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Synthesis of racemic 6-deoxy-6-fluoro-*chiro*-inositol 2,3,5-trisphosphate

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ABSTRACT

The synthesis of (±)-6-deoxy-6-fluoro-*chiro*-inositol 2,3,5-trisphosphate (**4**) is reported, starting from cyclohexa-1,4-diene. A key step involved the stereospecific 1,4-addition of singlet oxygen to *trans*-1,2-di-*O*-(2-methoxyethoxymethyl)cyclohexa-3,5-diene-1,2-diol (**7**) to afford (±)-1,2,4/3-2,3-di-*O*-(2-methoxyethoxymethyl)cyclohex-5-ene-1,2,3,4-tetrol (**9**). Benzylation of **9** followed by osmylation and selective protection of the equatorial hydroxyl group gave (±)-1,4-di-*O*-benzyl-2,3,5-tri-*O*-(2-methoxyethoxymethyl)-*chiro*-inositol (**12**), which reacted with diethylaminosulphur trifluoride (DAST) with retention of configuration, to yield the 6-deoxy-6-fluoro derivative **13**. Partial deprotection of **13**, followed by phosphorylation and hydrogenolysis, gave **4**.

INTRODUCTION

The biological activity of 1D-*myo*-inositol 1,4,5-trisphosphate (**1**) as a second messenger in the mobilisation of intracellular calcium ions is well established[1], and the role played by other inositol phosphates of the phosphoinositide cascade continues to be explored[2,3]. Currently, there is a need for inositol analogues which block specific phosphatase and kinase pathways, and this has led to the synthesis of various deoxyfluoroinositol[4–8] and azidodeoxyinositol isomers[9]. Most of the published inositol syntheses have started from *myo*-inositol or, in chiral routes, from the naturally occurring *O*-methyl-*chiro*-inositol isomers, D-pinitol and L-quebrachitol[8,10,11]. Several of the novel isomers show cell-growth-inhibitory properties[7,9]. Recently, there have been reports of the syntheses of deoxyfluoroinositol phosphates[12–15], notable amongst these being the route to 1D-3-deoxy-3-fluoro-*myo*-inositol 1,4,5-trisphosphate (**2**) from quebrachitol[12]. In a different approach, Ley et al.[15] presented a total synthesis of (±)-6-deoxy-6-fluoro-*myo*-inositol 1,4,5-

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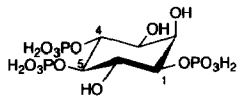

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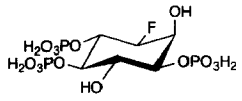

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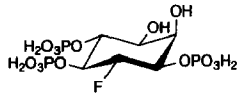
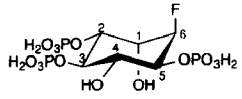


(±)-3



(±)-4

5

(±)-6 R = H

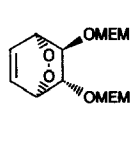
(±)-7 R = $CH_2OCH_2CH_2OMe$

trisphosphate (**3**) from benzene, via the microbial oxidation product *cis*-cyclohexa-3,5-diene-1,2-diol (**5**).

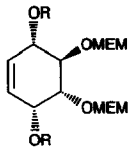
We now describe a route for the total synthesis of (±)-6-deoxy-6-fluoro-*chiro*-inositol 2,3,5-trisphosphate (**4**), using the *trans*-isomer (**6**) of **5**. Compound **4** was chosen as a target because it retains the three equatorial phosphate groups of **1**, but has a fluorine substituent which is isosteric[16] with HO-2. The fluorine substituent can accept but not donate a hydrogen bond involving the relevant enzyme[17]. In the phosphatidylinositol cycle, 1D-*myo*-inositol 1,4,5-trisphosphate (**1**) is converted by a 3-kinase into the 1,3,4,5-tetrakisphosphate. We have attempted to produce a 3-kinase inhibitor by replacing the equatorial HO-3 of **1** with an axial hydroxyl group (i.e., HO-1 in **4**). Significant biological activity of inositol phosphate analogues has recently been found by replacing the HO-3 of **1** by azide[9] or by an axial hydroxyl group[11].

RESULTS AND DISCUSSION

Any approach to the synthesis of an inositol trisphosphate stereoisomer from cyclohexa-1,4-diene must control the stereochemistry of the reaction in each step with good specificity. Thus, the synthesis of **4** began with cyclohexa-1,4-diene, which was converted[18] by bromination, vicinal hydroxylation, and dehydrobromination into the crystalline *trans*-diol **6** in five steps in an overall yield of ~ 50%. The diol **6** was then protected as its di-(2-methoxyethoxymethyl) ether **7** in good yield[19]. The key step in attaining the required stereochemistry was achieved by [2 + 4] cycloaddition of singlet oxygen to the diene system of **7**, to yield the endoperoxide

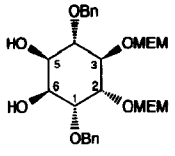


(±)-8

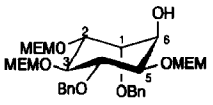


(±)-9 R = H

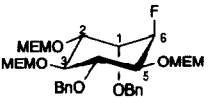
(±)-10 R = Bn



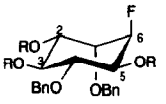
(±)-11



(±)-12



(±)-13



(±)-14 R = H

(±)-15 R = P(O)(OBn)$_2$

8 (82%) as a relatively stable compound that was purified by column chromatography. Smooth reduction of the endoperoxide ring to give the *cis*-1,4 diol **9** (70%) occurred on treatment of **8** with thiourea in methanol[20].

Benzylation of **9** using sodium hydride and benzyl bromide gave the fully protected derivative **10**. The ^{1}H NMR spectrum of **10** showed that the two $MeOCH_2CH_2OCH_2$ groups were in non-equivalent environments (2 s for OMe at δ 3.37 and 3.32). The ^{13}C NMR spectrum contained diagnostic signals at δ ~ 140 (2 C) for the quaternary carbons of the $PhCH_2$ groups, and at δ 97–96 (2 C) for the OCH_2O groups. *cis*-Hydroxylation of the double bond of **10**, using osmium tetroxide, gave a single isomer **11** (79%) having the *chiro*-inositol stereochemistry[21] resulting from attack by osmium tetroxide on the less hindered side of the ring, which is also *anti* to the allylic C–O bonds[22]. By using 1.4 equiv of 2-methoxyethoxymethyl chloride and *N*,*N*-diisopropylethylamine, it was possible to protect preferentially the equatorial HO-5 of **11** to give the derivative **12** (60%) with HO-6 unsubstituted, which was separated by column chromatography from 6% of the 2,3,5,6-tetra-*O*-(2-methoxyethoxymethyl) derivative[23].

Treatment of **12** with an excess of diethylaminosulphur trifluoride (DAST) in dichloromethane at −40° gave the 6-deoxy-6-fluoro derivative **13** (75%) with the original *chiro* stereochemistry. The configuration of **13** was shown by the ^{1}H NMR signal for H-6, visible downfield at δ 5.06, with $J_{6,F}$ 48, $J_{5,6}$ 4, and $J_{1,6}$ 2.5 Hz, the last two values being characteristic of equatorial/axial or equatorial/equatorial $^3J_{H,H}$ couplings. Although inversion of configuration of an alcohol on reaction with DAST is the more expected mode, examples are known where retention is the preferred pathway[13,24]. Retention of stereochemistry often reflects neighbouring group participation in the departure of the leaving group. Yang et al.[5] interpreted the retention of configuration on the reaction of a cyclitol derivative with DAST as due to participation of an adjacent bromomethyl group. The only obvious candi-

date for participation in the reaction **12** → **13** is the distal oxygen atom of the adjacent 2-methoxyethoxymethyl group. However, Prestwich and co-workers[13] have reported an example in the *scyllo*-inositol series where the reaction with DAST involved retention of configuration, although there were no notable groups (benzyl, allyl) which might participate.

The most efficient method found for removal of the 2-methoxyethoxymethyl groups from **13** involved treatment with hydrochloric acid in tetrahydrofuran overnight, to produce (±)-1,4-di-*O*-benzyl-6-deoxy-6-fluoro-*chiro*-inositol (**14**, 79%). The ^{1}H NMR data confirmed the *chiro* configuration of **14** (δ 4.68 for H-6 with $J_{6,F}$ 48.5, $J_{5,6}$ 4.3, and $J_{1,6}$ 2.7 Hz). The important step of phosphorylation of **14** was achieved best by generating the tri-sodium salt[25] in *N*,*N*-dimethylformamide at −20° in the presence of excess of tetrabenzyl pyrophosphate[26]. Repeated chromatography of the product gave 29% of 1,4-di-*O*-benzyl-6-deoxy-6-fluoro-*chiro*-inositol 2,3,5-tris(dibenzyl phosphate) (**15**), the ^{31}P NMR spectrum of which showed three non-equivalent phosphate groups, as expected. The final stage of deprotection was carried out by hydrogenolysis (Pd/C) of **15** in ethanol to give (±)-6-deoxy-6-fluoro-*chiro*-inositol 2,3,5-trisphosphate (**4**), isolated as the hexa-ammonium salt (71%). The 500-MHz ^{1}H NMR spectrum (D_2O) of **4** showed H-6 to have coupling constants similar to those for compounds **13**–**15**, but deprotection had simplified the spectrum of **4** to reveal the signal for H-5 at δ 4.26 (ddt, $J_{5,F}$ 30.8, $J_{4,5}$ 9, $J_{5,P}$ 9, and $J_{5,6}$ 2.5 Hz). The $J_{5,F}$ value is characteristic of a $^3J_{H5,F}$ axial/axial arrangement[27] and provides further proof of the axial position of F-6. The ^{31}P NMR spectrum of **4** revealed three signals, in the ratios 1:1:1, for the three phosphate groups. The biological activity of **4** is under investigation and will be reported elsewhere.

Manipulation of the intermediates **9** and **11** offers routes to stereo- and regio-isomers of fluorinated inositols. Since cyclohexa-1,4-diene is available readily from benzene by Birch reduction, the above sequence constitutes a total synthesis of **4** from benzene. In combination with a recent method[28] for the resolution of the chiral benzene *trans*-glycol **6**, a general route is provided for the preparation of enantiomerically pure inositol derivatives.

EXPERIMENTAL

General.—Melting points were determined with a Mettler FP 82 hot-stage apparatus and are uncorrected. Column chromatography was performed using SORBSIL™ C60-H silica gel (60–210 μm). TLC was carried out using Silica Gel 60 F_{254} (Merck), with detection by charring with sulphuric acid. NMR spectra were recorded with Jeol JNM GSX 270 and GSX 500 instruments. IR spectra were recorded with a Perkin-Elmer 597 instrument. Light petroleum refers to the fraction with bp 40–60°. Tetrabenzyl pyrophosphate was prepared by the method of Khorana and Todd[26]. *trans*-Cyclohexa-3,5-diene-1,2-diol (**6**) was prepared as

white platelets, mp 75–76° (lit. m.p. 77°) in five steps from cyclohexa-1,4-diene by the method of Platt and Oesch[18].

trans-*1,2-Di-O-(2-methoxyethoxymethyl)cyclohexa-3,5-diene-1,2-diol* (**7**).—To a solution of *trans*-cyclohexa-3,5-diene-1,2-diol (**6**; 0.36 g, 3.2 mmol) in CH_2Cl_2 (20 mL) was added *N,N*-diisopropylethylamine (1.20 g, 9.6 mmol) followed by 2-methoxyethoxymethyl chloride (1.20 g, 9.6 mmol). The mixture was stirred at room temperature for 16 h when TLC showed the reaction to be complete. The mixture was poured into ice–water (100 mL) and extracted with ether (3 × 100 mL), and the combined extracts were concentrated. Column chromatography (30% acetone in light petroleum) of the residue gave **7** (0.84 g, 91%), isolated as an oil, ν_{max}^{film} 3040, 2880, 2810, 1425, 1355, 1115, 1040, 930, and 850 cm^{-1}. NMR data ($CDCl_3$): ^1H (270 MHz), δ 5.95 (m, 4 H, H-3/6), 4.84 (s, 4 H, 2 OCH_2O), 4.46 (bs, 2 H, H-1,2), 3.80–3.55 (m, 8 H, 2 OCH_2CH_2O), 3.39 (s, 6 H, 2 OMe); ^{13}C (67.9 MHz), δ 127.52 and 124.68 (C-3/6), 94.69 (OCH_2O), 75.90 (C-1,2), 71.74 and 67.06 (OCH_2CH_2O), 59.02 (OMe).

Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.06; H, 8.47.

trans-*5,6-Di-(2-methoxyethoxymethoxy)-2,3-dioxabicyclo[2.2.2]oct-7-ene* (**8**).—A solution of **7** (0.73 g, 2.5 mmol) in CH_2Cl_2 (100 mL) was irradiated for 9.5 h with an external 500-W photo-flood lamp at −70° using Methylene Blue (10 mg) as the sensitiser whilst bubbling dry O_2 through the solution. The solvent was then evaporated. Column chromatography (30% acetone in light petroleum) of the residue gave **7** (347 mg) and **8** (349 mg, 43%; 82% based on recovered **7**), isolated as a yellow syrup. NMR data ($CDCl_3$): ^1H (270 MHz), δ 6.65 (m, 2 H, H-7,8), 4.90 (s, 2 H, OCH_2O), 4.81 (2 AB d, 2 H, *J* 7.2 Hz, OCH_2O), 4.01 (dd, 1 H, *J* 4.1 and 1.8 Hz) and 3.85 (m, 1 H), (H-5,6), 3.7–3.55 (m, 10 H, 2 OCH_2CH_2O and H-1,4), 3.39 and 3.38 (2 s, 6 H, 2 OMe); ^{13}C (67.9 MHz), δ 131.23 and 130.96 (C-7,8), 95.51 and 95.43 (OCH_2O), 78.84, 75.38, 75.33, and 72.41 (C-1,4,5,6), 71.64, 71.64, 67.51, and 67.29 (OCH_2CH_2O), 58.98 (OMe).

(±)-1,2,4 / 3-2,3-Di-O-(2-methoxyethoxymethyl)cyclohex-5-ene-1,2,3,4-tetrol (**9**).—A solution of **8** (349 mg, 1.10 mmol) in MeOH (25 mL) was stirred with thiourea (100 mg, 1.32 mmol) at room temperature for 8 h when TLC showed the reaction to be complete. The solvent was then evaporated. Column chromatography (20% acetone in light petroleum) of the residue gave **9** (245 mg, 70%), isolated as a colourless oil; ν_{max}^{film} 3400, 3030, 2900, 1620, 1450, 1365, 1040, 935, and 845 cm^{-1}. NMR data (CD_3COCD_3): ^1H (270 MHz), δ 5.79 (ddd, 1 H, *J* 10.2, 4.7, and 2 Hz, H-6), 5.71 (dd, 1 H, *J* 10.2 and 2.3 Hz, H-5), 4.91 (m, 4 H, 2 OCH_2O), 4.36 (dd, 1 H, *J* 8.5 and 4.7 Hz, H-2), 4.28 (d, 1 H, *J* 4.7 Hz, OH), 4.08 (bm, 1 H, H-4), 3.9–3.55 (m, 11 H, 2 OCH_2CH_2O, H-1,3 and OH), 3.35 (s, 6 H, 2 OMe); ^{13}C (67.9 MHz), δ 132.99 and 127.59 (C-5,6), 97.29 and 96.29 (OCH_2O), 80.62, 78.54, 72.79, and 72.55 (C-1/4), 72.55, 68.02, and 66.64 (OCH_2CH_2O), 58.76 (OMe).

(±)-1,2,4 / 3-1,4-Di-O-benzyl-2,3-di-O-(2-methoxyethoxymethyl)cyclohex-5-ene-1,2,3,4-tetrol (**20**).—A solution of **9** (188 mg, 0.58 mmol) in DMF (4 mL) was stirred with NaH (84 mg, 3.5 mmol) and benzyl bromide (350 mg, 2.05 mmol) at 0°

for 2 h, and then concentrated at 20°. Column chromatography (20% acetone in light petroleum) of the residue gave **10** (197 mg, 67%), isolated as a colourless oil, ν_{max}^{film} 3090, 3030, 2880, 1600, 1490, 1450, 1360, 1090, 735, and 700 cm^{-1}. NMR data: ^1H ($CDCl_3$, 270 MHz), δ 7.4–7.25 (m, 10 H, 2 Ph), 5.86 (m, 2 H, H-5,6), 4.98 (d, 1 H, *J* 6.3 Hz), 4.92 (d, 1 H, *J* 6.3 Hz), 4.88 (d, 1 H, *J* 7.0 Hz) and 4.82 (d, 1 H, *J* 7.0 Hz) (2 OCH_2O), 4.74 (d, 1 H, *J* 11.7 Hz), 4.70 (d, 1 H, *J* 12.1 Hz), 4.67 (d, 1 H, *J* 12.1 Hz) and 4.61 (d, 1 H, *J* 11.7 Hz) (2 PhCH_2O), 4.28 (dd, 1 H, *J* 10.2 and 7.0 Hz, H-3), 4.11 (t, 1 H, *J* 3.9 Hz, H-1), 4.07 (bd, 1 H, *J* 7 Hz, H-4), 3.75–3.42 (m, 9 H, 2 OCH_2CH_2O and H-2), 3.37 and 3.32 (2 s, each 3 H, 2 OMe); ^{13}C (CD_3COCD_3, 67.9 MHz), δ 140.41 and 139.95 (Ph C-1′), 131.04 and 127.59 (C-5,6), 129.05, 128.99, 128.56, 128.45, 128.18, and 128.13 (Ph), 96.89 and 96.02 (OCH_2O), 81.02, 77.62, 76.36, 74.14, 72.79, and 71.50 (C-1/4 and 2 PhCH_2O), 72.52 and 67.88 (OCH_2CH_2O), 58.82 and 58.74 (OMe).

Anal. Calcd for $C_{28}H_{38}O_8$: C, 66.91; H, 7.62. Found: C, 66.62; H, 7.55.

(±)-1,4-Di-O-benzyl-2,3-di-O-(2-methoxyethoxymethyl)-chiro-*inositol* (**11**).—To a stirred solution of **10** (189 mg, 0.38 mmol) and *N*-methylmorpholine *N*-oxide (53 mg, 0.45 mmol) in acetone (4 mL) and water (1 mL) was added osmium tetroxide (~ 5 mg) at room temperature. After 12 h, the solvents were evaporated. Column chromatography (40% acetone in light petroleum) of the residue afforded **11** (160 mg, 79%), ν_{max}^{film} 3430, 3030, 2900, 1600, 1490, 1450, 1360, 1090, 740 and 705 cm^{-1}. NMR data (CD_3COCD_3): ^1H (270 MHz), δ 7.4–7.25 (m, 10 H, 2 Ph), 4.89 (m, 4 H, 2 OCH_2O), 4.78 (m, 4 H, 2 PhCH_2O), 4.21 (d, 1 H, *J* 3.1 Hz, OH), 4.05 (t, 1 H, *J* 3 Hz, H-6), 4.0–3.9 (m, 2 H), 3.95–3.6 (m, 8 H), 3.51 (t, 2 H, *J* 5.0 Hz), 3.35 (m, 2 H), 3.30 and 3.22 (2 s, each 3 H, 2 OMe); ^{13}C (67.9 MHz), δ 140.57 and 140.06 (Ph C-1′), 129.02, 128.83, 128.40, 128.18, and 127.86 (Ph), 97.48 and 96.54 (OCH_2O), 83.42, 79.26, 78.38, 78.11, 75.47, 73.82, 72.85, and 71.20 (C-1/6 and 2 PhCH_2O), 72.55, 68.09, and 67.94 (OCH_2CH_2O), 58.85 and 58.71 (OMe).

(±)-1,4-Di-O-benzyl-2,3,5-tri-O-(2-methoxyethoxymethyl)-chiro-*inositol* (**12**).—To a solution of **11** (330 mg, 0.62 mmol) in CH_2Cl_2 (10 mL) was added *N,N*-diisopropylethylamine (120 mg, 0.93 mmol), followed by 2-methoxyethoxymethyl chloride (110 mg, 0.88 mmol). The mixture was stirred at room temperature for 12 h and then concentrated. Column chromatography (30% acetone in light petroleum) of the residue afforded **12** (230 mg, 60%), isolated as a colourless oil; ν_{max}^{film} 3450, 3030, 2880, 1450, 1365, 1100, 1020, 845, 740, and 700 cm^{-1}. NMR data: ^1H (CD_3COCD_3, 270 MHz), δ 7.4–7.25 (m, 10 H, 2 Ph), 4.95–4.75 (m, 10 H, 3 OCH_2O and 2 PhCH_2O), 4.34 (d, 1 H, *J* 3.5 Hz, OH), 4.20 (dd, 1 H, *J* 4.1 and 3.1 Hz, H-6), 4.07 (m, 1 H), 3.99 (dd, 1 H, *J* 10.0 and 3.1 Hz, H-5), 3.9–3.6 (m, 7 H), 3.50 (m, 6 H, 3 OCH_2CH_2O), 3.38 (m, 2 H), 3.31, 3.28, and 3.22 (3 s, each 3 H, OMe); ^{13}C ($CDCl_3$, 67.9 MHz), δ 138.98 and 138.55 (Ph C-1′), 128.32, 128.27, 128.21, 127.59, and 127.32 (Ph), 97.24, 96.27, and 95.24 (OCH_2O), 81.02, 80.97, 78.00, 77.87, 77.16, 75.33, 73.20, and 68.50 (C-1/6 and 2 PhCH_2O), 71.77 (3 C), 67.69, 67.48, and 67.21 (OCH_2CH_2O), 59.01, 58.90, and 58.84 (OMe).

Anal. Calcd for $C_{32}H_{48}O_{12}$: C, 61.52; H, 7.74. Found: C, 61.45; H, 7.85.

From earlier column fractions, (±)-1,4-di-*O*-benzyl-2,3,5,6-tetra-*O*-(2-methoxyethoxymethyl)-*chiro*-inositol (24 mg, 6%) was also isolated. NMR data ($CDCl_3$): inter alia, ^1H (270 MHz), δ 3.38, 3.36, 3.33, and 3.31 (4 s, each 3 H, 4 OMe); ^{13}C (67.9 MHz), δ 97.35, 96.29, 95.89, and 95.73 (OCH_2O).

(±)-1,4-Di-O-benzyl-6-deoxy-6-fluoro-2,3,5-tri-O-(2-methoxyethoxymethyl)-chiro-inositol (**13**).—To a stirred solution of **12** (124 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) at −40° in a teflon container was added DAST (Aldrich, 96 mg, 0.6 mmol). After 1 h, the mixture was neutralised with solid $NaHCO_3$, (0.5 g), stirred for 30 min, and then concentrated at 20°. Column chromatography (30% acetone in light petroleum) of the residue gave **13** (93 mg, 75%), isolated as a colourless oil. NMR data (CD_3COCD_3): ^1H (270 MHz), δ 7.38 (m, 10 H, 2 Ph), 5.06 (ddd, 1 H, *J* 48, 4, and 2.5 Hz, H-6), 4.95–4.72 (m, 10 H, 3 OCH_2O and 2 $PhCH_2O$), 4.18 (m, 1 H), 4.05–3.35 (m, 16 H, 3 OCH_2CH_2O and four ring protons), 3.31, 3.27, and 3.23 (3 s, each 3 H, OMe); ^{13}C (67.9 MHz), δ 139.92 and 139.38 (Ph C-1'), 129.15, 128.97, 128.67, 128.51, 128.40, and 128.10 (Ph), 97.48, 96.75, and 96.70 (OCH_2O), 89.81 (d, *J* 176 Hz, C-6), 81.73 (d, *J* 3.6 Hz), 77.48 (d, *J* 16.5 Hz, C-5), 76.36 (d, *J* 23.8 Hz, C-1), 77.89, 77.52, 76.01, and 74.22 (C-2,3 and 2 $PhCH_2O$), 72.47 (3 C), 68.15, 68.02, and 67.72 (OCH_2CH_2O), 58.84, 58.79, and 58.71 (OMe).

*(±)-1,4-Di-O-benzyl-6-deoxy-6-fluoro-*chiro*-inositol* (**14**).—A solution of **13** (85 mg, 0.135 mmol) in 4:1 THF and concd HCl (5 mL) was stirred at room temperature overnight, then concentrated, neutralised with solid K_2CO_3, and extracted with acetone (3 × 5 mL), and the combined extracts were concentrated. Column chromatography (30% acetone in light petroleum) of the residue gave **14** (39 mg, 79%), mp 116–118°. NMR data (CD_3OD): ^1H (270 MHz), δ 7.45–7.2 (m, 10 H, 2 Ph), 4.9–4.8 (m, 3 H), 4.68 (ddd, 1 H, *J* 48.5, 4.3, and 2.7 Hz, H-6), 4.62 (d, 1 H, *J* 12.1 Hz, 0.5 $PhCH_2O$), 3.8–3.4 (m, 5 H); ^{13}C (67.9 MHz), δ 140.41 and 139.63 (Ph C-1'), 129.40, 129.13, 128.97, 128.86 and 128.45 (Ph), 92.31 (d, *J* 177.8 Hz, C-6), 78.24 (d, *J* 23.6 Hz, C-1), 83.22 (d, *J* 3.7 Hz), 76.28, 75.28, 74.44, and 72.55 (C-2,3,4 and 2 $PhCH_2O$), 71.72 (d, *J* 16.5 Hz, C-5).

Anal. Calcd for $C_{20}H_{23}FO_5$: C, 66.28; H, 6.40. Found: C, 65.96; H, 6.36.

*(±)-1,4-Di-O-benzyl-6-deoxy-6-fluoro-*chiro*-inositol 2,3,5-tris(dibenzyl phosphate)* (**15**).—NaH (80%, 14 mg, 0.46 mmol) was added to a stirred mixture of **14** (29 mg, 0.08 mmol) and tetrabenzyl pyrophosphate (250 mg, 0.46 mmol) in dry DMF (2 mL) at −20°. The mixture was allowed to warm to room temperature during 1 h, then treated with 6 M HCl (0.1 mL), and concentrated. Column chromatography (30% acetone in light petroleum) of the residue gave slightly impure **15** (40 mg, 44%). Re-chromatography (50% EtOAc in light petroleum) gave **15** (26 mg, 29% overall yield), isolated as a colourless oil. NMR data (CD_3COCD_3): ^1H (270 MHz), δ 7.5–7.1 (m, 40 H, 8 Ph), 5.16 (ddd, 1 H, *J* 48, 4.9, and 2.5 Hz, H-6), 5.15–4.65 (m, 19 H), 4.55 (bm, 1 H, H-1), 3.98 (t, 1 H, *J* 9 Hz, H-4); ^{13}C (67.9 MHz), δ 139.11 and 138.44 (2 inositol ring OCH_2Ph C-1'), 137.44–137.09 (6 phosphate OCH_2Ph C-1'), 129.37, 129.29, 129.18, 128.99, 128.89, 128.75, 128.64, 128.54, and 128.13 (Ph), 88.76 (d, *J* 181.4 Hz, C-6), 78.47 (bd, *J* 4.5 Hz), 78.06 (m), 76.90 (dd, *J* 16.5, and 5.5 Hz,

C-5), 76.12 (t, *J* 4.5 Hz), 75.28 and 74.93 (2 inositol ring OCH_2Ph), 70.42–69.80 (C-1 and 6 phosphate OCH_2Ph); ^{31}P (109 MHz), δ 0.35, 0.01, and −0.29.

Anal. Calcd for $C_{62}H_{62}FO_{14}P_3$: C, 65.12; H, 5.47. Found: C, 65.40; H, 5.68.

*(±)-6-Deoxy-6-fluoro-*chiro*-inositol 2,3,5-trisphosphate* (**4**).—A solution of **15** (37 mg, 0.032 mmol) in EtOH (95%, 10 mL) was hydrogenated in the presence of 10% Pd/C (100 mg) at 50 p.s.i. for 4.5 h, then filtered, treated with aq ammonia to pH 9, and concentrated to give **4** as the hexa-ammonium salt (12 mg, 71%). NMR data (D_2O): ^1H (500 MHz), δ 5.16 (ddd, 1 H, *J* 47.3, 4.5, and 2.5 Hz, H-6), 4.52 (bm, 1 H, H-1), 4.26 (ddt, *J* 30.8, 9, 9, and 2.5 Hz, H-5), 4.15 (m, 2 H, H-2,3), 3.85 (t, 1 H, *J* 9 Hz, H-4); ^{13}C (67.9 MHz), δ 93.15 (d, *J* 173.2 Hz, C-6), 78.11 (bs) and 75.66–75.17 (m) (C-2/5), 70.68 (d, *J* 25.7 Hz, C-1); ^{31}P (109 MHz), δ 5.23, 3.92, and 3.65.

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