Synthesis and Tritium Radiolabelling of Fluorinated Analogues of *myo*-Inositol

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Syntheses have been developed for a set of six *myo*-inositol analogues from *myo*-inositol in which single hydroxy groups have been replaced by fluorine (monodeoxy-fluoro-*myo*-inositols). Except for 2-deoxy-2-fluoro-*myo*-inositol **32** and 1D-4-deoxy-4-fluoro-*myo*-inositol **23**, the monodeoxy-fluoro-*myo*-inositols were substrates for the enzyme inositol dehydrogenase [EC 1.1.1.18], which catalyses the oxidation of the axial 2-position of *myo*-inositol to give *scyllo*-inosose. This enzyme was used to exchange tritium radiolabel from *myo*-[2-^{3}H]inositol to the monodeoxy-fluoro-*myo*-inositol. 1D-4-Deoxy-4-fluoro-*myo*-inositol and 2-deoxy-2-fluoro-*myo*-inositol were radiolabelled chemically.

The hydrolysis of phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P_2] is one of the earliest responses to the activation of a wide range of cellular receptors by specific agonists. PtdIns(4,5)P_2 is formed by specific kinases which sequentially phosphorylate phosphatidylinositol (PtdIns) to phophatidylinositol 4-phosphate (PtdIns4P) and PtdIns(4,5)P_2. The hydrolysis of PtdIns(4,5)P_2 produces inositol 1,4,5-trisphosphate which releases Ca^{2+} from intracellular compartments and diacylglycerol which activates protein kinase C.[1] The hydrolysis of PtdIns(4,5)P_2 has been investigated in detail in many different cell systems, but no specific chemical inhibitors of the process have been developed. Such inhibitors are needed to determine which cellular responses depend upon PtdIns(4,5)P_2 breakdown as a required step in the signalling pathway. Other phosphorylated inositol phospholipids have been described; phosphatidylinositol 3-phosphate has recently been characterised[2] and other, more polar, 3-phosphorylated inositol lipids accumulate in response to growth factors in neutrophils, although these phospholipids are present in much smaller quantities than the other inositol phospholipids.[3] Inhibitors of the synthesis or breakdown of these 3-phosphorylated inositol lipids would be useful in defining their role in cellular responses.

We have synthesized the set of six systematically substituted monodeoxy fluoro analogues of *myo*-inositol with the aim of developing inhibitors of the formation and breakdown of the various inositol phospholipids. Alternative syntheses of 1-deoxy-1-fluoro-*myo*-inositol, 2-deoxy-2-fluoro-*myo*-inositol and 5-deoxy-5-fluoro-*myo*-inositol have been described previously.[4–6] It was assumed that the set of monodeoxy-fluoro-*myo*-inositols would be taken up into cells by the same mechanism as that undergone by *myo*-inositol and that they might be substrates for the PtdIns synthase and therefore be incorporated into phospholipid, except for 1D-1-deoxy-1-fluoro-*myo*-inositol which could not be linked to a phosphatidyl group at the 1-position but might be an inhibitor of PtdIns synthesis. The similarity of size between the C–F and C–OH bond lengths should allow the monodeoxy-fluoro-*myo*-inositols and any novel phospholipids formed by their incorporation to be processed by many of the enzymes normally acting on the unsubstituted inositol and the inositol phospholipids. The potential cellular effects of the monodeoxy-fluoro-*myo*-inositols are: (i) Inhibition of transport of *myo*-inositol into cells. (ii) Inhibition of PtdIns synthesis. (iii) The formation of modified inositol phospholipids which may act as inhibitors. For example, modified PtdIns(4,5)P_2 analogues may not be substrates for phosphoinositidide phospholipase C. (iv) The production of phosphorylated deoxy-fluoro-*myo*-inositols formed when cleaved from the parent phospholipid, which might be inhibitors of inositol phosphate signalling pathways. (v) Inhibition of the synthesis of PtdIns anchored cell-surface proteins, in which protein is attached through a glycan to the D-6 position of the inositol moiety.[7]

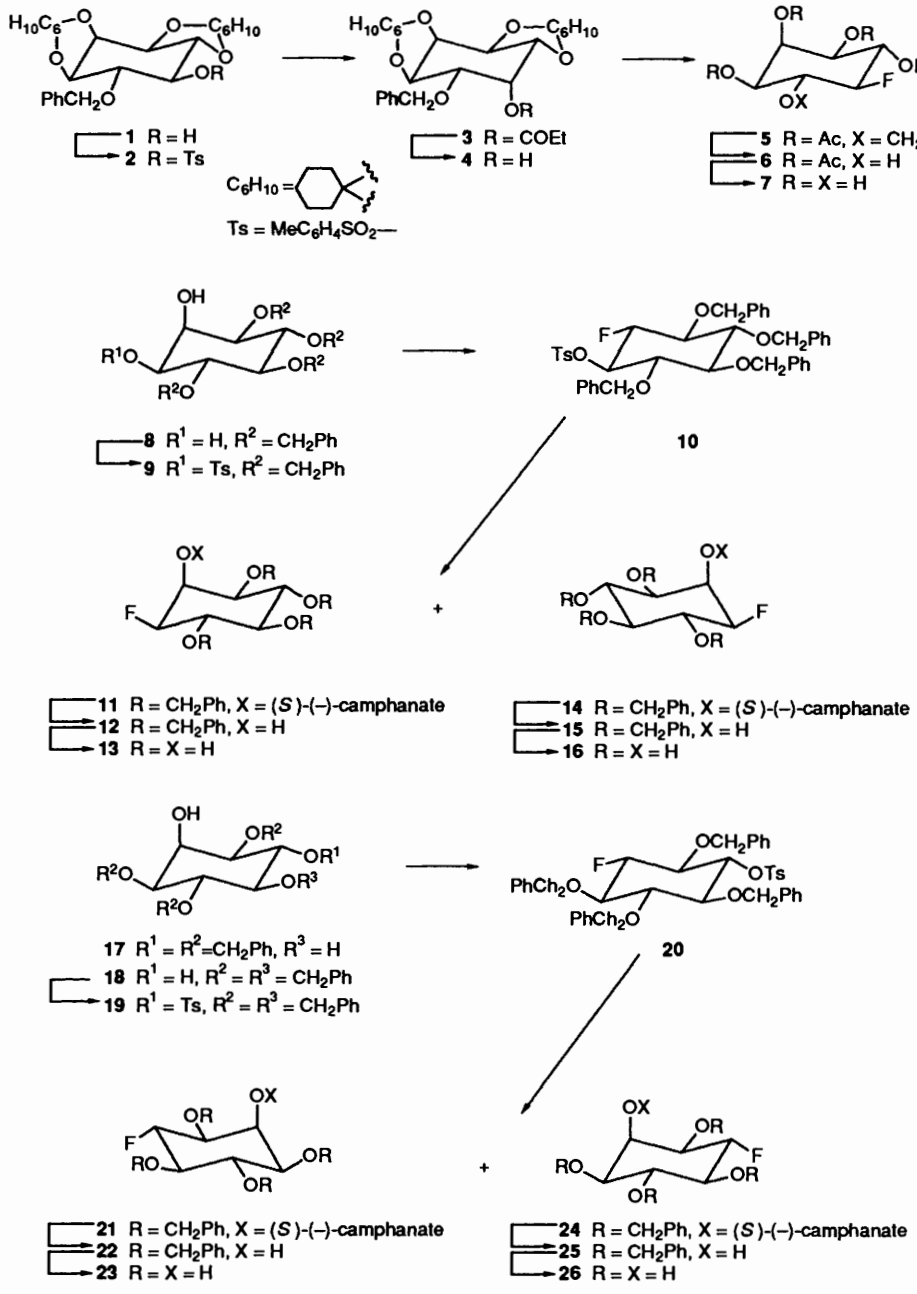
The synthesis of the tritium-radiolabelled monodeoxy-fluoro-*myo*-inositols was required to assay their ability to enter cells and become incorporated into phospholipids. We have used a novel enzymatic method for radiolabelling 1D-1-deoxy-1-fluoro-, 1D-3-deoxy-3-fluoro (= 1L-1-deoxy-1-fluoro-), 5-deoxy-5-fluoro- and 1D-6-deoxy-6-fluoro-*myo*-inositol (1L-4-deoxy-4-fluoro-*myo*-inositol). The 2-deoxy-2-fluoro- and 1D-4-deoxy-4-fluoro-*myo*-inositol were chemically radiolabelled by existing methods.[5,8]

Discussion

myo-Inositol was chosen as the starting material for these syntheses because of its availability and because its chemistry has been well developed in the search for synthetic routes to the inositol phosphates.[9] This choice and the use of the reagent diethylaminosulfur trifluoride (DAST) for fluorination dictated the strategy of the syntheses described. *myo*-Inositol is defined by a single axial hydroxy group and reactions with DAST usually occur with inversion[10] and consequent loss of the *myo*-configuration. The inversion of single hydroxy groups by the displacement of a leaving group using the caesium salt of a suitable acid in an aprotic solvent is a useful means of regenerating the initial configuration.[11] Inositol is an isocyclic ring and more stable to high temperatures than are its heterocyclic isomers. Tosyl derivatives of secondary hydroxy groups, which are easy to prepare but usually too unreactive to be displaced, can therefore be used with inositol in preference to triflates, which require strictly anhydrous conditions for their preparation.

myo-Inositol possesses a plane of symmetry between C-2 and C-5. Substitution either side of this plane of symmetry causes the loss of symmetry and the generation of enantiomers. The 1-deoxy-1-fluoro-*myo*-inositol, therefore, exists as D-1- and D-3-deoxy-fluoro-*myo*-inositol,* and 4-deoxy-4-fluoro-*myo*-inositol as D-4- and D-6-deoxy-fluoro-*myo*-inositol.† For use as potential inhibitors it was important to resolve these enantiomers, which introduces additional steps into the syntheses. Camphanate esters have been used successfully in cyclitol chemistry to resolve racemates[8] and we combined the inversion step required to regenerate the *myo*-configuration and the resolution step to separate enantiomers by using the caesium salt of (*S*)-(−)-camphanic acid which shortens the length of the synthesis. The camphanate displaces the tosyl

* Systematically, 1L-1-deoxy-1-fluoro-*myo*-inositol.
† Systematically, 1L-4-deoxy-4-fluoro-*myo*-inositol.



Scheme 1 Synthetic pathways to deoxy-fluoro-*myo*-inositols

leaving group with inversion of configuration, and the diastereoisomeric camphanate esters thus formed can be resolved by chromatography. The tosyl group has the additional function of protecting the position it occupies against fluorination.

The routes used to make 1-deoxy-1-fluoro-*myo*-inositol and 4-deoxy-4-fluoro-*myo*-inositol (Scheme 1) were very similar, differing only in the preparation of the protected inositol derivatives selected as starting materials. The starting material for the preparation of 1D- and 1L-1-deoxy-1-fluoro-*myo*-inositol **13** and **16** was the DL-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol* **8** available in three simple steps from *myo*-inositol. Tosylation gave exclusively the 1-*O*-tosyl derivative **9**.[12] Treatment of this tosyl derivative with DAST gave the *scyllo*-derivative **10**. (*S*)-(−)-Caesium camphanate was used to recover the *myo*-configuration and the diastereoisomers formed were separated by silica gel chromatography. Deprotection yielded the 1D- and 1L-1-deoxy-1-fluoro compounds in good yield. The absolute configuration of these compounds was determined by identifying which compound was incorporated into the inositol phospholipid, on the assumption that the 1D-substituted compound would be unable to form the phosphatidyl linkage and would not therefore be incorporated. The tritium-radiolabelled (+)-1-deoxy-1-fluoro-*myo*-inositol **16** was not incorporated into the lipid but radiolabelled (−)-1-deoxy-1-fluoro-*myo*-inositol **13** was incorporated, implying that the (+) compound had the 1D configuration and that the (−) compound had the 1L configuration.

For the 4-substituted derivative, DL-1,3,4,5-tetra-*O*-benzyl-*myo*-inositol **18** was used which can be prepared by several routes.[13] 1,4-Di-*O*-benzyl-*myo*-inositol was activated with dibutyltin oxide and partially benzylated to give the diol **18** as the major product. The 2- and 6-position were unprotected but tosylation produced the desired 6-*O*-monotosylated product **19**, notable for its very poor solubility in organic solvents. Fluorination with DAST gave a single product **20** and

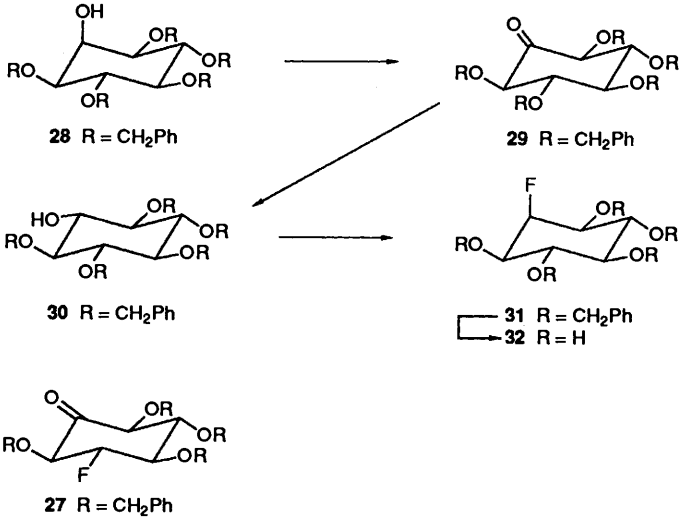
* DL-1,4,5,6-Tetra-*O*-benzyl-*myo*-inositol.

treatment of this with (*S*)-(−)-caesium camphanate gave the diastereoisomers. The camphanate esters could not be resolved by TLC but separation was observed using an HPLC system. Partial crystallisation also separated the two camphanate ester derivatives. Deprotection gave (+)-4-deoxy-4-fluoro-*myo*-inositol **23** and (−)-4-deoxy-4-fluoro-*myo*-inositol **26**. Two experimental observations were used to establish the absolute configurations of (+)- and (−)-4-deoxy-4-fluoro-*myo*-inositol. First, (−)-4-deoxy-4-fluoro-*myo*-inositol, **26**, was a substrate for inositol dehydrogenase but its enantiomer, **23**, was not. This enantiomer and the 2-deoxy-2-fluoro-*myo*-inositol were the only two monodeoxy-fluoro-*myo*-inositols of the set of six that were not substrates of inositol dehydrogenase. Magasanik *et al.*[14] formulated two rules for the stereochemical specificity of the oxidation of cyclitols by inositol dehydrogenase from *Acetobacter suboxydans*. The first rule was that only axial hydroxy groups are oxidised, which would exclude 2-deoxy-2-fluoro-*myo*-inositol from being a substrate. The second rule was that the carbon in the *meta* position anticlockwise to the axial hydroxy (positioned upwards) must carry an equatorial hydroxy group. The second rule applied to the deoxy-fluoro analogues predicts that the 1D-4-deoxy-4-fluoro analogue would not be a substrate but that its enantiomer would. On the basis of the second rule we assigned the (+)-4-deoxy-4-fluoro-*myo*-inositol **23** to the D-4 configuration and its enantiomer **26** to the L-4 configuration because only enantiomer **26** was a substrate for inositol dehydrogenase. However, this assignment of configuration was not definitive since the inositol dehydrogenase used in this study was from *Enterobachter aerogenes* and exceptions to the second rule have been observed.[15] However, a second observation consistent with the assigned configuration of the enantiomers was that when (−)-4-deoxy-4-fluoro-*myo*-inositol **26** was incorporated into cells it formed two modified lipids which ran on TLC at positions closely corresponding to PtdIns and PtdIns4*P*, whereas the (+)-4-deoxy-4-fluoro-*myo*-inositol **23** was not incorporated into phospholipid. The 1D-4-deoxy-4-fluoro-*myo*-inositol would be unable to form a 4-phosphorylated inositol lipid and on this basis the configuration of the (−) enantiomer **26** was assigned as L-4 (D-6).

5-Deoxy-5-fluoro-*myo*-inositol **7** is a *meso* compound and therefore no optical resolution is required. The synthesis required a protected inositol with the 5-position free. There are several such starting materials available but the 6-*O*-benzyl-1,2:3,4-di-*O*-cyclohexylidene-*myo*-inositol **1** prepared by dibutylstannylene-activated monobenzylation of the 1,2:3,4 diketal[16] was the most convenient. The 5-position was inverted by displacement of a tosyl leaving group with propionate and removal of the propionate group by treatment with base to give the *neo*-inositol derivative **4**. Treatment of this compound with DAST alone gave a single fluorine-substituted product with *myo*-configuration. Removal of the acid-sensitive ketal protecting groups and their replacement by acetates at this stage facilitated handling and purification of the intermediates and removal of the benzyl group by hydrogenolysis in the presence of acid. Deprotection of compound **6** with a catalytic amount of sodium methoxide gave 5-deoxy-5-fluoro-*myo*-inositol **7**.

[^{3}H]-*Labelling of the Monodeoxy-fluoro*-myo-*inositols*.—Inositol dehydrogenase catalyses the oxidation of *myo*-inositol to *scyllo*-inosose with NAD^+ as the electron acceptor[17] and the equilibrium for this reaction lies far towards the reduction of inosose. The activity of the dehydrogenase with the various *myo*-inositol analogues can be estimated from the initial rate of production of NADH assayed by its fluorescence. If the enzyme is added to the monodeoxy-fluoro-*myo*-inositol and *myo*-[2-^{3}H]inositol in the presence of NAD^+, the tritium radiolabel is exchanged from *myo*-inositol to the 2-equatorial position of the analogue *via* NADH. Experiments with 5-deoxy-5-fluoro-*myo*-inositol **7** demonstrated that this compound was tritiated under these conditions in 50% radiochemical yield. However, some of the tritium was lost to the dinucleotide and the extent of this reaction increased slowly with time. The conditions that produced the highest radiochemical yield with minimal loss of tritium into dinucleotide were those conditions required for a high steady-state concentration of the oxidised forms of the substrates, of high pH and high NAD^+ concentration. The final mixture was acetylated so that inositol and the fluoroinositol could be separated cleanly.

The inositol dehydrogenase was found to catalyse the radiolabelling of all of the monodeoxy-fluoro-*myo*-inositols to a high specific activity except 1D-4-deoxy-4-fluoro-*myo*-inositol **23**, which was labelled only to a very small extent, and 2-deoxy-2-fluoro-*myo*-inositol **32** (Scheme 2) which was not labelled to any detectable extent. These two compounds were [2-^{3}H]-labelled by chemical labelling procedures described previously[5,8] and modified as described in the Experimental section. The availability of the set of six monodeoxy-fluoro-*myo*-[2-^{3}H]inositols labelled to high specific activity has been used to characterise the incorporation of this compound into phospholipid and the phospholipids formed, which will be described elsewhere.



Scheme 2 Radiolabelling of 2-deoxy-2-fluoro-*myo*-inositol and 1D-4-deoxy-4-fluoro-*myo*-inositol

Experimental

Chemicals used were of standard laboratory grade. Pyridine was refluxed over KOH, distilled, and stored over 4 Å molecular sieves. Dimethylformamide (DMF) was distilled from CaH_2 and stored over 4 Å molecular sieves. Light petroleum was the fraction boiling in the range 40–60 °C. Caesium camphanate was prepared by mixing of a solution of caesium carbonate (7.4 g, 22.7 mmol) in methanol with (*S*)-(−)-camphanic acid (10 g, 46 mmol), evaporation of the methanol, and washing of the solid with diethyl ether to give caesium camphanate (16 g).

High-resolution NMR spectra were recorded on a Bruker AM 400 high-resolution spectrometer with $SiMe_4$ or sodium 3-(trimethylsilyl)propionate as the internal standard. *J*-Values are given in Hz. For TLC, silica gel precoated glass sheets (Merck plates $60F_{254}$) were used (0.25 mm; 2 mm for preparative TLC) and the compounds were detected by dipping of the plate into aq. ammonium sulfate and then charring on an electric hotplate, or by quenching of UV fluorescence. TLC plates were scanned for radioactivity by using a Berthold automatic TLC linear analyser. M.p.s were determined in open capillaries and are uncorrected. Optical rotations were measured between 20–24 °C on a Perkin-Elmer 241 polarimeter; $[\alpha]_D$-values are now to be understood as being in units of 10^{-1} deg dm^2 g^{-1}. HPLC analyses were carried out by using a steel column of 4.6 mm diameter handpacked with 5 μm silica (HPLC Technology Ltd.). Preparative HPLC was performed with an Alltech Econosil column of 22 mm diameter. *myo*-Inositol dehydrogenase [EC 1.1.1.18] from *Enterobacter aerogenes* was supplied by Sigma. *myo*-[2-^{3}H]Inositol (17.6 Ci/mmol) was from Amersham International. Evaporation of excess of solvent was performed on a rotary evaporator under reduced pressure.

Chemical Syntheses.—The synthetic pathways are summarised in Scheme 1.

DL-6-O-*Benzyl*-1,2:3,4-*di*-O-*cyclohexylidene*-myo-*inositol* **1**.—Compound **1** was prepared by the method of Garegg and Lindberg.[16] Briefly, DL-1,2:3,4-di-*O*-cyclohexylidene-*myo*-inositol (6.24 g, 18.4 mmol), prepared by the method of Garegg *et al.*,[18] was added to a mixture of dibutyltin oxide (20 g, 80 mmol) in toluene (100 cm^3) and the mixture was refluxed for 6 h with azeotropic removal of water using a Dean–Stark apparatus. The majority of the toluene was then evaporated off to leave a clear syrup (~20 cm^3). Benzyl bromide (6.3 g, 36 mmol) and tetrabutylammonium bromide (3.0 g, 9.2 mmol) were added and the mixture was stirred at 80 °C until the reaction had gone to completion [monitored by TLC with ethyl acetate–toluene (1:1) as developer]. Chromatography on silica gel (200 g) with ethyl acetate–toluene (1:9) as eluent and again on silica (600 g), with the same eluent, yielded *myo*-inositol **1** (3.98 g, 50.4%) m.p. 124 °C (from acetone–light petroleum) (lit.,[16] 125–126 °C) (Found: C, 69.5; H, 8.1. Calc. for $C_{25}H_{34}O_6$: C, 69.8; H, 8.0%); δ_H(400 MHz; $CDCl_3$) 1.20–1.85 (20 H, m, 10 × CH_2), 2.34 (1 H, d, OH), 3.69 (1 H, t, $J_{6,1}$ 4.6, 6-H), 3.78 (1 H, dd, $J_{3,4}$ 10, 3-H), 3.88 (1 H, m, $J_{5,6}$ 5.0, 5-H), 4.03 (1 H, t, $J_{4,5}$ 8.9, 4-H), 4.42 (1 H, t, $J_{1,2}$ 6, 1-H), 4.65 (1 H, t, $J_{2,3}$ 3.2, 2-H), 4.67 and 4.80 (2 H, 2 d, *J* 11.7, CH_2Ph) and 7.31–7.37 (5 H, m); *m/z* (EI) 430 (M$^+$); and DL-5-*O*-benzyl-1,2:3,4-di-*O*-cyclohexylidene-*myo*-inositol (43%) as a syrup; δ_H(400 MHz; $CDCl_3$) 1.20–1.80 (20 H, m, 10 × CH_2), 2.63 (1 H, s, OH), 3.53 (1 H, dd, $J_{5,6}$ 6.6, 5-H), 3.72 (1 H, dd, $J_{3,4}$ 9.9, 3-H), 3.87 (1 H, t, $J_{6,1}$ 5.5, 6-H), 4.07 (1 H, t, $J_{4,5}$ 9.2, 4-H), 4.20 (1 H, t, $J_{1,2}$ 5.6, 1-H), 4.62 (1 H, dd, $J_{2,3}$ 3.1, 2-H), 4.68 and 4.94 (2 H, 2 d, *J* 11.7, CH_2Ph) and 7.18–7.41 (5 H, m).

DL-6-O-*Benzyl*-1,2:3,4-*di*-O-*cyclohexylidene*-5-O-*tosyl*-myo-*inositol* **2**.—Compound **1** (6.0 g, 14 mmol) was dissolved in a minimum of dry pyridine at 0 °C and toluene-*p*-sulfonyl chloride (5.3 g, 28 mmol) was added at a rate that did not cause the temperature to rise above 10 °C. The reaction mixture was stirred and allowed to reach room temperature. After 12 h the solution was poured into ice-cold, saturated aq. $NaHCO_3$, followed by light petroleum (100 cm^3). The mixture was stirred and the crystals which had formed in the light petroleum phase were filtered off to give the tosate **2** (7.78 g, 95%), m.p. 127–130 °C (Found: C, 65.8; H, 7.0. $C_{32}H_{40}O_8S$ requires C, 65.8; H, 6.9%); δ_H(400 MHz; $CDCl_3$) 1.24–1.67 (20 H, m, 10 × CH_2), 2.43 (3 H, s, Me), 3.78 (1 H, dd, $J_{5,6}$ 10, 5-H), 4.07 (1.H dd, $J_{6,1}$ 8.0, 6-H), 4.09 (1 H, s, $J_{2,3}$ 3.0, 2-H), 4.44 (1 H, dd, $J_{3,4}$ 7.0, 3-H), 4.59 (1 H, dd, $J_{4,5}$ 3.5, 4-H) 4.63 and 4.8 (2 H, 2 d, *J* 11.8, CH_2Ph) 4.79 (1 H, d, $J_{1,2}$ 3.0, 1-H), 7.26–7.37 (7 H, m) and 7.31 and 7.86 (2 H, d, *J* 8.4); *m/z* (EI) 584 (M$^+$).

DL-6-O-*Benzyl*-1,2:3,4-*di*-O-*cyclohexylidene*-5-O-*propionyl*-neo-*inositol* **3**.—The tosate **2** (6.0 g, 10 mmol) and caesium propionate (10.6 g, 52 mmol) were dissolved in DMF (40 cm^3) and heated at 140 °C for 12 h. The mixture was partitioned with toluene (100 cm^3) and water (200 cm^3) and the organic layer was washed with saturated aq. NaCl (200 cm^3 × 2). The toluene was evaporated to give compound **3** as a red gum, δ_H(400 MHz; $CDCl_3$) 1.17 (3 H, t, *J* 7.6), 1.26–1.75 (20 H, m, 10 × CH_2), 2.39 and 2.40 (2 H, 2 q, *J* 7.6), 3.52 (1 H, dd, $J_{6,1}$ 7.0, 6-H), 3.95 (1 H, dd, $J_{4,5}$ 1.8, 4-H), 4.21 (1 H, dd, $J_{3,4}$ 10.4, 3-H), 4.24 (1 H, dd, $J_{1,2}$ 5.0, 1-H), 4.66 (1 H, t, $J_{2,3}$ 3.5, 2-H), 5.82 (1 H, t, $J_{5,6}$ 3.6, 5-H), 4.6 and 4.7 (2 H, 2 d, *J* 12.5, CH_2Ph), 7.25–7.38 (5 H, m); *m/z* (EI) 486 (M$^+$).

DL-6-O-*Benzyl*-1,2:3,4-*di*-O-*cyclohexylidene*-neo-*inositol* **4**.—Methanol (50 cm^3) and NaOH (5 mol dm^{-3}; 10 cm^3) were added to the crude propionate **3** and the mixture was stirred for 4 h. Crystals of compound **4** that precipiated during the reaction were filtered off, dried *in vacuo* and recrystallised from ethyl acetate. Methanol was evaporated off from the filtrate and the residue was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$), filtered, and the ethyl acetate was evaporated off to leave a solid, which was recrystallised from ethyl acetate. The two sets of crystals were combined to give compound **4** (4.25 g, 96% yield from **2**) m.p. 200 °C (Found: C, 69.7; H, 8.1. $C_{25}H_{34}O_6$ requires C, 69.8; H, 7.9%); δ_H(400 MHz; $CDCl_3$) 1.43–1.76 (20 H, m, 10 × CH_2), 2.33 (s, OH), 3.47 (1 H, dd, $J_{6,1}$ 7.0, 6-H), 3.90 (1 H, dd, $J_{4,5}$ 2.0, 4-H), 4.34 (1 H, t, $J_{1,2}$ 5.0, 1-H), 4.35 (1 H, dd, $J_{3,4}$ 10.0, 3-H), 4.39 (1 H, t, $J_{5,6}$ 3.4, 5-H), 4.64 (1 H, dd, $J_{2,3}$ 3.2, 2-H), 4.73 and 4.82 (2 H, 2 d, *J* 12.3, CH_2Ph) and 7.30–7.39 (5 H, m); *m/z* (EI) 430 (M$^+$).

DL-1,2,3,4-*Tetra*-O-*acetyl*-6-O-*benzyl*-5-*deoxy*-5-*fluoro*-myo-*inositol* **5**.—To stirred *neo*-derivative **4** (1.0 g, 2.3 mmol) under nitrogen at −20 °C (solid CO_2/CCl_4) was added DAST (5.0 g, 31 mmol). The reaction mixture was left to reach room temperature during 4 h; it was then carefully added dropwise to ice-cold, saturated aq. $NaHCO_3$ (250 cm^3) and partitioned between toluene (100 cm^3) and water. The toluene was evaporated off and the residue was added to acetic acid (80%; 100 cm^3) and refluxed for 3 h. The acetic acid was evaporated off and the residue was dried overnight in high vacuum. The dried residue was dissolved in dry pyridine (6 cm^3)–acetic anhydride (3 cm^3) and the solution was stirred at 65 °C for 3 h. TLC [ethyl acetate–toluene (1:4)] showed a single product, R_f 0.6. Chromatography on silica gel (80 g) with ethyl acetate–toluene (1:4) as eluent, followed by crystallisation from acetone–light petroleum, gave compound **5** (880 mg, 86%), m.p. 130–131 °C (Found: C, 57.25; H, 5.8. $C_{21}H_{25}FO_9$ requires C, 57.3; H, 5.7%); δ_H(400 MHz; $CDCl_3$) 1.98, 2.00, 2.11 and 2.17 (12 H, 4 s, 4 × Ac), 4.03 (1 H, dt, $J_{H,F}$ 13.2, $J_{6,1}$ 10.5, 6-H), 4.57 (1 H, dt,

$J_{H,F}$ 51, $J_{5,6}$ 9.0, 5-H), 4.66 and 4.86 (2 H, 2 d, J 11.6, CH_2Ph), 5.0 (1 H, dd, $J_{1,2}$ 3.0, 1-H), 5.0 (1 H, t, $J_{3,4}$ 10.5, 3-H), 5.53 (1 H, t, $J_{2,3}$ 3.0, 2-H), 5.57 (1 H, dt, $J_{H,F}$ 13.5, $J_{4,5}$ 9.0, 4-H) and 7.26–7.36 (5 H, m); m/z (EI) 440 (M^+).

DL-1,2,3,4-*Tetra*-O-*acetyl*-5-*deoxy*-5-*fluoro*-myo-*inositol* **6**.—Compound **5** (250 mg, 0.57 mmol) was hydrogenated at room temperature in a mixture of ethyl acetate (20 cm^3) and acetic acid (1 cm^3) in the presence of palladium-on-charcoal (10%; 150 mg) until consumption of hydrogen ceased. The catalyst was removed by filtration and the filtrate was evaporated off to leave a residue, which was crystallised from acetone–light petroleum to give *compound* **6** (192 mg, 97%), m.p. 138–140 °C (Found: C, 48.1; H, 5.5. $C_{14}H_{19}FO_9$ requires C, 48.0; H, 5.4%); δ_H(400 MHz; $CDCl_3$) 2.00, 2.09, 2.11 and 2.18 (12 H, 4 s, 4 × Ac), 2.67 (1 H, d, OH), 4.23 (1 H, m, $J_{H,F}$ 10.0, 6-H), 4.43 (1 H, dt, $J_{H,F}$ 50.8, $J_{5,6}$ 9.0, 5-H), 4.94 (1 H, dd, $J_{1,2}$ 2.7, 1-H), 5.03 (1 H, dd, $J_{3,4}$ 10.4, 3-H), 5.56 (1 H, m, 4-H) and 5.57 (1 H, t, $J_{2,3}$ 2.7, 2-H).

5-*Deoxy*-5-*fluoro*-myo-*inositol* **7**.—The acetate **6** (100 mg, 0.29 mmol) was dissolved in a minimum volume of methanol and sodium methoxide (100 mm^3; 0.1 mol dm^{-3}) was added to the stirred mixture. After 2 h the mixture was filtered and the solid obtained was redissolved in deionised water and neutralised with a mixed-bed resin, filtered, and crystallised from methanol to give title compound **7** (50 mg, 97%), m.p. 223–225 °C (lit.,[6] 222–224 °C) (Found: C, 39.8; H, 6.1. Calc. for $C_6H_{11}FO_5$: 39.6; H, 6.0%); δ_H(400 MHz; $CDCl_3$) 3.56 (2 H, dd, J 2.6, 1- and 3-H), 3.89 (2 H, dt, J_{HF} 14.2, J 10.2, 4- and 6-H), 4.04 (1 H, t, 2-H) and 4.21 (1 H, dt, J_{HF} 52, $J_{5,6}$ 9.0, 5-H); δ_F(376 MHz; D_2O) shift upfield from trifluoroacetic acid φ 122.5 ppm (dt, J 14, J 52).

DL-1,4,5,6-*Tetra*-O-*benzyl*-myo-*inositol* **8**.—To a stirred suspension of NaH (60%; 8.0 g) in DMF (100 cm^3) at room temperature, a solution of DL-1,2-isopropylidene-*myo*-inositol (10 g, 46 mmol), prepared by the method of Gigg *et al.*,[19] in DMF (100 cm^3) was added dropwise. After evolution of hydrogen had stopped, benzyl bromide (32 g, 187 mmol) in toluene (200 cm^3) was added dropwise, slowly and with stirring to prevent caking or overheating of the reaction mixture. The reaction was followed to completion with two TLC systems, the first using methanol–chloroform (3:7) to monitor the conversion of the starting material, R_f 0.4; and the second using ethyl acetate–toluene (1:4) to monitor the formation of the final product, R_f 0.6. Methanol was added slowly to destroy the excess of sodium hydride, and the mixture was poured into a mixture of saturated aq. sodium chloride (1.25 dm^3) and toluene–light petroleum (4:1; 300 cm^3). The organic layer was extracted and evaporated to give a yellow oil, which was dissolved in methanol (400 cm^3) with conc. HCl (10 cm^3) and was stirred overnight. TLC [ethyl acetate–toluene (3:1)] gave a single spot, R_f 0.6. The mixture was added to rapidly stirred light petroleum (1.5 dm^3) and ice/water (3 dm^3) to precipitate the product, which was filtered off, washed successively with water and toluene, and recrystallised from acetone–light petroleum to give compound **8** (21 g, 85%), m.p. 115–117 °C (lit.,[12] 115 °C).

DL-1,4,5,6-*Tetra*-O-*benzyl*-3-O-*tosyl*-myo-*inositol* **9**.—The diol **8** (5.0 g, 9.3 mmol) was dissolved in a minimum of dry pyridine at 0 °C and toluene-*p*-sulfonyl chloride (3.6 g, 19 mmol) was added at a rate that did not cause the reaction temperature to rise above 10 °C. The reaction was stirred overnight at room temperature and additional toluene-*p*-sulfonyl chloride (200 mg) was added to take the reaction to completion. After a further 12 h the mixture was poured onto ice-cold, saturated aq. $NaHCO_3$–light petroleum and stirred until the products crystallised. The mixture was filtered and the product was recrystallised from acetone–light petroleum to give DL-1,4,5,6-tetra-*O*-benzyl-3-*O*-tosyl-*myo*-inositol **9** (6.2 g, 96%), m.p. 115–117 °C (lit.,[12] 115–117 °C) (Found: C, 70.8; H, 6.1. Calc. for $C_{41}H_{42}O_8S$: C, 70.9; H, 6.05%); δ_H(400 MHz; $CDCl_3$) 2.35 (3 H, s, Me), 3.46 (1 H, t, $J_{5,6}$ 9.3, 5-H), 3.49 (1 H, dd, $J_{1,2}$ 2.4, 1-H), 3.96 (1 H, t, $J_{4,5}$ 9.4, 4-H), 4.04 (1 H, t, $J_{6,1}$ 9.6, 6-H), 4.47 (1 H, t, $J_{2,3}$ 2.6, 2-H), 4.49 (1 H, dd, $J_{3,4}$ 9.6, 3-H), 4.55–4.90 (8 H, m, 4 × CH_2Ph), 7.07–7.33 (20 H, m) and 7.14 and 7.71 (4 H, 2 d, J 8.2).

DL-2,3,4,5-*Tetra*-O-*benzyl*-1-*deoxy*-1-*fluoro*-6-O-*tosyl*-scyllo-*inositol* **10**.—To the stirred tosate **9** (1.0 g, 1.44 mmol) kept at −20 °C (solid CO_2/CCl_4) under dry nitrogen, DAST (5.0 g, 0.31 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and after 4 h was added dropwise to a stirred, ice-cold mixture of saturated aq. $NaHCO_3$ and light petroleum. As in the previous stage the product slowly crystallised from the petroleum layer; it was filtered off, and chromatography on silica gel (100 g) with ethyl acetate–toluene (1:9) as eluent gave the *fluoride* **10** (0.83 g, 83%), m.p. 134–136 °C (Found: C, 70.9; H, 5.9. $C_{41}H_{41}FO_7S$ requires C, 70.8; H, 5.9%); δ_H(400 MHz; $CDCl_3$) 2.38 (3 H, s), 3.48–3.64 (3 H, m, 3-, 4- and 5-H), 3.66 (1 H, dt, $J_{H,F}$ 13, J 9.5, 2-H), 4.46 (1 H, dt, $J_{H,F}$ 51, J 9.5, 1-H), 4.66–4.89 (9 H, m, 4 × CH_2Ph and 6-H), 7.19–7.30 (22 H, m) and 7.8 (2 H, d, J 8.2); m/z (EI) 605 (M − CH_2Ph).

(−)-1L-3,4,5,6-*Tetra*-O-*benzyl*-1-*deoxy*-1-*fluoro*-myo-*inositol Camphanate* **11** *and* (+)-1D-3,4,5,6-*Tetra*-O-*benzyl*-1-*deoxy*-1-*fluoro*-myo-*inositol Camphanate* **14**.—To the *scyllo*-inositol derivative **10** (4.0 g, 5.76 mmol) was added a mixture of caesium camphanate (8.0 g, 4 mol equiv.) in DMF (16 CM^3). The mixture was stirred at 160 °C for 2 h, cooled, and then partitioned between toluene and water. The toluene layer was dried ($MgSO_4$) and evaporated to give a solid, which was recrystallised from light petroleum, m.p. 125 °C. TLC with diethyl ether/dichloromethane (1:19) showed separation of the two *diastereoisomers* (**11** R_f 0.50; **14** R_f 0.55). Chromatography on deactivated silica gel (500 g; 10% water) equilibriated with diethyl ether–dichloromethane (1:9; 2.5 dm^3) as eluent, using an LKB 4700 Unicord for detection, yielded the separated diastereoisomers: **11** (2.0 g, 96%), m.p. 118 °C; HPLC t_R camphanate 66 min [dichloromethane–acetonitrile (98:2) 3.0 cm^3 min^{-1}]; $[\alpha]_D$ −21.5 (*c* 1, $CHCl_3$) (Found: C, 73.1; H, 6.5. $C_{44}H_{47}FO_8$ requires C, 73.1; H, 6.5%); δ_H(400 MHz; $CDCl_3$) 0.926 (3 H, s, Me), 0.932 (3 H, s, Me), 1.1 (3 H, s, Me), 1.68 (1 H, m), 1.90 (1 H, m), 2.07 (1 H, m), 2.41 (1 H, m), 3.47 (1 H, t, $J_{5,6}$ 8.8, 5-H), 3.55 (1 H, d, $J_{3,4}$ 9.0, 3-H), 3.75 (1 H, t, $J_{4,5}$ 10.1, 4-H), 4.01 (1 H, dt, J_{HF} 12.0, $J_{6,1}$ 9.7, 6-H), 4.57 (1 H, ddd, J_{HF} 47.5, $J_{1,2}$ 3.2, 1-H), 4 54–4.88 (8 H, 8 d, 4 × CH_2Ph), 5.98 (1 H, dt, J_{HF} 7.8, $J_{2,3}$ 3.0, 2-H) and 7.26–7.33 (20 H, m); and **14** (1.8 g, 87%), m.p. 115 °C; HPLC analysis of camphanate t_R 78 min [dichloromethane–acetonitrile (98:2), 3.0 cm^3 min^{-1}]; $[\alpha]_D$ +10.7 (*c* 1, $CHCl_3$) (Found: C, 73.1; H, 6.5%); δ_H(400 MHz; $CDCl_3$) 0.87 (3 H, s, Me), 1.04 (3 H, s, Me), 1.10 (3 H, s, Me), 1.69 (1 H, m), 1.90 (1 H, m), 2.04 (1 H, m), 2.36 (1 H, m), 3.47 (1 H, t, $J_{5,6}$ 8.8, 5-H), 3.56 (1 H, dd, $J_{3,4}$ 9.0, 3-H), 3.82 (1 H, t, $J_{4,5}$ 10.1, 4-H), 3.92 (1 H, dt, $J_{H,F}$ 12.0, $J_{6,1}$ 9.7, 6-H), 4.55 (1 H, ddd, $J_{H,F}$ 47.5, $J_{1,2}$ 3.2, 1-H), 4.54–4.88 (8 H, 8 d, 4 × CH_2Ph), 5.98 (1 H, dt, J_{HF} 7.8, $J_{2,3}$ 3.0, 2-H) and 7.30–7.40 (20 H, m).

(+)-1L-3,4,5,6-*Tetra*-O-*benzyl*-1-*deoxy*-1-*fluoro*-myo-*inositol* **12**.—The camphanate of higher R_f-value, **11** (1.8 g, 2.5 mmol) was dissolved in warm methanol (25 cm^3) and aq. NaOH (3 mol dm^{-3}; 5 cm^3) was added to the stirred solution.

When the reaction was complete, detected by TLC by the formation of a new zone at lower R_f [diisopropyl ether–dichloromethane (1:19)], water was added until the solution went milky and the mixture was stirred overnight to allow the product to crystallise. Water (100 cm^3) was added to the mixture again, to drive the crystallisation to completion. The mixture was stirred and filtered, and the solid product was washed with water and dried to give *compound* **12** (1.3 g, 95%), m.p. 115–117 °C; $[\alpha]_D$ +7 (*c* 1, $CHCl_3$) (Found: C, 75.2; H, 6.4. $C_{34}H_{35}FO_5$ requires C, 75.3; H, 6.5%); δ_H(400 MHz; $CDCl_3$) 2.51 (1 H, s, OH), 3.42–3.47 (2 H, m, 3- and 5-H), 3.98 (1 H, t, $J_{4,5}$ 9.5, 4-H), 4.15 (1 H, dt, $J_{H,F}$ 11.6, $J_{6,1}$ 9.5, 6-H), 4.34 (1 H, t, 2-H), 4.43 (1 H, ddd, $J_{H,F}$ 49.9, $J_{1,2}$ 2.8, 1-H), 4.68–4.89 (8 H, m, 4 × CH_2Ph) and 7.27–7.36 (20 H, m).

(−)-1L-1-*Deoxy*-1-*fluoro*-myo-*inositol* **13**.—The benzyl protecting groups were removed by dissolution of compound **12** (1.15 g, 2.1 mmol) in ethanol (95%; 25 cm^3) and hydrogenation using 10% palladium-on-carbon (500 mg) at room temperature and atmospheric pressure for two days. The catalyst was removed by filtration into Hyflo and washed successively with water (10 cm^3) and ethanol (10 cm^3) alternatively (3×). The filtrate was evaporated to a gum, which was dissolved in water (1 cm^3) and the solution was refiltered through Hyflo in a Pasteur pipette. This solution was evaporated to give a gum, which was dissolved in absolute ethanol (25 cm^3). The product was crystallised and filtered off, and the remaining mother liquors were concentrated to yield further crystals of product. The products of the two crystallisations were combined and recrystallised from ethanol to give title compound **13** (354 mg, 92%), m.p. 216 °C (Found: C, 39.7; H, 6.1. Calc. for $C_6H_{11}FO_5$: C, 39.6; H, 6.0%), $[\alpha]_D$ −6.9 (*c* 2, water); δ_H(400 MHz; D_2O) 3.29 (1 H, t, $J_{5,6}$ 9.6, 5-H), 3.54 (1 H, dd, $J_{3,4}$ 8.3, 3-H), 3.65 (1 H, t, $J_{4,5}$ 9.6, 4-H), 3.91 (1 H, dt, $J_{H,F}$ 12.7, $J_{6,1}$ 9.8, 6-H), 4.29 (1 H, dt, $J_{H,F}$ 8.2, $J_{2,3}$ 2.9, 2-H) and 4.45 (1 H, ddd, $J_{H,F}$ 47, $J_{1,2}$ 3.0, 1-H); δ_F(376 MHz; D_2O) shift upfield from trifluoroacetic acid δ 126.8 ppm (ddd, *J* 50.5, 13.0, 8.6).

(−)-1D-3,4,5,6-*Tetra*-O-*benzyl*-1-*deoxy*-1-*fluoro*-myo-*inositol* **15**.—The camphanate of lower R_f-value, **14** (1.65 g, 2.29 mmol) was hydrolysed in the same manner as its enantiomer **11** described above to give compound **15** (1.2 g, 96%); physical data were identical with those of its enantiomer **12** except $[\alpha]_D$ −7.9 (*c* 1, $CHCl_3$).

(+)-1D-1-*Deoxy*-1-*fluoro*-myo-*inositol* **16**.—The tetra-*O*-benzyl compound **15** was treated identically to its enantiomer **12** to give title compound **16** with the same physical data as those of its enantiomer **13**, except $[\alpha]_D$ +7.1 (*c* 2, water).

1,3,4,6-*Tetra*-O-*benzyl*-myo-*inositol* **17** *and* DL-1,3,4,5-*Tetra*-O-*benzyl*-myo-*inositol* **18**.—1,4-Di-*O*-benzyl-*myo*-inositol (6.0 g, 16.7 mmol), prepared by the method of Gigg *et al.*,[19] and dibutyltin oxide (10 g, 40 mmol) were dissolved in a mixture of toluene–methanol (2:1; 300 cm^3) and boiled under reflux with azeotropic removal of water for 4 h. The mixture was concentrated to a clear syrup (50 cm^3) and benzyl bromide (8.55 g, 50 mmol), tetrabutylammonium bromide (1 g) and toluene (200 cm^3) were added. The reaction mixture was stirred at 160 °C for two days with further azeotropic removal of water using a Dean–Stark apparatus. Four major products were detected by TLC using ethyl acetate–toluene (1:1). The products of highest R_f-values were identified as 1,2,3,4,6-penta-*O*-benzyl- (R_f 0.78) and 1,2,3,5,6-penta-*O*-benzyl-*myo*-inositol (R_f 0.73) by comparison of their R_f-values with those of samples of these compounds previously synthesized by other methods. Chromatography on silica gel (500 g) with ethyl acetate–toluene (3:7) as eluent yielded the two products of highest R_f on TLC as an unseparated mixture and 1,3,4,6-*tetra*-O-*benzyl*-myo-*inositol* **17**, R_f 0.67 (2 g, 22%), m.p. 125 °C (Found: C, 75.8; H, 6.7. $C_{34}H_{36}O_6$ requires C, 75.55; H, 6.7%); δ_H(400 MHz; $CDCl_3$) 2.57 (2 H, s, OH), 3.37 (2 H, dd, $J_{1,2}$ 2.7, $J_{3,4}$ 9.5), 3.50 (1 H, t, $J_{5,6}$ 9.5, 5-H), 3.86 (2 H, t, $J_{4,5}$ 9.3, 4- and 6-H), 4.22 (1 H, t, $J_{2,3}$ 2.7, 2-H), 4.69 (4 H, s, 2 × CH_2Ph), 4.80 and 4.90 (4 H, 2 d, *J* 11.2, 2 × CH_2Ph), 7.26–7.37 (20 H, m); and DL-1,3,4,5-tetra-*O*-benzyl-*myo*-inositol **18**, R_f 0.53 (3 g, 33%), m.p. 114–115 °C (lit.,[13] 116–118 °C) (Found: C, 75.4; H, 6.7. Calc. for $C_{34}H_{36}O_6$: C, 75.55; H, 6.7%); δ_H(400 MHz; $CDCl_3$) 2.44 (1 H, s, OH), 2.47 (1 H, OH), 3.23 (1 H, dd, $J_{3,4}$ 9.5, 1-H), 3.33 (1 H, dd, $J_{5,6}$ 9.5, 5-H), 3.41 (1 H, dd, $J_{1,2}$ 2.8, 3-H), 3.97 (1 H, t, $J_{4,5}$ 9.5, 4-H), 4.07 (1 H, t, $J_{6,1}$ 9.5, 6-H), 4.23 (1 H, t, $J_{2,3}$ 2.8, 2-H), 4.65–4.92 (8 H, m, 4 × CH_2Ph) and 7.36–7.25 (20 H, m).

DL-1,3,4,5-*Tetra*-O-*benzyl*-6-O-*tosyl*-myo-*inositol* **19**.—The diol **18** (600 mg, 1.1 mmol) was dissolved in a minimum of stirred pyridine at 0 °C and toluene-*p*-sulfonyl chloride (0.315 mg, 1.65 mmol) was added slowly. The reaction mixture was allowed to reach room temperature gradually and was stirred overnight, when it was poured onto ice–water, filtered, washed with water, dried ($MgSO_4$), and crystallised from toluene to give compound **19** (710 mg, 93%), m.p. 182–184 °C; δ_H(400 MHz; $CDCl_3$) 2.17 (3 H, s, Me), 3.25 (1 H, dd, $J_{1,2}$ 2.4, 1-H), 3.29 (1 H, dd, $J_{3,4}$ 9.7, 3-H), 3.41 (1 H, t, $J_{5,6}$ 9.6, 5-H), 4.00 (1 H, t, $J_{2,3}$ 2.4, 2-H), 4.02 (1 H, t, $J_{4,5}$ 9.2, 4-H), 4.32 and 4.37 (2 H, 2 d, *J* 12.1, CH_2Ph), 4.60–4.86 (6 H, m, 3 × CH_2Ph), 5.2 (1 H, t, $J_{6,1}$ 9.7, 6-H), 7.0 (2 H, d, *J* 8.2), 7.2–7.3 (20 H, m) and 7.8 (2 H, d, *J* 8.2).

DL-2,3,4,6-*Tetra*-O-*benzyl*-1-*deoxy*-1-*fluoro*-5-O-*tosyl*-scyllo-*inositol* **20**.—The tosate **19** (710 mg, 1.0 mmol) was treated with DAST (3 g, 18.6 mmol) as described for the tosate **9**. The single product was filtered off, washed with water, dried, and recrystallised from diisopropyl ether to yield *title compound* **20** (620 mg, 87%), m.p. 141–143 °C (Found: C, 70.7; H, 5.9. $C_{41}H_{41}FO_7S$ requires C, 70.7; H, 5.9%); δ_H(400 MHz; $CDCl_3$) 2.24 (3 H, s, Me), 3.52–3.57 (2 H, m, 3- and 4-H), 3.59–3.66 (2 H, m, 2- and 6-H), 4.59 (1 H, dt, J_{HF} 51.0, *J* 9.0, 1-H), 4.44–4.85 (8 H, m, 4 × CH_2Ph), 4.73 (1 H, dt, 5-H), 7.0 (2 H, d, *J* 8.3), 7.2–7.3 (20 H, m) and 7.7 (2 H, d, *J* 8.3).

(+)-1D-1,3,5,6-*Tetra*-O-*benzyl*-4-*deoxy*-4-*fluoro*-myo-*inositol Camphanate* **21** *and* (−)1L-1,3,5,6-*Tetra*-O-*benzyl*-4-*deoxy*-4-*fluoro*-myo-*inositol Camphanate* **24**.—To a solution of the *scyllo*-derivative **20** (580 mg, 0.83 mmol) in DMF (5 cm^3) was added (*S*)-(−)-caesium camphanate (1.2 g, 3.4 mmol) and the mixture was heated to 140 °C for 2 h, cooled, and partitioned between toluene and water. The toluene layer was dried ($MgSO_4$) and evaporated to give a solid, which was a mixture of the two diastereoisomers. Preparative HPLC [dichloromethane–acetonitrile (98:2) 3.0 cm^3 min^{-1}] separated the two *diastereoisomers* **21**, t_R 56 (220 mg, 73%), m.p. 116 °C; $[\alpha]_D$ +0.7 (*c* 4.5, $CHCl_3$) (Found: C, 73.2; H, 6.5. $C_{44}H_{47}FO_8$ requires C, 73.1; H, 6.5%); δ_H(400 MHz; $CDCl_3$) 0.84 (3 H, Me), 0.98 (3 H, Me), 1.08 (3 H, Me), 1.65 (1 H, m), 1.88 (1 H, m), 2.00 (1 H, m), 2.34 (1 H, m), 3.50–3.62 (3 H, m, 1-, 4- and 5-H), 3.72 (1 H, t, 6-H), 4.54–4.87 (9 H, m, 4 × CH_2Ph, 4-H), 5.92 (1 H, dd, 2-H) and 7.26–7.37 (20 H, m); and **24**, t_R 64 (200 mg, 67%), m.p. 126 °C; $[\alpha]_D$ −5.3 (*c* 1, $CHCl_3$) (Found: C, 73.2; H, 6.5%); δ_H(400 MHz; $CDCl_3$) 0.84 (3 H, Me), 0.98 (3 H, Me), 1.08 (3 H, Me), 1.66 (1 H, m), 1.88 (1 H, m), 2.03 (1 H, m), 2.39 (1 H, m), 3.51–3.62 (3 H, m, 1-, 4- and 5-H), 3.80 (1 H, t, 6-H), 4.57–4.87 (9 H, m, 4 × CH_2Ph, 4-H), 5.94 (1 H, dd, 2-H) and 7.29–7.37 (20 H, m).

(+)-1D-1,3,5,6-*Tetra*-O-*benzyl*-4-*deoxy*-4-*fluoro*-myo-*inositol* **22**.—The camphanate **21** (220 mg, 0.31 mmol) was dissolved

in methanol (20 cm^3), aq. NaOH (2.5 mol dm^{-3}; 1.0 cm^3) was added, and the mixture was stirred overnight. The product crystallised out slowly when water (60 cm^3) was added over a period of 1 h; it was filtered off, washed and dried *in vacuo* to yield title compound **22** (155 mg, 94%), m.p. 122 °C; $[\alpha]_D$ +9.1 (*c* 1, $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 3.40 (1 H, dd, $J_{1,2}$ 3.0, 1-H), 3.42 (1 H, dt, 3-H), 3.55 (1 H, dt, J_{HF} 14.5, $J_{5,6}$ 9.0, 5-H), 3.97 (1 H, t, $J_{6,1}$ 9.5, 6-H), 4.18 (1 H, t, 2-H), 4.67–4.86 (8 H, m, 4 × CH_2Ph), 4.96 (1 H, dt, J_{HF} 52, $J_{4,5}$ 9.0, 4-H) and 7.22–7.37 (20 H, m).

(+)-1D-4-*Deoxy*-4-*fluoro*-myo-*inositol* **23**.—The tetra-*O*-benzyl-protected inositol **22** (147 mg, 0.27 mmol) was treated identically to compound **12** as described above to yield *title compound* **23** (40 mg, 82%), m.p. 211 °C (Found: C, 39.75; H, 6.05. $C_6H_{11}FO_5$ requires C, 39.6; H, 6.0%); $[\alpha]_D$ +2.6 (*c* 1, water); δ_H(400 MHz; D_2O) 3.55–3.69 (3 H, m, *J* 4.5, 1-, 5- and 6-H), 3.83 (1 H, ddd, J_{HF} 12.3, $J_{3,4}$ 9.6, 3-H), 4.07 (1 H, dd, $J_{2,3}$ 3.0, 2-H) and 4.50 (1 H, dt, J_{HF} 53.0, $J_{4,5}$ 9.2, 4-H); δ_F(376 MHz; D_2O) shift upfield from trifluoroacetic acid δ 127 ppm (dtd, *J* 56.4, 13.6 and 4.9).

(−)-1L-1,3,5,6-*Tetra*-O-*benzyl*-4-*deoxy*-4-*fluoro*-myo-*inositol* **25**.—The camphanate **24** (200 mg, 0.28 mmol) was treated identically to isomer **21** as described above to yield compound **25** (145 mg, 96%). Physical data were identical with those of isomer **22**, except $[\alpha]_D$ −9.04 (*c* 0.7, $CHCl_3$).

(−)-1L-4-*Deoxy*-4-*fluoro*-myo-*inositol* **26**.—The tetra-*O*-benzyl compound **25** (137 mg, 0.25 mmol) was treated identically to isomer **22** as described above to give title compound **26** (32 mg, 70%), with identical physical data with those of its enantiomer, except $[\alpha]_D$ −2.0 (*c* 1, water).

2-*Deoxy*-2-*fluoro*-myo-*inositol* **32**.—This was synthesized by essentially the same method as Lowe and McPhee[5] and so is only briefly described here. The 2-hydroxy group of 1,3,4,5,6-penta-*O*-benzyl-*myo*-inositol **28** was inverted to give 1,2,3,4,5-penta-*O*-benzyl-*scyllo*-inositol **30** by displacement of a tosyl group with propionate, followed by removal of the propionyl group by treatment with base. These reactions occurred in almost quantitative yield. The *scyllo*-compound **30** was treated with DAST to give a low yield of 1,3,4,5,6-penta-*O*-benzyl-2-deoxy-2-fluoro-*myo*-inositol **31**. 2,5-Anhydro-1,3,4,6-tetra-*O*-benzyl-*myo*-inositol was a major side-product of this reaction. 1,3,4,5,6-Penta-*O*-benzyl-2-deoxy-2-fluoro-*myo*-inositol **31** was deprotected by hydrogenolysis to give 2-deoxy-2-fluoro-*myo*-inositol **32**.

Radiolabelling of Analogues.—1D-1-*Deoxy*-1-*fluoro*-myo-[2-^{3}H]*inositol*, 1L-1-*deoxy*-1-*fluoro*-myo-[2-^{3}H]*inositol*, 1L-4-*deoxy*-4-*fluoro*-myo-[2-^{3}H]*inositol and* 5-*deoxy*-5-*fluoro*-myo-[2-^{3}H]*inositol*. The monodeoxy-fluoro-*myo*-inositol (86 μmol) and *myo*-[2-^{3}H]inositol (17.5 Ci/mmol; 500 mm^3, 0.5 mCi) were evaporated to dryness and dissolved in sodium pyrophosphate buffer (50 mmol dm^{-3}; 100 mm^3) containing NAD^+ (30 mmol dm^{-3}) at pH 8.5. The enzyme inositol dehydrogenase [EC 1.1.1.18] was added (2 units) at room temperature. The exchange reaction was monitored by TLC with butan-1-ol–acetic acid–water (2:1:1) and a TLC plate scanner to detect the positions and intensities of the radiolabelled species. Equilibrium labelling was reached within 1 h. The specific activity of the monodeoxy-fluoro-*myo*-inositol was calculated by measuring the relative amounts of radiolabel present in the inositol, monodeoxy-fluoro-*myo*-inositol and dinucleotide using the TLC scanner.

The mixture was passed through a Pasteur pipette filled with mixed strong cation/strong anion exchange resin (Dowex MR-3 from Sigma) and the resin was washed with water. The eluate was evaporated to less than 100 mm^3 volume, acetic anhydride (1.0 g, 10 mmol) and pyridine (2.0 cm^3) were added and the mixture was stirred for 4 h at 50 °C, evaporated to dryness, and separated by TLC with ethyl acetate–toluene (1:1). The inositol hexaacetate (R_f 0.46) and monodeoxy-fluoro-*myo*-inositol pentaacetate (R_f 0.56) were easily separated on TLC. The position of the monodeoxy-fluoro-*myo*-inositol pentaacetate was detected by a TLC plate scanner and the silica gel in the appropriate area was scraped from the plate. The radiolabelled product was eluted from the silica with methanol–chloroform (1:1) and filtered. The filtrate was evaporated to dryness and the acetylated analogue was hydrolysed by the addition of a small amount of sodium methoxide to a methanolic solution of the analogue. This solution was passed through a short Pasteur pipette column of mixed strong cation/strong anion exchange resin (Dowex MR-3) and then evaporated to dryness to give the labelled monodeoxy-fluoro-*myo*-inositol. This method gave greater than 50% radiochemical yield and specific activities were: 1D-1-deoxy-fluoro-*myo*-[2-^{3}H]inositol, 4.0 Ci/mmol; 1L-1-deoxy-1-fluoro-*myo*-[2-^{3}H]inositol, 3.2 Ci/mmol; 5-deoxy-5-fluoro-*myo*-[2-^{3}H]inositol, 3.5 Ci/mmol and 1L-4-deoxy-4-fluoro-*myo*-[2-^{3}H]inositol, 4.1 Ci/mmol. The radiochemical purities of all the products were >99.9% by TLC.

(+)-1D-4-*Deoxy*-4-*fluoro*-myo-[2-^{3}H]*inositol*. Compound **22** (2.0 mg) was dissolved in acetone (1.0 cm^3) and treated with Jones' reagent (2.0 mm^3) for 1 h at room temperature to give the inosose **27**. The reaction mixture was then partitioned between toluene–water (50 cm^3; 1:1) and the toluene layer was washed with saturated aq. $NaHCO_3$, dried (Na_2CO_3) and evaporated. The residue was dissolved in ethanol, NaB^3H_4 (25 mCi; 8 Ci/mol) was added, and the reaction was left overnight and terminated by the addition of a trace of acetic acid; the mixture was evaporated to dryness and the products were isolated by preparative TLC (PLC) with ethyl acetate–toluene (1:9). The required radiolabelled analogue **22** was identified as the major band on TLC (R_f 0.23) with identical R_f-value to comigrating 'cold' **22**. Hydrogenolysis with 10% palladium-on-carbon (100 mg) in ethanol (20 cm^3) for 24 h removed the benzyl protecting groups. The product was contaminated with a trace of the less polar material, which was removed by the passage of the aq. solution over nonionic polymeric adsorbent resin (Dowex XAD-2) and recovered by evaporation. The specific activity of compound **23** was 2 Ci/mmol and radiochemical purity by TLC was >99.9%.

2-*Deoxy*-2-*fluoro*-myo-[2-^{3}H]*inositol*. The chemical radiolabelling of 2-deoxy-2-fluoro-*myo*-inositol is summarised in Scheme 2. This preparation was performed essentially as described by Lowe and MacPhee.[5] Briefly, 1,3,4,5,6-penta-*O*-benzyl-*myo*-inositol **28** (60 mg, 0.1 mmol), prepared by the method of Nashed and Anderson,[20] was treated in acetone with sodium dichromate (1 mol dm^{-3}) in sulfuric acid (150 mm^3; 4.5 mol dm^{-3}) for 1 h and partitioned between water–toluene (50 cm^3; 1:1). The toluene layer was washed with saturated aq. sodium hydrogen carbonate (50 cm^3), dried (Na_2CO_3), and evaporated to give a syrup of penta-*O*-benzylinosose, which was crystallised from methanol (50 mg, 83%), m.p. 160–162 °C (lit.,[12] 163–164 °C).

The penta-*O*-benzylinosose **29** was treated with excess of NaB^3H_4 (8 Ci/mmol) in ethanol (5 cm^3) overnight, and the reaction mixture was quenched with acetic acid and evaporated to dryness. TLC using ethyl acetate–toluene (1:9) and scanning for tritium showed ~80% *myo*- and 20% *scyllo*-inositol derivatives, identified by co-chromatography with 'cold' standards. The bulk of the *myo*-derivative **28** was removed by crystallisation (30 mg, 60%) from methanol and the *scyllo*-derivative **30** in the mother liquor was isolated by PLC using ethyl acetate–toluene (1:9), and was crystallised from methanol

(7.0 mg, 14%). The product was dissolved in DAST (0.5 cm^3) at −40 °C (solid CO_2/MeCN) and allowed to reach room temperature. The reaction was quenched by addition to saturated, ice-cold aq. $NaHCO_3$ (50 cm^3) and extracted with toluene (2 × 20 cm^3). The majority of the radiolabelled product isolated by PLC in ethyl acetate–toluene (1:19) was 2,5-anhydro-1,3,4,6-tetra-*O*-benzyl-*myo*-inositol (R_f 0.34), which was discarded along with the other side-product, penta-*O*-benzyl-1-deoxy-1-fluoro-*scyllo*-inositol (R_f 0.47). The area of silica gel containing the penta-*O*-benzyl-2-deoxy-2-fluoro-*myo*-inositol **31** (R_f 0.66) was scraped off the plate and the product was eluted from the silica with ethyl acetate. The product was deprotected and purified as for (+)-1D-4-deoxy-4-fluoro-*myo*-inositol **23** to give 2-deoxy-2-fluoro-*myo*-[2-^{3}H]inositol **32**. Radiochemical yield was 1%, specific activity 2 Ci/mmol, radiochemical purity was 99.9% by TLC.

Acknowledgements

This work was supported by a project grant from the Medical Research Council to J.C.M. J.L.O. held a Science and Engineering Research Council Studentship.

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Paper 2/00334A
Received 21*st January* 1992
Accepted 21*st January* 1992