D-mannose and 4-deoxy-4-fluoro-D-mannose by a similar chain-extension of 2-deoxy-2-fluoro-D-arabinose and 3-deoxy-3-fluoro-D-arabinose, respectively, are described.

RESULTS AND DISCUSSION

The decision to synthesize 3-deoxy-3-fluoro-D-mannose (**5**) and 4-deoxy-4-fluoro-D-mannose (**10**) by a one-carbon chain extension of the appropriate fluoroarabinose compounds was based on several considerations. First, literature precedent suggested that displacement reactions at C-3 of a protected altrose compound [10] or at C-4 of a protected talose compound[11] might be difficult. Second, satisfactory methods were available for the syntheses of the pentose intermediates 2-deoxy-2-fluoro-D-arabinose[12,13] and 3-deoxy-3-fluoro-D-arabinose[14]. Third, the groups of Kuhn and Barker had developed procedures for chain-extending aldoses that are a marked improvement over the classical Kiliani–Fischer method[9,15]. Finally, this route would allow facile incorporation of carbon-14 or tritium into a fluorohexose late in the reaction sequence[16]. This last feature was particularly important because radiolabeled analogs are required for many of the biochemical studies envisaged.

The syntheses of 2-deoxy-2-fluoro-D-arabinose (**1**) and 3-deoxy-3-fluoro-D-arabinose (**6**) followed literature procedures[12,14], with minor modifications. The conversion of **1** or **6** into the deoxyfluorohexoses **4** and **5**, or **9** and **10**, respectively, was accomplished by cyanohydrin formation and reduction essentially as described previously for 2-deoxy-D-*erythro*-pentose[8]. Briefly, addition of an excess of cyanide to either deoxyfluoropentose **1** or **6** at pH 7.8 resulted in nearly quantitative conversion of the aldose into an epimeric pair of cyanohydrins (**2** and **3** or **7** and **8**). After acidification to pH 4.2, and degassing to remove hydrogen cyanide, the mix-





ture of cyanohydrins was reduced over 5% palladium–barium sulfate to yield a pair of epimeric deoxyfluorohexoses (**4** and **5**, or **9** and **10**) contaminated with 1-amino-1-deoxyalditols. Treatment with Dowex-50W × 8 (H^+ form) removed the amines, and the hexoses were then separated by passage through a column of Dowex-50W × 8 (Ca^{2+} form). As with a mixture of D-glucose and D-mannose, the glucose analog **4** or **9** was eluted from the Dowex-50W (Ca^{2+}) column prior to its mannose epimer **5** or **10**. In this manner 2-deoxy-2-fluoro-D-arabinose (**1**) was converted into 3-deoxy-3-fluoro-D-glucose (**4**) and 3-deoxy-3-fluoro-D-mannose (**5**) in 25 and 40% isolated yields, respectively, and 3-deoxy-3-fluoro-D-arabinose (**6**) into 4-deoxy-4-fluoro-D-glucose (**9**) and 4-deoxy-4-fluoro-D-mannose (**10**) in 27 and 45% isolated yields, respectively. The ^{13}C-n.m.r. resonance observed for C-1 of the α and β anomer of each analog was similar to that obtained for D-glucose or D-mannose with respect to chemical shift and anomeric distribution (Table I and Fig. 1). This observation, together with the physical characterizations given next, confirm the assignments of *gluco* and *manno* epimers.

TABLE I

CARBON-13 CHEMICAL SHIFTS[a] AND ^{19}F–^{13}C COUPLING CONSTANTS[b] OF FLUOROHEXOSES[c]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
3-Deoxy-3-fluoro-D-mannose						
α anomer	94.2 (7 Hz)	68.9 (15 Hz)	92 3 (183 Hz)	65 4 (18 Hz)	72.0 (6 Hz)	60.7
β anomer	93.0 (11 Hz)	69 5 (17 Hz)	93.7 (183 Hz)	65.1 (19 Hz)	74.8 (7 Hz)	60.7
4-Deoxy-4-fluoro-D-mannose						
α anomer	94.0	71.4 (9 Hz)	68.7 (18 Hz)	88.5 (176 Hz)	69.9 (24 Hz)	60.5
β anomer	93.8	71.7 (11 Hz)	71.3 (18 Hz)	88.3 (176 Hz)	73.5 (24 Hz)	60.4

[a]In p.p.m. downfield from Me_4Si with methanol as internal standard. δ_{Me_4Si} for methanol, 49.0. [b]In parentheses under chemical-shift values. [c]Assignments were based on the magnitude of the ^{19}F–^{13}C coupling constants and position of D-mannose resonances.

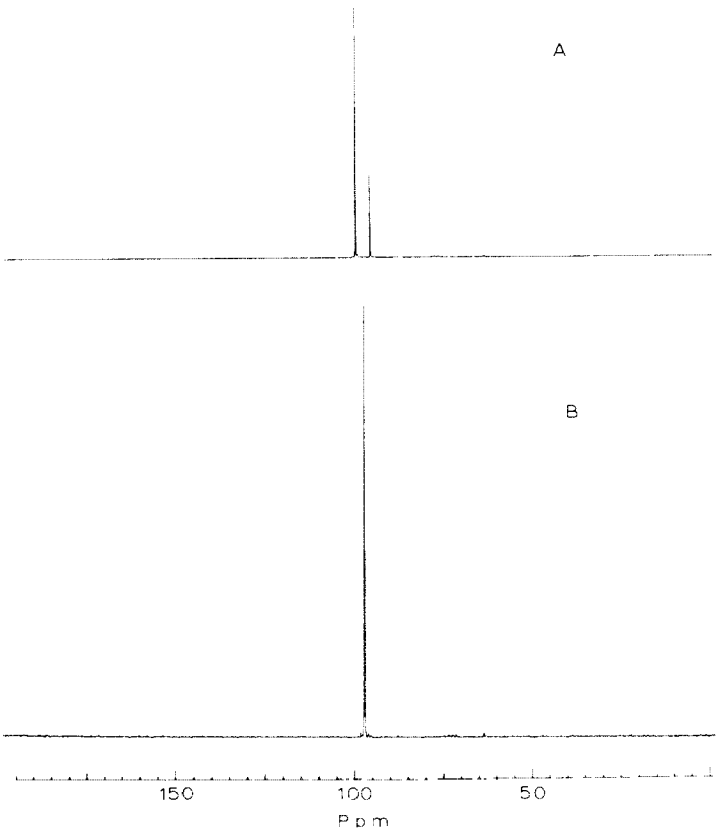


Fig. 1. The proton-decoupled, ^{13}C-n.m.r. spectra of purified (A) 4-deoxy-4-fluoro-D-[1-^{13}C]glucose (**9**) and (B) 4-deoxy-4-fluoro-D-[1-^{13}C]mannose (**10**).

Purified 3-deoxy-3-fluoro-D-glucose (**4**) was obtained as a thick, colorless syrup having $[\alpha]_D$ +69° (*c* 1.5, water), in agreement with the literature value[17]. Compound **5** crystallized from ethanol and was characterized by optical rotation measurements, elemental analysis, and ^{13}C-n.m.r. (Table I). Although the ^1H-n.m.r. spectrum of **5** at 300 MHz was complex, the resonances for the anomeric protons could be observed at δ 5.3 (α anomer) and 5.0 (β anomer). The magnitude of $J_{1,2}$ was small (<2 Hz) in each case. By observing the change in the relative intensities of these two resonances over a 60-min period immediately following the preparation of the n.m.r. sample, it was established that the crystalline 3-deoxy-3-fluoro-D-mannose was enriched in the α-pyranose form relative to the proportion observed in aqueous solution. We cannot rule out the possibility that a small amount of the β anomer co-crystallizes.

The 4-deoxy-4-fluoro-D-hexoses separated cleanly on the Dowex-50W (Ca^{2+}) column. Evaporation of the 4-deoxy-4-fluoro-D-glucose fractions yielded **9** as a crystalline solid, which, after recrystallization from ethanol, had m.p. 189–190° and $[\alpha]_D^{20}$ +46° (*c* 2.1, water), in agreement with literature values[18,19]. The pooled

fractions containing 4-deoxy-4-fluoro-D-mannose were concentrated to a thick syrup that failed to crystallize. Compound **10** was characterized by optical rotation measurement, ^{13}C-n.m.r. (Fig. 1 and Table I), and enzymic studies. The ^{13}C-n.m.r. spectrum of purified 4-deoxy-4-fluoro-D-[1-^{13}C]mannose prepared from 90% ^{13}C-enriched potassium cyanide (Fig. 1B) illustrates the purity of the product. The only unenriched compound that could reasonably be present in the sample applied to the column is 3-deoxy-3-fluoro-D-arabinose. This compound is eluted from the column prior to **9** and is not observed in the ^{13}C-n.m.r. spectra of nonenriched **10**. In spite of the apparent purity of **10**, elemental analysis was interpretable only if the syrupy compound contained residual water; prolonged drying *in vacuo* over phosphorous pentaoxide apparently does not remove the last traces of water.

The ^{13}C–^{19}F coupling constants observed in the ^{13}C-n.m.r. spectra of compounds **5** and **10** (Table I) support their proposed structures. A carbon atom bonded to fluorine generally exhibits a coupling constant of 150–400 Hz, whereas one coupled to fluorine through two bonds has a coupling constant of[20] 15–40 Hz. The value of J (^{13}C–^{19}F) for a carbon atom vicinal to fluorine shows a Karplus-type relationship[21], with a *trans* arrangement (180° dihedral angle) having J = 6–10 Hz and a gauche orientation (60° dihedral angle) having[22] J = 0–3 Hz. More-distant couplings are rarely observed.

The C-1 and C-6 resonances of compounds **5** and **10** could be assigned unambiguously. The C-1 signals were identified in the ^{13}C-n.m.r. spectra of the [1-^{13}C]-enriched products and the C-6 signals from their characteristic chemical shifts at the highest-field position. The ^{13}C–^{19}F coupling constants for C-1 of the α and β anomers of **5** (7 and 11 Hz) indicate a three-bond coupling to an equatorial fluorine. The presence of a second three-bond coupling implies that another carbon atom (C-5) is oriented *trans* to the equatorial fluorine. As expected, a singlet was observed for C-6.

In the ^{13}C-n.m.r. spectrum of **10**, there is only one, measurable three-bond ^{13}C–^{19}F coupling. The magnitude of the coupling in each anomer (9 and 11 Hz) again suggests an equatorial fluorine atom. The lack of ^{19}F coupling to C-1 or C-6 places the fluorine at C-4. C-1 is too distant from the fluorine, and the dihedral angle between C-6 and the fluorine (~60°) would be expected to give rise to little or no coupling.

The standard conditions for cyanohydrin formation[8,9] were modified for the synthesis of deoxyfluoro[1-^{14}C]hexoses. As excess of pentose **1** or **6** (3 molar equivalents) was employed to improve cyanide incorporation, and the reaction pH was controlled by use of a buffer rather than by periodic addition of acetic acid. Hepes [4-(2-hydroxyethyl)-1-piperazinylethanesulfonic acid] buffer gave satisfactory results, but it is possible that other buffers would be superior. This point was not investigated in detail. In a typical experiment, reaction of [^{14}C]KCN (0.9 mCi, specific activity 51.1 mCi/mmol) and 3-deoxy-3-fluoro-D-arabinose (50 μmol) in 0.2M Hepes buffer (pH 7.7) for 20 min followed by acidification, degassing and reduction over 5% palladium–barium sulfate gave 72% incorporation of [^{14}C]cyanide

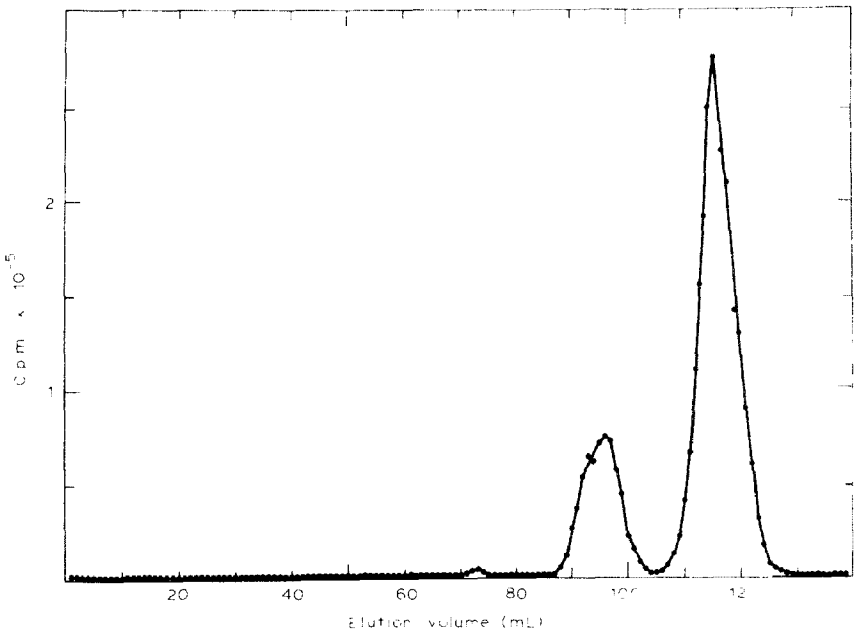


Fig. 2. The elution profile of 4-deoxy-4-fluoro-D-[1-^{14}C]glucose (**9**) and 4-deoxy-4-fluoro-D-[1-^{14}C]mannose (**10**) from a column of Dowex-50W × 8 (Ca^{2+}). Aliquots of 3 μL were counted. See text for experimental details.

into non-volatile products. Treatment of the reduction mixture with Dowex-50W (H^+ form) removed 26% of the isotopically labeled product (presumably 1-amino-1-deoxyalditols). The epimeric deoxyfluorohexoses were then separated on a column of Dowex-50W × 8 (Ca^{2+}). Fig. 2 shows the elution profile of 4-deoxy-4-fluoro-D-[1-^{14}C]glucose and 4-deoxy-4-fluoro-D-[1-^{14}C]mannose from the column. The isolated yields of radiolabeled **9** and **10** based on cyanide were 11 and 35%, respectively. Carbon-14-enriched 3-deoxy-3-fluoro-D-glucose and 3-deoxy-3-fluoro-D-mannose were prepared similarly. The radiochemical purity of each [1-^{14}C]deoxyfluorohexose was analyzed by paper chromatography (8:2:1 ethyl acetate–pyridine–water, v/v/v).

The activation of radiolabeled **10** to guanosine 5′-(4-deoxy-4-fluoro-D-[^{14}C]mannosyl diphosphate) *in vivo* by yeast cells has been observed. Details of this work and of studies of the effects of 3-deoxy-3-fluoro-D-mannose and 4-deoxy-4-fluoro-D-mannose on glycoprotein biosynthesis will be presented elsewhere.

The experimental simplicity and reliability of the reaction conditions reported by Barker and coworkers for the one-carbon chain-extension of aldoses[9] makes it practical to use this method both for preparative-scale and radiolabeled syntheses. For microscale reactions, we have modified the original protocol by controlling the reaction pH with a buffer. A disadvantage of the method is that a pair of epimers is produced, thus necessitating chromatographic separation and lowering the overall yield. In certain cases, it is possible to interconvert epimers by en-

zymic or chemical means[23]. We have applied this chain-extension reaction to the synthesis of deoxy and deoxyfluoro sugars, and it could no doubt be extended to additional classes of sugars not readily synthesized by other means.

EXPERIMENTAL

Materials and general methods. — Melting points were determined with a Thomas–Hoover capillary melting-point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. N.m.r. measurements were made in D_2O with a Bruker WM300 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc. Descending paper-chromatography was performed on Whatman 3M paper with 8:2:1 ethyl acetate–pyridine–water (v/v/v) as solvent. The R_F value for D-[1-^{14}C]mannose with this system was 0.21.

Palladium–barium sulfate (5%) was purchased from Sigma Chemical Co. and [^{14}C]potassium cyanide (specific activity 51.1 mCi/mmol) was obtained from New England Nuclear. The preparation of 2-deoxy-2-fluoro-D-arabinose[12] from methyl 2,3-anhydro-α-D-ribofuranoside[24] and of 3-deoxy-3-fluoro-D-arabinose[14] from methyl 2,3-anhydro-α-D-lyxofuranoside[24,25] followed literature procedures with minor modifications.

3-Deoxy-3-fluoro-D-glucose (**4**) *and 3-deoxy-3-fluoro-D-mannose* (**5**). — Treatment of 2-deoxy-2-fluoro-D-arabinose (**1**, 2 mmol) with potassium cyanide (6 mmol) followed by reduction over palladium-barium sulfate (150 mg) according to procedures described previously[8] produced an epimeric mixture of **4** and **5** contaminated with 1-amino-1-deoxyalditols. The amines were removed with Dowex-50W × 8 (H^+ form) and the deoxyfluorohexoses separated by passage through a column (3.4 × 100 cm) of Dowex-50W × 8 (200–400 mesh, Ca^{2+} form)[26]. The column was eluted with water at a flow rate of 0.4 mL/min. Six-mL fractions were collected. Hexose-containing fractions were detected with phenol–sulfuric acid reagent[27]. Fractions 88-93 contained pure 3-deoxy-3-fluoro-D-glucose (91 mg, 25%) and fractions 97–104 pure 3-deoxy-3-fluoro-D-mannose (145 mg, 40%). Fractions 94–96 contained a mixture of **4** and **5** (35 mg).

After concentration and drying *in vacuo*, 3-deoxy-3-fluoro-D-glucose was obtained as a thick, nearly colorless syrup having $[\alpha]_D^{20}$+69° (*c* 1.5, water); R_F 0.54; [lit.[17] $[\alpha]_D^{22}$ +64° (*c* 1.0, water)]. The fractions containing pure **5** were pooled and concentrated to a syrup. The syrup was dissolved in ethanol and concentrated to remove residual water. After several days, the product crystallized. Recrystallization from a small amount of ethanol yielded fine, colorless needles of 3-deoxy-3-fluoro-D-mannose, m.p. 172–173°, $[\alpha]_D^{20}$ +27.5 → +23.5° (4 → 20 min, *c* 2.0, water); R_F 0.57; ^{13}C-n.m.r.-spectral data are listed in Table I.

Anal. Calc. for $C_6H_{11}FO_5$: C, 39.53; H, 6.09; F, 10.43. Found: C, 39.34; H, 6.02; F, 10.42.

4-Deoxy-4-fluoro-D-glucose (**9**) *and 4-deoxy-4-fluoro-D-mannose* (**10**). — In a

manner analogous to the chain extension of **1**, 3-deoxy-3-fluoro-D-arabinose (**6**, 2 mmol) was converted into a mixture of the epimeric deoxyfluorohexoses **9** and **10**. The fluoro sugars were separated on a column (3.4 × 100 cm) of Dowex-50W × 8 (200–400 mesh, Ca^{2+} form). The column was eluted with water at a flow rate of 0.3 mL/min, and 6-mL fractions were collected. Pooled fractions 79–89 were evaporated *in vacuo* to give crystalline 4-deoxy-4-fluoro-D-glucose (100 mg, 27%), which, after recrystallization from ethanol, had m.p. 189–190°, $[\alpha]_D^{20}$ +46° (equil. *c* 2.1, water); R_f 0.46; lit.[18] m.p. 189–190°, $[\alpha]_D^{23}$ +50° (equil. *c* 1.0, water). Fractions 97–106 were evaporated *in vacuo* to give **10** as a thick, colorless syrup (164 mg, 45%), $[\alpha]_D^{20}$ +3.7° (*c* 3.5, water); R_f 0.56; ^{13}C-n.m.r. spectral data are tabulated in Table I (also see Fig. 1).

4-Deoxy-4-fluoro-D-[*1*-^{14}C]*glucose and 4-deoxy-4-fluoro*-D-[*1*-^{14}C]*mannose.* — Compound **1** (7.5 mg) in 0.1 mL of water was added to a stirred and stoppered solution of [^{14}C]potassium cyanide (0.9 mCi, 51.1 mCi/mmol) in 0.5 mL of 0.24M Hepes buffer (pH 7.7). After 20 min, 0.3 mL of 50% acetic acid was added and the solution was degassed for 4 h with a stream of nitrogen introduced below the surface of the stirred solution. Methanolic potassium hydroxide was used to trap the purged hydrogen cyanide. The degassed solution was reduced over 5% palladium–barium sulfate (100 mg in 4 mL of water) for 4 h at a pressure of one atmosphere. After filtration to remove the catalyst, the solution contained ~0.65 mCi of C-14 (72% incorporation). Dowex-50W × 8 (H^+ form, 8 mL) was added to remove 1-amino-1-deoxyalditols produced by over-reduction. After filtration to remove the resin, the filtrate contained 0.48 mCi of ^{14}C-enriched deoxyfluorohexoses **9** and **10** (54% yield based on cyanide). This solution was concentrated to 0.4 mL and applied to a column (1.5 × 75 cm) of Dowex-50W × 8 (Ca^{2+} form). The column was eluted with water at a flow rate of 0.08 mL/min. Fractions (1 mL) were collected. Fig. 2 shows the elution profile of the labeled sugars. The yield of 4-deoxy-4-fluoro-D-[1-^{14}C]glucose and 4-deoxy-4-fluoro-D-[1-^{14}C]mannose based on cyanide was 0.10 mCi (11%) and 0.32 mCi (35%), respectively. The recovery of carbon-14 material applied to the Ca^{2+} column was 86%. Each sugar gave a single peak when analyzed by descending paper-chromatography.

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