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REACTION OF 1,2-ANHYDRO-3,4:5,6-DI-*O*-ISOPROPYLIDENE-1-*C*-NITRO-D-MANNITOL WITH POTASSIUM HYDROGENFLUORIDE IN ETHYLENE GLYCOL: A SYNTHESIS OF 2-DEOXY-2-FLUORO-D-GLUCOSE*

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ABSTRACT

The reaction of 1,2-anhydro-3,4:5,6-di-*O*-isopropylidene-1-*C*-nitro-D-mannitol (**2**) with potassium hydrogenfluoride in ethylene glycol under anhydrous conditions provides a route to 2-deoxy-2-fluoro-D-glucose, the ^{18}F-labeled analog of which is an important radiopharmaceutical of use in medical imaging. The reaction is accompanied to a minor extent by epimerization at C-2 of the initially formed fluoro aldehyde and also results in an attack by solvent at C-2 in **2**.

INTRODUCTION

The recognition that hydrogen may be replaced by fluorine in natural compounds with a dramatic, concomitant change in their biological properties has given great impetus to the investigation of synthetic methods for the preparation of fluorinated carbohydrates[2–4]. In recent years, the synthesis of 2-deoxy-2-fluoro-D-glucose (**8**) and of its ^{18}F-labeled analog have attracted considerable attention because of the latter's central importance in the development of positron emission tomography (PET)[5–7] in which it has been exploited for the measurement of myocardial[8] and regional cerebral[9] glucose metabolism. Several syntheses of **8** have been published[10–23]. The present article describes the reaction of 1,2-anhydro-3,4:5,6-di-*O*-isopropylidene-1-*C*-nitro-D-mannitol (**2**) with potassium hydrogenfluoride in ethylene glycol under scrupulously anhydrous conditions. The major course of the reaction involves attack by fluoride ion at C-2 in **2** to give preponderantly 2-deoxy-2-fluoro-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose (**3**). The reaction is also accompanied to a small extent by epimerization at C-2 of the initially formed **3**; a minor product (**4**) results from attack by solvent at C-2 in **2**. The method provides a route to 2-deoxy-2-fluoro-D-glucose (**8**) and, indeed, has been adapted[24] for the preparation of the ^{18}F-labeled analog; however, the present

*For a preliminary report of part of this work, see ref. 1.

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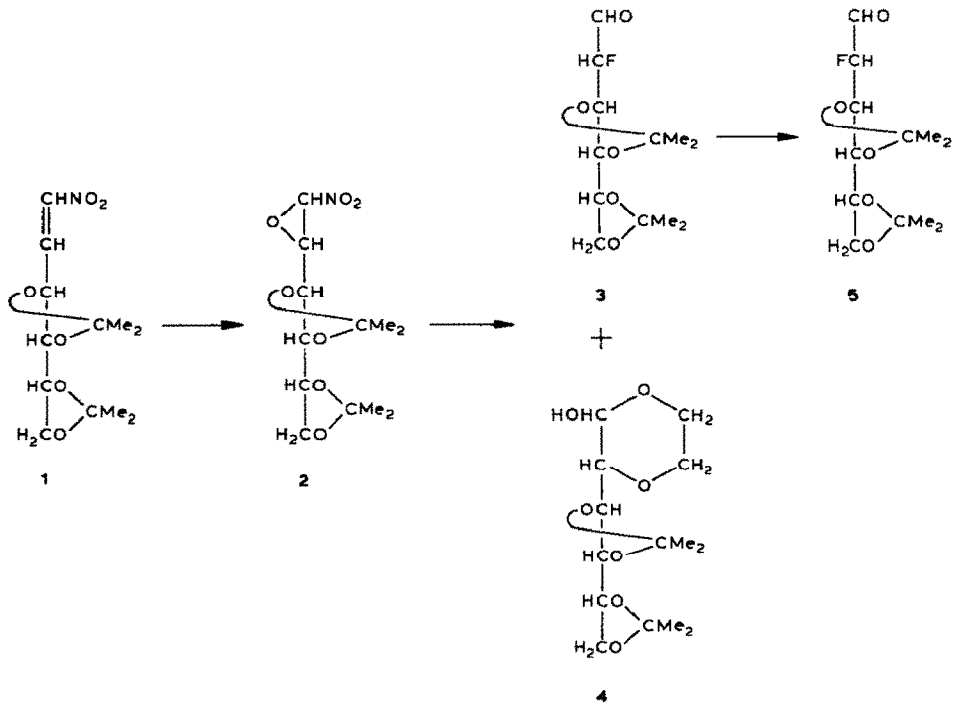
work clearly establishes that the ^{18}F-labeled *manno* isomer must have been formed concomitantly.

RESULTS AND DISCUSSION

1,2-Dideoxy-3,4:5,6-di-*O*-isopropylidene-1-*C*-nitro-D-*arabino*-hex-1-enitol (**1**), a known[25] compound, was prepared by two different sequences of reactions. Condensation of 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose with nitromethane in alkaline methanol gave a mixture of 1-deoxy-3,4:5,6-di-*O*-isopropylidene-1-*C*-nitro-D-mannitol and -D-glucitol; the nitroalkene (**1**) was obtained by subsequent treatment with either acetic anhydride–sodium acetate[26] or methanesulfonyl chloride–triethylamine[25,27]. Alternatively, the mixture of β-nitro alcohols was obtained by condensation[28] of D-arabinose with nitromethane in alkaline methanol, and then treatment with acetone–concentrated sulfuric acid (see ref. 29). The ^1H-n.m.r. spectrum of **1** showed $^3J_{1,2}$ to be 13.4 Hz, indicative of the *trans* configuration[30]. Treatment of **1** with 30% hydrogen peroxide and aqueous sodium hydrogencarbonate[31] gave 87% of a mixture of 1,2-anhydro-3,4:5,6-di-*O*-isopropylidene-1-*C*-nitro-D-mannitol (**2**) and -D-glucitol, from which crystalline **2** was isolated in 72% yield.

To obtain higher yields of the target 2-deoxy-2-fluoro-D-glucose (**8**), and greater simplicity of the product-mixture, it was crucial to employ scrupulously dry



glassware, reagents, and solvent. Thus, treatment of the α-nitroepoxide **2** with potassium hydrogenfluoride in ethylene glycol for 20 min at ~112° converted the starting material into a product, t.l.c. of which gave a long, tailing spot (R_F 0.40–0.53) and a more-intense spot (R_F 0.33); these were separated by column chromatography on silica gel. The fraction corresponding to the tailing spot was found to be comprised of 2-deoxy-2-fluoro-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose (**3**) and the D-*manno* analog (**5**) in the ratio of ~4:1, respectively, as judged by the relative ^{1}H-n.m.r. intensities of the apparent doublets at δ 9.78 and 9.72 attributable to H-1 in **3*** and **5**; the two compounds had ^{19}F chemical-shift values of 216.4 and 205.2 p.p.m., respectively. Storage of this fraction in the neat state or in chloroform solution led to decomposition, as indicated by the appearance of other signals in the ^{19}F-n.m.r. spectrum. The second fraction having R_F 0.33 appeared to consist of a compound to which the structure of the hemiacetal **4** has been assigned, and a fluorine-containing substance†.

The mixture of fluoro aldehydes (R_F 0.40–0.53) was deacetalated by treatment with 80% trifluoroacetic acid for 5 min and the product was acetylated with acetic anhydride–pyridine to afford, after column chromatography, 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranoses (**6**) and the D-*manno* analogs (**7**); from a sample of the former the β-D-*gluco* anomer could be isolated crystalline.

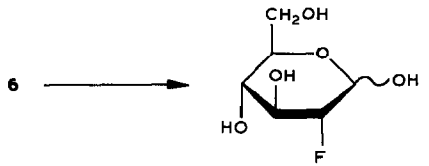
The ^{18}F- and ^{1}H-n.m.r. spectra of the acetylated compounds, and the melting point and specific rotation of the crystalline material, were in accord with the corresponding data reported in the literature (see Experimental section). The acetylation procedure was occasioned by the fact that the deacetalated product, namely a mixture of 2-deoxy-2-fluoro-D-glucose (**8**) and -D-mannose, migrated as a single component (R_F 0.42) in t.l.c. (solvent *F*). *O*-Deacetylation of **6** by treatment with boiling M hydrochloric acid for 40 min, or with sodium methoxide in methanol for 7 min at room temperature, afforded **8**; ^{19}F-n.m.r. spectroscopy did not indicate the presence of any of the *manno* isomer. Thus, the method described in this article does provide a route to 2-deoxy-2-fluoro-D-glucose.

In an effort to establish the origin of the *manno* isomer in the reaction of the α-nitroepoxide **2** with potassium hydrogenfluoride, a sample of 2-deoxy-2-fluoro-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose (**3**) was prepared by a different route and subjected to the conditions employed for the reaction with the α-nitroepoxide **2**. This sample of **3** was obtained by conversion of 2-deoxy-2-fluoro-D-glucose (**8**) into its diethyl dithioacetal **9**, formation of 2-deoxy-2-fluoro-3,4:5,6-di-*O*-isopropylidene-D-glucose diethyl dithioacetal (**10**), and demercaptalation. A solution of **3** in solvent *G* was passed through a column of silica gel; significantly,

*The ^{1}H-n.m.r. data attributed to 2-deoxy-2-fluoro-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose in ref. 1 do not, in fact, correspond to that compound.

†It must be recognized that the obtaining of the *gluco* (**3**) and *manno* (**5**) isomers in the ratio of ~4:1, respectively, does not establish unambiguously the configuration of the starting α-nitroepoxide; however, the formation of the hemiacetal **4** as the sole product from the reaction of the α-nitroepoxide with ethylene glycol (see below) does indicate the *manno* configuration for the α-nitroepoxide as shown in **2**.

6 R^1 = H, R^2 = F
7 R^1 = F, R^2 = H



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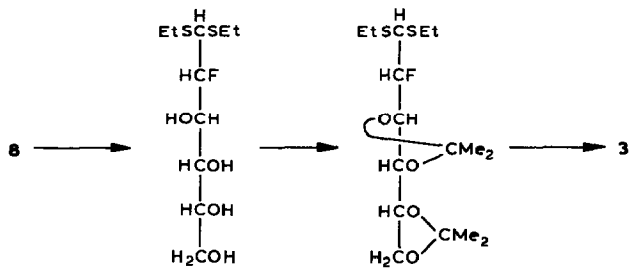
no epimerization at C-2 was detected by ^{1}H-n.m.r. spectroscopy. However, when a solution of **3** in ethylene glycol was treated with potassium hydrogenfluoride for 17 min at 112–117°, the ^{1}H-n.m.r. spectrum indicated the presence of **3** and its D-*manno* analog (**5**) in ~3:1 ratio, establishing that epimerization at C-2 had occurred under the conditions of the α-nitroepoxide opening.



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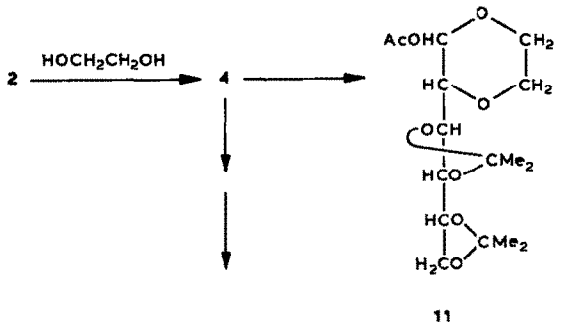
It has already been mentioned that the fraction having R_F 0.33 appeared to consist of hemiacetal **4** and a fluorine-containing substance. Compound **4** was considered to have arisen by the reaction of the solvent (ethylene glycol) with the α-nitroepoxide **2**. An authentic sample of **4** (R_F 0.33) was obtained by performing the reaction separately and was characterized by conversion into the acetate **11**. Also, treatment of authentic **4** with 80% trifluoroacetic acid, and acetylation of the resultant product with acetic anhydride–pyridine, afforded 2-*O*-(2-acetoxyethyl)-1,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranoses (**12**). The ^{1}H-n.m.r. spectrum of the original fraction from the reaction of the α-nitroepoxide **2** with potassium hydrogenfluoride in ethylene glycol contained the same signals as those of the spectrum of

authentic **4**, as well as some additional signals. The ^{19}F-n.m.r. spectrum of the fraction also indicated the presence of a fluorine-containing substance. Further evidence for the heterogeneity of this fraction was obtained by acetylation (acetic anhydride–pyridine) to give a product shown by t.l.c. to consist of a component that comigrated with authentic acetate **11** plus a more-polar component, and material that migrated with the solvent front. The more-polar component could not be obtained homogeneous; however, its ^{19}F-n.m.r. spectrum indicated that it contained fluorine. Hydrolysis of the original fraction with 80% trifluoroacetic acid gave material which appeared in t.l.c. (solvent *F*) as essentially one diffuse spot having R_F ~0.1.



Although more than one compound was formed in the particular system investigated in the present study, a salient feature of the work is the rapidity of the ring-opening reaction of the α-nitroepoxide **2**. The synthetic utility of this potentially versatile carbohydrate intermediate remains to be exploited.

EXPERIMENTAL

General methods. — Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 automatic polarimeter for solutions in a 1.0- or 0.1-dm cell at 23 ±3°. I.r. spectra were recorded with a Perkin–Elmer 180, or a Beckman Acculab 6 spectrophotometer. Proton (^{1}H-n.m.r.) and fluorine (^{19}F-n.m.r.) n.m.r. spectra were recorded with a Bruker AM-400 spectrometer at 400 and 376.5 MHz, respectively, unless stated otherwise, for solutions in chloroform-*d*; tetramethylsilane (Me_4Si) was used as the internal standard for ^{1}H-n.m.r. spectra, and tri-

chlorofluoromethane ($CFCl_3$) as the external standard for ^{19}F-n.m.r. spectra. Chemical shifts are given in δ (^1H) or ϕ (^{19}F) values relative to the standards.

Solvents were evaporated under diminished pressure and <40°. Analytical t.l.c. was performed on glass plates precoated with Merck silica gel 60 F-254 as the adsorbent (layer thickness 0.25 mm). The developed plates were air-dried and sprayed with a solution of cerium sulfate (1%) and molybdic acid (1.5%) in 10% aqueous sulfuric acid, and heated at 150°. Column chromatography was performed on silica gel 60 (70–230 mesh, Merck); for flash chromatography the mesh was 230–400. The following solvent systems (v/v) were used: (*A*) 1:1, (*B*) 5:1, (*C*) 7:1, (*D*) 15:1, and (*E*) 20:1 toluene–ethyl acetate; (*F*) 19:1 acetonitrile–water; (*G*) 1:1, (*H*) 2:1, and (*I*) 3:2 hexanes–ethyl acetate; (*J*) 3:1, and (*K*) 7:1 hexanes–ether.

*1-Deoxy-3,4:5,6-di-*O*-isopropylidene-1-*C*-nitro-*D*-mannitol and -*D*-glucitol.* — To a solution of 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose[32] (15.1 g) in methanol (19.8 mL) and nitromethane (35.6 mL) was added methanolic sodium methoxide prepared by the reaction of sodium (2.07 g) with methanol (69 mL). The solution was stirred under nitrogen for 20 h at room temperature, after which time the presence of the starting material could not be detected by t.l.c. (solvent *I*). The solution was diluted with water (30 mL) and the mixture was extracted with CH_2Cl_2 (6 × 200 mL). The extracts were washed with water (3 × 100 mL), dried ($MgSO_4$), and evaporated to a yellow syrup (17.8 g) which was chromatographed on a column of silica gel (solvent *B*) to afford a mixture of the title compounds as a light-yellow syrup (16.8 g), R_F 0.35 (solvent *B*), contaminated by a trace of a component having R_F 0.4. This mixture was used in the next experiment without further purification. A sample, obtained by further chromatography on silica gel, had $[\alpha]_D$ +10.8° (*c* 2.1, chloroform) [lit.[25] $[\alpha]_D^{20}$ +9° (*c* 0.8, chloroform)]; ν_{max}^{film} 3450 (OH), and 1555 and 1380 (NO_2) cm^{-1}; ^1H-n.m.r. (200 MHz): δ 1.34–1.42 (12 H, 2 CMe_2), 3.23 (d, exchanged in D_2O, OH), and 3.75–4.70 (9 H, OH and stem H's).

Anal. Calc. for $C_{12}H_{21}NO_7$: C, 49.48; H, 7.27; N, 4.81. Found: C, 49.61; H, 7.32; N, 4.84.

*1,2-Dideoxy-3,4:5,6-di-*O*-isopropylidene-1-*C*-nitro-*D*-arabino-hex-1-enitol* (**1**). — (*a*) To a cold (0°) solution of the foregoing mixture of β-nitro alcohols (13.6 g, 46.7 mmol) in dry CH_2Cl_2 (48 mL) was added methanesulfonyl chloride (13.0 mL, 166 mmol). Triethylamine (31.0 mL, 0.222 mol) was added gradually to the solution and the mixture was stirred under nitrogen for 2 h at 0°. Dichloromethane (150 mL) was added and the mixture was washed successively with aqueous sodium hydrogencarbonate (2 × 100 mL), saturated aqueous sodium chloride (2 × 100 mL), and water (2 × 100 mL), dried ($MgSO_4$), and evaporated to a syrup (13.2 g). Purification by column chromatography with solvent *D* gave nitroalkene **1** as a faintly yellow syrup (10.85 g, 85%) having R_F 0.54 (solvent *C*), $[\alpha]_D$ −21.0° (*c* 0.7, chloroform) [lit.[25] $[\alpha]_D^{20}$ −46° (*c* 1, chloroform)]; ν_{max}^{film} 1655 (C=C), and 1530 and 1350 (NO_2) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 230 nm; ^1H-n.m.r. (200 MHz): δ 1.35–1.44 (12 H, 2 CMe_2), 3.68 (t, 1 H, $^3J_{4,3} = {}^3J_{4,5}$ 8.2 Hz, H-4), 3.92–4.21 (3 H, H-5, -6, -6'), 4.63 (ddd, 1 H, $^4J_{3,1}$ 1.5, $^3J_{3,2}$ 3.4, $^3J_{3,4}$ 8.2 Hz, H-3), 7.24 (dd, 1 H, $^4J_{1,3}$ 1.5, $^3J_{1,2}$ 13.4 Hz, H-1), and 7.37 (dd, 1 H, $^3J_{2,1}$ 13.4, $^3J_{2,3}$ 3.4 Hz, H-2).

Anal. Calc. for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.88; H, 7.34; N, 4.97.

(*b*). A mixture of the β-nitro alcohols (17.53 g, 60.2 mmol) and anhydrous sodium acetate (150 g) in acetic anhydride (271 mL) was stirred for 72 h at room temperature and poured into an aqueous solution of sodium hydrogencarbonate (3.5 L). The mixture was extracted with CH_2Cl_2 (4 × 250 mL); the combined extract was washed with water (2 × 200 mL) and then with 0.1M hydrochloric acid (200 mL), dried ($MgSO_4$), and evaporated to a syrup (14.5 g) that was chromatographed (solvent *D*) to afford the nitroalkene **1** as a faintly yellow syrup (12.5 g, 76%).

*1,2-Anhydro-3,4:5,6-di-*O*-isopropylidene-1-*C*-nitro-*D*-mannitol* (**2**) *and* -D-*glucitol*. — To a solution of the nitroalkene **1** (10.0 g) in abs. ethanol (475 mL) was added 30% aqueous hydrogen peroxide (60 mL), with stirring at room temperature. The pH of the mixture was adjusted to ~8.5 by the dropwise addition of saturated, aqueous sodium hydrogencarbonate. After 50 min, the mixture was extracted exhaustively with CH_2Cl_2. The extract was washed twice with water, dried (Na_2SO_4), and evaporated to give a white solid which was collected by filtration. The residue was washed with hexanes (15 mL) and abs. ethanol (3 mL); these washings were retained for further processing. Compound **2**, which was retained by the filter paper as a white solid (7.63 g, 72%), could be recrystallized from ethyl acetate or ether–hexanes. Compound **2** and the starting nitroalkene **1** had essentially the same R_F value (0.54 in solvent *C*); however, the former was only faintly visible when a t.l.c. plate was irradiated with u.v. light but appeared as a deep-black spot when the plate was sprayed with reagent (see General methods section), whereas the latter was strongly u.v.-active and appeared as a brownish spot on spraying. Compound **2** also had m.p. 112.5–113°, $[\alpha]_D$ −29.0° (*c* 1.0, chloroform); ν_{max}^{KBr} 1565 (NO_2) cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 1.35–1.42 (12 H, 2 CMe_2), 3.74 (dd, 1 H, $^3J_{4,3}$ 7.6, $^3J_{4,5}$ 8.2 Hz, H-4), 3.83 (dd, 1 H, $^3J_{2,1}$ 0.9, $^3J_{2,3}$ 2.1 Hz, H-2), 3.96 (dd, 1 H, $^2J_{6,6'}$ 8.2, $^3J_{6,5}$ 4.0 Hz, H-6), 4.06 (ddd, 1 H, $^3J_{5,4}$ 8.2, $^3J_{5,6}$ 4.0, $^3J_{5,6'}$ 5.8 Hz, H-5), 4.18 (dd, 1 H, $^2J_{6',6}$ 8.2, $^3J_{6',5}$ 5.8 Hz, H-6'), 4.24 (dd, 1 H, $^3J_{3,2}$ 2.1, $^3J_{3,4}$ 7.6 Hz, H-3), and 5.54 (bs, 1 H, H-1).

Anal. Calc. for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 49.68; H, 6.56; N, 4.92.

The foregoing washings were concentrated to a yellow syrup that was chromatographed on a column of silica gel (solvent *E*) to give the D-*gluco* isomer as a colorless syrup (1.69 g, 15.9%), R_F 0.54 (solvent *C*), $[\alpha]_D$ +18.0° (*c* 1.0, chloroform); ν_{max}^{film} 1560 (NO_2) cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 1.35–1.45 (12 H, 2 CMe_2), 3.68 (dd, 1 H, $^3J_{2,1}$ 0.8, $^3J_{2,3}$ 3.2 Hz, H-2), 3.82–4.13 (m, 3 H, H-5, -6, -6'), 4.08 (dd, 1 H, $^3J_{3,2}$ 3.2, $^3J_{3,4}$ 8.0 Hz, H-3), 4.17 (dd, 1 H, $^3J_{4,3}$ 8.0, $^3J_{4,5}$ 5.6 Hz, H-4), and 5.46 (d, 1 H, $^3J_{1,2}$ 0.8 Hz, H-1).

Anal. Calc. for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 49.88; H, 6.66; N, 4.98.

Reaction of **2** *with potassium hydrogenfluoride in ethylene glycol*. — The

initial preparations for the utilization of the materials and glassware were as follows. Ethylene glycol (Fisher Scientific Ltd., 1L) was boiled under reflux overnight in the presence of magnesium turnings (12 g) and then distilled into a storage flask containing 4-Å molecular sieves; just prior to its utilization a portion (~10 mL) was transferred using a dry syringe, a few (~5) sodium spheres (diameter ~1.5–6 mm) were added, and the ethylene glycol was distilled into a three-necked, round-bottom, 25-mL reaction flask. Potassium hydrogenfluoride (BDH Chemicals) was heated at ~155° overnight, and then finely powdered, and the required amount was heated for 6 h at ~155° and then used immediately. The α-nitroepoxide **2** was dried over P_2O_5 under diminished pressure (13 Pa) for 6 h immediately before use. All of the assembled glassware was dried using a propane torch, while being ventilated with a stream of dry argon, for 0.5 h.

Dry potassium hydrogenfluoride (0.59 g, 7.6 mmol) was added to freshly distilled ethylene glycol (~4 mL) and the mixture was stirred for ~15 min at ~112° under a slow stream of dry argon. The dry α-nitroepoxide **2** (0.14 g, 0.48 mmol) was added in one portion and stirring was continued for 20 min. The mixture was cooled to room temperature, diluted with water, and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated to give a faintly yellow syrup. The product appeared in t.l.c. (solvent *A*) as a long, tailing spot (R_F 0.40–0.53) and a more-intense spot (R_F 0.33); unless adequate amounts of the product were applied to the chromatographic plate the former spot was only faintly or not visible. The starting α-nitroepoxide **2** has an R_F value of 0.78 in solvent *A*. Column chromatography using solvent *I* and then solvent *G* as eluants afforded 0.060 g of the faster-moving fraction and 0.034 g of the slower-moving fraction. The faster-moving fraction was subsequently identified as a mixture (47% yield) of 2-deoxy-2-fluoro-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose (**3**) and the D-*manno* (**5**) isomer. The ^{1}H-n.m.r. spectrum of this fraction showed signals, amongst others, at δ 9.78 ($J_{1,F}$ 5.7 Hz) and 9.72 ($J_{1,F}$ 5.5 Hz) having relative intensities of ~4:1, respectively; on expansion of the spectrum the signals exhibited further splitting ($J_{1,2}$ <1.0 Hz). The two signals were assigned to H-1 in **3** and **5**, respectively. The ^{19}F-n.m.r. spectrum of this fraction exhibited signals at φ 216.3 (ddd, $J_{F,1}$ 5.6, $J_{F,3}$ 28.3, $J_{F,2}$ 47.7 Hz) and at 205.2 (ddd, $J_{F,1}$ 5.1, $J_{F,3}$ 21.3, $J_{F,2}$ 48.5 Hz) which have been assigned to the D-*gluco* (**3**) and D-*manno* (**5**) isomers, respectively. On storage of this fraction in the neat state or in chloroform solution, some decomposition occurred, as indicated by the appearance of other signals in the ^{19}F-n.m.r. spectrum.

A sample (45 mg, 0.17 mmol) of the faster-moving fraction was treated with 80% trifluoroacetic acid (2 mL) for 5 min at room temperature, and the acid was then evaporated. Water was added to the residue, and the solution was made neutral with Amberlite IRA-400 (OH^-) ion-exchange resin; the resin was removed by filtration, washed with water, and the filtrate and washings were evaporated. T.l.c. (solvent *F*) revealed the presence of a component which appeared as a diffuse spot centered at R_F 0.42. As shown subsequently, this component was comprised

of 2-deoxy-2-fluoro-D-glucose and 2-deoxy-2-fluoro-D-mannose; an authentic sample of 2-deoxy-2-fluoro-D-glucose migrated in t.l.c. (solvent *F*) at R_F 0.42. The residue from the hydrolysis reaction was conventionally acetylated with acetic anhydride–pyridine to afford, after column chromatography (solvent *H*), 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranoses (**6**) (27 mg, 45%), 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-α,β-D-mannopyranoses (**7**) (10 mg, 16.8%), and a fraction (5 mg, 8.4%) consisting of **6** and **7**. The *gluco* acetates **6** had R_F 0.31 (solvent *H*), $[\alpha]_D$ +90.1° (*c* 1.11, chloroform) [lit., for the α anomer[20] $[\alpha]_D$ +146° (*c* 1, chloroform), for the β anomer[11] $[\alpha]_D$ +50° (*c* ~1, chloroform)]; crystallization from hexanes–ether afforded the β anomer, m.p. 88–90°, $[\alpha]_D$ +44.5° (*c* 1.91, chloroform) (lit.[11] m.p. 91–92°). The *manno* acetates **7** had R_F 0.21 (solvent *H*), $[\alpha]_D$ +39.3° (*c* 1.00, chloroform) [lit.[11], for the α anomer $[\alpha]_D$ +60° (*c* ~1, chloroform), for the β anomer $[\alpha]_D$ −14° (*c* ~1, chloroform)]. The ^{19}F- and ^{1}H-n.m.r. spectra of **6** and **7** were in accord with the corresponding data recorded in the literature[11,20,33,34].

A solution of the acetates **6** in methanol was treated with sodium methoxide for 7 min at room temperature, and the solvent was then evaporated. Water was added to the residue, and the solution was made neutral with Dowex 50X2-400 (H^+) ion-exchange resin. The ^{19}F-n.m.r. spectrum of the product (**8**) in deuterium oxide was identical to that of an authentic sample of 2-deoxy-2-fluoro-D-glucose (see also, refs. 23, 35); no signals attributable to the D-*manno* isomer were observed. A sample of **6** was treated also with M hydrochloric acid at reflux temperature for 40 min, and the solution was made neutral with Amberlite IRA-400 (OH^{-1}) ion-exchange resin; the ^{19}F-n.m.r. spectrum of the product in deuterium oxide did not show any signals attributable to 2-deoxy-2-fluoro-D-mannose (see also, refs. 11, 36).

The original slower-moving fraction, having R_F 0.33 (solvent *A*), from the reaction of the α-nitroepoxide **2** with potassium hydrogenfluoride in ethylene glycol, was shown by the following experiments to consist of a compound to which the structure of the hemiacetal **4** has been assigned, and a fluorine-containing substance. The ^{1}H-n.m.r. spectrum of this fraction contained signals the same as those of the spectrum of authentic (see later) **4**, as well as some additional signals; in particular, the spectrum of the mixture showed a doublet (*J* 18.2 Hz) at δ 9.30 and doublet of doublets (*J* 34.0 and 8.0 Hz) at δ 5.96, signals not present in the spectrum of authentic **4**. The ^{19}F-n.m.r. spectrum of this fraction exhibited a doublet of doublets (*J* 32.7 and 17.4 Hz) at φ 128.8. Conventional acetylation of the original slower-moving fraction with acetic anhydride–pyridine afforded a product consisting (t.l.c.) of a component migrating at the same rate as the authentic (see later) acetate **11** (R_F 0.74, solvent *G*) and of a component having R_F 0.60, in addition to material that migrated with the solvent front; in this solvent the hemiacetal **4** had R_F 0.42. The component having R_F 0.60 could not be obtained homogeneous by column chromatograhy; the ^{19}F-n.m.r. spectrum exhibited a doublet of doublets (*J* 31.8 and 16.2 Hz) at φ 126.7.

A sample of the original slower-moving fraction was hydrolysed with 80% trifluoroacetic acid at room temperature to give material that appeared in t.l.c. (solvent *F*) as mainly one diffuse spot having R_F ~0.1; a number of very faint spots were also observed at higher R_F values.

*2-Deoxy-2-fluoro-*D*-glucose diethyl dithioacetal* (**9**). — To a solution of 2-deoxy-2-fluoro-D-glucose (Calbiochem–Behring Corporation, 180 mg, 0.99 mmol) in concentrated hydrochloric acid (1 mL) at 0° was added ethanethiol (1 mL), and the mixture was stirred for 1 h. The resultant white precipitate was removed by filtration, washed with cold (0°) ethanol (1 mL), and air-dried to afford compound **9** (220 mg, 77%). Recrystallized from ethanol, the product had m.p. 150–151.5°, $[\alpha]_D$ −12.3° (*c* 1.5, dimethyl sulfoxide); ^{19}F-n.m.r. (dimethyl sulfoxide-d_6): ϕ 194.65 (ddd, $J_{F,2}$ 47.5, $J_{F,1(3)}$ 12.5, $J_{F,3(1)}$ 27.0 Hz).

Anal. Calc. for $C_{10}H_{21}O_4S_2F$: C, 41.65; H, 7.34; S, 22.23. Found: C, 41.84; H, 7.44; S, 22.22.

*2-Deoxy-2-fluoro-3,4:5,6-di-*O*-isopropylidene-*D*-glucose diethyl dithioacetal* (**10**). — A mixture of **9** (190 mg, 0.659 mmol), 2,2-dimethoxypropane (8 mL), and 4 drops of a solution of concentrated sulfuric acid (0.5 mL) in anhydrous acetone (20 mL) was stirred for 3 h. Triethylamine was added until the solution was slightly basic, and the mixture was evaporated. Compound **10** was isolated by flash chromatography (solvent *K*) as a syrup (110 mg, 45.3%), R_F 0.63 (solvent *J*), $[\alpha]_D$ −17.4° (*c* 1.1, chloroform); ^{19}F-n.m.r. ϕ 190.7 (ddd, $J_{F,2}$ 46.2, $J_{F,1(3)}$ 7.0, $J_{F,3(1)}$ 26.5 Hz).

Anal. Calc. for $C_{16}H_{29}O_4S_2F$: C, 52.14; H, 7.93; S, 17.41. Found: C, 52.40; H, 7.90; S, 17.65.

Demercaptalation of compound **10**. — A mixture of **10** (60 mg, 0.163 mmol), mercuric chloride (110 mg), and mercuric oxide (130 mg) in acetone (5 mL) containing 5 drops of water was stirred for 3 h. After the usual processing, fluoro aldehyde **3** was isolated by flash chromatography (solvent *G*) as a syrup (~2 mg, 4.7%), R_F 0.56 (solvent *A*), $[\alpha]_D$ +9.4° (*c* 2.32, chloroform); ^{1}H-n.m.r. δ 9.79 (apparent d, 1 H, $J_{1,F}$ 6.0, $^3J_{1,2}$ ~0.5 Hz, H-1), 4.93 (apparent d, 1 H, $J_{2,F}$ 47.5, $^3J_{2,3}$ 1.0 Hz, H-2), 4.35 (apparent dd, 1 H, $J_{3,F}$ 28.0, $^3J_{3,2}$ 1.5, $^3J_{3,4}$ 7.5 Hz, H-3), 4.24–3.97 (m, H-4, -5, -6, -6′), and 1.49–1.31 (12 H, 2 CMe_2); ^{19}F-n.m.r. ϕ 216.3 (ddd, $J_{F,2}$ 47.5, $J_{F,1}$ 5.7, $J_{F,3}$ 28.1 Hz).

A solution of **3** in solvent *G* was passed through a column of silica gel; the ^{1}H-n.m.r. spectrum was identical to that of the starting compound, **3**. A solution of **3** in ethylene glycol was treated with potassium hydrogenfluoride for 17 min at 112–117°; in this case the ^{1}H-n.m.r. spectrum showed an apparent doublet at δ 9.79 and at δ 9.72 in the approximate ratio of 3:1, respectively.

Reaction of α-nitroepoxide **2** *and ethylene glycol.* — A mixture of α-nitroepoxide **2** (0.36 g, 1.24 mmol) and 3-Å molecular sieves (0.36 g) in dry ethylene glycol (8 mL) was stirred for 20 min at 112°. The sieves were removed by filtration, water was added to the filtrate, and the solution was extracted with chloroform; the extracts were dried ($MgSO_4$) and evaporated. Column chromatography (solvent

G) afforded hemiacetal **4** as a syrup (0.115 g, 30.4%), R_F 0.33 (solvent *A*), $[\alpha]_D$ +24.4° (*c* 9.0, chloroform); ^{1}H-n.m.r. δ 1.32–1.45 (12 H, 2 CMe_2), 3.29–4.45 (11 H), 4.85 (apparent t, 0.5 H, *J* 7.0 and 7.1 Hz), and 5.06 (d, 0.5 H, *J* 4.0 Hz).

Anal. Calc. for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: C, 54.52; H, 8.13.

*1-(2-Acetoxy-1,4-dioxan-3-yl)-1,2:3,4-di-*O*-isopropylidene-*D-arabino-*tetrol* (**11**). — The hemiacetal **4** (0.09 g, 0.30 mmol) was conventionally acetylated at room temperature with acetic anhydride–pyridine to give, after column chromatography (solvent *H*), the acetate **11** as a syrup (0.08 g, 78%), R_F 0.74 (solvent *G*), $[\alpha]_D$ +30.8° (*c* 4.35, chloroform); ^{1}H-n.m.r. δ 1.34–1.41 (12 H, 2 CMe_2), 2.15 (s, 3 H, OAc), 3.50 (dd, 1 H, $^3J_{3',2'}$ 7.6, $^3J_{3',1}$ 2.0 Hz, H-3'), 3.59–4.15 (9 H), and 5.78 (d, 1 H, $^3J_{2',3'}$ 7.6 Hz, H-2').

Anal. Calc. for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.16; H, 7.76.

*2-*O*-(2-Acetoxyethyl)-1,3,4,6-tetra-*O*-acetyl-α,β-*D*-glucopyranoses* (**12**). — Compound **4** (0.10 g, 0.33 mmol) was treated with 80% trifluoroacetic acid (3 mL) for 5 min, and the acid was then evaporated. Water was added to the residue, and the solution was made neutral with Amberlite IRA-400 (OH^-) ion-exchange resin; the resin was removed by filtration, washed with water, and the filtrate and washings were evaporated. The residue was treated with 1:2 (v/v) acetic anhydride–pyridine overnight at room temperature. Toluene was added and the mixture was evaporated; this procedure was repeated three times. The residual syrup was chromatographed (solvent *G*) to give **12** as a syrup (0.090 g, 63.1%), R_F 0.30 (solvent *G*), $[\alpha]_D$ +58.8° (*c* 5.53, chloroform); ^{1}H-n.m.r. δ 2.01–2.10 (15 H, 5 OAc), 3.50 (apparent t, $^3J_{2,1}$ 8.3, $^3J_{2,3}$ 9.2 Hz, H-2 of the β anomer), 3.64 (dd, $^3J_{2,1}$ 3.8, $^3J_{2,3}$ 9.7 Hz, H-2 of the α anomer), 3.67–4.33 (m, H-5, -6, -6' and OCH_2CH_2O), 5.03 (apparent t, *J* 9.6 and 9.8 Hz), 5.07 (apparent t, *J* 9.5 and 9.8 Hz), 5.20 (apparent t, *J* 9.3 and 9.5 Hz) and 5.36 (apparent t, *J* 9.5 and 9.7 Hz) (H-3 and H-4 in both anomers), 5.62 (d, $^3J_{1,2}$ 8.0 Hz, H-1 of the β anomer), and 6.38 (d, $^3J_{1,2}$ 3.8 Hz, H-1 of the α anomer).

Anal. Calc. for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03. Found: C, 49.44; H, 6.12.

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