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Synthesis of racemic 5-phosphonate analogues of *myo*-inositol 1,4,5-tris- and 1,3,4,5-tetrakis-phosphate

Cornelis E. Dreef, Jan-Pieter Jansze, Cornelius J.J. Elie, Gijs A. van der Marel and Jacques H. van Boom

Gorlaeus Laboratories, Department of Chemistry, Leiden University, P.O. Box 9502, 2300 RA Leiden (Netherlands)

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ABSTRACT

(±)-2,3,6-Tri-*O*-benzyl-5-*O*-*p*-methoxybenzyl-*myo*-inositol and (±)-2,6-di-*O*-benzyl-5-*O*-*p*-methoxybenzyl-*myo*-inositol, accessible readily from (±)-3,6-di-*O*-allyl-1,2-*O*-cyclohexylidene-*myo*-inositol, were phosphitylated with dibenzyl *N*,*N*-di-isopropylphosphoramidite, and the resulting phosphite triesters were oxidised with *tert*-butyl hydroperoxide to give the corresponding fully protected *myo*-inositol 1,4-bis- (**12**) and 1,3,4-tris-phosphate (**13**) derivatives. Cleavage of the *p*-methoxybenzyl group from **12** and **13**, phosphonylation with bis[6-(trifluoromethyl)benzotriazol-1-yl] methylphosphonate or (difluoromethyl)phosphonic di(1,2,4-triazolide), followed by treatment in situ with benzyl alcohol, and then hydrogenolysis of the benzyl groups gave the 5-methylphosphonate and 5-[(difluoromethyl)phosphonate] analogues of *myo*-inositol 1,4,5-tris- and 1,3,4,5-tetrakis-phosphate. The 5-methylphosphonate analogue of *myo*-inositol 1,4,5-trisphosphate acted as a calcium antagonist in permeabilized human platelets.

INTRODUCTION

The intracellular second messenger D-*myo*-inositol 1,4,5-trisphosphate (Ins[1,4,5]P_3)[1,2] is released by the action of phospholipase C on phosphatidylinositol 4,5-bisphosphate after stimulation of cells by hormones, growth factors, and neurotransmitters[3]. Ins[1,4,5]P_3 is responsible for the release of calcium ions from intracellular storage sites and may be deactivated by two different pathways. The major pathway involves dephosphorylation by a specific 5-phosphatase[4] to give D-*myo*-inositol 1,4-bisphosphate (Ins[1,4]P_2), which is then degraded to *myo*-inositol by other phosphatases. Alternatively, phosphorylation of Ins[1,4,5]P_3 by a specific 3-kinase[5] yields the putative second messenger D-*myo*-inositol 1,3,4,5-te-

Correspondence to: Professor J.H. van Boom, Gorlaeus Laboratories, Department of Chemistry, Leiden University, P.O. Box 9502, 2300 RA Leiden, Netherlands.

trakisphosphate (Ins[1,3,4,5]P_4)[6]. Hydrolysis of the 5-phosphate affords D-*myo*-inositol 1,3,4-trisphosphate (Ins[1,3,4]P_3)[7], which is also degraded to *myo*-inositol.

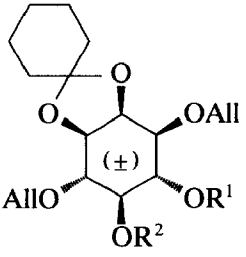
The importance of Ins[1,4,5]P_3 as a calcium-mobilizing second messenger has evoked interest[8,9] in the synthesis of Ins[1,4,5]P_3 and derivatives thereof. The role of the three hydroxyl groups of Ins[1,4,5]P_3 in determining receptor binding and calcium release has been investigated using the 2-[10], 3-[11], and 6-deoxy[12] Ins[1,4,5]P_3 analogues. Thus, deletion of HO-2[10] or HO-3[11] is accompanied by only a small decrease in calcium-releasing activity. On the other hand, HO-6 is important[12] for the release of calcium, but is not a key polar group.

The vicinal D-4,5-bisphosphate system is essential[13] for the calcium-releasing activity, whereas the affinity for the receptor is enhanced by the 1-phosphate. Therefore, Ins[1,4,5]P_3 analogues having modified phosphate groups at positions 4 and/or 5 may be of value in probing the role of the phosphate groups in determining receptor binding and calcium release. In this context, the preparation of the 5-phosphorothioate[14] and 5-methylenephosphonate[15] analogues of Ins[1,4,5]P_3, which act as long-lived agonists, have been reported.

As part of a programme on the synthesis of *myo*-inositol phosphates and analogues thereof[16–20], we now describe the synthesis of the racemic 5-phosphonate analogues (**20** and **24**) of Ins[1,4,5]P_3, and the corresponding analogues (**21** and **25**) of Ins[1,3,4,5]P_4.

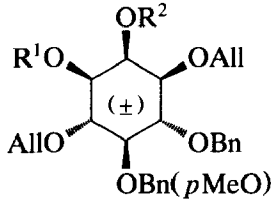
RESULTS AND DISCUSSION

The preparation of the target analogues requires suitably protected *myo*-inositol derivatives that not only allow the introduction of the natural phosphate functions at the respective 1,4- and 1,3,4-positions, but also the modified phosphate function at position 5. Hence, the *myo*-inositol derivatives **10** and **11** were synthesised.

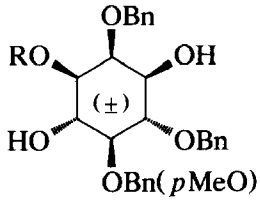


1 $R^1 = R^2 = H$
2 $R^1 = R^2 = Bn$
3 $R^1 = Bn$; $R^2 = H$
4 $R^1 = H$; $R^2 = Bn$
5 $R^1 = Bn$; $R^2 = Bn(pMeO)$

All = allyl

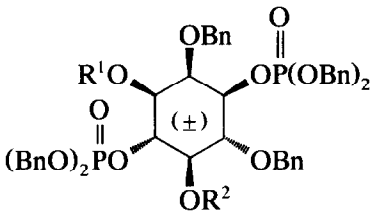


6 $R^1 = R^2 = H$
7 $R^1 = R^2 = Bn$
8 $R^1 = All$; $R^2 = H$
9 $R^1 = All$; $R^2 = Bn$



10 R = Bn
11 R = H

The route to **10** and **11** commences with the preparation of the key intermediate **6** from known (±)-3,6-di-*O*-allyl-1,2-*O*-cyclohexylidene-*myo*-inositol[16,18] (**1**). Thus, regioselective benzylation of **1**, under phase-transfer conditions[21], afforded a 3:2 mixture of the mono-*O*-benzyl derivatives **3** and **4** together with a small proportion of the di-*O*-benzyl derivative **2**. Column chromatography of the mixture on silica gel gave the 4-*O*-benzyl derivative **3** (53%). *p*-Methoxybenzylation of **3** (→ **5**) followed by mild methanolysis of the cyclohexylidene group afforded the crystalline key-intermediate diol **6** (87%). Di-*O*-benzylation of **6** furnished **7** in high yield, and regioselective allylation of **6**, by treatment of the corresponding stannylidene complex[22] with allyl bromide in the presence of cesium fluoride[23], gave **8** (83%). Benzylation of **8** then afforded fully protected derivative **9**. Isomerisation[24] of the allyl groups in **7** and **9** with (1,5-cyclooctadiene)bis(methyldiphenylphosphine)-iridium hexafluorophosphate[25], followed by methanolysis of the resulting *trans*-prop-1-enyl groups, gave the crystalline *myo*-inositol 1,4-diol **10** and 1,3,4-triol **11**, respectively, in excellent yields.

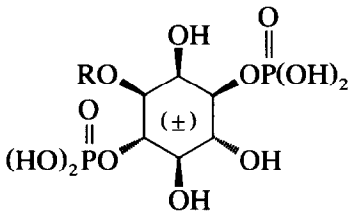


12 R^1 = Bn; R^2 = Bn(*p*MeO)

13 R^1 = P(O)(OBn)$_2$; R^2 = Bn(*p*MeO)

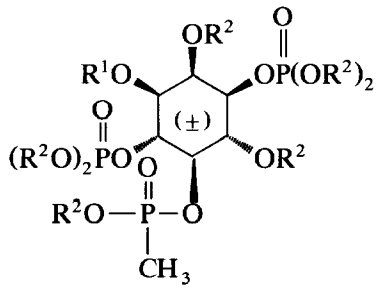
14 R^1 = Bn; R^2 = H

15 R^1 = P(O)(OBn)$_2$; R^2 = H



16 R = H

17 R = P(O)(OH)$_2$

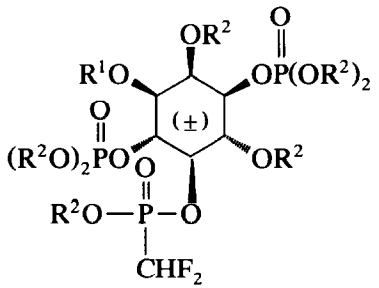


18 R^1 = R^2 = Bn

19 R^1 = P(O)(OBn)$_2$; R^2 = Bn

20 R^1 = R^2 = H

21 R^1 = P(O)(OH)$_2$; R^2 = H

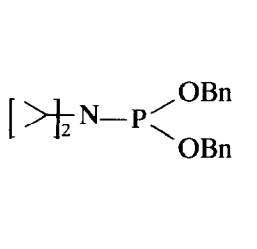


22 R^1 = R^2 = Bn

23 R^1 = P(O)(OBn)$_2$; R^2 = Bn

24 R^1 = R^2 = H

25 R^1 = P(O)(OH)$_2$; R^2 = H



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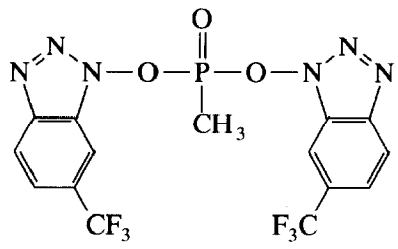
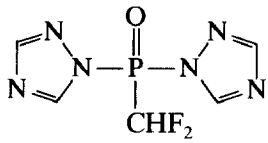


27



28

Phosphate groups were introduced at the 1,4- and 1,3,4-positions by 1*H*-tetrazole-mediated phosphitylation of **10** and **11**, respectively, with dibenzyl *N*,*N*-di-isopropylphosphoramidite[17,26] (**26**) and then oxidation of the phosphite triesters with *tert*-butyl hydroperoxide[27] to give, after column chromatography, the fully protected 1,4-bis- (**12**) and 1,3,4-tris-phosphate (**13**) derivatives in high overall yields. Cleavage of the 5-*O*-*p*-methoxybenzyl from **12** and **13** with 2.5% trifluoroacetic acid in dichloromethane afforded the respective derivatives **14** and **15**, each with HO-5 unsubstituted. The identities of the racemic derivatives **14** and **15** were established, after hydrogenolysis of the benzyl groups, by ^{1}H and ^{31}P NMR spectroscopy of the 1,4-bis- (**16**) and 1,3,4-tris-phosphate (**17**), respectively. The NMR data were in excellent agreement[28,29] with the proposed structures.

Likewise, reaction of **14** or **15** with bis[6-(trifluoromethyl)benzotriazol-1-yl] methylphosphonate[30] (**27**) for 15 min gave the corresponding 5-[6-(trifluoromethyl)benzotriazol-1-yl] methylphosphonate intermediate, treatment of which in situ with benzyl alcohol in the presence of *N*-methylimidazole for 1 h gave the 5-methylphosphonate derivative **18** or **19** in high overall yield. Hydrogenolysis removed the benzyl groups from **18** and **19** to afford the 5-methylphosphonate 1,4-bisphosphate **20** and the 5-methylphosphonate 1,3,4-trisphosphate **21**, without phosphate or phosphonate migration (^{1}H NMR data). The structures of **20** and **21** were established by ^{1}H NMR spectroscopy with selective phosphorus-decoupling.

Treatment of **14** or **15** with (difluoromethyl)phosphonic di(1,2,4-triazolide)[20] (**28**) for 15 min, followed by the addition of benzyl alcohol to the intermediate (difluoromethyl)phosphonic 1,2,4-triazolides in the presence of *N*-methylimidazole, afforded the derivative **22** or **23** in high overall yield. Hydrogenolysis of the benzyl groups in **22** and **23** then furnished the 5-[(difluoromethyl)phosphonate] 1,4-bisphosphate (**24**) and the 5-[(difluoromethyl)phosphonate] 1,3,4-trisphosphate (**25**), respectively, the ^{1}H and ^{31}P NMR data of which accorded with the proposed structures; the (difluoromethyl)phosphonate group was characterised[31,32] by the resonance for C*H*F_2 at 6.09 ppm (dt, $J_{H,F}$ 49.0, $J_{H,P}$ 24.0 Hz).

Biological evaluation indicated that the methylphosphonate analogue **20** antagonised Ins[1,4,5]P_3-stimulated calcium release in a pH-dependent manner in permeabilised human platelets. The antagonistic effect was not due to a chelation of calcium. The methylphosphonate analogue **24** was a weak antagonist. Furthermore, **20** was a competitive inhibitor of the binding of ^{3}H-Ins[1,4,5]P_3 to mem-

branes from bovine adrenocortical microsomes. Full biological data for **20** and **24** will be published elsewhere, and the biological properties of the corresponding Ins[1,3,4,5]P_4 analogues **21** and **25** are under investigation.

The 5-phosphonate analogues of Ins[1,4,5]P_3 and Ins[1,3,4,5]P_4 are accessible readily from the common precursors **10** and **11**. Furthermore, the *myo*-inositol derivatives **14** and **15**, with HO-5 unsubstituted, can be used to prepare other analogues of Ins[1,4,5]P_3 and Ins[1,3,4,5]P_4, having a modified phosphate function at the 5-position[19].

EXPERIMENTAL

General procedures.—Acetonitrile, dichloromethane, pyridine, and triethylamine were dried by heating with CaH_2 (10 g/L), under reflux, for 16 h, and then distilled. Pyridine was redistilled from *p*-toluenesulfonyl chloride (60 g/L), and KOH (25 g/L). *N,N*-Dimethylformamide was stirred with CaH_2 (10 g/L) for 16 h, and then distilled under reduced pressure. Dioxane and 1,2-dichloroethane were distilled from $LiAlH_4$ (5 g/L). Acetonitrile, dichloromethane, pyridine, *N,N*-dimethylformamide, and 1,2-dichloroethane were stored over molecular sieves 4A. Dioxane was stored over molecular sieves 5A. Triethylamine was stored over CaH_2. Methanol was dried by boiling under reflux with magnesium methoxide, then distilled, and stored over molecular sieves 3A. Toluene was distilled from P_2O_5, and stored over sodium wire. Benzyl alcohol, *N*-methylimidazole, and trifluoroacetic acid were distilled before use. 1*H*-Tetrazole was purchased from Janssen (Belgium). 1,2,4-Triazole (Janssen) was dried in vacuo over P_2O_5 for 70 h at 50°. *tert*-Butyl hydroperoxide (80% solution in di-*tert*-butyl peroxide) was purchased from Merck–Schuchardt (Germany). Pd/C (10%) was purchased from Fluka (Switzerland), and Sephadex C-25 from Pharmacia (Sweden).

Triethylammonium hydrogen carbonate buffer (TEAB, 2 M) was prepared by saturating a mixture of triethylamine (825 mL) and H_2O (2175 mL) with carbon dioxide gas at 0° to pH 7.0. TLC was performed on DC Fertigfolien F 1500 LS 254 (Schleicher & Schüll, Germany) with *A*, hexane–Et_2O (50:50); *B*, hexane–EtOAc (50:50); *C*, EtOAc, *D*, CH_2Cl_2–acetone (97:3); *E*, CH_2Cl_2–MeOH (95:5); and detection by UV light, and by spraying with $KMnO_4$ (10 g) in aq 2% Na_2CO_3 (1000 mL) or ammonium molybdate (25 g) and ceric ammonium sulfate (10 g) in aq 10% H_2SO_4 (1000 mL) followed by heating at 100°. Column chromatography was performed on Merck Kieselgel 60 (230–400 mesh, ASTM). Melting points are uncorrected. ^1H NMR spectra (300 MHz) were recorded with a Bruker WM-300 spectrometer, equipped with an ASPECT-2000 computer operating in the FT mode. The ^{13}C (50.1 MHz) and ^{31}P NMR spectra (80.7 MHz) were recorded with a Jeol JNM-FX 200 spectrometer on line with a JEC 980B computer. The ^1H and ^{13}C chemical shifts are given relative to that for internal Me_4Si, and ^{31}P chemical shifts relative to that for external aq 85% H_3PO_4.

(±)-3,6-Di-O-allyl-4,5-di-O-benzyl-1,2-O-cyclohexylidene-myo-*inositol* (**2**), *(±)-3,6-di-O-allyl-4-O-benzyl-1,2-O-cyclohexylidene*-myo-*inositol* (**3**), *and (±)-3,6-di-O-allyl-5-O-benzyl-1,2-O-cyclohexylidene*-myo-*inositol* (**4**).—To a solution of **1**[18] (6.80 g, 20 mmol) and tetrabutylammonium hydrogen sulfate (6.78 g, 20 mmol) in CH_2Cl_2 (200 mL) were added benzyl bromide (3.00 mL, 25.23 mmol) and aq 5% NaOH (200 mL). The mixture was boiled under reflux for 24 h, and the organic layer was separated, washed with H_2O, M $NaHCO_3$, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (140 g of silica gel, hexane–Et_2O 100:0 → 50:50) of the residue afforded **2** (0.52 g, 5%), isolated as an oil, R_F 0.52 (solvent *A*), R_F 0.61 (solvent *D*). NMR data ($CDCl_3$): ^1H, δ 1.27–1.80 (m, 10 H, 5 CH_2, cyclohexylidene), 3.37 (dd, 1 H, $J_{5,6}$ 9.5 Hz, H-5), 3.63 (dd, 1 H, $J_{3,4}$ 8.5 Hz, H-3), 3.68 (dd, 1 H, $J_{1,6}$ 7.0 Hz, H-6), 3.87 (dd, 1 H, $J_{4,5}$ 8.5 Hz, H-4), 4.07 (dd, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 4.18–4.29 (m, 3 H, 1.5 CH_2=CHCH_2), 4.34–4.43 (m, 1 H, 0.5 CH_2=CHCH_2), 4.39 (dd, 1 H, $J_{2,3}$ 4.0 Hz, H-2), 4.77–4.85 (m, 4 H, PhCH_2), 5.14–5.20 (m, 4 H, 2 CH_2=CHCH_2), 5.89–6.05 (m, 2 H, 2 CH_2=C*H*CH_2), 7.25–7.38 (m, 10 H, 2 Ph); ^{13}C, δ 23.48, 23.80, 24.94, 35.07, and 37.23 (5 CH_2, cyclohexylidene), 72.18, 72.80, 75.04, and 75.19 (4 O*C*H_2, All and Bn), 73.93, 77.03, 78.58, 80.65, 82.05, and 82.34 (C-1/6), 110.32 (Cq, cyclohexylidene), 116.60 and 117.30 (2 *C*H_2=CH), 127.46–128.19 (10 C, 2 Ph), 134.87 and 135.17 (2 CH_2=*C*H), 138.52 (2 Cq, Bn).

Anal. Calcd for $C_{32}H_{40}O_6$: C, 73.82; H, 7.74. Found: C, 74.08; H, 7.86.

Compound **3** (4.56 g, 53%), isolated as an oil, had R_F 0.38 (solvent *A*), R_F 0.42 (solvent *D*). NMR data ($CDCl_3$): ^1H, δ 1.25–1.82 (m, 10 H, 5 CH_2, cyclohexylidene), 2.69 (d, 1 H, exchangeable, HO-5), 3.46 (ddd, 1 H, $J_{5,6}$ 9.5, $J_{5,OH}$ 2.0 Hz, H-5), 3.60 (dd, 1 H, $J_{1,6}$ 7.0 Hz, H-6), 3.64 (dd, 1 H, $J_{3,4}$ 8.0 Hz, H-3), 3.76 (dd, 1 H, $J_{4,5}$ 8.0 Hz, H-4), 4.07 (dd, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 4.19–4.25 (m, 3 H, 1.5 CH_2=CHCH_2), 4.37–4.43 (m, 1 H, 0.5 CH_2=CHCH_2), 4.41 (dd, 1 H, $J_{2,3}$ 4.0 Hz, H-2), 4.77–4.91 (m, 2 H, PhCH_2), 5.17–5.33 (m, 4 H, 2 CH_2=CHCH_2), 5.90–6.01 (m, 2 H, 2 CH_2=C*H*CH_2), 7.25–7.41 (m, 5 H, Ph); ^{13}C, δ 23.45, 23.83, 24.94, 34.95, and 37.11 (5 CH_2, cyclohexylidene), 71.86, 72.12, and 74.46 (3 O*C*H_2, All and Bn), 73.20, 73.93, 77.12, 78.37, 80.45, and 81.29 (C-1/6), 110.32 (Cq, cyclohexylidene), 117.03 and 117.27 (2 *C*H_2=CH), 127.46–128.25 (5 C, Ph), 134.73 and 134.87 (2 CH_2=*C*H), 138.41 (Cq, Bn).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.83; H, 7.82.

Compound **4** (3.10 g, 36%), isolated as an oil, had R_F 0.25 (solvent *A*), R_F 0.36 (solvent *D*). NMR data ($CDCl_3$): ^1H, δ 1.26–1.76 (m, 10 H, 5 CH_2, cyclohexylidene), 2.63 (d, 1 H, exchangeable, HO-4), 3.25 (dd, 1 H, $J_{5,6}$ 9.0 Hz, H-5), 3.50 (dd, 1 H, $J_{3,4}$ 10.0 Hz, H-3), 3.60 (dd, 1 H, $J_{1,6}$ 7.0 Hz, H-6), 3.97 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{4,OH}$ 1.5 Hz, H-4), 4.08 (dd, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.19–4.26 (m, 3 H, 1.5 CH_2=CHCH_2), 4.33–4.40 (m, 1 H, 0.5 CH_2=CHCH_2), 4.42 (dd, 1 H, $J_{2,3}$ 4.0 Hz, H-2), 4.72–4.92 (m, 2 H, PhCH_2), 5.15–5.35 (m, 4 H, 2 CH_2=CHCH_2), 5.89–6.02 (m, 2 H, 2 CH_2=C*H*CH_2), 7.25–7.42 (m, 5 H, Ph); ^{13}C, δ 23.51, 23.80, 24.91, 35.13, and 37.46 (5 CH_2, cyclohexylidene), 71.39, 72.65, and 74.99 (3 O*C*H_2, All and Bn),

71.28, 73.20, 76.80, 78.84, 81.64, and 82.40 (C-1/6), 110.43 (Cq, cyclohexylidene), 116.80 and 117.68 (2 CH_2=CH), 127.63–128.30 (5 C, Ph), 134.79 and 135.02 (2 CH_2=CH), 138.44 (Cq, Bn).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.62; H, 7.84.

*(±)-1,4-Di-*O*-allyl-6-*O*-benzyl-5-*O*-p-methoxybenzyl-*myo*-inositol* (**6**).—To a solution of **3** (4.30 g, 10 mmol) and NaH (0.30 g, 12.50 mmol) in dry *N,N*-dimethylformamide (50 mL) was added *p*-methoxybenzyl chloride (1.50 mL, 11.07 mmol) dropwise at 0°. The mixture was stirred for 2 h at 20°, excess of NaH was destroyed with MeOH, and the mixture was concentrated in vacuo. A solution of the residue in CH_2Cl_2 was washed with H_2O, M $NaHCO_3$, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. To a solution of the crude **5** in MeOH (25 mL) was added 0.1 M HCl in MeOH (25 mL, 2.50 mmol); the mixture was stirred for 5 h at 20°, then neutralised with Et_3N, and concentrated in vacuo. A solution of the residue in CH_2Cl_2 was washed with H_2O, M $NaHCO_3$, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (60 g of silica gel, CH_2Cl_2–MeOH 100:0 → 95:5) of the crude product afforded **6** (4.09 g, 87%), R_F 0.10 (solvent *D*), R_F 0.39 (solvent *E*), mp 97–98° (from Et_2O–hexane). NMR data ($CDCl_3$): ^1H, δ 2.52 (bs, 1 H, exchangeable, HO-2), 2.55 (d, 1 H, exchangeable, HO-3), 3.36 (dd, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 3.39 (dd, 1 H, $J_{5,6}$ 9.5 Hz, H-5), 3.46 (ddd, 1 H, $J_{3,4}$ 9.5, $J_{3,OH}$ 4.5 Hz, H-3), 3.68 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.80 (s, 3 H, OMe), 3.86 (dd, 1 H, $J_{1,6}$ 9.5 Hz, H-6), 4.13–4.29 (m, 3 H, 1.5 CH_2=CHCH_2), 4.22 (bdd, 1 H, $J_{2,3}$ 3.0, $J_{2,OH}$ 1.0 Hz, H-2), 4.40–4.47 (m, 1 H, 0.5 CH_2=CHCH_2), 4.70–4.89 [m, 4 H, 2 OCH_2, Bn and Bn(*p*MeO)], 5.17–5.34 (m, 4 H, 2 CH_2=CHCH_2), 5.87–6.03 (m, 2 H, 2 CH_2=CHCH_2), 6.82–6.87 and 7.21–7.37 (m, 9 H, aromatic); ^{13}C, δ 55.10 (OCH_3), 69.23 and 71.51 (C-2,3), 71.63, 74.17, 75.22, and 75.72 [4 OCH_2, All, Bn, and Bn(*p*MeO)], 79.57, 80.83, 81.38, and 82.72 (C-1,4,5,6), 113.62 [2 C, Bn(*p*MeO)], 116.92 and 117.44 (2 CH_2=CH), 127.43–129.39 (7 C, aromatic), 130.58 [Cq, Bn(*p*MeO)], 134.44 and 134.96 (2 CH_2=CH), 138.58 (Cq, Bn), 158.99 [Cq, Bn(*p*MeO)].

Anal. Calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28. Found: C, 69.04; H, 7.34.

*(±)-1,4-Di-*O*-allyl-2,3,6-tri-*O*-benzyl-5-*O*-p-methoxybenzyl-*myo*-inositol* (**7**).—To a solution of **6** (1.75 g, 3.72 mmol) and NaH (0.23 g, 9.58 mmol) in dry *N,N*-dimethylformamide (20 mL) was added benzyl bromide (1.00 mL, 8.41 mmol) dropwise at 0°. The mixture was stirred for 2 h at 20°, excess of NaH was destroyed with MeOH, and the mixture was concentrated in vacuo. A solution of the residue in CH_2Cl_2 was washed with H_2O, M $NaHCO_3$, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (30 g of silica gel, hexane–Et_2O 100:0 → 50:50) of the crude product yielded **7** (2.30 g, 95%), R_F 0.44 (solvent *A*), mp 69.5–70.5° (from pentane). NMR data ($CDCl_3$): ^1H, δ 3.23 (dd, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 3.30 (dd, 1 H, $J_{3,4}$ 10.0 Hz, H-3), 3.38 (dd, 1 H, $J_{5,6}$ 9.0 Hz, H-5), 3.79 (s, 3 H, OMe), 3.91 (dd, 1 H, $J_{4,5}$ 9.0 Hz, H-4), 3.96 (dd, 1 H, $J_{1,6}$ 10.0 Hz, H-6), 3.99 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 4.03–4.13 (m, 2 H, CH_2=CHCH_2), 4.29–4.44 (m, 2 H, CH_2=CHCH_2), 4.58–4.90 [m, 8 H, 4 OCH_2, Bn and Bn(*p*MeO)], 5.13–5.32 (m, 4

H, 2 CH_2=CHCH_2), 5.83–6.06 (m, 2 H, 2 CH_2=CHCH_2), 6.82–6.86, and 7.22–7.41 (m, 19 H, aromatic); ^{13}C, δ 55.07 (OCH_3), 71.48, 72.71, 73.85, 74.40, 75.48, and 75.63 [6 OCH_2, All, Bn, and Bn(*p*MeO)], 74.28 (C-2), 80.56, 80.68, 81.35, 81.50, and 83.28 (C-1,3,4,5,6), 113.62 [2 C, Bn(*p*MeO)], 116.27 and 116.45 (2 CH_2=CH), 127.14–129.44 (17 C, aromatic), 130.99 [Cq, Bn(*p*MeO)], 134.85 and 135.43 (2 CH_2=CH), 138.44, 138.88, and 138.93 (3 Cq, 3 Bn), 159.02 [Cq, Bn(*p*MeO)].

Anal. Calcd for $C_{41}H_{46}O_7$: C, 75.67; H, 7.12. Found: C, 75.62; H, 7.19.

*(±)-1,3,4-Tri-*O*-allyl-6-*O*-benzyl-5-*O*-*p*-methoxybenzyl-*myo*-inositol* (**8**).—A solution of **6** (2.00 g, 4.26 mmol) and dibutyltin oxide (1.20 g, 4.82 mmol) in dry MeOH (25 mL) was boiled under reflux for 2.5 h, then concentrated in vacuo. Toluene (3 × 25 mL) was evaporated from the residue which was dissolved in dry *N*,*N*-dimethylformamide (45 mL), and cesium fluoride (0.85 g, 5.59 mmol) and allyl bromide (0.55 mL, 6.50 mmol) were added. The mixture was stirred for 16 h at 20°, then concentrated in vacuo. A solution of the residue in Et_2O was washed with H_2O, M $NaHCO_3$, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (30 g of silica gel, hexane–EtOAc 100:0 → 50:50) of the crude product afforded **8** (1.81 g, 83%), R_F 0.13 (solvent *A*), R_F 0.44 (solvent *B*), mp 77–78° (from Et_2O–pentane). NMR data ($CDCl_3$): ^{1}H, δ 2.42 (bs, 1 H, exchangeable, HO-2), 3.25 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 3.29 (dd, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 3.36 (dd, 1 H, $J_{5,6}$ 9.5 Hz, H-5), 3.77 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.80 (s, 3 H, OMe), 3.87 (dd, 1 H, $J_{1,6}$ 9.5 Hz, H-6), 4.18–4.22 (m, 4 H, 2 CH_2=CHCH_2), 4.21 (bdd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 4.25–4.39 (m, 2 H, CH_2=CHCH_2), 4.72–4.87 [m, 4 H, 2 OCH_2, Bn and Bn(*p*MeO)], 5.14–5.35 (m, 6 H, 3 CH_2=CHCH_2), 5.88–6.05 (m, 3 H, 3 CH_2=CHCH_2), 6.82–6.87 and 7.23–7.38 (m, 9 H, aromatic); ^{13}C, δ 55.04 (OCH_3), 71.66, 74.31, 75.42, and 75.66 [5 OCH_2, All, Bn, and Bn(*p*MeO)], 67.74 (C-2), 79.31, 79.48, 80.68, 80.91, and 82.61 (C-1,3,4,5,6), 113.56 [2 C, Bn(*p*MeO)], 116.30, 117.00, and 117.12 (3 CH_2=CH), 127.34–129.39 (7 C, aromatic), 130.79 [Cq, Bn(*p*MeO)], 134.58 and 135.23 (3 CH_2=CH), 138.70 (Cq, Bn), 158.96 [Cq, Bn(*p*MeO)].

Anal. Calcd for $C_{30}H_{38}O_7$: C, 70.57; H, 7.50. Found: C, 70.46; H, 7.53.

*(±)-1,3,4-Tri-*O*-allyl-2,6-di-*O*-benzyl-5-*O*-*p*-methoxybenzyl-*myo*-inositol* (**9**).—To a solution of **8** (1.75 g, 3.43 mmol) and NaH (0.11 g, 4.58 mmol) in dry *N*,*N*-dimethylformamide (20 mL) was added benzyl bromide (0.45 mL, 3.78 mmol) dropwise at 0°. The mixture was stirred for 2 h at 20°, excess of NaH was destroyed with MeOH, and the mixture was concentrated in vacuo. A solution of the residue in CH_2Cl_2 was washed with H_2O, M $NaHCO_3$, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (30 g of silica gel, hexane–Et_2O 100:0 → 50:50) of the crude product yielded **9** (1.96 g, 95%), isolated as an oil, R_F 0.46 (solvent *A*), mp 39.5–40.5° (solidified). NMR data ($CDCl_3$): ^{1}H, δ 3.19 (dd, 1 H, $J_{3,4}$ 10.0 Hz, H-3), 3.24 (dd, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 3.37 (dd, 1 H, $J_{5,6}$ 9.0 Hz, H-5), 3.79 (s, 3 H, OMe), 3.86 (dd, 1 H, $J_{4,5}$ 9.0 Hz, H-4), 3.96 (dd, 1 H, $J_{1,6}$ 10.0 Hz, H-6), 3.99 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 4.02–4.16 (m, 4 H, 2 CH_2=CHCH_2), 4.26–4.41 (m, 2 H, CH_2=CHCH_2), 4.69–4.90 [m, 6 H, 3 OCH_2, Bn and

Bn(*p*MeO)], 5.13–5.34 (m, 6 H, 3 CH_2=CHCH$_2$), 5.85–6.06 (m, 3 H, 3 CH$_2$=C*H*CH$_2$), 6.82–6.86 and 7.23–7.44 (m, 14 H, aromatic); ^{13}C, δ 55.13 (OCH_3), 71.57, 73.88, 74.43, 75.48, and 75.69 [6 O*C*H$_2$, All, Bn, and Bn(*p*MeO)], 74.28 (C-2), 80.47, 80.56, 81.35, 81.53, and 83.25 (C-1,3,4,5,6), 113.65 [2 C, Bn(*p*MeO)], 116.30 and 116.45 (3 *C*H$_2$=CH), 127.17–129.62 (12 C, aromatic), 131.05 [Cq, Bn(*p*MeO)], 134.93 and 135.49 (3 CH$_2$=*C*H), 138.93 (Cq, Bn), 159.02 [Cq, Bn(*p*MeO)].

Anal. Calcd for $C_{37}H_{44}O_7$: C, 73.98; H, 7.38. Found: C, 73.80; H, 7.31.

(±)-2,3,6-Tri-O-benzyl-5-O-p-methoxybenzyl-myo-inositol (**10**).—To a solution of **7** (1.95 g, 3.00 mmol) in 1,2-dichloroethane (15 mL) under He was added a solution of (1,5-cyclooctadiene)bis(methyldiphenylphosphine)iridium hexafluorophosphate[25] (20 mg) in 1,2-dichloroethane (0.5 mL). The catalyst was activated by passing a stream of H_2 for 2 min, and the solution was degassed and left under a stream of Ar for 4 h. The mixture was concentrated in vacuo to give crude (±)-2,3,6-tri-*O*-benzyl-5-*O*-*p*-methoxybenzyl-1,4-di-*O*-*trans*-prop-1-enyl-*myo*-inositol, R_F 0.53 (solvent *A*), to a solution of which in CH_2Cl_2 (15 mL) was added 0.2 M HCl in MeOH (15 mL, 3.00 mmol). The mixture was stirred for 1 h at 20°, then neutralised with Et_3N, and concentrated in vacuo. A solution of the residue in CH_2Cl_2 was washed with H_2O, M $NaHCO_3$, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (25 g of silica gel, CH_2Cl_2–acetone, 100:0 → 97:3) of the crude product afforded **10** (1.58 g, 92%), R_F 0.29 (solvent *D*), mp 97.5–98.5° (from Et_2O–hexane). NMR data ($CDCl_3$): ^{1}H, δ 2.28 (d, 1 H, exchangeable, HO-1), 2.52 (d, 1 H, exchangeable, HO-4), 3.30 (dd, 1 H, $J_{3,4}$ 10.0 Hz, H-3), 3.38 (dd, 1 H, $J_{5,6}$ 9.0 Hz, H-5), 3.52 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{1,OH}$ 6.5 Hz, H-1), 3.78 (dd, 1 H, $J_{1,6}$ 9.5 Hz, H-6), 3.80 (s, 3 H, OMe), 4.07 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 4.14 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{4,OH}$ 1.5 Hz, H-4), 4.59–4.94 [m, 8 H, 4 O*C*H$_2$, Bn and Bn(*p*MeO)], 6.84–6.89 and 7.21–7.40 (m, 19 H, aromatic); ^{13}C, δ 55.16 (OCH_3), 72.39, 74.52, 74.78, and 75.31 [4 O*C*H$_2$, Bn and Bn(*p*MeO)], 72.53, 73.17, 76.15, 80.33, 81.79, and 82.90 (C-1/6), 113.76 [2 C, Bn(*p*MeO)], 127.49–129.47 (17 C, aromatic), 130.79 [Cq, Bn(*p*MeO)], 137.79 and 138.52 (3 Cq, 3 Bn), 159.11 [Cq, Bn(*p*MeO)].

Anal. Calcd for $C_{35}H_{38}O_7$: C, 73.66; H, 6.71. Found: C, 73.48; H, 6.66.

(±)-2,6-Di-O-benzyl-5-O-p-methoxybenzyl-myo-inositol (**11**).—To a solution of **9** (1.80 g, 3.00 mmol) in 1,2-dichloroethane (15 mL) under He was added (1,5-cyclooctadiene)bis(methyldiphenylphosphine)iridium hexafluorophosphate[25] (20 mg) in 1,2-dichloroethane (0.5 mL). The catalyst was activated by passing a stream of H_2 for 2 min, and the solution was degassed and left under a stream of Ar for 4 h. The mixture was concentrated in vacuo to give crude (±)-2,6-di-*O*-benzyl-5-*O*-*p*-methoxybenzyl-1,3,4-tri-*O*-*trans*-prop-1-enyl-*myo*-inositol, R_F 0.53 (solvent *A*), which was treated as for **10**. Column chromatography (20 g of silica gel, CH_2Cl_2–MeOH 100:0 → 95:5) of the crude product afforded **11** (1.31 g, 91%), R_F 0.33 (solvent *E*), mp 108.5–109.5° (from CH_2Cl_2–hexane). NMR data ($CDCl_3$): ^{1}H, δ

exchangeable, HO-4), 3.32 (dd, 1 H, $J_{5,6}$ 9.0 Hz, H-5), 3.46 (ddd, 1 H, $J_{3,4}$ 9.5, $J_{3,OH}$ 7.0 Hz, H-3), 3.57 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{1,OH}$ 5.0 Hz, H-1), 3.77 (dd, 1 H, $J_{1,6}$ 9.5 Hz, H-6), 3.80 (s, 3 H, OMe), 3.82 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{4,OH}$ 2.0 Hz, H-4), 4.01 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 4.71–4.95 [m, 6 H, 3 OCH_2, Bn and Bn(*p*MeO)], 6.85–6.89 and 7.25–7.39 (m, 14 H, aromatic); ^{13}C, δ 55.10 (OCH_3), 72.33, 72.59, 73.96, 79.10, 81.73, and 82.64 (C-1/6), 74.72, 75.07, and 75.19 [3 OCH_2, Bn and Bn(*p*MeO)], 113.79 [2 CH, Bn(*p*MeO)], 127.57–129.47 (12 C, aromatic), 130.55 [Cq, Bn(*p*MeO)], 138.38 and 138.50 (2 Cq, 2 Bn), 159.14 [Cq, Bn(*p*MeO)].

Anal. Calcd for $C_{28}H_{32}O_7$: C, 69.98; H, 6.71. Found: C, 69.82; H, 6.64.

*(±)-2,3,6-Tri-*O*-benzyl-5-*O*-*p*-methoxybenzyl-*myo*-inositol 1,4-bis(dibenzyl phosphate)* (**12**).—Toluene (2 × 25 mL) was evaporated from a mixture of **10** (1.43 g, 2.51 mmol) and dibenzyl *N,N*-diisopropylphosphoramidite[17,26] (**26**; 2.60 g, 7.54 mmol), which was then dissolved in CH_2Cl_2 (20 mL), and a solution of 1*H*-tetrazole (0.65 g, 9.29 mmol) in MeCN (20 mL) was added. The mixture was stirred for 15 min when ^{31}P NMR spectroscopy revealed resonances at δ 141.04, and 141.88 (P-1,4). The mixture was cooled to 0°, *tert*-butyl hydroperoxide (3.75 mL) was added, and the mixture was stirred for 45 min at 0°. The mixture was diluted with CH_2Cl_2, washed with H_2O, M TEAB, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (35 g of silica gel, hexane–EtOAc 100:0 → 25:75) of the crude product afforded **12** (2.57 g, 94%), isolated as an oil, R_F 0.21 (solvent *B*). ^{31}P NMR data ($CDCl_3$): δ −1.03 (P-1,4).

Anal. Calcd for $C_{63}H_{64}O_{13}P_2$: C, 69.35; H, 5.91; P, 5.68. Found: C, 69.18; H, 5.83; P, 5.51.

*(±)-2,6-Di-*O*-benzyl-5-*O*-*p*-methoxybenzyl-*myo*-inositol 1,3,4-tris(dibenzyl phosphate* (**13**).—A mixture of **11** (1.20 g, 2.50 mmol) was treated with dibenzyl *N,N*-diisopropylphosphoramidite[17,26] (**26**; 3.90 g, 11.30 mmol) and 1*H*-tetrazole (1.00 g, 14.29 mmol) as described for **10**. ^{31}P NMR spectroscopy revealed resonances at δ 141.10, 141.19, and 142.55 (P-1,3,4). Treatment of the product with *tert*-butyl hydroperoxide (5.65 mL) as described for **10**, with column chromatography (40 g of silica gel, hexane–EtOAc 100:0 → 25:75) of the crude product, afforded **13** (2.74 g, 87%), isolated as an oil, R_F 0.14 (solvent B). ^{31}P NMR data ($CDCl_3$): δ −1.45, −1.12, and −0.82 (P-1,3,4).

Anal. Calcd for $C_{70}H_{71}O_{16}P_3$: C, 66.66; H, 5.67; P, 7.37. Found: C, 66.54; H, 5.73; P, 7.28.

*(±)-2,3,6-Tri-*O*-benzyl-*myo*-inositol 1,4-bis(dibenzyl phosphate)* (**14**).—To a solution of **12** (2.18 g, 2.00 mmol) in CH_2Cl_2 (48.75 mL) was added trifluoroacetic acid (1.25 mL). The mixture was stirred for 30 min at 20°, then diluted with CH_2Cl_2, washed with H_2O, M TEAB, and H_2O dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (25 g of silica gel, hexane–EtOAc 100:0 → 25:75) of the crude product afforded **14** (1.59 g, 82%), isolated as an oil, R_F 0.59 (solvent *C*). ^{31}P NMR data ($CDCl_3$): δ −1.24 and 0.76 (P-1,4).

Anal. Calcd for $C_{55}H_{56}O_{12}P_2$: C, 68.03; H, 5.81; P, 6.38. Found: C, 67.92; H, 5.69; P, 6.29.

(±)-2,6-Di-O-benzyl-myo-inositol 1,3,4-tris(dibenzyl phosphate) (**15**).—Compound **13** (2.52 g, 2.00 mmol) was treated with trifluoroacetic acid, and the product was purified, as described for **12**, to afford **15** (1.78 g, 78%), isolated as an oil, R_F 0.55 (solvent *C*). ^{31}P NMR data ($CDCl_3$): δ −1.30 and 0.82 (P-1,3,4).

Anal. Calcd for $C_{62}H_{63}O_{15}P_3$: C, 65.26; H, 5.56; P, 8.14. Found: C, 65.10; H, 5.48; P, 8.21.

(±)-myo-Inositol 1,4-bisphosphate (Na^+ salt) (**16**).—A solution of **14** (215 mg, 0.22 mmol) in a 4:1 mixture of MeOH and H_2O (50 mL) was hydrogenolysed over 10% Pd/C (0.20 g) at 500 kPa for 16 h at 20°. The solution was filtered, and concentrated in vacuo at 30° to a small volume. Cation-exchange with Sephadex C-25 (Na^+ form, 4.0 g, 9.2 mmol) and lyophilisation gave **16** (90 mg, 95%), as a white solid. NMR data (D_2O, pH 2.00): ^1H, δ 3.51 (dd, 1 H, $J_{5,6}$ 9.5 Hz, H-5), 3.71 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 3.81 (dd, 1 H, $J_{1,6}$ 10.0 Hz, H-6), 3.99 (ddd, 1 H, $J_{1,2}$ 3.0, $J_{H,P}$ 8.5 Hz, H-1), 4.20 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{H,P}$ 8.5 Hz, H-4), 4.27 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2); ^{31}P, δ 0.34 and 1.52 (P-1,4).

Anal. Calcd for $C_6H_{10}Na_4O_{12}P_2$: P, 14.47. Found: P, 14.28.

(±)-myo-Inositol 1,3,4-trisphosphate (Na^+ salt) (**17**).—Compound **15** (225 mg, 0.20 mmol) was hydrogenolysed, as described for **14**, to give **17** (102 mg, 94%), as a white solid. NMR data (D_2O, pH 2.00): ^1H, δ 3.56 (dd, 1 H, $J_{5,6}$ 9.5 Hz, H-5), 3.84 (dd, 1 H, $J_{1,6}$ 10.0 Hz, H-6), 4.04 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{H,P}$ 8.5 Hz, H-1), 4.17 (ddd, 1 H, $J_{3,4}$ 9.5, $J_{H,P}$ 9.5 Hz, H-3), 4.36 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{H,P}$ 8.5 Hz, H-4), 4.44 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H-2); ^{31}P, δ 0.23, 0.45, and 0.89 (P-1,3,4).

Anal. Calcd for $C_6H_9Na_6O_{15}P_3$: P, 16.83. Found: P, 16.98.

(±)-2,3,6-Tri-O-benzyl-myo-inositol 5-(benzyl methylphosphonate) 1,4-bis(dibenzyl phosphate) (**18**).—A solution of bis[6-(trifluoromethyl)benzotriazol-1-yl] methylphosphonate[30] (**27**) in dioxane (0.2 M, 3.5 mL, 0.70 mmol) was added to **14** (0.34 g, 0.35 mmol), which had been dried by repeated evaporation of pyridine therefrom. The mixture was stirred for 30 min at 20°, benzyl alcohol (0.15 mL, 1.45 mmol) and *N*-methylimidazole (0.15 mL, 1.88 mmol) were added, and the mixture was stirred for 1 h at 20°. After the addition of M TEAB, the mixture was diluted with CH_2Cl_2, washed with H_2O, M TEAB, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (5 g of silica gel, hexane–EtOAc 100:0 → 25:75) of the crude product afforded **18** (0.30 g, 75%), isolated as an oil, R_F 0.44 (solvent *C*). ^{31}P NMR data ($CDCl_3$): δ −1.27 (P-1,4), 31.31, and 32.88 (1:3 ratio, P-5).

Anal. Calcd for $C_{63}H_{65}O_{14}P_3$: C, 66.43; H, 5.75; P, 8.16. Found: C, 66.61; H, 5.67; P, 8.02.

(±)-2,6-Di-O-benzyl-myo-inositol 5-(benzyl methylphosphonate) 1,3,4-tris(dibenzyl phosphate) (**19**).—Compound **15** (0.40 g, 0.35 mmol) was treated with a solution of **27**[30] in dioxane (0.2 M, 3.5 mL, 0.70 mmol), then with benzyl alcohol (0.15 mL, 1.45 mmol), and *N*-methylimidazole (0.15 mL, 1.88 mmol), as described for **14**, to afford **19** (0.29 g, 63%), isolated as an oil, R_F 0.49 (solvent *C*). ^{31}P NMR data ($CDCl_3$): δ −1.45, −1.21, and −0.70 (P-1,3,4), 31.46, and 33.12 (1:3 ratio, P-5).

Anal. Calcd for $C_{70}H_{72}O_{17}P_4$: C, 64.22; H, 5.54; P, 9.46. Found: C, 64.30; H, 5.46; P, 9.32.

*(±)-*myo*-Inositol 5-methylphosphonate 1,4-bisphosphate (Na^+ salt)* (**20**).—A solution of **18** (225 mg, 0.20 mmol) in a 4:1 mixture of MeOH and H_2O (50 mL) was hydrogenolysed over 10% Pd/C (0.20 g) at 500 kPa for 16 h at 20°, then filtered, and concentrated in vacuo at 30° to a small volume. Cation-exchange with Sephadex C-25 (Na^+ form, 4.5 g, 10.4 mmol) and lyophilisation gave **20** (101 mg, 97%), as a white solid. NMR data (D_2O, pH 2.00): ^1H, δ 1.48 (d, 3 H, $J_{H,P}$ 17.5 Hz, Me), 3.75 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 3.88 (dd, 1 H, $J_{1,6}$ 10.0 Hz, H-6), 4.03 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{H,P}$ 8.5 Hz, H-1), 4.12 (ddd, 1 H, $J_{5,6}$ 9.5, $J_{H,P}$ 9.0 Hz, H-5), 4.28 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 4.34 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{H,P}$ 9.0 Hz, H-4); ^{31}P, δ 0.29 and 1.20 (P-1,4), 31.68 (P-5).

Anal. Calcd for $C_7H_{12}Na_5O_{14}P_3$: P, 17.60. Found: P, 17.48.

*(±)-*myo*-Inositol 5-methylphosphonate 1,3,4-trisphosphate (Na^+ salt)* (**21**).—Hydrogenolysis of **19** (215 mg, 0.16 mmol), as described for **18**, gave **21** (102 mg, 95%), as a white solid. NMR data (D_2O, pH 2.00): ^1H, δ 1.48 (d, 3 H, $J_{H,P}$ 17.5 Hz, Me), 3.90 (dd, 1 H, $J_{1,6}$ 10.0 Hz, H-6), 4.08 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{H,P}$ 8.5 Hz, H-1), 4.18 (ddd, 1 H, $J_{5,6}$ 9.5, $J_{H,P}$ 9.0 Hz, H-5), 4.20 (ddd, 1 H, $J_{3,4}$ 9.5, $J_{H,P}$ 9.5 Hz, H-3), 4.44 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 4.50 (ddd, 1 H, $J_{4,5}$ 9.5, $J_{H,P}$ 9.5 Hz, H-4); ^{31}P, δ 0.25, and 0.43 (P-1,3,4), 31.76 (P-5).

Anal. Calcd for $C_7H_{11}Na_7O_{17}P_4$: P, 19.00. Found: P, 19.13.

*(±)-2,3,6-Tri-O-benzyl-*myo*-inositol 5-[benzyl (difluoromethyl)phosphonate] 1,4-bis(dibenzyl phosphate)* (**22**).—A solution of (difluoromethyl)phosphonic di(1,2,4-triazolide) (**28**) in dioxane (0.2 M, 3.5 mL, 0.70 mmol) was added to **14** (0.34 g, 0.35 mmol), which had been dried by repeated evaporation of pyridine therefrom. The mixture was stirred for 30 min at 20°, benzyl alcohol (0.15 mL, 1.45 mmol) and *N*-methylimidazole (0.15 mL, 1.88 mmol) were added, and the mixture was stirred for 1 h at 20°. After the addition of M TEAB, the mixture was diluted with CH_2Cl_2, washed with H_2O, M TEAB, and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (5 g of silica gel, hexane–EtOAc 100:0 → 25:75) of the crude product afforded **22** (0.29 g, 70%), isolated as an oil, R_F 0.17 (solvent *B*), R_F 0.62 (solvent *C*). ^{31}P NMR data ($CDCl_3$): δ −1.45, −1.36, −1.18, and −1.00 (P-1,4), 4.32 ($J_{P,F}$ 93.0 Hz), and 6.66 ($J_{P,F}$ 85.5, $J_{P,F}$ 97.5 Hz) (1:1 ratio, P-5).

Anal. Calcd for $C_{63}H_{63}F_2O_{14}P_3$: C, 64.39; H, 5.40; P, 7.91. Found: C, 64.58; H, 5.31; P, 7.86.

*(±)-2,6-Di-O-benzyl-*myo*-inositol 5-[benzyl (difluoromethyl)phosphonate] 1,3,4-tris(dibenzyl phosphate)* (**23**).—Treatment of **15** (0.40 g, 0.35 mmol) with **28**, as described for **14**, afforded **23** (0.29 g, 61%), isolated as an oil, R_F 0.16 (solvent *B*), R_F 0.63 (solvent *C*). ^{31}P NMR data ($CDCl_3$): δ −1.39, −1.15, −0.97, and 0.79 (P-1,3,4), 4.35 ($J_{P,F}$ 95.0 Hz), and 6.86 ($J_{P,F}$ 88.0, $J_{P,F}$ 102.5 Hz) (1:1 ratio, P-5).

Anal. Calcd for $C_{70}H_{70}F_2O_{17}P_4$: C, 62.50; H, 5.25; P, 9.21. Found: C, 62.32; H, 5.31; P, 9.16.

(±)-myo-Inositol 5-[(difluoromethyl)phosphonate] 1,4-bisphosphate (Na^+ salt) (**24**).—A solution of **22** (220 mg, 0.19 mmol) in a 4:1 mixture of MeOH and H_2O (50 mL) was hydrogenolysed over 10% Pd/C (0.20 g) at 500 kPa for 16 h at 20°, then filtered, and concentrated in vacuo at 30° to a small volume. Cation-exchange with Sephadex C-25 (Na^+ form, 4.0 g, 9.2 mmol), and lyophilisation gave **24** (0.10 g, 95%), as a white solid. NMR data (D_2O, pH 2.00): ^1H, δ 3.78 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 3.89 (dd, 1 H, $J_{1,6}$ 10.0 Hz, H-6), 4.03 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{H,P}$ 8.5 Hz, H-1), 4.13 (ddd, 1 H, $J_{5,6}$ 9.5, $J_{H,P}$ 9.0 Hz, H-5), 4.27 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 4.34 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{H,P}$ 9.0 Hz, H-4), 6.09 (dt, 1 H, $J_{H,F}$ 49.0, $J_{H,P}$ 24.0 Hz, CHF_2); ^{31}P, δ 0.27, and 1.16 (P-1,4), 4.68 ($J_{P,F}$ 85.0 Hz, P-5).

Anal. Calcd for $C_7H_{10}F_2Na_5O_{14}P_3$: P, 16.47. Found: P, 16.23.

(±)-myo-Inositol 5-[(difluoromethyl)phosphonate] 1,3,4-trisphosphate (Na^+ salt) (**25**).—Hydrogenolysis of **23** (240 mg, 0.18 mmol), as described for **22**, gave **25** (114 mg, 93%), as a white solid. NMR data (D_2O, pH 2.00): ^1H, δ 3.91 (dd, 1 H, $J_{1,6}$ 10.0 Hz, H-6), 4.07 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{H,P}$ 8.5 Hz, H-1), 4.20 (ddd, 1 H, $J_{5,6}$ 9.5, $J_{H,P}$ 9.0 Hz, H-5), 4.22 (ddd, 1 H, $J_{3,4}$ 9.5, $J_{H,P}$ 9.5 Hz, H-3), 4.42 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 4.53 (ddd, 1 H, $J_{4,5}$ 9.5, $J_{H,P}$ 9.5 Hz, H-4), 6.09 (dt, 1 H, $J_{H,F}$ 49.0, $J_{H,P}$ 24.0 Hz, CHF_2); ^{31}P, δ 0.21, 0.62, and 0.62 (P-1,3,4), 4.81 ($J_{P,F}$ 85.5 Hz, P-5).

Anal. Calcd for $C_7H_9F_2Na_7O_{17}P_4$: P, 18.01. Found: P, 17.93.

(Difluoromethyl)phosphonic di(1,2,4-triazolide) (**28**).—A solution of (difluoromethyl)phosphonic dichloride[32] (0.85 g, 5.03 mmol) in anhyd dioxane (5 mL) was added dropwise to a stirred solution of dry 1,2,4-triazole (0.85 g, 12.32 mmol) and Et_3N (1.40 mL, 10.06 mmol) in anhyd dioxane (20 mL) at 20°. The solution was stirred for 1 h at 20°, and the salts were removed by filtration. The resulting 0.2 M stock solution of **28** in dioxane [^{31}P NMR: δ −3.01 ($J_{P,F}$ 106.0 Hz)] could be stored for several weeks at −20°.

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