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Stereoselective synthesis of 2,6-dideoxy; 3,6-dideoxy; 2,3,6-trideoxy-inositol 1,4,5-trisphosphate and 6-deoxy-inositol 1,3,4,5-tetrakisphosphate analogues from 6-deoxy-D-inositol precursors

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This article is dedicated to the memory of Stéphane Dov Gero, who passed away on 16 November 1998

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Abstract—The novel 2,6-dideoxy-2,2-difluoro; 2,6-dideoxy-2-fluoro; and 2,3,6-trideoxy-2,3-difluoro-Ins(1,4,5)tris(dibutyl)phosphates and 6-deoxy-D-*chiro*-inositol 1,3,4,5-tetrakis(dibutyl)phosphate analogues were synthesized in optically pure form. Modification of Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4 analogues by lipophilic substituents has been investigated in order to produce neutral phosphate derivatives aimed to be incorporated in cell membrane for in vivo evaluation.

It is conceivable that inhibitors of the key enzymes of the phosphoinositide cascade, as phosphatases or kinases, could be of medicinal interest. For example, intracellular signaling pathways mediating the effects of oncogenes on cell growth and transformation offer novel targets for the development of anticancer drugs.[1]

As a result of the stimulation of cell surface receptors by a variety of ligands, the membrane-located phosphatidylinositol 4,5-bisphosphate is hydrolyzed by phospholipase C to 1D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] and diacylglycerol. The further metabolism of Ins(1,4,5)P_3 is quite complex and involves the action of various kinases and phosphatases. An important initial transformation is the phosphorylation of Ins(1,4,5)P_3 through the action of an ATP-dependent 3-kinase to give 1D-*myo*-inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P_4]. While the role of this metabolite is still under study, the suggestion has been made that it may play a role in refilling the intracellular Ca^{2+} stores with extracellular Ca^{2+}.[2]

A major challenge is now the elucidation of the structural basis for interaction of Ins(1,4,5)P_3 both with its receptor and with the metabolic enzymes Ins(1,4,5)P_3 3-kinase and 5-phosphatase, and the rational chemical design of agonists, antagonists and enzyme inhibitors.

Several inositol ring-modified and phosphate-modified analogues have been synthesized and progress has been made in understanding the role of phosphate and hydroxyl groups in determining activity of second messengers.[3]

The D-3-substituted *myo*-inositol analogues are selective inhibitors of the growth of v-*sis*-transformed NIH 3T3 cells.[4] Furthermore the 6-deoxy Ins(1,4,5)P_3 has already been shown to be a full agonist for Ca^{2+} release in permeabilized SH-SY5Y human neuroblastoma cells, a relatively potent Ins(1,4,5)P_3 5-phosphatase inhibitor and a weak substrate for Ins(1,4,5)P_3 3-kinase.[5]

The optically active starting material, 6-deoxy Ins(1,5) diol **1**, was prepared from D-galactose (Scheme 1) according to our earlier developed methodology, using Ferrier rearrangement in the stereoselective sugar to cyclitol transformation step.[6]

1. Results and discussion

In view of the inhibition of the 3-kinase and 5-phosphatase by 2-, 3- or 6-deoxy substituted Ins(1,4,5)P_3 derivatives and after the success accounted on the transmembrane incorporation of lipophilic derivatives of Ins(1,4,5)P_3,[3] the

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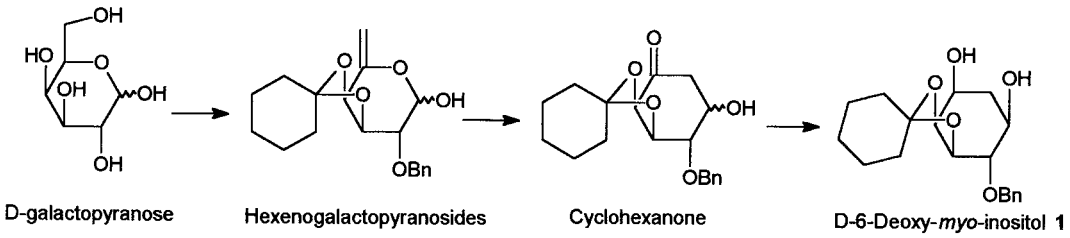


Scheme 1.

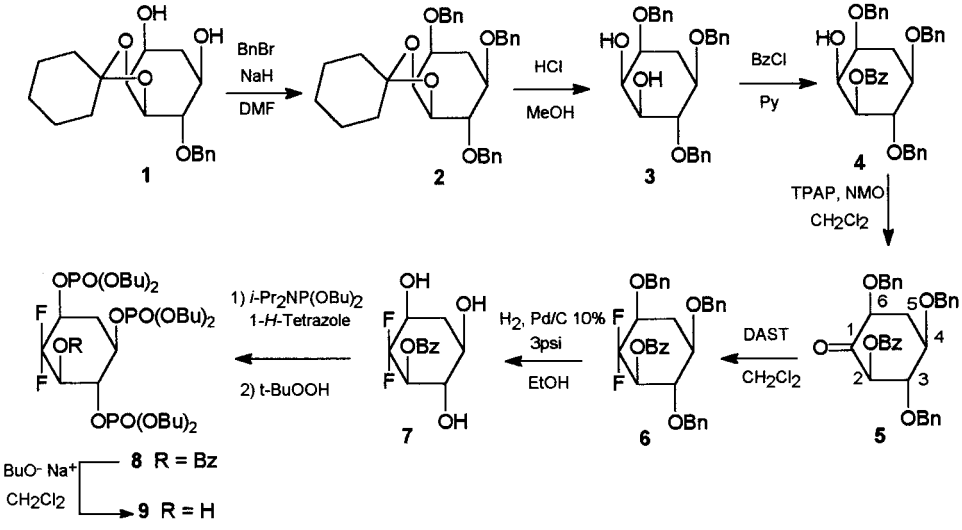
preparation of the 2-, 3- and 6-deoxy Ins(1,4,5)P_3 derivatives in more lipophilic forms seemed attractive. Additionally, the fluorine atom is a suitable isostere for a hydroxy group. Such an isosteric replacement was viewed as giving rise to a compound which in terms of its physiochemical properties should still be close enough to inositol to enter into the cell via a carrier-mediated process. Furthermore in the last decade a number of deoxy-fluoro-*myo*-Ins(1,4,5)P_3 and deoxy-fluoro-*scyllo*-Ins(1,4,5)P_3 analogues have shown interesting biological results.[7]

Keeping these considerations in mind, we justified the synthesis of 2,6-dideoxy-2,2-difluoro-Ins(1,4,5)tris(dibutyl)-phosphate **9**, 2,6-dideoxy-2-fluoro-Ins(1,4,5)tris(dibutyl)-phosphate **17** and 2,3,6-trideoxy-2,3-difluoro-Ins(1,4,5)-tris(dibutyl)phosphate **14** and 6-deoxy-D-*chiro*-Ins(1,3,4,5)-tetrakis(dibutyl) phosphate **22**.

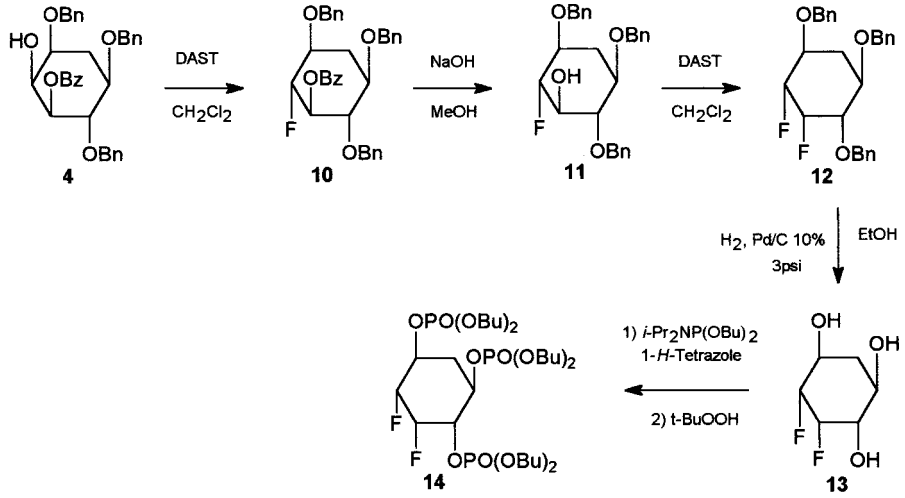
Compound **1** was treated with benzyl bromide and sodium hydride in DMF to give the tri-*O*-benzyl derivative **2** in 93% yield (Scheme 2). Hydrolysis of the cyclohexylidene ketal, under mildly acidic conditions, afforded the protected deoxy *myo*-inositol **3**, in 95% yield, which presented two free hydroxyls at the 2 and 3 positions. The benzoylation of diol **3** was carried out, in 96% yield, by treatment with benzoyl chloride in pyridine to give the intermediate **4**, which was oxidized in the presence of TPAP/NMO to give the 2-inosose **5** in 80% yield. Conversion of this ketone into the 2,2-difluoro derivative **6** was accomplished in 62% yield using (diethylamino)sulfur trifluoride (DAST). The hydrogenolysis of the protected 2,2-difluoro **6**, in the presence of Pd/C 10%, produced the 3-*O*-benzoyl-2,6-dideoxy-2,2-difluoro-*myo*-inositol **7**. The latter compound was phosphorylated by reaction with bisbutyloxy(diisopropylamino)phosphine and tetrazole, followed by oxidation with *t*-BuOOH, leading to the protected 2,2-difluoro-tris(dibutyl)phosphate **8** in 55% yield. Saponification of the ester intermediate **8**, under basic medium in dichloromethane, afforded the 2,2-difluoro-tris(dibutyl)-phosphate **9** in quantitative yield.

In order to produce the 2,3,6-trideoxy-2,3-difluoro-Ins(1,4,5)tris(dibutyl)phosphate **14** the following methods were adopted (Scheme 3). The alcohol **4** was treated with the (diethylamino)sulfurtrifluoride (DAST) with inversion of configuration to yield the 3-*O*-benzoyl-1,4,5-tri-*O*-benzyl-2,6-dideoxy-2-fluoro-*scyllo*-inositol **10**, in 90% yield. Removal of the benzoyl group on **10** under basic conditions gave **11**, in 76% yield, which was fluorinated with DAST, with inversion of configuration to yield the 2,3-difluoro **12** in 75% yield. Hydrogenolysis of the benzyl groups afforded the 2,3-difluoro **13** in 55% yield, which was allowed to be phosphorylated in the presence of bisbutyloxy(diisopropylamino)phosphine and tetrazole, followed by oxidation with *t*-BuOOH, leading to **14** in 55% yield.

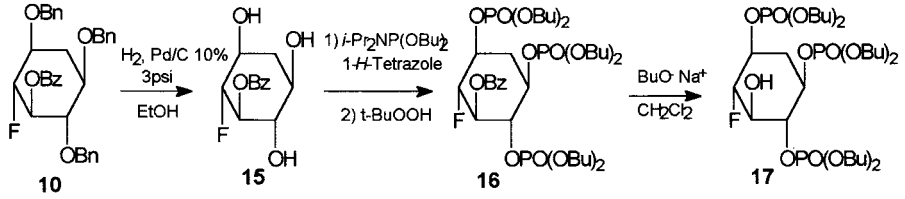
The deprotection of the intermediate **10** was achieved by hydrogenolysis of benzyl groups to give **15** in quantitative yield (Scheme 4). The 2,6-dideoxy-2-fluoro-Ins(1,4,5)tris-(dibutyl)phosphate **16** was prepared from the triol **15**, in 73% yield, by the same phosphorylation procedure described above. Cleavage of benzoyl group of **16** was



Scheme 2.



Scheme 3.



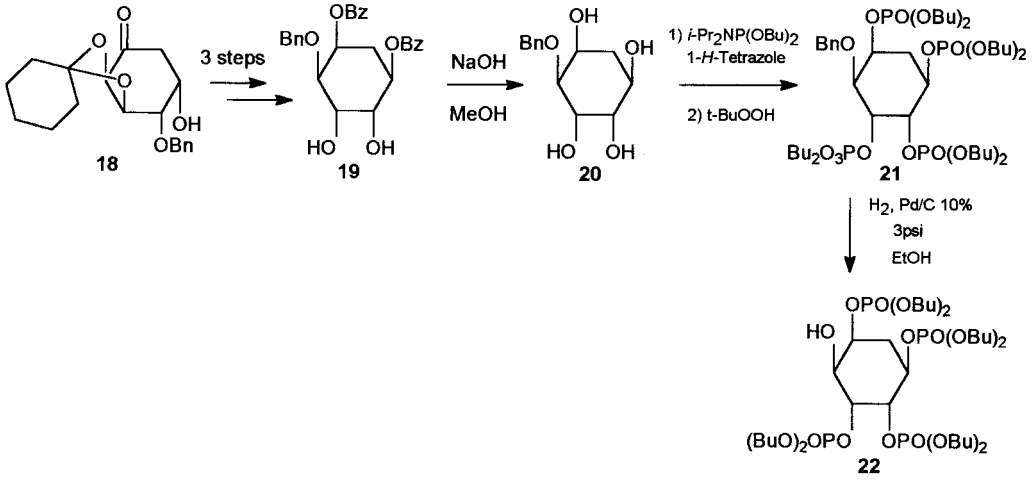
Scheme 4.

accomplished in 95% yield by treatment with sodium *n*-butoxide in dichloromethane.

As described recently,[8] the protected 6-deoxy Ins(3,4)diol **19** is easily available from cyclohexanone α-hydroxyl (Scheme 1). Saponification of the diester intermediate **19** (Scheme 5), under basic medium, afforded the tetrol **20** in 86% yield, which was allowed to be phosphorylated in the presence of bisbutyloxy(diisopropylamino)phosphine and tetrazole, followed by oxidation with *t*-BuOOH, leading to the tetrakis(dibutyl)phosphate **21** in 55% yield. Hydrogenolysis, in the presence of Pd/C 10% in AcOEt, of intermediate **21** furnished the lipophilic tetrakis(dibutyl)-phosphate **22** in 85% yield.

2. Conclusion

We have illustrated the potentiality of deoxy cyclitol precursors, stereoselectively produced from D-galactose,[8,9] to be used for the synthesis of optically pure 2,6-dideoxy-2,2-difluoro; 2,6-dideoxy-2-fluoro and 2,3,6-trideoxy-2,3-difluoro-Ins(1,4,5)tris(dibutyl)phosphates and 6-deoxy-D-*chiro*-inositol 1,3,4,5-tetrakis(dibutyl)phosphate analogues. The 6-deoxy analogues of the well-known second messenger Ins(1,4,5)P_3, possessing a promising biological effect on permeabilized cells,[3] have been transformed into lipophilic forms in order to assume their incorporation through the membrane of intact cells.



Scheme 5.

Preliminary success encountered in vivo in the incorporation of lipophilic analogues of Ins(1,4,5)P_3 into cell membrane encouraged the investigation of lipophilic 2,6-dideoxy, 3,6-dideoxy, 2,3,6-trideoxy Ins(1,4,5)P_3 and 6-deoxy Ins(1,3,4,5)P_4 analogues on Ca^{2+} mobilization.

3. Experimental

3.1. 1,4,5-Tri-*O*-benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol 2

NaH (250 mg, 10.4 mmol) was added, under argon, to diol **1** (1.14 g, 2.22 mmol) dissolved in *N*,*N*-dimethylformamide (15 mL). The mixture was stirred for 10 min before benzylbromide (2.46 mL, 10 mmol) was added. The solution was stirred for 12 h then methanol was added. The reaction mixture was extracted and the organic layer concentrated to dryness. Flash chromatography on silica gel (eluent: AcOEt/heptane) gave the *myo*-inositol **2** (93%). $[\alpha]_D=-39°$ (*c* 0.27; CH_2Cl_2); ^{1}H NMR (250 MHz; $CDCl_3$) δ: 4.3 (t, 1H, H-2, $J_{2-1}=J_{2-3}=3$); 4.1 (dd, 1H, H-3, $J_{3-4}=12$); 3.6 (m, 2H, H-4, H-1); 3.3 (m, 1H, H-5); 2.1 (m, 1H, H-6eq); 1.9 (q, 1H, H-6ax, $J_{6ax-1}=J_{6ax-5}=J_{6ax-6eq}=12$); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ: 85 (C-4); 80 (C-3); 77 (C-5); 74 (C-2); 72 (C-1); 30 (C-6); (Found C, 76.86; H, 7.52; $C_{33}H_{38}O_5$ requires C, 77.01; H, 7.44%).

3.2. 1,4,5-Tri-*O*-benzyl-6-deoxy-D-*myo*-inositol 3

Methanol (10 mL, 0.23 mol) and HCl (0.6 mL, 0.02 mmol) were added to the inositol **2** (1.0 g, 1.9 mmol). The solution was stirred at 60°C for 15 h. The reaction mixture was extracted and the organic layer concentrated to dryness. The residue was purified by flash chromatography on silica gel (eluent: AcOEt/heptane) to give the inositol **3** (98%). $[\alpha]_D=4.9°$ (*c* 1.0; $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 4.7 (d, 1H, H-3, $J_{2-3}=0$, $J_{3-4}=9$); 4.2 (sl, 1H, H-2); 3.8 (t, 1H, H-4, $J_{4-5}=9$); 3.5 (m, 2H, H-1, H-5); 2.2 (dt, 1H, H-6eq, $J_{6eq-5}=J_{6eq-1}=3$, $J_{6eq-6ax}=12$); 2.0 (q, 1H, H-6ax, $J_{6ax-5}=J_{6ax-1}=J_{6ax-6eq}=12$); ^{13}C NMR (75.50 MHz, $CDCl_3$) δ: 82 (C-4); 78 (C-5); 75 (C-2); 74 (C-3); 70 (C-1); 30 (C-6); (Found C, 74.24; H, 7.01; $C_{27}H_3O_5$ requires C, 74.63; H, 7.00%)

3.3. 1,4,5-Tri-*O*-benzyl-3-*O*-benzoyl-6-deoxy-D-*myo*-inositol 4

To a solution of diol **3** (725 mg, 1.6 mmol) in pyridine (10 mL) was added benzoyl chloride (0.3 mL, 2.10 mmol). The solution was stirred at 10°C for 20 min, extracted with CH_2Cl_2 (2×50 mL) and the organic layer was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: AcOEt/heptane) to afford the benzoylated inositol **4** (80%). $[\alpha]_D=47.0°$ (*c* 1.0; $CHCl_3$); mp 135–136°C; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 5.1 (d, 1H, H-3, $J_{3-4}=10$); 4.5 (sl, 1H, H-2); 4.2 (t, 1H, H-4, $J_{4-5}=10$); 3.6 (m, 2H, H-1, H-5); 2.3 (m, 1H, H-6eq); 2.1 (q, 1H, H-6ax, $J_{6ax-5}=J_{6ax-6eq}=J_{6ax-1}=12$); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 80 (C-4); 78 (C-5); 75 (C-3); 74 (C-1); 69 (C-2); 30 (C-6); (Found C, 73.56; H, 6.41; $C_{34}H_{34}O_6$ requires C, 73.36; H, 6.19%).

3.4. 3,4,6-Tri-*O*-benzyl-2-*O*-benzoyl-1-one-5-deoxy-D-*myo*-inositol 5

N-oxy-4-methylmorpholine (67.25 mg, 0.57 mmol), tetra-*n*-propylammonium perruthenate (13 mg, 0.04 mmol) and molecular sieves (200 mg) were added to a solution of **4** (200 mg, 0.38 mmol) in anhydrous dichloromethane (4 mL). The mixture was stirred for 12 h before addition of isopropanol (1 mL). The stirring was maintained for 30 min before concentration and filtration through silica gel (eluent: AcOEt/heptane). The filtrate was concentrated under reduced pressure and used without further purification (80%); $[\alpha]_D=14.1°$ (*c* 1.0; $CHCl_3$); mp 122–125°C; IR 1750 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ: 5.5 (d, 1H, H-2, $J_{2-3}=10$); 4.2 (dd, 1H, H-6, $J_{6-5eq}=4$, $J_{6-5ax}=10$); 3.9 (m, 2H, H-4, H-3); 2.6 (m, 1H, H-5eq); 1.8 (q, 1H, H-5ax, $J_{5ax-4}=J_{5ax-5eq}=10$); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 199 (C-1); 82 (C-4); 80 (C-6); 78 (C-2); 75 (C-3); 34 (C-5); (Found C, 76.36; H, 6.17; $C_{34}H_{32}O_6$ requires C, 76.10; H, 6.01%).

3.5. 1,4,5-Tri-*O*-benzyl-3-*O*-benzoyl-2,2-difluoro-6-deoxy-D-*myo*-inositol 6

Diethylaminosulfur trifluoride (0.3 mL, 2 mmol) was added to a solution of the ketone **5** (500 mg, 0.9 mmol) in anhydrous dichloromethane (5 mL). The solution was stirred for 20 h at room temperature before addition of methanol (5 mL). The reaction mixture was extracted and the organic layer concentrated to dryness. Flash chromatography on silica gel (eluent: AcOEt/heptane) gave the difluoro **6** (62%). $[\alpha]_D=22.3°$ (*c* 1.0; $CHCl_3$); mp 60–62°C; ^{1}H NMR (200 MHz; $CDCl_3$) δ: 5.4 (m, 1H, H-3); 3.8 (t, 1H, H-4, $J_{4-5}=J_{3-4}=9$); 3.7–3.5 (m, 2H, H-1, H-5); 2.6 (m, 1H, H-6eq); 1.8 (q, 1H, H-6ax, $J_{6ax-1}=J_{6ax-6eq}=J_{6ax-5}=12$); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 123–120–116 (C-2, $J_{2-F}=252$); 81 (C-4, $J_{4-F}=7$); 76 (C-5); 73 (C-1, $J_{1-F}=19$); 71 (C-3, $J_{3-F}=19$); 32 (C-6, $J_{6-F}=7$); (Found C, 72.17; H, 6.02; $C_{34}H_{32}F_2$ requires C, 71.94; H, 5.86%).

3.6. 3-*O*-Benzoyl-2,6-dideoxy-2,2-difluoro-D-*myo*-inositol 7

Difluoro **6** (250 mg, 0.4 mmol) was dissolved in the minimum amount of AcOEt and hydrogenated for 2 h under 3 psi, in the presence of Pd/C 10% (36 mg). The catalyst was removed by filtration on silica gel (eluent: AcOEt) and the solvent evaporated to afford the desired compound **7** in 93% yield. $[\alpha]_D=9.2°$ (*c* 0.6; CH_3OH); mp 194–196°C; ^{1}H NMR (300 MHz; CD_3OD) δ: 5.2 (dd, 1H, H-3, $J_{3-4}=10$); 4.5–4.3 (dt, 1H, H-2, $J_{2-F}=52$); 3.9 (m, 1H, H-5); 3.6 (m, 1H, H-1); 3.5 (t, 1H, H-4, $J_{4-5}=10$); 2.2 (m, 1H, H-6eq); 0.8 (q, 1H, H-6ax, $J_{6ax-1}=J_{6ax-6eq}=12$); ^{13}C NMR (75.50 MHz; CD_3OD) δ: 169 (C=O); 136–130 (Ph); 122–119–115 (C-2, $J_{2-F}=224$); 77 (C-4); 75 (C-3); 71 (C-5); 69 (C-1); 32 (C-6); (Found C, 54.31; H, 5.05; $C_{13}H_{14}O_5F_2$ requires C, 54.19; H, 4.90%).

3.7. 3-*O*-Benzoyl-2,6-dideoxy-2,2-difluoro-D-*myo*-inositol-1,4,5-tris(dibutyl)phosphate 8

To difluoro **7** (86 mg, 0.3 mmol) was added dibutoxy(diisopropylamino)phosphine (480 mg, 1.7 mmol) and the

mixture was dried for 0.5 h under vacuum (0.05 mmHg). Sublimated tetrazole (389 mg, 5.55 mmol), dissolved in dry acetonitrile (10 mL) was added under argon to the mixture. The solution was stirred under argon at room temperature for 3 h. The solution was diluted with CH_2Cl_2 before *t*-BuOOH (1.07 mL, 11.12 mmol) was added. The solution was stirred under argon at room temperature for 12 h. Aqueous sodium thiosulfate was added for neutralization. The product was separated by chromatography on silica gel (eluent: AcOEt/heptane 8:2) (73%). $[\alpha]_D$=14.6° (*c* 1.0; $CHCl_3$); mp 62–65°C; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 5.5 (m, 1H, H-3); 4.8 (m, 2H, H-1, H-2); 4.4 (m, 1H, H-4); 4.1 (m, 12H, $OCH_2CH_2CH_2CH_3$); 2.7 (q, 1H, H-6eq, $J_{6eq-5}=J_{6eq-1}=J_{6ax-6eq}$=8); 2.1 (m, 1H, H-6ax); 1.7 (m, 12H, $OCH_2CH_2CH_2CH_3$); 1.4 (m, 12H, $OCH_2CH_2CH_2CH_3$); 0.9 (m, 18H, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 120–117–114 (C-2, J_{2-F}=201); 79 (C-5); 75 (C-4); 72 (C-1); 69 (C-3); 68 ($OCH_2CH_2CH_2CH_3$); 34 (C-6); 32 ($OCH_2CH_2CH_2CH_3$); 19 ($OCH_2CH_2CH_2CH_3$); 13 ($OCH_2CH_2CH_2CH_3$); (Found C, 50.83; H, 7.41; $C_{37}H_{65}O_{14}P_3F_2$ requires C, 50.83; H, 7.61%).

3.8. 2,6-Dideoxy-2,2-difluoro-D-*myo*-inositol-1,4,5-tris(dibutyl)-phosphate 9

A solution of sodium butoxide (0.1 mol/L) in dichloromethane was added to compound **8** (86 mg, 0.1 mmol) and the mixture was stirred for 6 h. The reaction mixture was extracted and the organic layer concentrated to dryness. The residue was purified by flash chromatography on silica gel (eluent: AcOEt/heptane 8:2) to furnish the triphosphate **9** (67%). $[\alpha]_D$=0.44° (*c* 2.5; $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 4.4 (m, 3H, H-1, H-4, H-5); 4.1 (m 12H, $OCH_2CH_2CH_2CH_3$); 3.7 (m, 1H, H-3); 2.6 (m, 1H, H-6eq); 2.1 (m, 1H, H-6ax); 1.7 (m, 12H, $OCH_2CH_2CH_2CH_3$); 1.4 (m, 12H, $OCH_2CH_2CH_2CH_3$); 0.9 (t, 18H, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (62.50 MHz, $CDCl_3$) δ: 80 (C-1); 71-70 (C-3, C-4, C-5); 68 ($OCH_2CH_2CH_2CH_3$); 33–32 ($OCH_2CH_2CH_2CH_3$); 30 (C-6); 19 ($OCH_2CH_2CH_2CH_3$); 14 ($OCH_2CH_2CH_2CH_3$); (Found C, 47.38; H, 8.16; $C_{30}H_{61}O_{13}P_3F_2$ requires C, 47.36; H, 8.08%).

3.9. 1,4,5-Tri-*O*-benzyl-3-*O*-benzoyl-2,6-dideoxy-2-fluoro-*scyllo*-inositol 10

A solution of *myo*-inositol **4** (1.22 g, 2.26 mmol) in anhydrous dichloromethane (25 mL) was cooled to 0°C before addition of diethylaminosulfur trifluoride (0.6 mL, 4.5 mmol) under argon. The solution was stirred for 2 h under argon at room temperature before addition of methanol (10 mL). The mixture was extracted and the organic layer concentrated to dryness. The residue was chromatographed on silica gel (eluent: AcOEt/heptane) to give the monofluoro **10** (90%). $[\alpha]_D$=0.8° (*c* 1.0; $CHCl_3$); mp 94–95°C; ^{1}H NMR (300 MHz; C_6D_6) δ: 5.6 (dd, 1H, H-3, J_{2-3}=9, J_{3-4}=12); 4.5 (m, 1H, H-2, J_{2-F}=50); 3.3 (t, 1H, H-4, J_{4-5}=12); 3.1 (m, 2H, H-1, H-5); 2.0 (m, 1H, H-6eq); 1.3 (q, 1H, H-6ax, $J_{6ax-6eq}=J_{6ax-1}=J_{6ax-5}$=12); ^{13}C NMR (75.50 MHz; C_6D_6) δ: 92 (C-2, J_{2-F}=187); 81 (C-4, J_{4-F}=7); 73 (C-5); 72 (C-1, J_{1-F}=19); 71 (C-3, J_{3-F}=19); 31 (C-6, J_{6-F}=9); (Found C, 75.59; H, 6.22; F, 3.20; $C_{34}H_{33}O_5F$ requires C, 75.53; H, 6.19; F, 3.51%).

3.10. 1,4,5-Tri-*O*-benzyl-2,6-dideoxy-2-fluoro-*scyllo*-inositol 11

To a solution of compound **10** (140 mg, 0.26 mmol) in AcOEt (5 mL) was added a solution of sodium hydroxide (200 mg) in methanol (10 mL). The mixture was stirred for 24 h at room temperature before concentration and filtration through silica (eluent: ethyl acetate). The filtrate was concentrated under reduced pressure and used without further purification (76%). $[\alpha]_D$=−2.9° (*c* 0.8; $CHCl_3$); mp 82–85°C; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 4.4 (dt, 1H, H-2, J_{2-F}=51; $J_{2-1}=J_{2-3}$=10); 3.5 (m, 4H, H-3, H-4, H-1, H-5); 2,4 (m, 1H, H-6eq); 1.5 (m, 1H, H-6ax); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 100–99 (C-2, J_{2-F}=183); 85 (C-4, J_{4-F}=9); 78 (C-3); 76 (C-5); 75 (CH_2Ph); 74 (C-1); 33 (C-6, J_{6-F}=9); (Found C, 74.30; H, 6.84; $C_{27}H_{29}O_4F$ requires C, 74.28; H, 6.69%).

3.11. 1,4,5-Tri-*O*-benzyl-2,3,6-trideoxy-2,3-difluoro-*neo*-inositol 12

Diethylaminosulfur trifluoride (0.08 mL, 0.60 mmol) was added to a solution of monofluoro **11** (100 mg, 0.23 mmol) in anhydrous dichloromethane (6 mL). The mixture was stirred for 10 h under argon at room temperature before addition of methanol (10 mL). The reaction mixture was extracted and the organic layer concentrated to dryness. Flash chromatography on silica gel (eluent: AcOEt/heptane) of the residue gave the difluoro **12** (75%). $[\alpha]_D$=3.4° (*c* 1.0; $CHCl_3$); mp 104–106°C; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 5.0 (dd, 1H, H-3, J_{3-F3}=51); 4.4 (dd, 1H, H-2, J_{2-3}=3, J_{2-F2}=47); 4.0–3.8 (m, 2H, H-1, H-5); 3.4 (dd, 1H, H-4, J_{3-4}=3); 2.4 (m, 1H, H-6eq); 1.4 (m, 1H, H-6ax); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 95 (C-2, J_{2-F2}=189, J_{2-F3}=24); 92 (C-3, J_{3-F3}=189, J_{3-F2}=24); 80 (C-4); 76 (C-5); 75 (C-1); 32 (C-6); (Found C, 73.69; H, 6.64; $C_{27}H_{28}O_3F_2$ requires C, 73.95; H, 6.43%).

3.12. 2,3,6-Trideoxy-2,3-difluoro-*neo*-inositol 13

Compound **12** (80 mg, 0.48 mmol) dissolved in the mixture of AcOEt/MeOH (10 mL, 1:1) was hydrogenated by the same procedure described to obtain **7** from **6** (90%). $[\alpha]_D$=−11.1° (*c* 1.0; CH_3OH); mp 193–196°C; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 4.9 (m, 1H, H-3); 4.2 (m, 1H, H-2); 3.9 (m, 1H, H-1); 3.6 (m, 1H, H-5); 3.3 (m, 1H, H-4); 2.1 (m, 1H, H-6eq); 1.2 (m, 1H, H-6ax); ^{13}C NMR (75.50 MHz, $CDCl_3$) δ: 96 (C-2, J_{2-F}=168); 93 (C-3, J_{3-F}=168); 75 (C-4); 69 (C-5); 68 (C-1); 38 (C-6, J_{6-F}=9).

3.13. 2,3,6-Trideoxy-2,3-difluoro-*neo*-inositol-1,4,5-tris(dibutyl)-phosphate 14

The difluoro **13** (30 mg, 0.18 mmol) was added to dibutoxy-(diisopropylamino)phosphine (300 mg, 1 mmol) and the mixture was dried for 0.5 h under reduced pressure (0.05 mmHg). Sublimated tetrazole (0.08 mg, 11.4 mmol), dissolved in dry acetonitrile (5 mL) was added under argon to the mixture. The solution was stirred under argon for 3 h and diluted with CH_2Cl_2 before *t*-BuOOH (0.21 mL, 2.1 mmol) was added. The solution was stirred under argon at room temperature for 20 h. Aqueous thiosulfate and sodium solution was added for neutralization. After

extraction with dichloromethane the organic layer was purified by chromatography on silica gel (eluent: AcOEt/heptane 8:2) to yield **14** in 55% yield. $[\alpha]_D=-8.6°$ (*c* 0.8; $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$) δ: 4.5–4.2 (dd, 1H, H-3, $J_{3-F}=51$, $J_{3-4}=12$); 4.7 (m, 1H, H-5); 4.6–4.1 (m, 3H, H-1, H-4, H-2); 4.2 (m, 12H, $OCH_2CH_2CH_2CH_3$); 2.8 (m, 1H, H-6eq); 1.7 (m, 13H, H-6ax, $OCH_2CH_2CH_2CH_3$); 1.4 (m, 12H, $OCH_2CH_2CH_2CH_3$); 0.9 (m, 18H, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 92 and 89 (C-3, $J_{3-F}=180$); 91 and 88 (C-2, $J_{2-F}=180$); 76 (C-4); 72–71 (C-1, C-5); 68 ($OCH_2CH_2CH_2CH_3$); 34 (C-6); 33 ($OCH_2CH_2CH_2CH_3$); 20 ($OCH_2CH_2CH_2CH_3$); 15 ($OCH_2CH_2CH_2CH_3$); (Found C, 48.51; H, 8.12; $C_{30}H_{61}O_{12}P_3F_2$ requires C, 48.38; H, 8.24%).

3.14. 3-*O*-Benzoyl-2,6-dideoxy-2-fluoro- *scyllo*-inositol 15

Monofluoro **10** (1.10 g, 2.03 mmol) dissolved in a mixture of AcOEt/EtOH (10 mL, 8:2) was hydrogenated for 2 h under 3 psi, in the presence of the Pd/C (800 mg). The catalyst was removed by filtration in celite and the filtrate was evaporated to dryness to afforded **15** in quantitative yield. $[\alpha]_D=11.7°$ (*c* 1.0; $CHCl_3$). mp 183–185°C, ^1H NMR (300 MHz; CD_3OD) δ: 5.35 (dd, 1H, H-3, $J_{3-2}=9$, $J_{3-4}=12$); 4.5 (dt, 1H, H-2, $J_{2-F}=52$, $J_{2-1}=9$); 4.0 (m, 1H, H-4); 3.7 (m, 2H, H-1, H-5); 2.3 (m, 1H, H-6eq); 1.6 (q, 1H, H-6ax, $J_{6ax-1}=J_{6ax-5}=12$); ^{13}C NMR (75.50 MHz; CD_3OD) δ: 167 (*O*COPh); 97 (C-2, $J_{2-F}=184$); 76 (C-4, $J_{4-F}=9$); 75 (C-1, $J_{1-F}=18$); 70 (C-5); 68 (C-3, $J_{3-F}=18$); 37 (C-6); (Found C, 53.54; H, 5.85; $C_{13}H_{15}O_5F\cdot 5/4H_2O$ requires C, 53.64; H, 5.94%).

3.15. 3-*O*-Benzoyl-2,6-dideoxy-2-fluoro-*scyllo*-inositol-1,4,5-tris(dibutyl)phosphate 16

Compound **15** (250 mg, 0.93 mmol) was phosphorylated in 73% yield by the same procedure described to obtain **14** from **13**. $[\alpha]_D=-8.6°$ (*c* 0.8; $CHCl_3$); mp 44–46°C; ^1H NMR (300 MHz; $CDCl_3$) δ: 5.5 (t, 1H, H-3, $J_{3-4}=J_{3-2}=12$); 4.7 (m, 3H, H-1, H-2, H-5); 4.4 (m, 1H, H-4); 4.1 (m, 12H, $OCH_2CH_2CH_2CH_3$); 2.9 (m, 1H, H-6eq); 1.9 (m, 1H, H-6ax); 1.6 (12H, $OCH_2CH_2CH_2CH_3$); 1.4 (m, 12H, $OCH_2CH_2CH_2CH_3$); 0.9 (m, 18H, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 165 (Ph*C*=O); 91 (C-2, $J_{2-F}=186$); 77 (C-4); 71 (C-5, C-3); 70 (C-1); 67 ($OCH_2CH_2CH_2CH_3$); 32 ($OCH_2CH_2CH_2CH_3$); 31 (C-6); 18 ($OCH_2CH_2CH_2CH_3$); 13 ($OCH_2CH_2CH_2CH_3$); (Found C,52.48; H, 7.69; P, 10.84; F, 2.16; $C_{37}H_{66}O_{14}P_3F$ requires C, 52.47; H, 7.85; P, 10.97; F, 2.24%).

3.16. 2,6-Dideoxy-2-fluoro-*scyllo*-inositol-1,4,5-tris(dibutyl)-phosphate 17

To a solution of monofluoro **16** (165 mg, 0.2 mmol) in dichloromethane anhydrous (12 mL) was added a solution of sodium *n*-butoxide (0.1 mol/L) in *n*-butyl alcohol. The solution was stirred for 1 h, extracted with CH_2Cl_2 and the organic layer concentrated to dryness. Flash chromatography on silica gel (eluent: AcOEt/heptane 8:2) of the residue gave the *scyllo*-inositol **17** (71%). $[\alpha]_D=-2.2°$ (*c* 1.0; $CHCl_3$); mp 105–108°C; ^1H NMR (300 MHz; $CDCl_3$) δ: 4.8 (m, 12H, $OCH_2CH_2CH_2CH_3$); 4.6–4.0 (m, 4H, H-1, H-2, H-4, H-5); 3.7 (t, 1H, H-3, $J_{3-4}=J_{3-2}=10$); 2.6 (m, 1H, H-6eq); 1.9 (m, 1H, H-6ax); 1.7 (m, 12H, $OCH_2CH_2CH_2CH_3$); 1.4 (m, 12H, $OCH_2CH_2CH_2CH_3$); 0.9 (m, 18H, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 92–90 (C-2); 74 (C-5); 72 (C-1); 70–68 (C-3, C-4); 32 (C-6); (Found C, 47.71; H, 8.19; P, 12.35; $C_{30}H_{62}O_{13}P_3F$ requires C, 47.92; H, 8.44; P, 12.36%).

3.17. 2-*O*-Benzyl-6-deoxy-D-*chiro*-inositol 20

To a solution of *chiro*-inositol **19** (2.8 g, 6 mmol) in ethyl acetate (10 mL) was added a solution of sodium hydroxide (400 mg) in methanol (10 mL). The mixture was stirred for 4 h at room temperature before concentration and purification by chromatography on RP8 (eluent: AcOEt/MeOH) (90%). $[\alpha]_D=-2.8°$ (*c* 1.2; CH_3OH); ^1H NMR (300 MHz; CD_3OD) δ: 4.8 (m, 2H, OCH_2Ph); 4.0 (m, 2H, H-1, H-3); 3.6 (m, 2H, H-2, H-5); 3.5 (m, 1H, H-4); 2.8 (m, 2H, H-6eq, H-6ax); ^{13}C NMR(75.50 MHz; CD_3OD) δ: 80 (C-2); 74 (C-4); 70 (C-3); 68 (C-5); 66 (C-1); 38 (C-6); (Found C, 60.16; H, 7.17; $C_{13}H_{18}O_5\cdot 1/3H_2O$ requires C, 60.33; H, 7.23%).

3.18. 2-*O*-Benzyl-6-deoxy-D-*chiro*-inositol-1,3,4,5-tetra(dibutyl)-phosphate 21

The tetrol **20** (100 mg, 0.4 mmol) was dissolved in THF (7 mL) and cooled to 0°C under argon. *n*-Butyllithium 1.6 M solution in hexane was added (0.1 mL, 1.0 mmol). The temperature was cooled to −40°C and di-*n*-butyl phosphoryl chloride (0.72 g, 3.14 mmol) was added. The mixture was stirred for 1 h extracted with CH_2Cl_2 and the organic layer concentrated to dryness. The product was separated by chromatography on silica gel (eluent: AcOEt/heptane 8:2) (30%). $[\alpha]_D=-13.2°$ (*c* 1.0; CH_3OH). ^1H NMR (300 MHz; $CDCl_3$) δ: 4.8–4.4 (m, 5H, H-1, H-3, H-2, H-5, H-4); 3.9 (m, 16H, $OCH_2CH_2CH_2CH_3$); 2.5–2.0 (m, 2H, H-6eq, H-6ax); 1.5 (m, 16H, $OCH_2CH_2CH_2CH_3$); 1.2 (m, 16H, $OCH_2CH_2CH_2CH_3$); 0.7 (m, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 74 (C-1); 73 (C-3); 72 (C-2); 71 (C-5, C-4); 66 ($OCH_2CH_2CH_2CH_3$); 31 ($OCH_2CH_2CH_2CH_3$); 30 (C-6); 19 ($OCH_2CH_2CH_2CH_3$); 14 ($OCH_2CH_2CH_2CH_3$); (Found C, 53.21; H, 8.73; $C_{45}H_{86}O_{17}P_4$ requires C, 52.83; H, 8.47%).

3.19. 6-Deoxy-D-*chiro*-inositol-1,3,4,5-tetra(dibutyl)-phosphate 22

The tetraphosphate **21** (100 mg, 0.1 mmol) dissolved in AcOEt/EtOH (10 mL, 3:1) was hydrogenated for 3 h under 3 psi, in the presence of the Pd/C catalyst (100 mg). The catalyst was removed by filtration in silica (eluent: AcOEt) and the solvent evaporated to obtain **22** in quantitative yield. $[\alpha]_D=-17°$ (*c* 1.9; $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$) δ: 4.9 (m, 1H, H-4); 4.6 (m, 3H, H-2, H-1, H-5); 4.3 (m, 1H, H-3); 4.1 (m, 16H, $OCH_2CH_2CH_2CH_3$); 3.6 (m, 1H, OH); 2.4 (m, 1H, H-6eq); 2.3 (m, 1H, H-6ax); 1,7 (m, 16H, $OCH_2CH_2CH_2CH_3$); 1.3 (m, 24H, $OCH_2CH_2CH_2CH_3$); 1.0 (m, 24H, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (75.50 MHz; $CDCl_3$) δ: 75 (C-4, C-3); 72 (C-2); 69 (C-1, C-5); 68 ($OCH_2CH_2CH_2CH_3$); 32 ($OCH_2CH_2CH_2CH_3$); 30 (C-6); 19 ($OCH_2CH_2CH_2CH_3$); 14 ($OCH_2CH_2CH_2CH_3$); (Found

C, 49.01; H, 8.59; P, 13.32; $C_{38}H_{80}O_{17}P_4$ requires C, 48.92; H, 8.64; P, 13.28%).

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