Synthesis of 3,4,5,6-tetrakisphosphates of DL-1,2-dideoxy-1,2-difluoro-*myo*-inositol and DL-1,2-dideoxy-1,2-difluoro-*scyllo*-inositol as analogues of DL-*myo*-inositol 3,4,5,6-tetrakisphosphate

Kevin R. H. Solomons,[a] Sally Freeman,*[,a] David R. Poyner[b] and Farid Yafai[b]

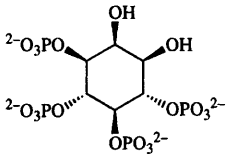
[a] *Department of Pharmacy, University of Manchester, Oxford Road, Manchester M13 9PL, UK*

[b] *Department of Pharmaceutical and Biological Sciences, Aston University, Birmingham B4 7ET, UK*

DL-1,2-Dideoxy-1,2-difluoro-*myo*-inositol was prepared from DL-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol in five steps in an overall yield of 36%. The fluoro substituents were introduced with DAST in separate steps by displacement of hydroxy substituents with inversion of stereochemistry. Difluorination could not be achieved in one step because of competing formation of a 1,4-anhydro derivative. DL-1,2-Dideoxy-1,2-difluoro-*scyllo*-inositol was prepared in 42% overall yield using similar chemistry, with the required inversion of one stereocentre being accomplished by displacement of a tosyl group with caesium propionate. Both difluoroinositol analogues increased the levels of phytic acid (InsP_6) in a skeletal muscle cell line. Each compound was tetraphosphorylated with dibenzyl *N*,*N*-diisopropylphosphoramidite in the presence of 1*H*-tetrazole, with subsequent oxidation of the phosphite with MCPBA. The P–OBn groups were removed by H_2/Pd–C, and the sodium salts of the tetrakisphosphates of the difluoroinositol analogues were obtained by cation exchange.

Introduction

The discovery that *myo*-inositol 1,4,5-trisphosphate is the second messenger linking receptor activation to the mobilisation of calcium from intracellular stores[1] has led to widespread interest into the metabolism and effects of inositol phosphates.[2,3] Recent findings have implicated *myo*-inositol 3,4,5,6-tetrakisphosphate (Ins[3,4,5,6]P_4, **1**) in the long-term uncoupling of chloride secretion from intracellular calcium levels.[4] It has also been shown to be a potent inhibitor of *myo*-inositol 1,3,4-trisphosphate 5/6-kinase activity.[5] In addition, levels of its enantiomer, *myo*-inositol 1,4,5,6-tetrakisphosphate (Ins[1,4,5,6]P_4, **2**), may increase after cell transformation with



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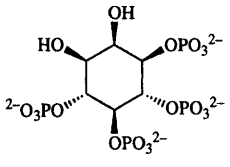

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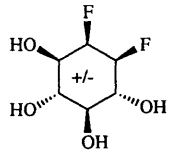
the *src* oncogene,[6] and also after treatment with phosphoinositidase C (PIC)-linked agonists.[7] These tetrakisphosphates are linked with the metabolism of *myo*-inositol 1,3,4,5,6-pentakisphosphate (Ins[1,3,4,5,6]P_5) and phytic acid (InsP_6),[8] which are the most abundant inositol phosphates in mammalian cells, about which little is known in terms of their cellular effects.

The isosteric and isoelectronic replacement of a hydroxy group with a fluoro group has been adopted as a common strategy in the preparation of analogues of inositol and its phosphates.[9–20] Although *gem*-difluoro analogues of *myo*-inositol have been prepared,[10,13,14] no syntheses of *myo*-inositol derivatives with two fluoro groups on different carbons have been reported. As an unexpected side-product, a 1,5-dideoxy-1,5-difluoro-*neo*-inositol derivative has been isolated.[15]

Here, we report the syntheses of DL-1,2-dideoxy-1,2-difluoro-*myo*-inositol† **3** and DL-1,2-dideoxy-1,2-difluoro-*scyllo*-inositol



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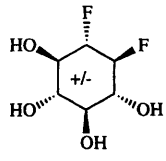

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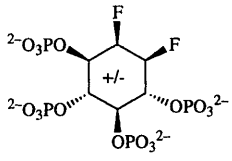

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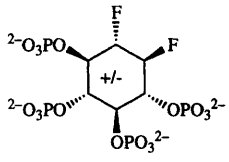

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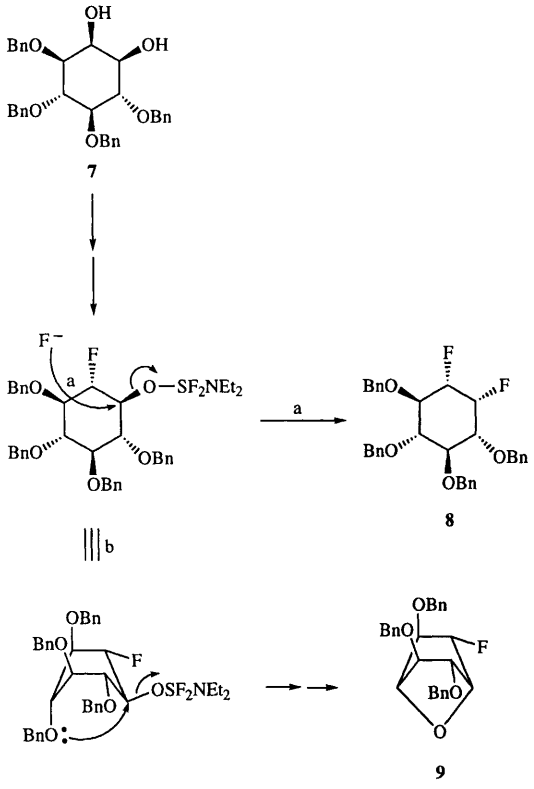
4, in order to investigate their ability to enter cells *via* the inositol transporter, and if so, to examine their actions on the levels of higher inositol phosphates. The tetrakisphosphates of the difluoroinositol derivatives, **5** and **6**, were also prepared. These may mimic the physiological responses of the parent tetrakisphosphates **1** and **2**, and inhibit the kinases and phosphatases that participate in their metabolism.

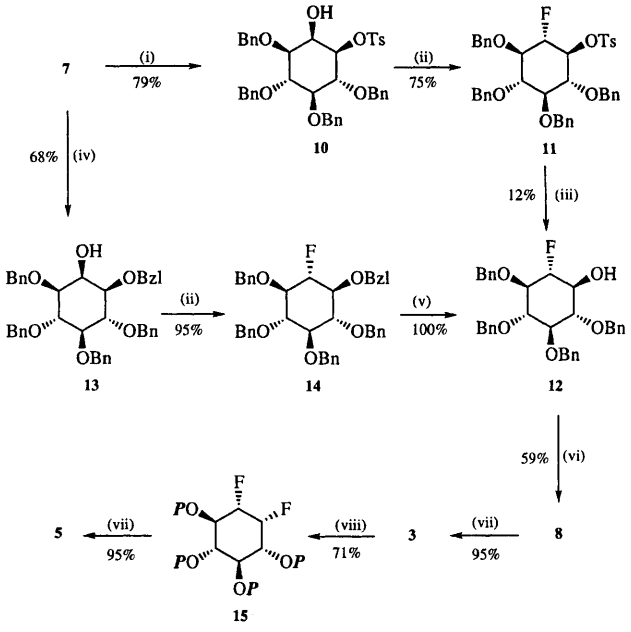
Results and discussion

DL-3,4,5,6-Tetra-*O*-benzyl-*myo*-inositol **7** was prepared in three steps from *myo*-inositol by the method of Baker *et al.*[21] Attempts to fluorinate this compound directly to the 1,2-difluoro analogue **8** by using (diethylamino)sulfur trifluoride (DAST) resulted in a mixture of products, two of which were separated by flash chromatography. Analysis by NMR spectroscopy indicated that the required product **8** had been obtained (< 5% yield), together with the anhydro derivative **9** (14%). These products can be accounted for by the route shown in Scheme 1. The anhydro compound **9** gave an unusual pattern

† All racemic structures of inositols are drawn in the D-form.



Scheme 1 Suggested route for the formation of compounds **8** and **9** from the reaction of DAST with diol **7**



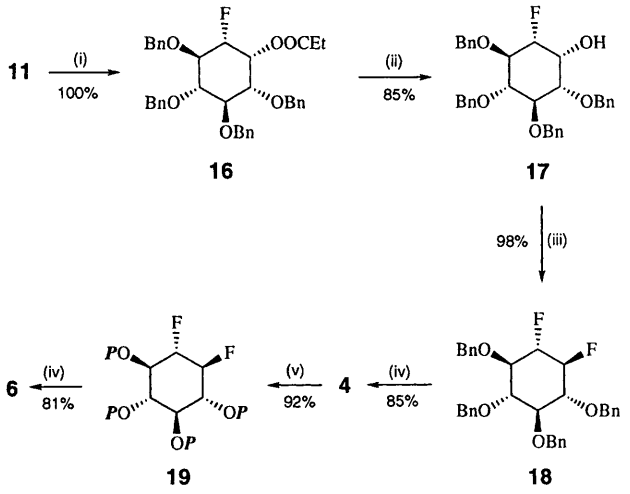
Scheme 2 Synthesis of DL-1,2-dideoxy-1,2-difluoro-*myo*-inositol **3** and its tetrakisphosphate **5**. ***P*** = $(BnO)_2P(O)$–. *Reagents:* (i) TsCl, pyridine; (ii) DAST, CH_2Cl_2; (iii) Na, naphthalene, THF; (iv) PhCOCl, pyridine, DMAP; (v) 5 M aq. NaOH, MeOH; (vi) DAST, CH_2Cl_2, Et_3N; (vii) H_2, Pd–C; (viii) $(BnO)_2PNPr^i_2$, then MCPBA.

by ^{19}F NMR spectroscopy. Conformational analysis‡ of compound **9** gave dihedral angles between the fluorine and neighbouring protons consistent with the observed ddd pattern. Geminal coupling between F and H-1 was 54.1 Hz. The vicinal coupling constants, $J_{F/6\text{-}H}$ and $J_{F/2\text{-}H}$, were 29.7 and 13.8 Hz, respectively, which are consistent with the corresponding calculated dihedral angles of 3.2° and 37.9°. The formation of anhydro by-products has previously been observed in the preparation of 2-deoxy-2-fluoro-*myo*-inositol.[9] These are likely to arise when a boat conformation can be adopted in which the benzyloxy group at position 4 is axial, with the DAST-activated hydroxy group on position-1 equatorial, thereby allowing nucleophilic attack by the benzyl oxygen (Scheme 1). Failure to obtain a reasonable yield of difluoride **8** by direct fluorination of diol **7** led us to investigate its preparation by two separate monofluorination reactions (Scheme 2).

DL-3,4,5,6-Tetra-*O*-benzyl-1-*O*-tosyl-*myo*-inositol **10** and DL-3,4,5,6-tetra-*O*-benzyl-2-deoxy-2-fluoro-1-*O*-tosyl-*scyllo*-inositol **11** were prepared from diol **7** by using methods similar to that described by Offer *et al.*[9] in yields of 79 and 75%, respectively. The fluorination of compound **10**, mediated by DAST, proceeded with inversion of stereochemistry. In order to regenerate the *myo*-configuration during the second fluorination with DAST, it was necessary to remove the tosyl protecting group to give DL-2,3,4,5-tetra-*O*-benzyl-1-deoxy-1-fluoro-*scyllo*-inositol **12**. An attempt was made to remove the tosyl group from compound **11** with S–O bond cleavage by irradiation with a mercury lamp in the presence of triethylamine;[22] however, reaction was not observed. In contrast, deprotection with sodium naphthalenide[23] gave the required compound **12**, albeit in a low (12%) yield, which led us to consider alternative strategies for its preparation. Thus, DL-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol **13** was prepared in 68% yield by the reaction of diol **7** with benzoyl chloride.[24] Fluorination of compound **13** with DAST proceeded in excellent yield (95%) to give DL-2-*O*-benzoyl-3,4,5,6-tetra-*O*-benzyl-1-deoxy-1-fluoro-*scyllo*-inositol**14**.[20] Alkaline hydrolysis of compound **14** removed the benzoyl group to give the alcohol **12** in quantitative yield. Fluorination of alcohol **12** with DAST in dichloromethane gave a mixture of DL-3,4,5,6-tetra-*O*-benzyl-1,2-dideoxy-1,2-difluoro-*myo*-inositol **8** and DL-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro-*myo*-inositol **9**. Offer *et al.*[9] reported the formation of an anhydro side-product during the preparation of 1,3,4,5,6-penta-*O*-benzyl-2-deoxy-2-fluoro-*myo*-inositol when using analogous DAST fluorination conditions. In contrast, Lowe and McPhee[12] did not detect the anhydro compound when triethylamine was added to the reaction mixture. In agreement with this study, fluorination of compound **12** with DAST in the presence of triethylamine proceeded with inversion of stereochemistry to give difluoride **8** in 59% yield, without the formation of the anhydro derivative **9**. Removal of the benzyl protecting groups from compound **8** by hydrogenolysis over palladium-on-charcoal afforded DL-1,2-dideoxy-1,2-difluoro-*myo*-inositol **3** in 95% yield.

The *scyllo* analogue was also of interest to probe whether stereochemistry of the inositol ring was important. The preparation of DL-1,2-dideoxy-1,2-difluoro-*scyllo*-inositol **4** is outlined in Scheme 3. Unlike the *myo* synthesis, problems associated with anhydro formation during fluorination were not envisaged: the DAST-activated hydroxy group and the benzyloxy group on positions one and four, respectively, could only be diaxial or diequatorial in the boat form. When compared with the *myo* route, the formation of the *scyllo* configuration required an additional inversion step within the synthetic strategy. Caesium salts of carboxylic acids have been shown to displace tosyl groups with inversion of configuration,[25] and this reaction was utilised here. DL-3,4,5,6-Tetra-*O*-benzyl-2-deoxy-2-fluoro-1-*O*-tosyl-*scyllo*-inositol **11** was treated with caesium propionate to give the *myo*-inositol product **16**. Alkaline hydrolysis to remove the ester yielded the alcohol **17** in good yield, which was fluorinated with neat DAST to give DL-3,4,5,6-tetra-*O*-benzyl-1,2-dideoxy-1,2-

‡ Conformational analysis with energy minimalisation using the Tripos forcefield (0.209 kJ $Å^{-1}$) was performed on SYBYL (Version 6.2, Tripos Associates, 1699 Hanley Rd., St. Louis, MO 63144, USA).



Scheme 3 Synthesis of DL-1,2-dideoxy-1,2-difluoro-*scyllo*-inositol **4** and its tetrakisphosphate **6**. ***P*** = $(BnO)_2P(O)$–; (i) $EtCO_2^-Cs^+$, DMF; (ii) 5 M aq. NaOH, MeOH; (iii) DAST, CH_2Cl_2; (iv) H_2, Pd–C; (v) $(BnO)_2PNPr^i_2$, then MCPBA.

difluoro-*scyllo*-inositol **18** in 98% yield. Hydrogenolysis with palladium-on-charcoal removed the four benzyl protection groups to give DL-1,2-dideoxy-1,2-difluoro-*scyllo*-inositol **4**.

The tetraols **3** and **4** were phosphorylated with dibenzyl *N*,*N*-diisopropylphosphoramidite,[26] and the phosphite intermediates were oxidised with *m*-chloroperbenzoic acid (MCPBA) to give the corresponding 1,2-dideoxy-1,2-difluoroinositol 3,4,5,6-tetrakis(dibenzyl phosphates), **15** and **19**, in 71 and 92% yield, respectively (Schemes 2 and 3). Deprotection reactions of compounds **15** and **19** were achieved by hydrogenolysis in tetrahydrofuran (THF)–water in the presence of Pd–C catalyst. The resulting free acids of the phosphates were passed down a Dowex-50 cation-exchange column (sodium form) to give the sodium salts of tetrakisphosphates **5** and **6**.

For the syntheses of difluorides **3**–**6**, the novel intermediates and final products were characterised by ^1H, ^{13}C, ^{19}F and ^{31}P NMR spectroscopy, mass spectrometry, and elemental analysis. Derivatives containing the DL-1,2-dideoxy-1,2-difluoro-*scyllo*-inositol moiety gave an unusual symmetrical multiplet in the ^{19}F NMR (^1H-coupled) spectrum. However, the ^1H-decoupled spectrum gave a singlet, confirming the equivalence of the two fluoro substituents.

The effects of both the *myo*- and *scyllo*-1,2-dideoxy-1,2-difluoroinositol analogues, **3** and **4**, were examined on the biosynthesis of InsP_6 in a skeletal muscle cell line (L6 myocytes). Both compounds had a tendency to increase [^3H]InsP_6 levels: the presence of 1 mM 1,2-dideoxy-1,2-difluoro-*scyllo*-inositol **4** increased InsP_6 by 137 ± 5% (n = 2), whereas 1 mM 1,2-dideoxy-1,2-difluoro-*myo*-inositol **3** gave a larger increase of 176 ± 6% (n = 3). These results must be treated with caution in view of the small number of replicates involved, but are nonetheless interesting, as they show that these compounds appear to be transported into cells. InsP_6 metabolism is poorly understood, but it appears to be controlled by a series of futile cycles involving both InsP_5 isomers and pyrophosphate derivatives of InsP_6.[8] If either an InsP_6 phosphatase or kinase were to be inhibited, this could explain the increase in InsP_6 levels observed. This requires further investigation.

The 1,2-difluoroinositol tetrakisphosphates **5** and **6** are currently being evaluated as agonists/antagonists of the receptors or inhibitors/substrates of the enzymes that utilise the corresponding tetrakisphosphates, **1** and **2**,[27] and studies are currently underway to prepare the single enantiomers of these compounds.

Experimental

NMR spectra were recorded on a JEOL EX-270 MHz spectrometer at ^1H (270.0 MHz), ^{19}F (254.0 MHz), ^{31}P (109.2 MHz) and ^{13}C (67.8 MHz), or a Varian Unity 500 spectrometer at ^1H (500 MHz). ^1H and ^{13}C (^1H-decoupled) NMR spectra were referenced to tetramethylsilane at 0 ppm unless otherwise stated, ^{19}F NMR spectra were referenced to $CFCl_3$ at 0 ppm and are ^1H-coupled unless otherwise stated, and ^{31}P NMR spectra were referenced to 85% H_3PO_4 at 0 ppm. The ^1H NMR spectra were assigned with the aid of ^1H–^1H homonuclear chemical-shift correlation (COSY) spectra, and ^{13}C NMR spectra were assigned with the aid of distortionless en-hancement by polarisation transfer (DEPT) spectra. *J*-Values are given in Hz. Mass spectra were recorded on a Kratos Concept 1-S mass spectrometer using xenon as a carrier gas and 3-nitrobenzyl alcohol as a matrix for fast-atom bombardment (FAB), or a Fisons VG Trio spectrometer for chemical ionisation (CI) (ammonia carrier gas) and electron impact (EI). A VG Quattro quadropole mass spectrometer/MassLynx data system (VG Organic) fitted with an upgraded electrospray ionisation source was used for negative-ion electrospray (−ES) mass spectrometry. Mps were measured on a Gallenkamp digital capillary apparatus, and are uncorrected. Elemental analyses were measured at the Micro Analytical Laboratory, Department of Chemistry, University of Manchester. Flash column chromatography[28] was performed using Sorbsil C60 40/60H silica gel. TLC was performed using Merck aluminium-backed silica gel 60 plates containing a fluorescent indicator. Spots were visualised under 254 nm UV light or with a phosphomolybdic acid or molybdic acid dip. The following solvents were purified by heating under reflux, followed by distillation over the appropriate drying reagent: dichloromethane (P_2O_5), THF (Na/benzophenone) and pyridine (KOH). All chemicals were obtained from Aldrich Chemical Company, including dry dimethylformamide (DMF), except DAST which was obtained from Fluorochem.

DL-2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro-*myo*-inositol 9

Neat DAST (0.488 cm^3, 3.7 mmol) was added to a solution of DL-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol[21] **7** (200 mg, 0.37 mmol) in dry dichloromethane (2 cm^3) at −78 °C under argon. The reaction mixture was allowed to warm to room temp. over a period of 1 h, and after 6 days it was added dropwise to ice-cold saturated aq. sodium hydrogen carbonate (10 cm^3). The solution was extracted with dichloromethane (3 × 10 cm^3), and the organic layers were combined, washed with water (10 cm^3), dried (Na_2SO_4), and evaporated to dryness. Flash chromatography on silica with diethyl ether–hexane (30:70) as eluent gave compound **9** (23 mg, 14%), which was recrystallised from methanol to give crystals, mp 84–85 °C (Found: C, 72.2; H, 6.3. $C_{27}H_{27}FO_4$ requires C, 74.6; H, 6.3%. $C_{27}H_{27}FO_4{\cdot}0.5H_2O$ requires C, 71.9; H, 6.6%); $\delta_H(CDCl_3)$ 3.73 (1 H, d, $J_{3/4}$ 2.3, 3-H), 4.1–4.2 (1 H, m, 4-H), 4.24 (1 H, ddq, J_{HF} 29.7, $J_{6/5}$ 4.95, $J_{6/1} \sim J_{6/4} \sim J_{6/2} \sim$ 1.65, 6-H), 4.4–4.65 (8 H, m, 3 × CH_2Ph, 2- and 5-H), 4.79 (1 H, dd, J_{HF} 54.1, $J_{1/6}$ 1.65, 1-H) and 7.25–7.35 (15 H, m, Ph); δ_C 71.3 (CH_2), 73.0 (CH_2), 73.2 (CH_2), 74.9 (d, $^3J_{CF}$ 4.9, C-3 or -5), 82.5 (d, $^3J_{CF}$ 4.9, C-5 or -3), 86.2 (d, $^2J_{CF}$ 23.2, C-2 or -6), 87.1 (s, C-4), 87.3 (d, $^2J_{CF}$ 22.0, C-6 or -2), 96.4 (d, $^1J_{CF}$ 190.4, C-1), 127.8–128.5 (15 × arom CH), 137.2 (arom C), 137.3 (arom C) and 137.6 (arom C); δ_F −178.6 (ddd, $^1J_{F/H\text{-}1}$ 54.1, $^2J_{F/H\text{-}6}$ 29.7, $^2J_{F/H\text{-}2}$ 13.8); *m*/*z* (CI) 452 ($M + NH_4^+$, 2%), 435 ($M + H^+$, 3) and 91 (100); *m*/*z* (EI) 343 ($M^+ - 91$, 6%) and 91 (100). Further elution of the column with the same solvent system gave DL-3,4,5,6-tetra-*O*-benzyl-1,2-dideoxy-1,2-difluoro-*myo*-inositol **8** (9 mg, 4.5%), with identical NMR spectra to those described for **8** below.

DL-1-*O*-Benzoyl-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol 13

Prepared in a similar manner to that outlined by Schevchenko *et al.*[24] A solution of DL-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol **7**[21] (2.0 g, 3.7 mmol), 4-(dimethylamino)pyridine (DMAP) (0.226 g, 1.85 mmol) and benzoyl chloride (0.45 cm^3, 3.9 mmol) in dry pyridine (20 cm^3) was stirred at room temperature for 4 h under argon. The reaction mixture was diluted with dichloromethane (100 cm^3), washed successively with saturated aq. sodium hydrogen carbonate (100 cm^3) and water (100 cm^3), dried (Na_2SO_4), and evaporated. Flash chromatography on silica with ethyl acetate–hexane (35:65) as eluent gave compound **13** as a solid, which was crystallised from ethyl acetate–hexane (1.61 g, 68%), mp 145 °C (lit.,[29] 144–145 °C) (Found: C, 76.2; H, 6.1. Calc. for $C_{41}H_{40}O_7$: C, 76.4; H, 6.25%); $\delta_H(CDCl_3)$ 2.45 (1 H, s, OH), 3.61 (1 H, t, $J_{5/4} \sim J_{5/6} \sim 9.6$, 5-H), 3.63 (1 H, dd, $J_{3/4}$ 9.6, $J_{3/2}$ 2.3, 3-H), 4.01 (1 H, t, $J_{4/3} \sim J_{4/5} \sim 9.6$, 4-H), 4.24 (1 H, t, $J_{6/1} \sim J_{6/5} \sim 9.9$, 6-H), 4.43 (1 H, t, $J_{2/1} \sim J_{2/3} \sim 2.0$, 2-H), 4.7–4.9 (8 H, m, 4 × CH_2Ph), 5.11 (1 H, dd, $J_{1/6}$ 10.2, $J_{1/2}$ 2.0, 1-H), 7.1–7.35 (21 H, m, Ph), 7.44 (1 H, t, J_{HH} 7.6, 3′- or 5′-H of benzoyl Ph), 7.58 (1 H, t, J_{HH} 7.2, 5′-or 3′-H of benzoyl Ph) and 8.07 (2 H, d, J_{HH} 7.3, 2′- and 6′-H of benzoyl Ph); δ_C 67.9 (inositol CH), 72.9 (CH_2), 73.8 (inositol CH), 75.8 (CH_2), 76.0 (2 × CH_2), 79.0 (inositol CH), 80.0 (inositol CH), 81.2 (inositol CH), 83.2 (inositol CH), 127.5–128.5 (m, 22 × arom CH), 129.7 (arom C), 129.8 (2 × arom CH), 133.2 (arom CH), 137.4 (arom C), 138.1 (arom C), 138.5 (arom C), 138.55 (arom C) and 165.9 (C=O); *m/z* (CI) 662 ($M + NH_4^+$, 100%).

DL-2-*O*-Benzoyl-3,4,5,6-tetra-*O*-benzyl-1-deoxy-1-fluoro-*scyllo*-inositol 14

Prepared by a related method communicated by Yang *et al.*[20] Neat DAST (0.41 cm^3, 3.10 mmol) was added to a stirred solution of compound **13** (200 mg, 0.310 mmol) in dry dichloromethane (1.5 cm^3) at −78 °C under argon. The reaction mixture was warmed to room temp. over a period of 1 h then was stirred for 2 h after which time it was added dropwise to ice-cold saturated aq. sodium hydrogen carbonate (10 cm^3). The solution was extracted with dichloromethane (2 × 25 cm^3), and the combined organic layers were washed with water (10 cm^3), dried (Na_2SO_4), and evaporated to dryness. Flash chromatography on silica and elution with hexane–ethyl acetate (75:25) gave fluoride **14** as a clear gum. This crystallised to a solid on storage (190 mg, 95%), which was recrystallised from methanol, mp 135–136 °C (lit.,[20] 134.5–135.5 °C) (Found: C, 75.3; H, 6.2. Calc. for $C_{41}H_{39}FO_6$: C, 76.1; H, 6.1%. Calc. for $C_{41}H_{39}FO_6 \cdot 0.5H_2O$: C, 75.1; H, 6.15%); $\delta_H(CDCl_3)$ 3.59 (1 H, t, $J_{4/3} \sim J_{4/5} \sim 8.9$, 4-H), 3.65 (1 H, t, $J_{5/4} \sim J_{5/6} \sim 8.9$, 5-H), 3.68 (1 H, t, $J_{3/2} \sim J_{3/4} \sim 8.9$, 3-H), 3.80 (1 H, dt, $^3J_{HF}$ 12.5, $J_{6/1} \sim J_{6/5} \sim 9.2$, 6-H), 4.61 (1 H, dt, J_{HF} 51.5, $J_{1/2} \sim J_{1/6} \sim 9.2$, 1-H), 4.6–5.0 (8 H, m, 4 × OCH_2Ph), 5.52 (1 H, dt, J_{HF} 11.9, $J_{2/1} \sim J_{2/3} \sim 9.6$, 2-H), 7.2–7.6 (23 H, m, Ph) and 8.0–8.05 (2 H, m, 2′- and 6′-H of benzoyl Ph); δ_C 72.6 (d, $^2J_{CF}$ 18.3, C-2 or -6), 75.5 (d, $^4J_{CF}$ 2.6, CH_2), 75.6 (CH_2), 76.0 (CH_2), 76.1 (CH_2), 79.1 (d, $^3J_{CF}$ 11.0, C-3 or -5), 80.7 (d, $^2J_{CF}$ 17.1, C-6 or -2), 81.2 (d, $^3J_{CF}$ 12.2, C-5 or - 3), 82.5 (s, C-4), 93.2 (d, $^1J_{CF}$ 186.7, C-1), 127.7–128.4 (m, 22 × arom CH), 129.6 (arom C), 129.8 (2 × arom CH), 133.2 (arom CH), 137.5 (arom C), 137.9 (arom C), 138.1 (arom C), 138.15 (arom C) and 165.5 (C=O); δ_F −196.5 (dt, $^2J_{FH}$ 51.5, $^3J_{F/H-2} \sim {}^3J_{F/H-6}$ 12.9); *m/z* (CI) 664 ($M + NH_4^+$, 100%); *m/z* (EI) 555 ($M^+ - 91$, 3%) and 91 (100).

DL-2,3,4,5-Tetra-*O*-benzyl-1-deoxy-1-fluoro-*scyllo*-inositol 12

Prepared using a similar method to that communicated by Yang *et al.*[20] Aq. sodium hydroxide (5 M; 5 cm^3) was added to a stirred solution of benzoate **14** (171 mg, 0.29 mmol) in methanol (15 cm^3). After 3 h at room temp., methanol was removed by evaporation *in vacuo* and the residue was partitioned between dichloromethane (2 × 25 cm^3) and water (10 cm^3). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated off to give title fluoride **12** in quantitative yield. Recrystallisation from ethyl acetate–hexane gave crystals, mp 113–114 °C (lit.,[20] 113.5–114.5 °C) (Found: C, 75.2; H, 6.7. Calc. for $C_{34}H_{35}FO_5$: C, 75.3; H, 6.5%); $\delta_H(CDCl_3)$ 2.49 (1 H, s, OH), 3.40 (1 H, t, $J_{4/3} \sim J_{4/5} \sim 9.0$, 4-H), 3.5–3.8 (4 H, m, 2-, 3-, 5- and 6-H), 4.42 (1 H, dt, J_{HF} 52.4, $J_{1/2} \sim J_{1/6} \sim 9.0$, 1-H), 4.75–4.95 (8 H, m, 4 × CH_2Ph) and 7.25–7.35 (20 H, m, Ph); δ_C 72.5 (d, $^2J_{CF}$ 18.3, C-2 or -6), 75.3 (CH_2), 75.7 (CH_2), 76.9 (CH_2), 76.1 (CH_2), 79.1 (d, $^3J_{CF}$ 11.0, C-3 or -5), 80.85 (d, $^2J_{CF}$ 15.9, C-6 or -2), 81.0 (d, $^3J_{CF}$ 12.2, C-5 or -3), 82.4 (s, C-4), 95.2 (d, $^1J_{CF}$ 181.8, C-1), 127.7–128.6 (m, 20 × arom CH), 138.0 (arom C), 138.1 (arom C), 138.15 (arom C) and 138.2 (arom C); δ_F −196.3 (dt, $^2J_{FH}$ 51.7, $^3J_{F/H-2} \sim {}^3J_{F/H-6} \sim 13.0$); *m/z* (CI) 560 ($M + NH_4^+$, 100%); *m/z* (EI) 451 [$M^+ - 91$ (Bn), 12%], 181 (60) and 91 (100). [Compound **12** was also prepared in 12% yield by the reaction of tosyl ester **11**[9] (0.144 mmol) with 0.3 M sodium naphthalenide (0.432 mmol)].

DL-3,4,5,6-Tetra-*O*-benzyl-1,2-dideoxy-1,2-difluoro-*myo*-inositol 8

Neat DAST (0.75 cm^3, 5.68 mmol) was added to a stirred solution of compound **12** (250 mg, 0.46 mmol) and triethylamine (0.65 cm^3, 4.66 mmol) in dry dichloromethane (2.5 cm^3) at 0 °C under argon. The reaction mixture was warmed to room temperature over a period of 1 h and was stirred for a further 64 h, after which time it was added dropwise to ice-cold saturated aq. sodium hydrogen carbonate (50 cm^3). The reaction mixture was extracted with dichloromethane (50 cm^3), which was washed with water (2 × 50 cm^3), dried (Na_2SO_4), and evaporated to dryness. Flash chromatography on silica and elution with hexane–ethyl acetate (80:20) gave *title compound* **8** as a liquid (148 mg, 59%), which crystallised on storage. Recrystallisation from ethanol gave needles, mp 112–113 °C (Found: C, 75.3; H, 6.5. $C_{34}H_{34}F_2O_4$ requires C, 75.0; H, 6.3%); $\delta_H(CDCl_3)$ 3.45 (1 H, br dd, $^3J_{3/F-2}$ 28.0, $J_{3/4}$ 9.5, 3-H), 3.47 (1 H, t, $J_{5/4} \sim J_{5/6} \sim 9.4$, 5-H), 3.97 (1 H, td, $J_{4/3} \sim J_{4/5} \sim 9.6$, $^4J_{4/F-2}$ 1.3, 4-H), 4.04 (1 H, dtd, $^3J_{6/F-1}$ 9.9, $J_{6/1} \sim J_{6/5} \sim 9.6$, $^4J_{6/F-2}$ 1.3, 6-H), 4.42 (1 H, dddd, $^2J_{HF}$ 46.5, $^3J_{HF}$ 27.7, $J_{1/6}$ 9.7, $J_{1/2}$ 1.8, 1-H), 4.7–4.95 (8 H, m, 4 × CH_2Ph), 5.02 (1 H, ddt, $^2J_{HF}$ 53.1, $^3J_{HF}$ 9.6, $J_{2/1} \sim J_{2/3} \sim 1.6$, 2-H) and 7.25–7.35 (20 H, m, Ph); δ_C 73.0 (CH_2), 75.6 (CH_2), 76.1 (2 × CH_2), 77.3 (dd, $^2J_{CF}$ 17.1, $^3J_{CF}$ 9.8, C-3 or -6), 79.6 (dd, $^2J_{CF}$ 15.6, $^3J_{CF}$ 3.7, C-6 or -3), 80.7 (d, $^3J_{CF}$ 4.9, C-4 or -5), 81.5 (d, $^3J_{CF}$ 13.4, C-5 or -4), 88.5 (dd, $^1J_{CF}$ 181.8, $^2J_{CF}$ 17.0, C-1 or -2), 91.2 (dd, $^1J_{CF}$ 189.3, $^2J_{CF}$ 17.0, C-2 or -1), 127.8–128.6 (6 peaks, 20 × arom CH) and 137.3–138.3 (3 peaks, 4 × arom C); δ_F −202.1 (ddt, $^2J_{FH}$ 46.5, $^3J_{FF}$ 16.3, $^3J_{F/H-2} \sim {}^3J_{F/H-6} \sim 10.6$, F-1) and −212.7 (ddt, $^2J_{FH}$ 53.1, $^3J_{FF}$ 16.5, $^3J_{F/H-1} \sim {}^3J_{F/H-3} \sim 27.6$, F-2); *m/z* (CI) 562 ($M + NH_4^+$, 28%), 453 (18), 108 (31) and 91 (100).

DL-1,2-Dideoxy-1,2-difluoro-*myo*-inositol 3

Compound **8** (100 mg, 0.184 mmol) was dissolved in ethanol (20 cm^3) and the solution was stirred with 10% palladium-on-charcoal (200 mg) under a positive pressure of hydrogen for 4 days. The mixture was filtered through Celite, the filter pad was washed with ethanol (30 cm^3), and the combined filtrate and washings were evaporated to dryness. Flash chromatography on silica gel and elution with ethanol–ethyl acetate (1:9) gave *title tetraol* **3** as a solid (32.2 mg, 95%), mp 147–148 °C (Found: C, 39.3; H, 5.7. $C_6H_{10}F_2O_4$ requires C, 39.1; H, 5.5%); $\delta_H(D_2O$; referenced to benzene at δ_H 7.44) 3.3–3.45 (1 H, m, 3-H), 3.6–3.8 (2 H, m, 4- and 5-H), 3.8–4.1 (1 H, m, 6-H), 4.59 (1 H, dddd, $^2J_{HF}$ 46.2, $^3J_{HF}$ 28.0, $J_{1/6}$ 9.9, $J_{1/2}$ 2.0, 1-H) and 5.13 (1 H, br dd, $^2J_{HF}$ 53.1, $^3J_{HF}$ 8.6, 2-H); $\delta_C(D_2O$, referenced to benzene at δ_C 128.5) 69.1 (dd, $^2J_{CF}$ 17.1, $^3J_{CF}$ 9.7, C-3 or -6), 70.6 (dd, $^2J_{CF}$ 18.9, $^3J_{CF}$ 4.3, C-6 or -3), 72.1 (d, $^3J_{CF}$ 4.8, C-4 or -5), 72.7 (d, $^3J_{CF}$ 12.3, C-5 or -4), 91.2 (dd, $^1J_{CF}$ 183.1, $^2J_{CF}$ 16.5, C-1 or -2) and 91.5 (dd, $^1J_{CF}$ 177.0, $^3J_{CF}$ 17.1, C-2 or -1); δ_F −204.5

(ddt, $^2J_{FH}$ 45.9, $^3J_{FF}$ 11.1, $^3J_{F/H-2}$ ~ $^3J_{F/H-6}$ ~ 12.8, F-1) and −214.6 (m, F-2); *m/z* (CI) 202 ($M + NH_4^+$, 100%).

DL-3,4,5,6-Tetra-*O*-benzyl-1-deoxy-1-fluoro-2-*O*-propionyl-*myo*-inositol 16

A solution of **11**[9] (200 mg, 0.29 mmol) and caesium propionate (296 mg, 1.44 mmol, $C_2H_5CO_2Cs{\cdot}xC_2H_5CO_2H$) in dry DMF (1.5 cm^3) was heated at 140 °C for 20 h. On cooling, the mixture was partitioned between toluene (5 cm^3) and water (10 cm^3), and the organic layer was washed with saturated aq. sodium chloride (2 × 10 cm^3). After drying (Na_2SO_4), the solvent was evaporated off to give *title ester* **16** as a solid in quantitative yield. A small amount was recrystallised from ethyl acetate–hexane, mp 95–96 °C (Found: C, 74.1; H, 6.6. $C_{37}H_{39}FO_6$ requires C, 74.2; H, 6.6%); δ_H($CDCl_3$) 1.18 (3 H, t, J_{HH} 7.4, CH_2CH_3), 2.44 (2 H, q, J_{HH} 7.6, CH_2CH_3), 3.48 (1 H, t, J_{HH} 9.6, 4- or 5-H), 3.5–3.55 (1 H, m, 3-H), 3.85 (1 H, t, J_{HH} 9.6, 5- or 4-H), 4.02 (1 H, dt, $^3J_{HF}$ 11.9, $J_{6/1}$ ~ $J_{6/5}$ ~ 9.4, 6-H), 4.49 (1 H, d, J_{gem} 11.2, OCH^AH^BPh), 4.52 (1 H, ddd, J_{HF} 46.9, $J_{1/6}$ 9.6, $J_{1/2}$ 3.0, 1-H), 4.7–4.95 (7 H, m, OCH_2Ph), 5.88 (1 H, dt, $^3J_{HF}$ 8.6, $J_{2/1}$ ~ $J_{2/3}$ ~ 3.0, 2-H) and 7.15–7.4 (20 H, m, Ph); δ_C 9.2 (s, CH_2CH_3), 27.6 (s, CH_2CH_3), 67.65 (d, $^2J_{CF}$ 17.0, C-2 or -6), 72.2 (s, OCH_2Ph), 75.4 (d, $^4J_{CF}$ 2.4, OCH_2Ph), 76.0 (s, OCH_2Ph), 76.3 (s, OCH_2Ph), 77.2 (d, $^3J_{CF}$ 9.8, C-3 or -5), 80.1 (d, $^2J_{CF}$ 18.3, C-6 or -2), 81.1 (s, C-4), 81.65 (d, $^3J_{CF}$ 12.2, C-5 or -3), 90.8 (d, $^1J_{CF}$ 190.5, C-1), 127.7–128.4 (m, 20 × arom CH), 137.4 (s, arom C), 138.1 (s, arom C), 138.2 (s, arom C), 138.4 (s, arom C) and 173.4 (C=O); δ_F −201.2 (br dt, $^2J_{FH}$ 44.8, $^3J_{F/H-6}$ ~ $^3J_{F/H-2}$ ~ 10.0); *m/z* (CI) 616 ($M + NH_4^+$, 100%); *m/z* (EI) 507 [M^+ − 91 (Bn), 17%], 401 (52) and 91 (100).

DL-3,4,5,6-Tetra-*O*-benzyl-1-deoxy-1-fluoro-*myo*-inositol 17

Using a different procedure, compound **17** has previously been prepared by Offer *et al.* in its two enantiomerically pure forms.[9] Aq. sodium hydroxide (5 M; 0.35 cm^3) was added to a solution of ester **16** (171 mg, 0.29 mmol) in methanol (5 cm^3) and the mixture was stirred at room temp. for 2 h. Further aq. sodium hydroxide (5 M; 0.15 cm^3) was added to complete the reaction. Methanol was evaporated off and the residue was washed with water. The product was recrystallised from methanol–water to give alcohol **17** as crystals (133 mg, 85% [from **11**]), mp 113–114 °C; δ_H($CDCl_3$) 2.48 (1 H, s, OH), 3.4–3.5 (2 H, m, 3- and 5-H), 3.98 (1 H, t, $J_{4/5}$ ~ $J_{4/3}$ ~ 9.5, 4-H), 4.15 (1 H, dt, $^3J_{HF}$ 11.6, $J_{6/1}$ ~ $J_{6/5}$ ~ 9.5, 6-H), 4.3–4.4 (1 H, m, 2-H), 4.42 (1 H, ddd, $^2J_{HF}$ 47.5, $J_{1/6}$ 9.6, $J_{1/2}$ 3.0, 1-H), 4.65–4.9 (8 H, m, 4 × CH_2Ph) and 7.25–7.4 (20 H, m, Ph); δ_F −201.8 (dt, $^2J_{F/H-1}$ 47.5, $^3J_{F/H-6}$ ~ $^3J_{F/H-2}$ ~ 10.4).

DL-3,4,5,6-Tetra-*O*-benzyl-1,2-dideoxy-1,2-difluoro-*scyllo*-inositol 18

Neat DAST (0.30 cm^3, 2.27 mmol) was added to compound **17** (100 mg, 0.184 mmol) and the mixture was stirred at room temp. for 17 h under argon. The reaction mixture was added dropwise to ice-cold saturated aq. sodium hydrogen carbonate (10 cm^3). The solution was extracted with dichloromethane (30 cm^3), and the combined organic layers were washed with water (2 × 10 cm^3), dried ($MgSO_4$), and evaporated to dryness. Flash chromatography on silica and elution with light petroleum (distillation range 40–60 °C)–ethyl acetate (82.5:17.5), followed by crystallisation from ethanol gave *difluoride* **18** (98 mg, 98%), mp 103–104 °C (Found: C, 74.7; H, 6.3. $C_{34}H_{34}F_2O_4$ requires C, 75.0; H, 6.3%); δ_H($CDCl_3$) 3.5–3.7 (4 H, m, 3-, 4-, 5- and 6-H), 4.45–4.75 (2 H, m, 1- and 2-H), 4.7–4.9 (8 H, m, 4 × CH_2Ph) and 7.2–7.35 (20 H, m, Ph); δ_C 75.5 (s, CH_2), 76.1 (s, 2 × CH_2), 79.7 (t, $^2J_{CF}$ ~ $^3J_{CF}$ ~ 14.0, C-3 and -6), 81.0 (t, $^3J_{CF}$ ~ $^4J_{CF}$ ~ 4.9, C-4 and -5), 93.1 (dd, $^1J_{CF}$ 186.8, $^2J_{CF}$ 19.5, C-1 and -2), 127.7–128.4 (m, 20 × arom CH), 137.8 (s, 2 × arom C) and 138.1 (s, 2 × arom C); δ_F −196.6 to −197.1 (m); δ_F(^{1}H-decoupled) −196.85 (s); *m/z* (CI) 562 ($M + NH_4^+$, 100%); *m/z* (EI) 453 [M^+ − 91 (Bn), 3%], 181 (5) and 91 (100).

DL-1,2-Dideoxy-1,2-difluoro-*scyllo*-inositol 4

A mixture of DL-3,4,5,6-tetra-*O*-benzyl-1,2-dideoxy-1,2-difluoro-*scyllo*-inositol **18** (98 mg, 0.18 mmol) and palladium-on-charcoal (10%; 100 mg) in methanol (10 cm^3) was stirred for 70 h under a positive pressure of hydrogen. Filtration through Celite, followed by washing of the filter pad with methanol (50 cm^3), gave *title tetraol* **4** (28 mg, 85%), mp 215–216 °C (Found: C, 38.2; H, 5.9. $C_6H_{10}F_2O_4$ requires C, 39.1; H, 5.5%. $C_6H_{10}F_2O_4{\cdot}0.25\ H_2O$ requires C, 38.2; H, 5.6%); δ_H(500 MHz; D_2O, referenced to benzene at δ_H 7.44) 3.4–3.5 (2 H, dt, $^4J_{HF}$ 7.0, $J_{4/3}$ ~ $J_{4/5}$ ~ 10.0, 4- and 5-H), 3.6–3.75 (2 H, m, 3- and 6-H) and 4.4–4.75 (2 H, m, 1- and 2-H); δ_C(D_2O, referenced to benzene at δ_C 128.5) 74.1 (2 C, t, $^2J_{CF}$ ~ $^3J_{CF}$ ~ 14.6, C-3 and -6), 75.4 (2 C, t, $^3J_{CF}$ ~ $^4J_{CF}$ ~ 4.3, C-4 and -5) and 95.6 (2 C, dd, $^1J_{CF}$ 181.3, $^2J_{CF}$ 19.0, C-1 and -2); δ_F(D_2O, referenced to CF_3CO_2H at δ_F −76.5) −199.8 to −200.3 (m); δ_F(D_2O, referenced to CF_3CO_2H at δ_F −76.5; ^{1}H-decoupled) −200.1 (s); *m/z* (CI) 202 ($M + NH_4^+$, 100%).

DL-1,2-Dideoxy-1,2-difluoro-*myo*-inositol 3,4,5,6-tetrakis-(dibenzyl phosphate) 15

A solution of tetraol **3** (10 mg, 0.0543 mmol), 1*H*-tetrazole (46.6 mg, 0.665 mmol) and dibenzyl *N,N*-diisopropylphosphoramidite[26] (187.5 mg, 0.543 mmol) in freshly distilled THF (0.8 cm^3) was stirred under argon at room temp. for 17 h. The reaction mixture was cooled to −78 °C and a solution of MCPBA (165 mg; 57–86%; >0.545 mmol) in THF (0.6 cm^3) was added. The solution was allowed to warm to room temp. over a period of 1 h, then was stirred for a further 100 min. Ethyl acetate (20 cm^3) was added and the reaction mixture was washed successively with aq. $NaHSO_3$ (10% w/v; 10 cm^3), saturated aq. $NaHCO_3$ (10 cm^3) and water (10 cm^3). The organic layer was dried (Na_2SO_4) and the solvent was evaporated off *in vacuo*. The residue was purified by flash column chromatography on silica gel and elution with ethyl acetate–hexane (2:1), to give *title compound* **15** as an oil (47 mg, 71%) (Found: C, 60.8; H, 5.2. $C_{62}H_{62}F_2O_{16}P_4$ requires C, 60.8; H, 5.1%); δ_H($CDCl_3$) 4.15–4.35 (1 H, m, inositol H), 4.4–4.65 (1 H, m, inositol H), 4.85–5.1 (19 H, m, 8 × CH_2Ph and 3 × inositol H), 5.35 (1 H, br dd, $^2J_{HF}$ 51.1, $^3J_{HF}$ 8.9, 2-H) and 7.1–7.4 (40 H, m, Ph); δ_C 69.7–69.75 (4 × CH_2), 69.95 (CH_2), 70.0 (CH_2), 70.05 (CH_2), 70.1 (CH_2), 72.45–72.9 (1 C, m), 74.5–74.65 (1 C, m), 74.8–75.3 (2 C, m), 87.3 (1 C, dd, $^1J_{CF}$ 193.6, $^2J_{CF}$ 17.7, C-1 or -2), 87.5 (1 C, dd, $^1J_{CF}$ 187.5, $^2J_{CF}$ 18.9, C-2 or -1), 127.9–128.8 (40 × arom CH) and 135.1–138.8 (8 × arom C); δ_F(^{1}H-coupled) −202.2 (ddt, $^2J_{FH}$ 45.1, $^3J_{FF}$ 15.5, $^3J_{F/H-2}$ ~ $^3J_{F/H-6}$ ~ 9.2, F-1) and −213.3 (ddt, $^2J_{FH}$ 51.5, $^3J_{FF}$ 16.5, $^3J_{F/H-1}$ ~ $^3J_{F/H-3}$ ~ 16.6, F-2); δ_P(^{1}H-decoupled) −0.72 (s), −0.88 (s), −1.63 (s) and −1.73 (s); δ_P(^{1}H-coupled) −0.71 (sextet, J_{PH} 8.8), −0.87 (sextet, J_{PH} 8.8), −1.63 (sextet, J_{PH} 8.0) and −1.73 (sextet, J_{PH} 8.0); *m/z* (FAB) 1247 ($M + Na^+$, 100%) and 1225 ($M + H^+$, 17%).

DL-1,2-Dideoxy-1,2-difluoro-*scyllo*-inositol 3,4,5,6-tetrakis-(dibenzyl phosphate) 19

A solution of tetraol **4** (50 mg, 0.271 mmol), 1*H*-tetrazole (287 mg, 4.10 mmol) and dibenzyl *N,N*-diisopropylphosphoramidite[26] (470 mg, 1.36 mmol) in THF (2 cm^3) was stirred under argon at room temp. for 90 min. The reaction mixture was cooled to −78 °C and a solution of MCPBA (575 mg; 57–86%; >1.90 mmol) in THF (2 cm^3) was added. The solution was allowed to warm to room temp. over a period of 30 min, then was stirred for a further 30 min. Ethyl acetate (50 cm^3) was added and the reaction mixture was washed successively with aq. $NaHSO_3$ (10% w/v; 2 × 20 cm^3), saturated aq. $NaHCO_3$ (2 × 10 cm^3) and water (10 cm^3). The organic layer was dried (Na_2SO_4) and the solvent was evaporated off *in vacuo*. The

residue was purified by flash column chromatography on silica gel and elution with ethyl acetate–toluene (2:3) to give compound **19** as a solid, which was recrystallised from ethanol (306 mg, 92%), mp 126–128 °C (Found: C, 60.3; H, 5.25. $C_{62}H_{62}F_2O_{16}P_4$ requires C, 60.8; H, 5.1%. $C_{62}H_{62}F_2O_{16}P_4{\cdot}0.5H_2O$ requires C, 60.3; H, 5.15%); $\delta_H(CDCl_3)$ 4.55–4.8 (6 H, m, 6 × inositol H), 4.9–5.15 (16 H, m, 8 × OCH_2Ph) and 7.15–7.3 (40 H, m, Ph); δ_C 69.7–70.0 (5 peaks, 8 × CH_2), 74.6–75.45 (4 C, m, C-3, -4, -5 and -6), 90.5 (2 C, dd, $^1J_{CF}$ 190.5, $^2J_{CF}$ 22.1, C-1 and -2), 127.85–128.5 (40 C, m, arom CH) and 135.4–135.6 (8 C, m, arom C); δ_F(^{1}H-decoupled) −194.5 (s); δ_F −194.35 to −194.65 (m); δ_P(^{1}H-decoupled) −0.99 (2 P, s) and −1.49 (2 P, s); δ_P(^{1}H-coupled) −1.00 (2 P, sextet, J_{PH} 8.0) and −1.51 (2 P, sextet, J_{PH} 8.0); *m/z* (FAB) 1225 ($M + H^+$, 100%).

Sodium salt of DL-1,2-dideoxy-1,2-difluoro-*myo*-inositol 3,4,5,6-tetrakisphosphate 5

A solution of compound **15** (53 mg, 0.0432 mmol) in a mixture of freshly distilled THF (5 cm^3) and water (5 cm^3) was stirred with Pd–C catalyst (10%; 200 mg) under H_2 for 25 h at room temp. The catalyst was removed by filtration through Celite and the filtrate was concentrated under vacuum. The residue was dissolved in water (3 cm^3) and applied to a cation-exchange column (Dowex 50-X8, mesh 20–50; 50 cm^3; Na^+ form) which was eluted with water (250 cm^3). The water was evaporated off under vacuum to give compound **5** as a solid (27.8 mg, 95%), mp > 300 °C; $\delta_H(D_2O$; referenced to benzene at δ_H 7.44) 4.2–4.3 (2 H, m, inositol H), 4.35–4.65 (2 H, m, inositol H), 4.59 (1 H, ddd, $^2J_{HF}$ 46.8, $^3J_{HF}$ 29.0, $J_{1/6}$ 9.4, 1-H) and 5.45 (1 H, dd, $^2J_{HF}$ 52.1, $^3J_{HF}$ 8.9, 2-H); δ_C 70.4–71.1 (m, C-3 or -6), 74.0 (br d, $^2J_{CF}$ 19.5, C-6 or -3), 75.1 (br s, C-4 or -5), 75.7 (br s, C-5 or -4), 88.6 (dd, $^1J_{CF}$ 186.8, $^2J_{CF}$ 15.9, C-1 or -2) and 89.9 (dd, $^1J_{CF}$ 178.2, $^2J_{CF}$ 17.1, C-2 or -1); $\delta_F(D_2O$; referenced to CF_3CO_2H at δ_F −76.5; ^{1}H-decoupled) −203.1 (s) and −214.3 (s); $\delta_F(D_2O$; referenced to CF_3CO_2H at δ_F −76.5) −202.8 to −203.4 (m) and −214.0 to −214.7 (m); δ_P(^{1}H-decoupled) 0.6 (s), 1.25 (s), 1.45 (s) and 2.55 (s); *m/z* (ES) 568.3 ($[M^{8-} + 4H^+ + 3Na^+]^-$, 5%), 546.4 ($[M^{8-} + 5H^+ + 2Na^+]^-$, 3), 524.4 ($[M^{8-} + 6H^+ + Na^+]^-$, 2), 502.4 ($[M^{8-} + 7H^+]^-$, 2), 466.4 ($[M^{8-} + 5H^+ - HPO_3 + 2Na^+]^-$, 3), 444.5 ($[M^{8-} + 6H^+ - HPO_3 + Na^+]^-$, 9), 422.5 ($[M^{8-} + 7H^+ - HPO_3]^-$, 21), 272.6 ($[M^{8-} + 4H^+ + 2Na^+]^{2-}$, 13), 261.6 ($[M^{8-} + 5H^+ + Na^+]^{2-}$, 50) and 250.7 ($[M^{8-} + 6H^+]^{2-}$, 100).

Sodium salt of DL-1,2-dideoxy-1,2-difluoro-*scyllo*-inositol 3,4,5,6-tetrakisphosphate 6

This was prepared in the same manner as compound **5**, from compound **19** in 81% yield, mp 190–195 °C (decomp.) (Elemental analysis not correct. Found: C, 11.2; H, 2.3; Na, 14.1; P, 15.0. $C_6H_9F_2Na_5O_{16}P_4$ requires C, 11.8; H, 1.0; Na, 18.8; P, 20.3%. $C_6H_9F_2Na_5O_{16}P_4{\cdot}10\,H_2O$ requires C, 9.1; H, 3.3; Na, 14.5; P, 15.7%); $\delta_H(D_2O$; referenced to benzene at δ_H 7.44; 20 °C) 4.2–4.3 (2 H, m, 4- and 5-H), 4.3–4.5 (2 H, m, 3- and 6-H) and 4.65–4.95 (2 H, m§, 1- and 2-H); δ_C 74.4 (dt, J_{CP} ~ 3, $^2J_{CF}$ ~ $^3J_{CF}$ ~ 14.6, C-3 and -6), 75.6 (br s, C-4 and -5) and 90.9 (dd, $^1J_{CF}$ 185.5, $^2J_{CF}$ 20.7, C-1 and -2); $\delta_F(D_2O$; referenced to CF_3CO_2H at δ_F −76.5; ^{1}H-decoupled) −199.7 (s); $\delta_F(D_2O$; referenced to CF_3CO_2H at δ_F −76.5) −199.5 to −199.8 (m); δ_P(^{1}H-decoupled) 0.91 (2 P, s) and 2.35 (2 P, s); δ_P(^{1}H-coupled) 0.91 (2 P, d, J_{PH} 9.4) and 2.35 (2 P, d, J_{PH} 7.0); *m/z* (ES) 568.3 ($[M^{8-} + 4H^+ + 3Na^+]^-$, 15%), 546.4 ($[M^{8-} + 5H^+ + 2Na^+]^-$, 9), 524.4 ($[M^{8-} + 6H^+ + Na^+]^-$, 7), 502.4 ($[M^{8-} + 7H^+]^-$, 3), 466.4 ($[M^{8-} + 5H^+ - HPO_3 + 2Na^+]^-$, 13), 444.5 ($[M^{8-} + 6H^+ - HPO_3 + Na^+]^-$, 26), 422.5 ($[M^{8-} + 7H^+ - HPO_3]^-$, 15), 272.6 ($[M^{8-} + 4H^+ + 2Na^+]^{2-}$, 82), 261.6 ($[M^{8-} + 5H^+ + Na^+]^{2-}$, 100) and 250.7 ($[M^{8-} + 6H^+]^{2-}$, 81).

Biological method

InsP_6 synthesis was investigated in rat L6 skeletal myocytes. These were grown to confluence in 6-well plates in a medium consisting of Dulbecco's Modified Eagle Medium/5% foetal calf serum. They were then labelled for 24–48 h in the same medium supplemented with 5 μCi [^{3}H]-*myo*-inositol in the presence of 1 mM **3** or **4**, along with a control. Cells were then ruptured with 0.5 cm^3 5% perchloric acid, neutralised with 4 M aq. KOH, and the supernatants were analysed by HPLC on a Partisil SAX column (Jones chromatography) with a linear gradient of 0–100% 3.5 M aq. ammonium formate, pH 3.8.[30] Fractions were counted to determine radiochemical levels of InsP_6.

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§ At 20 °C the water peak in the ^{1}H NMR spectrum obscured most of this signal. Acquisition of the spectrum at 60 °C shifted the water signal upfield to reveal the characteristic multiplet shown by 1,2-dideoxy-1,2-difluoro-*scyllo*-inositol derivatives.

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