Carbohydrate Research, 207 (1990) 277–285
Elsevier Science Publishers B.V., Amsterdam

Fluorinated cyclitols. An improved synthesis of 5-deoxy-5-fluoro-*myo*-inositol, its deuterium labeling, and synthesis of a 5,5-*gem*-difluoro analogue

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(Received January 10th, 1990; accepted for publication March 20th, 1990)

ABSTRACT

An improved synthesis of 5-deoxy-5-fluoro-*myo*-inositol is provided *via* the reaction of diethylaminosulfur trifluoride (DAST) with the versatile intermediate, 1,4,6-tri-*O*-benzyl-2,3-*O*-cyclohexylidene-*neo*-inositol (I), followed by appropriate deprotection reactions. Reaction of DAST with the 5-*keto* analogue of I gave the *gem*-difluoro compound, which upon deprotection afforded 5-deoxy-5,5-difluoro-*myo*-inositol. A ^{1}H-n.m.r. study of the deuteration of 5-deoxy-5-fluoro-*myo*-inositol with Raney nickel–deuterium oxide revealed that the equatorial H-2 proton was most rapidly exchanged, followed by the sterically identical H-1 and H-3 protons, which exchanged at a significantly slower rate.

INTRODUCTION

5-Deoxy-5-fluoro-*myo*-inositol (**3**) has been shown to be a useful probe for studies on the biochemistry of the inositol cycle[1,2]. The compound is unique among analogues of *myo*-inositol in that it is a reasonably good substrate for phosphatidylinositol (PI) synthase (CDPdiacylglycerol–inositol 3-phosphatidyltransferase, EC 2.7.8.11), the key enzyme of phosphatidylinositol biosynthesis. Studies with **3** have demonstrated[1,2] that the compound has about 26% of the substrate activity of *myo*-inositol in a standard assay using rat-brain microsomal PI synthase. Furthermore, from studies using intact L1210 cells, definitive evidence has been presented[1,2] showing that a new, more lipophilic phosphatidylinositol, which was subsequently converted to a monophosphate, was formed upon incubation of the cells with **3**. Thus, the compound does indeed function as a surrogate for *myo*-inositol, through at least the first two steps of the PI pathway. Given the fact that none of the diastereomers of *myo*-inositol are substrates for PI synthase[3], precluding their incorporation into the respective phosphatidylinositol derivatives, there is considerable interest in pursuing research with this biochemical probe.

A previous paper[4] reported a synthesis of **3** from *myo*-inositol that proceeded *via*

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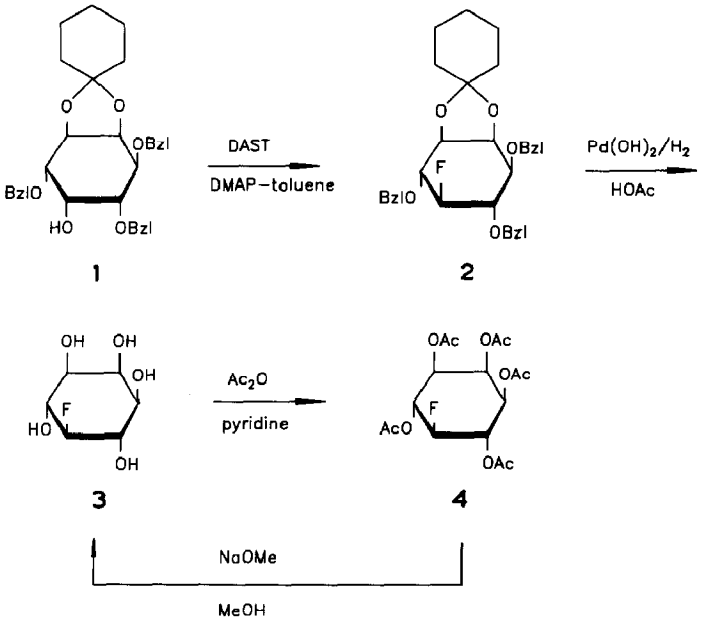
0008-6215/90/$ 03.50

6-*O*-benzyl-1,2:3,4-di-*O*-cyclohexylidene-*myo*-inositol (compound **9** in the reference cited), which gave the compound as one of the products of fluorodehydroxylation with diethylaminosulfur trifluoride (DAST). However, the yield of *myo*isomer was low (14.5%), and problems were encountered in handling the sensitive diacetal. The *trans* 3,4-*O*-cyclohexylidene group was particularly labile under the conditions of reaction and workup. Thus, an improved route to **3** was desired. In addition, interest was generated in evaluating other deoxyfluoro analogues, such as the *gem*-difluoro compound **8**.

RESULTS AND DISCUSSION

An improved synthesis of 5-deoxy-5-fluoro-myo-*inositol* (**3**). — In order to circumvent the major problems in the synthesis of 5-deoxy-5-fluoro-*myo*-inositol as outlined in the preceding paragraph, a more versatile intermediate, 1,4,6-tri-*O*-benzyl-2,3-*O*-cyclohexylidene-*neo*-inositol (**1**) was identified as a viable alternative to the diacetal previously used. This compound had served well in the preparation of the previously reported[4] 5-chloro- and 5-bromo-5-deoxy *myo*-analogues, and its synthesis was relatively straightforward (see ref. 4). Thus reaction of **1** with DAST in toluene in the presence of 4-dimethylaminopyridine (DMAP) afforded 1,4,6-tri-*O*-benzyl-2,3-*O*-cyclohexylidene-5-deoxy-5-fluoro-*myo*-inositol (**2**) in 61% yield (Scheme 1). The most significant signal in the ^{1}H-n.m.r. spectrum of **2** was that of H-5 at δ 4.45, which appeared as a

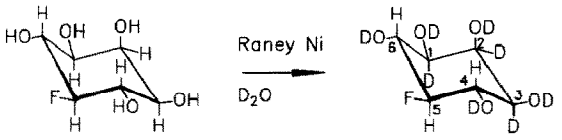


Scheme 1

doublet of apparent triplets having $J_{H,F}$ = 50.53 Hz, reflecting the large geminal coupling of H-5 with F-5, and vicinal proton couplings ($J_{4,5}$, $J_{5,6}$) of ~8.5 Hz, diagnostic for the *trans* diaxial arrangement of H-4, H-5, and H-6, which confirmed the *myo* configuration.

Deprotection of **2** was effected *via* a one-step hydrogenolysis–hydrolysis procedure in acetic acid (using palladium hydroxide-on-charcoal as the hydrogenolysis catalyst) to give **3** in 85% yield. The compound was shown to be identical, by m.p. and ^{1}H-n.m.r. spectrum, with samples produced earlier[4]. An analysis of the product by gas-liquid chromatography of its pentakis-*O*-(trimethylsilyl) derivative revealed that it was contaminated with 2–3% of *myo*-inositol. Simple recrystallization did not significantly improve the purity of **3**, but purification was achieved by converting it to its penta-*O*-acetyl derivative with acetic anhydride and pyridine. Careful crystallization gave the pure acetyl derivative (**4**) in 94% yield, and deacetylation of the purified **4** with sodium methoxide in methanol gave **3** in 79% yield, 99–99.5% pure by g.l.c. analysis. The stubborn persistence of a per cent or so of *myo*-inositol in the sample could suggest the occurrence during manipulation of an intramolecular displacement of fluorine by an OH group to form an epoxide, with subsequent opening of the epoxide by water to give the parent cyclitol. However, no evidence for this mechanism has been found, and the fact that no additional isomeric products were detected by n.m.r. and g.l.c. analysis would indicate that the *myo*-inositol does not arise by an epoxide-opening process.

Deuteration studies on 5-deoxy-5-fluoro-myo-*inositol* (**3**). — For biological studies with **3**, a tritium-labeled compound was desired. By way of evaluating a possible process for tritium-labeling of **3**, deuterium-labeling studies were undertaken to ascertain (*i*) the rates of, and conditions for, incorporation of the label, (*ii*) the position(s) labeled by the isotopic substitution, and (*iii*) the degree of epimerization that might occur in the labeling reaction. The procedure chosen was that of Koch and Stuart[5,6], which makes use of Raney nickel and isotopically labeled water for the exchange. This process has been used in deuterium-labeling of both sugars[5,6] and cyclitols[6,7], where labeling has been shown to occur with retention of configuration and with a minimum of epimerization, provided that reaction times and conditions are controlled. Thus a sample of **3** (see Scheme 2) was heated at 65° in deuterium oxide with Raney nickel (which had previously been washed with deuterium oxide), and the exchange was followed by examining the mixture at fixed time periods of 0, 40, 160, and 280 min by ^{1}H-n.m.r. spectroscopy, and at 0 and 280 min by ^{13}C-n.m.r. spectroscopy. The ^{1}H-n.m.r. data allow, by simple integration of the resonance signals, the determination that H-2, the only equatorial hydrogen in the molecule, is most rapidly exchanged (Scheme 2). The



Scheme 2

flanking H-1 (H-3) hydrogens* were observed to exchange, albeit somewhat more slowly, while H-4 and H-6, as well as the H-5 protons, underwent no perceptible exchange. The results are presented in Table I. These observations, in general, are in accord with the earlier findings of Angyal and Odier[7], as well as those of Balza and Perlin[8]. As H-5 is geminal to the fluorine atom, it is not expected to exchange (refer to the proposed mechanism for the protium–deuterium exchange[6]). Therefore, H-5 was allowed to serve as the reference for integration of the ^{1}H-n.m.r. spectra that generated the data in Table I.

TABLE I

Deuterium labeling of 5-deoxy-5-fluoro-*myo*-inositol (**3**)

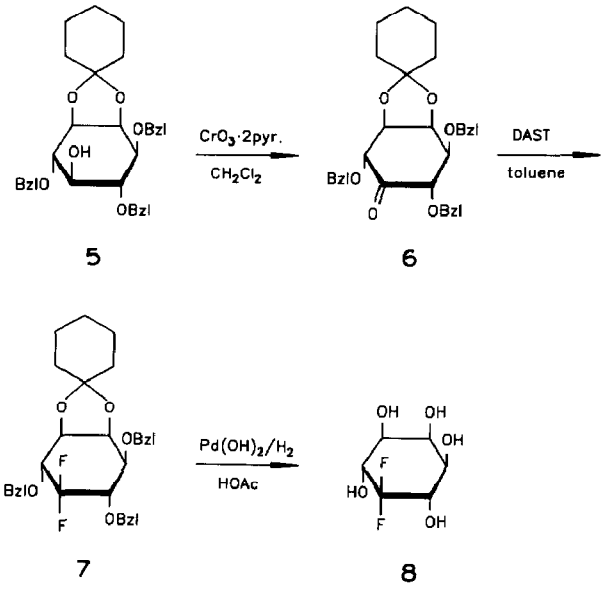
Time (min)	*Percent replacement by ^2H*[a]	
	H-1,H-3	*H-2*
40	0	0
160	41	68
280	64	89

[a] Percentages of deuterium replacement were determined by integration of the ^{1}H-n.m.r. spectrum, with H-5 set equal to 1.0 H. No detectable deuteration was observed at C-4 (C-6). The velocity of the exchange reaction varied from one experiment to another, presumably owing to variations in the activity of the catalyst.

Synthesis of 5-deoxy-5,5-difluoro-myo-*inositol* (**8**). — From tests of a number of modified cyclitols as substrates for PI synthase[1,2], the developing structure–activity relationships indicated that a small substituent placed at the *myo*-5 position would likely be compatible with the enzyme. Both 5-deoxy-5-fluoro-*myo*-inositol (**3**) and its *neo* epimer were shown to be substrates for PI synthase, with the former, whose fluorine is in a position to accept an H-bond in much the same way as the 5-OH group in *myo*-inositol, being the better substrate. Thus the idea of evaluating a *gem*-difluoro analogue such as **8** was generated.

The synthesis of compound **8** is shown in Scheme 3. 1,4,6-Tri-*O*-benzyl-2,3-*O*-cyclohexylidene-*myo*-inositol (**5**, ref. 4) was oxidized with the chromium trioxide–dipyridine complex, as developed for sugars[9] and further modified by Garegg and coworkers[10], to give the inosose **6** in good yield. The compound was fully characterized by both spectroscopy and elemental analysis. Fluorination with DAST gave the *gem*-difluoro derivative, 1,4,6-tri-*O*-benzyl-2,3-*O*-cyclohexylidene-5-deoxy-5,5-difluoro-*myo*-inositol (**7**) in 51% yield. The structure of the product was determined from its ^{1}H-n.m.r. spectrum, which showed distinct *cis* and *trans* couplings of the fluorine atoms with the adjacent H-4 and H-6 protons (see Experimental section). Deprotection of **7** was effected as for **2** *via* hydrogenolysis over palladium hydroxide in acetic acid solution

* Note that H-1 and H-3, as well as H-4 and H-6, are equivalent by symmetry.



Scheme 3

to give 5-deoxy-5,5-difluoro-*myo*-inositol (**8**) in 83% yield. This symmetrical molecule gave rise to a simplified ^{1}H-n.m.r. spectrum that revealed *cis* and *trans* couplings of 21.6 and 4.8 Hz, respectively, with the adjacent H-4 and H-6 protons, as well as other resonances indicative of the structure. The structure was further substantiated *via* mass spectrometry of its pentakis-*O*-(trimethylsilyl) derivative (*m/z* 560) and by elemental analysis.

Evaluation of **8** as a substrate for PI synthase was carried out as previously described[1], and the results have been reported[2]. Interestingly, the compound was a very poor substrate for the enzyme, in contrast to the substrate activity shown by both **3** and its *neo* epimer.

EXPERIMENTAL

General procedures. — For general procedures, including conditions for chromatography, see ref. 4. Toluene and dichloromethane were distilled from calcium hydride and stored over 4A molecular sieves. 4-Dimethylaminopyridine (Riley) was recrystallized from ether prior to use.

^{1}H-N.m.r. spectra were recorded at 200 MHz or at 360 MHz, using respectively a Nicolet NT-200 or a Bruker AM360 n.m.r. spectrometer. Chemical shifts are reported in δ-units downfield from internal tetramethylsilane ($CDCl_3$ solutions), or from external sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) in D_2O, for samples in D_2O. Multiplicities are first-order values (in Hz); the symbol ψt is used to indicate a "pseu-

dotriplet", *i.e.*, a doublet of doublets having equal J values. Proton-decoupled ^{13}C-n.m.r. spectra were recorded at 90.5 MHz on the Bruker instrument. Solutions were typically 1–2% for both ^{1}H- and ^{13}C-n.m.r. determinations.

1,4,6-Tri-O-benzyl-2,3-O-cyclohexylidene-5-deoxy-5-fluoro-myo-*inositol* (**2**). — To a stirred solution of 1,4,6-tri-*O*-benzyl-2,3-*O*-cyclohexylidene-*neo*-inositol [**1** (ref. 4); 2.1 g, 4.0 mmol] in dry toluene (100 mL), maintained under an atmosphere of dry nitrogen, was added 4-dimethylaminopyridine (1.0 g, 8.2 mmol). The solution was cooled to −30°, and diethylaminosulfur trifluoride (DAST, Aldrich; 1.0 mL, 7.6 mmol) was slowly added. The mixture was warmed to room temperature, then heated for 2 h at 60–65° (still under nitrogen), at the end of which time it was again cooled to −30°, and saturated aq. sodium bicarbonate (20 mL) was added. This mixture was poured into 2:1 ethyl acetate–water (150 mL), and the organic layer was separated and dried over magnesium sulfate. Evaporation of the solvent gave a syrup that was purified by column chromatography (silica gel, 60 g), using dichloromethane as the eluent, to give **2** (1.3 g, 61%) as a syrup, R_F 0.16 (CH_2Cl_2); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 1.41–1.67 (10 H), 3.69 (dd, 1 H, $J_{1,2}$ 3.6, $J_{1,6}$ 8.2 Hz, H-1), 3.95 [m, 2 H, H-4(H-6)], 4.10 (ψt, 1 H, $J_{3,4}$ 6.1 Hz, H-3), 4.28 (dd, 1 H, $J_{2,3}$ 5.1 Hz, H-2), 4.45 (dψt, 1 H, $J_{H,F}$ 50.53, $J_{4,5} = J_{5,6} = 8.5$ Hz, H-5), 4.75–4.86 (m, 6 H, PhCH_2), and 7.27–7.36 (m, 15 H, Ph-H).

Anal. Calc. for $C_{33}H_{37}FO_5$: C, 74.41; H, 7.00. Found: C, 74.26; H, 7.06.

Preparation of 5-deoxy-5-fluoro-myo-*inositol* (**3**). — *A. From compound* **2**. To a solution of **2** (1.2 g, 2.25 mmol) in 80% aq. acetic acid (50 mL) was added 20% palladium hydroxide-on-charcoal (Aldrich; 450 mg). The mixture was shaken under hydrogen at 65 psi for 48 h at room temperature, at the end of which time the catalyst was removed by filtration through a Celite pad, and the filter cake was washed with ethanol (30 mL), followed by water (50 mL). The clear, light-yellow filtrate was evaporated to give a light-yellow solid, to which chloroform (30 mL) and water (50 mL) were added. The layers were separated, and the aqueous layer was evaporated to dryness to give a white solid, to which absolute ethanol (2 × 50 mL) was added and subsequently evaporated to remove traces of acetic acid. The residue was crystallized from 90% aq. ethanol to give **3** (349 mg, 85%) as analytically pure, colorless crystals, m.p. 222–24° (lit.[4] 222–24°). For ^{1}H-n.m.r. data identical to those previously reported[4], and ^{13}C-n.m.r. data, see the section, below, describing deuteration experiments on **3**.

B. From the penta-O-acetyl derivative **4**. To a solution of sodium methoxide in methanol, prepared by dissolving a small sphere of sodium metal (3 mm, Aldrich) in dry methanol (25 mL) at 0°, was added **4** (545 mg, 1.4 mmol). The mixture was stirred in an ice bath for 1 h, at the end of which time the reaction was quenched by addition of Dowex 50-X2 (H^+) cation-exchange resin. The resin was filtered off and rinsed with methanol (10 mL). The solvent was evaporated, and the residue was dissolved in water and freeze-dried, yielding **3** (200 mg, 1.1 mmol, 79%). The product was identical by m.p. and ^{1}H-n.m.r. spectroscopy with that obtained by procedure *A*. The ^{1}H-n.m.r. data were identical to those previously reported[4]. G.l.c. analysis of the product, derivatized using *N*-(trimethylsilyl)imidazole[4,11] showed 99% pure pentakis-*O*-(trimethylsilyl)-**3**.

Preparation of 1,2,3,4,6-penta-O-acetyl-5-deoxy-5-fluoro-myo-*inositol* (**4**). — To

a solution of **3** (600 mg, 3.29 mmol) in dry pyridine (20 mL), maintained under a dry nitrogen atmosphere, was added acetic anhydride (3 mL). The mixture was stirred for 6 h at 60°, at the end of which time the pyridine and excess acetic anhydride were evaporated. Ethanol (3 × 20 mL) was added to and evaporated from the residue to remove any remaining reagents. The resulting white solid on crystallization from ethanol provided pure **4** (1.20 g, 3.08 mmol, 94%) as colorless needles, m.p. 182–184° (lit.[4] m.p. 180–181°).

*(2,6/3,4,5)-2,3,6-Tri-*O*-benzyl-4,5-*O*-cyclohexylidenepentahydroxycyclohexanone* (**6**). — To a clear, burgundy-colored solution of chromium trioxide–dipyridine complex, prepared by mixing under rigorously dry conditions chromium trioxide (1.0 g, 10 mmol, dried at 140 ° in vacuo), dry pyridine (1.6 mL, 20 mmol), and acetic anhydride (1.0 mL, 10 mmol) in dry dichloromethane (25 mL), was added 1,4,6-tri-*O*-benzyl-2,3-*O*-cyclohexylidene-*myo*-inositol[4] (**5**, 2.0 g, 3.8 mmol). The mixture was stirred for 2 h at room temperature, at the end of which time the reaction was quenched by pouring the mixture into ethyl acetate (30 mL). The mixture was then filtered through a 2-cm layer of silica gel contained in a 7-cm Buchner funnel. The silica gel was washed with ethyl acetate (150 mL), and the combined filtrates were washed with 3% (v/v) hydrochloric acid (100 mL), followed by saturated aq. sodium hydrogencarbonate (100 mL). The organic extract was then dried over magnesium sulfate. The solvent was evaporated to give a syrup which was purified by column chromatography (silica gel, 100 g) using 1:9 ethyl acetate–petroleum ether as the eluent to give **6** (1.5 g, 75%) as a syrup, R_F 0.44 (1:9 ethyl acetate–petroleum ether); i.r. (neat):710 (s), 940 (m), 1100 (s), 1280 (s), 1370 (m), 1450 (m), 1600 (m), 1730 (s), and 2940 (s) cm^{-1}; ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 1.42–1.59 (10 H), 4.02 (d, 1 H, $J_{3,4}$ 4.8 Hz, H-4), 4.15 [s, 2 H, H-1(H-6)], 4.28 (ψt, 1 H, $J_{2,3}$ 6.3 Hz, H-3), 4.51 (d, 1 H, H-2), 4.75–4.85 (m, 6 H, PhCH_2), and 7.3 (m, 15 H, Ph-H).

Anal. Calc. for $C_{33}H_{36}O_6 \cdot 0.25\ H_2O$: C, 74.34; H, 6.90. Found: C, 74.44; H, 6.90.

*1,4,6-Tri-*O*-benzyl-2,3-*O*-cyclohexylidene-5-deoxy-5,5-difluoro-*myo*-inositol* (**7**). — To a solution of **6** (1.4 g, 2.65 mmol) in dry toluene (30 mL), maintained under a dry nitrogen atmosphere, was added DAST (0.40 mL, 0.49 g, 3.0 mmol). The mixture was stirred for 3 h at 60°, then cooled to 0°, and cold, saturated aq. sodium hydrogencarbonate (20 mL) was added. The mixture was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was evaporated to give a yellow syrup, which was purified by column chromatography (silica gel, 100 g) using dichloromethane as the eluent to furnish pure **7** (0.75 g, 51%) as a syrup, R_F 0.22 (dichloromethane); i.r. (neat): 690 (s), 710 (s), 910 (m), 1080 (s), 1230 (s), 1340 (s), 1440 (s), 1480 (m), 2900 (s), and 300 (m) cm^{-1}; ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 1.40–1.57 (10 H), 3.68 (ddd, 1 H, $J_{3,4}$ 7.3, $J_{4,F(trans)}$ 24, $J_{4,F(cis)}$ 3.3 Hz, H-4), 3.82 (dψt, 1 H, $J_{1,6}$ 10.2, $J_{1,F}$ 2.8 Hz, H-1), 3.98 (ddd, 1 H, $J_{6,F(trans)}$ 19.7, $J_{6,F(cis)}$ 3.1 Hz, H-6), 4.07 (ψt, 1 H, H-3), 4.24 (ψt, 1 H, $J_{1,2} = J_{2,3}$ = 4.4 Hz, H-2), 4.67–4.93 (m, 6 H, PhCH_2), and 7.32–7.39 (m, 15 H, Ph-H); m.s.: *m/z* (%) 550 (M, 0.4), 521 (0.3), 507 (1.3), 459 (M − 91, 11), and 91 (C_7H_7, 100).

Anal. Calc. for $C_{33}H_{36}F_2O_5$: C, 71.98; H, 6.59. Found: C, 72.09; H, 6.61.

*5-Deoxy-5,5-difluoro-*myo*-inositol* (**8**). — To a solution of **7** (700 mg, 1.27 mmol)

dissolved in ethanol (5 mL) and 80% aq. acetic acid (30 mL) was added 20% palladium hydroxide-on-charcoal (Aldrich; 400 mg). The mixture was shaken under hydrogen at 65 psi for 48 h at room temperature, at the end of which time the catalyst was filtered off (Celite), and the filter cake was washed with ethanol (20 mL), then with water (20 mL). The clear, colorless filtrate was evaporated to give a white solid to which absolute ethanol (50 mL) was added, then evaporated, to remove traces of acetic acid. Crystallization of the product from 95% aq. ethanol yielded **8** (210 mg, 83%) in two crops of white crystals, m.p. 264–266° (dec.); i.r. (KBr): 790 (s), 840 (m), 895 (m), 915 (m), 1035 (s), 1140 (s), 1240 (s), 1389 (m), and 3250 (s) cm^{-1}; ^{1}H-n.m.r. (D_2O): δ 3.67 [dd, 2 H, $J_{1,6}$ ($J_{3,4}$) 10.3 Hz, H-1 (H-3)], 3.99 [ddd, 2 H, $J_{4,F(trans)}$($J_{6,F(trans)}$ 21.6 Hz, $J_{4,F(cis)}$ ($J_{6,F(cis)}$) 4.8 Hz, H-4, (H-6)], 4.10 [t, 1 H, $J_{1,2}$ ($J_{2,3}$) 3.1 Hz, H-2]; g.l.c. [pentakis-*O*-(trimethylsilyl) derivative] T_R 2.21 min; g.l.c.–m.s. [pentakis-*O*-(trimethylsilyl) derivative]: *m/z* (%) 560 (M, 0.6), 545 (M − Me, 0.7), 73 (Me_3Si, 88), and 68 (100).

Anal. Calc. for $C_6H_{10}F_2O_5$: C, 36.01; H, 5.04; F, 18.99. Found: C, 35.94; H, 5.08; F, 19.01.

Deuterated Raney nickel. — According to the method of Koch and Stuart[5], commercial Raney Ni (Aldrich, cat. no. 22,167-8; 5 mL wet volume) was washed in a sintered glass funnel, first with distilled water until neutral to pH paper, then with copious amounts of D_2O. The Raney Ni was then suspended in D_2O and kept in the refrigerator at 4° (sealed bottle for storage longer than overnight). The D_2O was replaced with fresh D_2O just before use.

Deuteration of 5-deoxy-5-fluoro-myo-*inositol* (**3**). — Compound **3** (25 mg, 0.14 mmol) was dissolved in D_2O (3.0 mL) and stirred with deuterated Raney Ni (0.1 mL wet volume, prepared as just described) for 40 min at 65°. The solution was filtered through a cotton plug, then through a 0.45-μm Swinney filter (Teflon filter disc). The D_2O was removed by lyophilization to give an amorphous white solid. The cyclitol was prepared for ^{1}H- and ^{13}C-n.m.r. analyses by dissolving the product in D_2O (0.6 mL). The DSS shift reference was contained in a coaxial capillary tube. After the ^{1}H- and ^{13}C-n.m.r. spectra were recorded, the cyclitol solution was recovered and subjected to the deuteration conditions for an additional 2 h (160 min, total time), and again for an additional 4 h (280 min, total time). ^{1}H-n.m.r. data (D_2O) at time = 0 min: δ 4.20 (dψt, 1 H, $J_{5,6(4)}$ 9.1, $J_{5,F}$ 52.1 Hz, H-5), 4.03 (ψt, 1 H, $J_{2,3(1)}$ 2.8 Hz, H-2), 3.87 [ddd, 2 H, $J_{4(6),F}$ 14.3 Hz, H-4 (H-6)], 3.54 [dd, 2 H, $J_{3(1),4(6)}$ 9.9 Hz, H-1 (H-3)]. H-2 is ~89% replaced by ^{2}H at 280 min, giving a broad doublet at δ 4.03. As H-1 and H-3 are replaced by ^{2}H, their resonances widen into a broad doublet, making spin–spin couplings difficult to determine. ^{13}C-n.m.r. data (D_2O) at time = 0 min: δ 98.1 (d, $J_{5,F}$ 177.2 Hz, C-5), 74.6 (s, $J_{2,F}$ 0 Hz, C-2), 73.4 [d, $J_{4(6),F}$ 17.6 Hz, C-4 (C-6)], 72.7 [d, $J_{1(3),F}$ 11.4 Hz, C-1 (C-3)]. As ^{1}H is replaced by ^{2}H, the C-2 resonance becomes greatly attenuated, and the C-4 (C-6) and C-1 (C-3) resonances show primary ^{2}H-^{13}C coupling (as dd's, $J_{1(3),D}$ 4.9 Hz and $J_{4(6),D}$ 5 Hz).

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