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First derivatives of *myo*-inositol 1,4,6-trisphosphate modified at positions 2 and 3: structural analogues of D-*myo*-inositol 1,4,5-trisphosphate

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Abstract—Novel, structurally modified potential mimics of the second messenger D-*myo*-inositol 1,4,5-trisphosphate, based on the biologically active regioisomer D-*myo*-inositol 1,4,6-trisphosphate, were synthesised. DL-5-*O*-Benzyl-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol was the key intermediate for the preparation of the following compounds: DL-3-deoxy-, DL-3-deoxy-2-*O*-methyl-, DL-3-*O*-(2-hydroxyethyl)-, DL-3-*O*-(3-hydroxypropyl)- and DL-3-*O*-(4-hydroxybutyl)-*myo*-inositol 1,4,6-trisphosphate. DL-1,4,6-Tri-*O*-allyl-5-*O*-benzyl-*myo*-inositol was used to prepare DL-2-*O*-methyl-*myo*-inositol 1,4,6-trisphosphate. Deoxy-compounds were prepared by reduction of the corresponding tosylated intermediate using Super Hydride. The hydroxyalkyl groups were introduced at the C-3 of *myo*-inositol using the corresponding benzyl protected hydroxy alkyl bromide via the *cis*-2,3-*O*-dibutylstannylene acetal. Methylation and benzylation at C-2 was accomplished using methyl iodide and benzyl bromide, respectively, in the presence of sodium hydride. Deblocking of *p*-methoxybenzyl groups was accomplished with TFA in dichloromethane and the allyl groups were removed by isomerisation to the *cis*-prop-1-enyl derivative, which was hydrolysed under acidic conditions to give the corresponding 1,4,6-triol.

The 1,4,6-triols were phosphitylated with the P(III) reagent bis(benzyloxy)(diisopropylamino)phosphine in the presence of 1*H*-tetrazole then oxidised with 3-chloroperoxybenzoic acid followed by deblocking by hydrogenolysis to give DL-2-*O*-methyl-, DL-3-*O*-deoxy-, DL-3-*O*-deoxy-2-*O*-methyl-, DL-3-*O*-(2-hydroxyethyl)-, DL-3-*O*-(3-hydroxypropyl)- and DL-3-*O*-(4-hydroxybutyl)-*myo*-inositol 1,4,6-trisphosphate, respectively.

Keywords: Biological signal transduction; Cyclitols; *myo*-Inositol polyphosphates; D-*myo*-Inositol-1,4,5-trisphosphate; Stannylene acetals

1. Introduction

Phosphatidylinositol 4,5-bisphosphate is the precursor to the second messengers D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3, Fig. 1] and diacylglycerol.[1] Ins-(1,4,5)P_3 is produced in response to stimulation from a wide variety of agonists[2] and mediates a large number of calcium-regulated signal transduction events.[3] Rapid deactivation of this process is essential and occurs by one of two pathways. First, phosphorylation of Ins-(1,4,5)P_3 by a 3-kinase gives D-*myo*-inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P_4] and second, a 5-phosphatase converts Ins(1,4,5)P_3 into D-*myo*-inositol 1,4-bisphosphate, which is further dephosphorylated to *myo*-inositol. Both metabolic pathways are considered as 'off signals' since these compounds do not release Ca^{2+} ions. The primary signal function of Ins(1,4,5)P_3 is the mobilisation of Ca^{2+} through ligand-gated Ca^{2+} channels in which the receptor and ion channel form a structural unit; three dimensional structural data on this receptor are now becoming available.[4]

One metabolite from the inositol phosphate pathway is *myo*-inositol 1,3,4,6-tetrakisphosphate [Ins(1,3,4,6)P_4, **2**],

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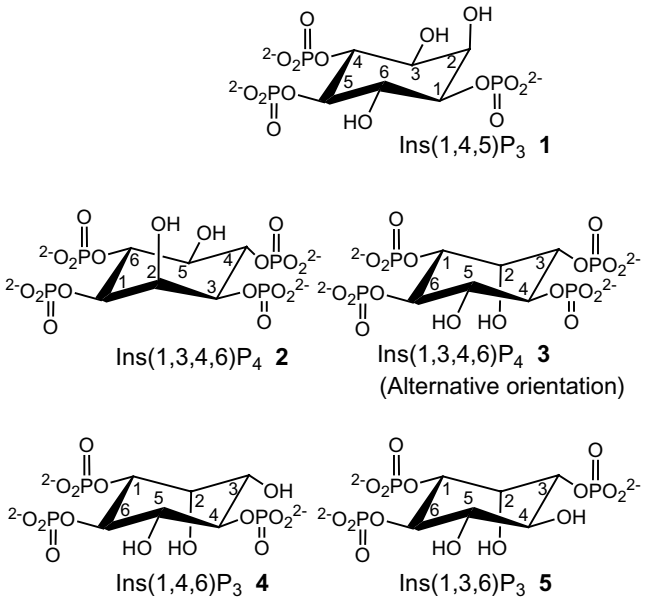
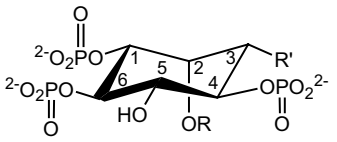


Figure 1. *myo*-Inositol phosphates.

which has Ca^{2+}-mobilising activity despite the apparent absence of the 4,5-bisphosphate motif.[5] We previously rationalised this finding by considering two alternative receptor binding orientations for Ins-(1,3,4,6)P_4, where the vicinal 1,6-bisphosphate mimics the normal 4,5-bisphosphate in Ins(1,4,5)P_3.[6] Both the 1-phosphate group and equatorial 6-hydroxyl group of Ins(1,4,5)P_3 are responsible for enhanced binding, thus one orientation, represented by (**3** in Fig. 1) is likely to be responsible for most of the Ca^{2+}-release activity, since an axial OH group at the 3-position [to give L-*chiro*-Ins(2,3,5)P_3] only results in a 10-fold decrease in Ca^{2+} mobilisation relative to Ins(1,4,5)P_3.[7] Based on these considerations D-*myo*-inositol 1,4,6-trisphosphate **4** and D-*myo*-inositol 1,3,6-trisphosphate **5** [Ins(1,4,6)P_3 and Ins(1,3,6)P_3], respectively, can be derived from Ins-(1,3,4,6)P_4. Both compounds mobilise Ca^{2+}, since the vicinal 1,6-bisphosphate of each compound can mimic the 4,5-bisphosphate of Ins(1,4,5)P_3. We have synthesised Ins(1,4,6)P_3[8] and Ins(1,3,6)P_3,[9] which allowed us to investigate Ca^{2+} release from permeabilised platelets, where Ins(1,4,6)P_3 was only two- to three-fold weaker than Ins(1,4,5)P_3[10a] and Ins(1,3,6)P_3 was 12-fold less potent than Ins(1,4,5)P_3 and both of these compounds specifically displaced bound [^{3}H]Ins(1,4,5)P_3 from the Ins(1,4,5)P_3 receptor on rat cerebellar membranes. Another study has demonstrated that the trisphosphorothioate derivative of Ins(1,4,6)P_3 is a partial agonist at the platelet Ins(1,4,5)P_3 receptor.[10b]

By rotating and inverting the molecule, the 1, 4 and 6 phosphates of Ins(1,4,6)P_3 can be superimposed on positions 4, 1 and 5 of Ins(1,4,5)P_3, respectively. Likewise, the hydroxyl groups at positions 3 and 2 of Ins(1,4,6)P_3 can be superimposed on positions 2 and 3 of Ins-(1,4,5)P_3, respectively, but with inversion of stereochemistry at the relevant carbon. SAR studies have revealed that position 3 of Ins(1,4,5)P_3 can be modified to some degree, without dramatically affecting activity, since both 3-deoxy-Ins(1,4,5)P_3[11] and L-*chiro*-Ins-(2,3,5)P_3[12] [with an axial orientation of the 3-hydroxyl group of Ins(1,4,5)P_3], are full agonists [EC_{50} 1.4 μM, L-*chiro*-Ins(2,3,5)P_3, cf. 0.12 μM, Ins(1,4,5)P_3], at the Ins (1,4,5)P_3 receptor and potent inhibitors of Ins(1,4,5)P_3 3-kinase. 3-Deoxy-Ins(1,4,5)P_3 is a good substrate for Ins(1,4,5)P_3 5-phosphatase but L-*chiro*-Ins(2,3,5)P_3 is a potent inhibitor of this enzyme.[12a,b,13a] The *chiro*-inositol analogue binds to the Ins(1,4,5)P_3 receptor from bovine adrenal cortex with high affinity [K_i value of 60.4 nM cf. Ins(1,4,5)P_3 K_d 5.9 nM].[13a] Similarly, the analogues[13b] 3-deoxy-Ins(1,4,5)P_3 and 2,3-dideoxy-Ins(1,4,5)P_3 are potent agonists with K_i values for binding to bovine adrenal cortex of 23.4 and 39.6 nM, respectively, and EC_{50} values for Ca^{2+} release from SH-SY5Y cells of 155.7 and 185.7 nM, respectively [cf. Ins(1,4,5)P_3, K_d 6.3 nM and EC_{50} 52.1 nM]. The 2,3,6-trideoxy-Ins-(1,4,5)P_3 analogue exhibited substantially weaker binding affinity (K_i 3948 nM) and was a poor Ca^{2+} agonist (EC_{50} > 10,000 nM) thus demonstrating the major role of the 6-hydroxyl in the activity of Ins(1,4,5)P_3. The 3-halogeno substituted Ins(1,4,5)P_3 analogues, 3-deoxy-3-bromo-Ins(1,4,5)P_3 [3-Br-Ins(1,4,5)P_3] and 3-deoxy-3-chloro-Ins(1,4,5)P_3 [3-Cl-Ins(1,4,5)P_3] and the 3-methoxy Ins(1,4,5)P_3 analogue [3-OMe-Ins(1,4,5)P_3] have also been evaluated for competitive Ins(1,4,5)P_3 binding and Ca^{2+} release in permeabilised SH-SY5Y neuroblastoma cells.[13c] 3-Cl-Ins(1,4,5)P_3, 3-Br-Ins(1,4,5)P_3 and 3-OMe-Ins(1,4,5)P_3 all exhibited receptor binding and Ca^{2+} release. However, as the steric bulk of the 3-substituent increases the activity of the Ins(1,4,5)P_3 analogue decreases (IC_{50} values of 32.0, 69.5 and 271.1 nM, respectively). Other studies show that modifications at position 2 of Ins(1,4,5)P_3 are well tolerated and the hydroxyl group can be inverted (to give a *scyllo*-derivative), deleted (to give a *deoxy*-derivative), or substituted (with small or large groups, polar or nonpolar), without adversely affecting Ca^{2+} release.[14]

No direct analogues of Ins(1,4,6)P_3 have been reported, and consequently we have modified positions 2 and 3 of Ins(1,4,6)P_3 by deoxygenation, alkylation and hydroxyalkylation, in order to probe the interactions of these new molecules with the Ins(1,4,5)P_3 receptor and the enzymes 3-kinase and 5-phosphatase. We report here the synthesis of the following molecules as racemic mixtures, modified at positions 2 and 3 based on the Ins(1,4,6)P_3 structure: 3-deoxy-Ins(1,4,6)P_3 **6**, 3-deoxy-2-OMe-Ins(1,4,6)P_3 **7**, 2-OMe-Ins(1,4,6)P_3 **8**, 3-*O*-(EtOH)-Ins(1,4,6)P_3 **9**, 3-*O*-(PrOH)-Ins(1,4,6)P_3 **10** and 4-*O*-(BuOH)-Ins(1,4,6)P_3 **11** (Fig. 2).



6 3-Deoxy-Ins(1,4,6)P_3, R = H, R' = H;
7 3-Deoxy-2-*O*-Me-Ins(1,4,6)P_3, R = Me, R = H;
8 2-*O*-Me-Ins(1,4,6)P_3, R = Me, R' = OH;
9 3-*O*-(EtOH)-Ins(1,4,6)P_3, R = H, R' = $O(CH_2)_2OH$;
10 3-*O*-(PrOH)-Ins(1,4,6)P_3, R = H, R' = $O(CH_2)_3OH$;
11 3-*O*-(BuOH)-Ins(1,4,6)P_3, R = H, R' = $O(CH_2)_4OH$;

Me = Methyl, EtOH = Hydroxyethyl,
PrOH = Hydroxypropyl, BuOH = Hydroxybutyl.

All compounds are racemic

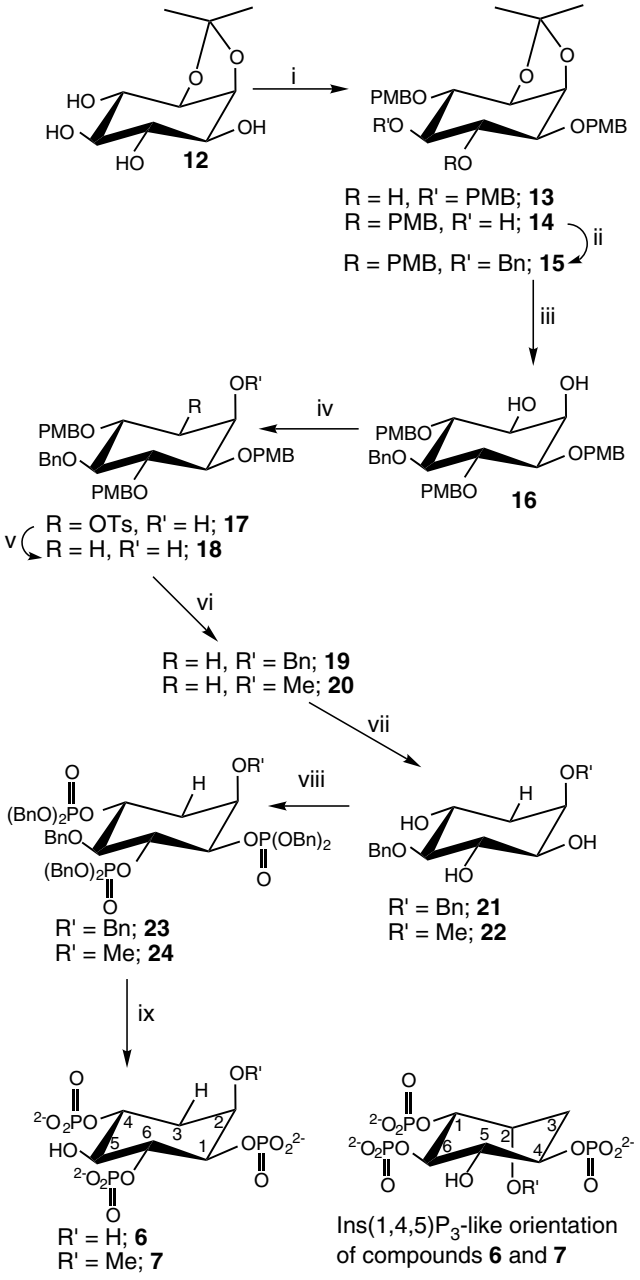
Figure 2. The 2- and 3-modified analogues of *myo*-inositol 1,4,6-trisphosphate.

2. Results and discussion

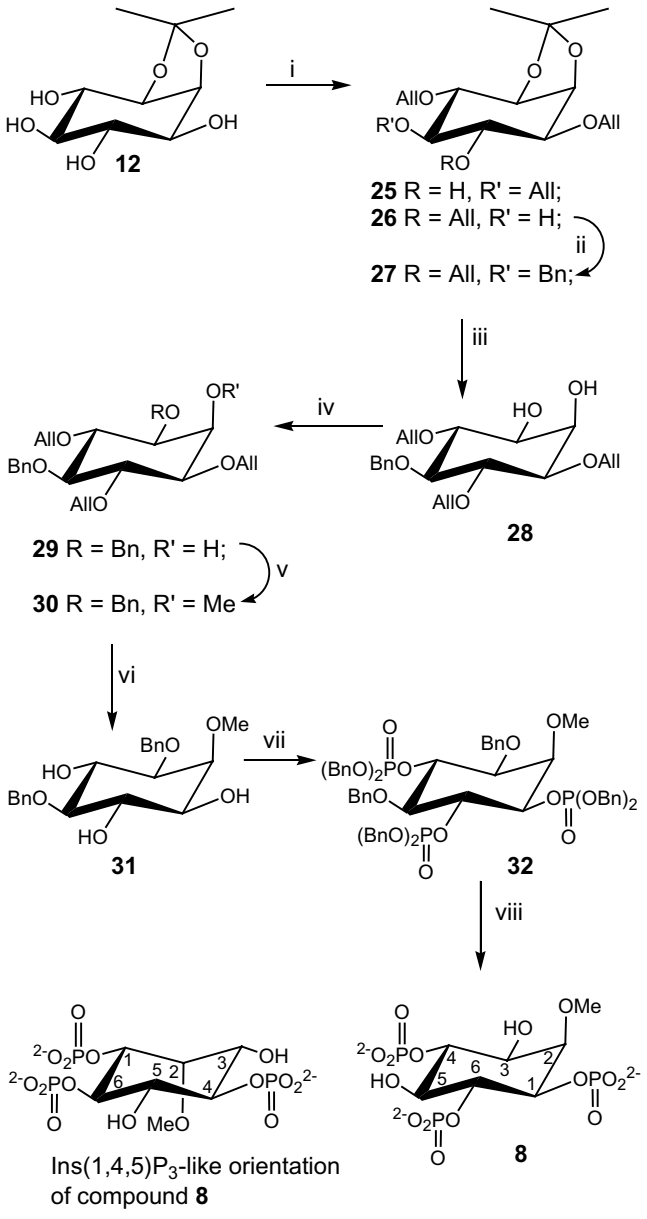
myo-Inositol 1,4,6-trisphosphate derivatives **6–11** were synthesised using DL-1,2-*O*-isopropylidene-*myo*-inositol **12** as the common intermediate, and prepared from *myo*-inositol in one step (35–50%).[15] Selective alkylation of **12** was achieved by using *p*-methoxybenzyl chloride or allyl bromide in the presence of tetrabutylammonium iodide and dibutyltin oxide[16] to give two sets of two major products **13** and **14** (*p*-methoxybenzyl, Scheme 1) and **25** and **26** (allyl, Scheme 2) in moderate yield (**14**, 41%, **13**, 32%; **26**, 24%, **25**, 21%). These yields are not surprising but notably the various regioisomers produced are useful in other syntheses, so overall the route chosen is economical. We recently used compound **13** to synthesise 6-deoxy-Ins(1,3,4,5)P_4.[17]

Benzylation of compound **14** with benzyl bromide in *N*,*N*-dimethylformamide (DMF) at room temperature with sodium hydride (NaH) as base (conditions used for all benzylations in this paper), gave the fully protected *myo*-inositol derivative DL-5-*O*-benzyl-2,3-*O*-isopropylidene-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol **15**, in 92% yield. The *cis*-isopropylidene protecting group was removed using aqueous HCl in THF at reflux to provide diol **16**, a suitable intermediate for selective deoxygenation and regioselective alkylation.

Deoxygenation of sugar hydroxyl groups is usually carried out by metal hydride reduction of halides, sulfonates and epoxides[18] and radical deoxygenation of thiocarbonyl derivatives using the Barton–McCombie method.[19] Our initial attempts at deoxygenation involved generating the thiocarbonyl derivative of DL-5-*O*-benzyl-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol **16**, followed by radical reduction. However, treatment of diol **16** with phenyl chlorothionoformate in the presence of dibutyltin oxide[20] failed to give the required thioacyl derivative and an alternative procedure was sought. Previously, lithium triethylborohydride was reported to reduce *p*-toluenesulfonate esters of both cyclic and



Scheme 1. Reagents and conditions: (i) Bu_2SnO, PMBCl, Bu_4NBr, toluene, reflux 16 h (**14**, 41%; **13**, 32%); (ii) BnBr, NaH, DMF, rt, 2 h (**15**, 92%); (iii) THF–1 M aq HCl (1:1) reflux 1 h (**16**, 93%); (iv) Bu_2SnO, TsCl, $BnNEt_3Br$, MeCN, rt, 24 h (**17**, 76%); (v) Super Hydride, THF, reflux, 1 h (**18**, 67%); (vi) NaH, BnBr, DMF, rt (**19**, 93%), NaH, MeI, DMF, rt (**20**, 71%); (vii) TFA–CH_2Cl_2 (1:9) rt (**21**, 80%; **22**, 81%); (viii) $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_2Cl_2, rt, 1 h, then MCPBA (**23**, 61%; **24**, 57%); (ix) $Pd(OH)_2$ (20% on carbon) MeOH–H_2O (9:1), H_2, 20 psi, 16 h, then purification by Q-Sepharose Fast Flow ion exchange chromatography (**6** and **7** quantitative). All compounds are racemic.

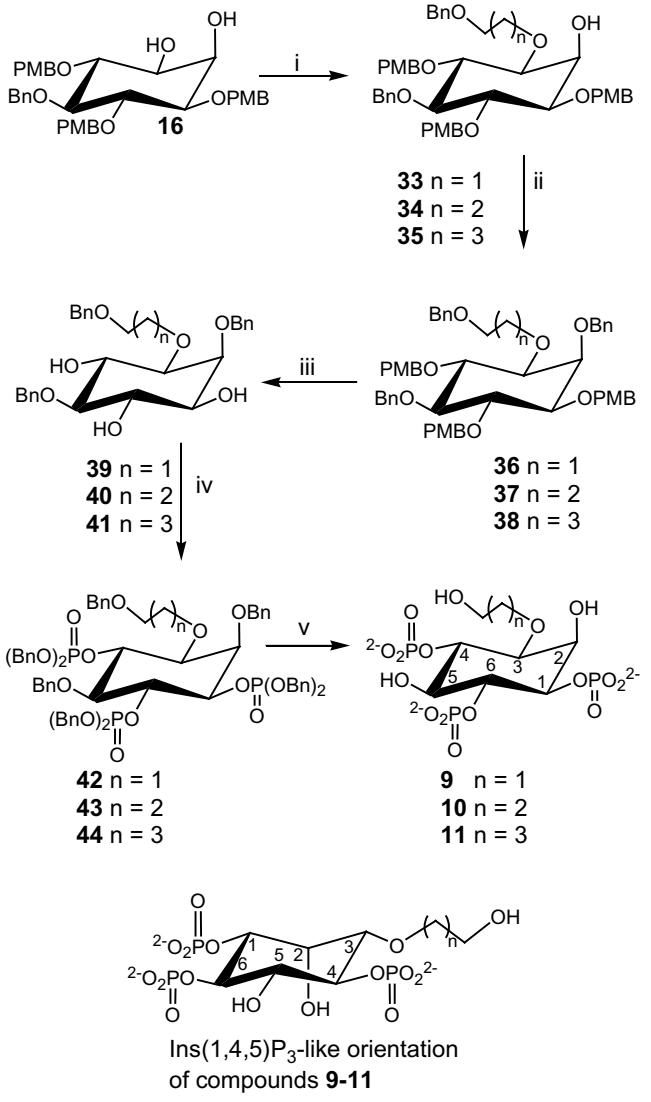


Scheme 2. Reagents and conditions: (i) Bu_2SnO, AllBr, Bu_4NI, MeCN, reflux (**26**, 24%; **25**, 21%); (ii) NaH, BnBr, DMF, rt, 2 h (**27**, 82%); (iii) MeOH–1 M aq HCl (9:1) reflux, 1 h (**28**, 98%); (iv) Bu_2SnO, Bu_4NBr, BnBr, MeCN, reflux, 24 h (**29**, 80%); (v) NaH, MeI, DMF, rt, 2 h (**30**, 91%); (vi) Bu^tOK, Me_2SO, 60 °C, 6 h, then workup and purification followed by MeOH–1 M aq HCl (9:1) reflux, 30 min (**31**, 68%); (vii) $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_2Cl_2, rt, then MCPBA (**32**, 96%); (viii) 10% Pd/C, MeOH–H_2O (9:1), H_2, 30 psi, 20 h, then purification by Q-Sepharose Fast Flow ion-exchange chromatography to give compound **8**. All compounds are racemic.

acyclic alcohols to afford the corresponding alkanes in excellent yield and this procedure was then applied to tosylates derived from hindered alcohols.[21] Subsequently, this methodology was used to synthesise 2- and 3-deoxy sugars[22] and regioselective deoxygenation of *myo*-inositol.[23] Treatment of diol **16** with *p*-toluenesulfonyl chloride in the presence of dibutyltin oxide and benzyltriethylammonium bromide using acetonitrile as solvent, gave the 3-*O*-tosyl derivative **17** in good yield. The regioselective mono-tosylation of nucleosides under phase-transfer conditions was shown to be dependent on the solvent and the nature of the quaternary ammonium salt.[24] However in our syntheses, the best yields were achieved when acetonitrile was used as the solvent, rather than benzene or toluene. In all cases benzyltriethylammonium bromide was shown to be the preferred quaternary ammonium salt. For all our experiments, the deoxygenation of the 3-*O*-*p*-toluenesulfonyl ester was carried out using lithium triethylborohydride (Super Hydride), which produced the corresponding deoxy-derivative DL-5-*O*-benzyl-3-deoxy-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol **18**, in 67% yield. Compound **18** was then alkylated with either benzyl bromide or methyl iodide to give the fully protected derivatives DL-2,5-di-*O*-benzyl-3-deoxy-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol **19** and DL-5-*O*-benzyl-3-deoxy-1,4,6-tri-*O*-*p*-methoxybenzyl-2-*O*-methyl-*myo*-inositol **20** in 93% and 71% yield, respectively. Subsequent removal of the *p*-methoxybenzyl groups using 10% trifluoroacetic acid in dichloromethane for 30 min provided the triols DL-2,5-di-*O*-benzyl-3-deoxy-*myo*-inositol **21** and DL-5-*O*-benzyl-3-deoxy-2-*O*-methyl-*myo*-inositol **22**, respectively.

Compound **8** was synthesised from DL-1,4,6-tri-*O*-allyl-2,3-*O*-isopropylidene-*myo*-inositol **26**. Benzylation of compound **26** (Scheme 2) then deprotection of the *cis*-isopropylidene with methanolic aqueous HCl gave DL-1,4,6-tri-*O*-allyl-5-*O*-benzyl-*myo*-inositol **28**, in 98% yield. Compound **28** was selectively benzylated in 80% yield on the equatorial hydroxyl to give DL-1,4,6-tri-*O*-allyl-3,5-di-*O*-benzyl-*myo*-inositol **29**. Methylation of compound **29** using MeI and NaH in DMF gave fully protected *myo*-inositol derivative **30** in 91% yield. The allyl groups were removed in a two-step procedure; first, potassium *tert*-butoxide in anhydrous dimethylsulfoxide isomerised the allyl functionality to give the 1,4,6-tri-*O*-*cis*-prop-1-enyl ether derivative, which was quickly purified by flash chromatography to remove any remaining dimethyl sulfoxide. This intermediate was hydrolysed under acidic conditions to provide the triol DL-3,5-di-*O*-benzyl-2-*O*-methyl-*myo*-inositol **31**, in 68% yield for the two step process.

The 3-*O*-(hydroxyalkyl) derivatives **9**–**11**, were synthesised using DL-5-*O*-benzyl-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol **16** as the common intermediate (Scheme 3). Selective alkylation of compound **16** was achieved via the 2,3-*O*-dibutylstannylene derivative under phase transfer conditions using benzyl-2-bromoethyl ether, benzyl-3-bromopropyl ether or benzyl-4-bromobutyl ether and tetrabutylammonium bromide in refluxing toluene to give the following compounds: DL-5-*O*-benzyl-3-*O*-(2-benzyloxy-ethyl)- **33**, DL-5-*O*-benzyl-3-*O*-(3-benzyloxy-propyl)- **34** and DL-5-*O*-benzyl-3-*O*-(4-benzyloxy-butyl)-2,3-*O*-isopropylidene-*myo*-inositol



Scheme 3. Reagents and conditions: (i) Bu_2SnO, Bu_4NBr, toluene, $Br(CH_2)_nOBn$, reflux ($n = 2$, **33**, 72%; $n = 3$, **34**, 63%; $n = 4$, **35**, 81%); (ii) NaH, BnBr, DMF, rt, 4 h (**36**, 89%; **37**, 83%; **38**, 93%); (iii) TFA–CH_2Cl_2 (1:9), rt, 30 min (**39**, 71%; **40**, 67%; **41**, 75%); (iv) $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_2Cl_2, rt, 1 h, then MCPBA, −78 °C, 1 h (**42**, 71%; **43**, 57%; **44**, 68%); (v) $Pd(OH)_2$ (20% on carbon), MeOH–H_2O (9:1), H_2, 20 psi, then purification by Q-Sepharose Fast Flow ion-exchange chromatography to give compounds **9**–**11** (quantitative). All compounds are racemic.

35, respectively. Benzylation of **33**–**35** and removal of the *p*-methoxybenzyl protecting groups with 10% TFA in dichloromethane for 30 min afforded the triols DL-2,5-di-*O*-benzyl-3-*O*-(2-benzyloxy-ethyl)- **39**, DL-2,5-di-*O*-benzyl-3-*O*-(3-benzyloxy-propyl)- **40** and DL-2,5-di-*O*-benzyl-3-*O*-(4-benzyloxy-butyl)-*myo*-inositol **41**, respectively.

Compounds **21**, **22**, **31** and **39**–**41** were phosphitylated with bis(benzyloxy)(diisopropylamino)phosphine[25,26] in the presence of 1*H*-tetrazole to form the trisphosphite. Oxidation of the trisphosphite intermediate with MCPBA afforded the fully protected trisphosphate compounds **23**, **24**, **32**, **42**, **43** and **44**, respectively. All the benzyl groups were removed in one step by hydrogenolysis using 20% palladium hydroxide on carbon or 10% palladium on carbon. The residue of each compound was purified by ion-exchange chromatography on Q-Sepharose Fast Flow using a gradient of aqueous triethylammonium bicarbonate (TEAB) 0–1 M as eluent. The inositol 1,4,6-trisphosphates (**6**–**11**) eluted between 55% and 75% 1 M TEAB and the appropriate fractions were pooled and the solvent was evaporated to give the trisphosphates as their triethylammonium salts. In all cases the final *myo*-inositol 1,4,6-trisphosphate compounds **6**–**11** were quantified by total phosphate assay using a modified Briggs test[27] in order to determine the amount of compound present. This assay has a greater degree of accuracy for determining the amount of inositol phosphate, compared to the weighing of hygroscopic sodium and potassium salts of inositol polyphosphates, since the amount of *myo*-inositol polyphosphate is determined by graphical methods. This is a critical stage in the analysis of inositol polyphosphates since micromolar amounts of compound are used to investigate enzyme inhibition, Ca^{2+} release and receptor binding, thus, precise quantities are required in order to provide accurate and reproducable data.

Compounds **6**–**11** were synthesised in order to investigate how modifications at positions 2 and 3 of Ins-(1,4,6)P_3 affect the interaction of this molecule at the Ins(1,4,5)P_3 receptor and metabolic enzymes 3-kinase and 5-phosphatase. Preliminary biological evaluation of racemic **8** on cerebellar receptor binding indicated an affinity some 100-fold lower than Ins(1,4,5)P_3. Given that we expect the D-enantiomer of **8** to be the active one of the pair this could then be 50-fold weaker than Ins-(1,4,5)P_3. It is therefore likely that D-2-*O*-methyl-Ins-(1,4,6)P_3 will prove to be a low affinity agonist in Ca^{2+} release. Full results of these biological investigations will be reported in due course.

3. Experimental

3.1. General methods

Toluene and dichloromethane were distilled from calcium hydride and stored over 4 Å molecular sieves; acetonitrile was distilled from phosphorous pentoxide and stored over 3 Å molecular sieves; tetrahydrofuran was distilled from sodium/benzophenone and ether is diethylether. Molecular sieves (3 and 4 Å) were pre-dried in an oven and activated for 1 h under vacuum at 250 °C. All aqueous (aq) solutions were saturated unless otherwise stated. Reactions were carried out at room temperature under nitrogen in pre-dried glassware. Sodium hydride (NaH) was used in a 60% dispersion of mineral

oil. Super Hydride was purchased from the Aldrich Chemical Company. Analytical thin-layer chromatography (TLC) was performed on pre-coated plates (Merck TLC aluminium sheets silica 60 F_{254}, Art. No. 5554): the products were visualised by ultraviolet radiation and stained with ethanolic phosphomolybdic acid, or ethanolic sulfuric acid followed by charring. Column chromatography was carried out under pressure using BDH silica gel for flash chromatography. NMR spectra (^{31}P, ^{1}H, ^{13}C, COSY, HETCOR) were recorded on a Varian Mercury 400 spectrometer and signals were assigned by 1D, DEPT, and 2D spectra (COSY, HETCOR). Chemical shifts were measured in parts per million (ppm) relative to tetramethylsilane (TMS) in *d*-chloroform ($CDCl_3$). The other deuterated solvents used included the following: deuterium oxide (D_2O), dimethyl sulfoxide (Me_2SO-d_6) and methanol (CD_3OD-d_4). The ^{31}P NMR shifts were measured in ppm relative to external 85% phosphoric acid. High and low resolution mass spectra were recorded by the University of Bath Mass Spectrometry Service using +ve and −ve fast atom bombardment (FAB) with 3-nitrobenzyl alcohol (NBA) as the matrix. Elemental analyses were carried out by the Microanalysis Service at the University of Bath. Ion-exchange chromatography was performed on an LKB-Pharmacia medium pressure ion exchange chromatograph using Q-Sepharose Fast Flow and gradients of 0–1 M TEAB as eluent. Fractions were assayed for phosphate by a modification of the Briggs phosphate test.[27]

3.2. DL-2,3-*O*-Isopropylidene-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (14) and DL-2,3-*O*-isopropylidene-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (13)

A mixture of compound **12** (4.4 g, 10 mmol), Bu_2SnO (22.6 g, 90 mmol), Bu_4NBr (18 g, 56 mmol), *p*-methoxybenzyl chloride (18.48 g, 118 mmol) and toluene (150 mL) was heated under reflux with 4 Å molecular sieves in a Soxhlet apparatus for 16 h. TLC (ether–hexane, 2:1) revealed two major products with R_f values of 0.28 and 0.19. The solution was cooled and washed with H_2O, brine, then dried ($MgSO_4$) and concentrated in vacuo. The crude syrup was purified by flash chromatography (ether–hexane, 2:1) to provide compound **13** as a white crystalline solid (3.7 g, 32%) and compound **14** as a colourless syrup (4.76 g, 41%). **13**: TLC, $R_f = 0.19$ (ether–hexane, 2:1); mp 89 °C; ^{1}H NMR ($CDCl_3$): δ 7.33–6.80 (m, 12H, $3\times CH_2C_6H_4OMe$), 4.80–4.61 (m, 4H, $2\times CH_2C_6H_4OMe$), 4.78, 4.64 (AB, 2H, $CH_2C_6H_4OMe$), 4.25 (dd, 1H, $J_{2,3}$ 6.6 Hz, H-2), 4.08 (t, 1H, $J_{3,4}$ 6.6 Hz, H-3), 3.99 (dd, 1H, $J_{1,6}$ 9.7 Hz, H-6), 3.77 (s, 9H, $3\times CH_2C_6H_4OMe$), 3.65 (dd, 1H, $J_{4,5}$ 9.0 Hz, H-4), 3.51 (dd, 1H, $J_{1,2}$ 3.9 Hz, H-1), 3.24 (t, 1H, $J_{5,6}$ 9.0 Hz, H-5), 1.47, 1.33 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 159.49, 159.35, 159.26 (C_q, CH_2PhOMe), 130.77, 130.68, 130.22 (C_q, CH_2PhOMe), 129.85, 129.81, 129.72 (CH_2PhOMe), 114.06, 113.89 (CH_2PhOMe), 110.00 ($C(CH_3)_2$), 82.39, 81.71, 79.67, 76.71, 74.30, 71.95 (6×*myo*-inositol ring carbons), 74.98, 73.59, 72.51 (CH_2PhOMe), 55.59 ($CH_2C_6H_4OMe$), 28.28, 26.27 ($C(CH_3)_2$); MS: (FAB^+) *m*/*z* 603.3, 579.2, 459.2, 121.1; (HRMS, FAB^+) *m*/*z* Calcd for $C_{33}H_{41}O_9$, $[M+H]^+$ 581.2750. Found: 581.2690; Anal. Calcd for $C_{33}H_{40}O_9$: C, 68.26; H, 6.94. Found: C, 68.4; H, 6.93.

14: TLC, $R_f = 0.28$ (ether–hexane, 2:1); ^{1}H NMR ($CDCl_3$): δ 7.30–6.84 (m, 12H, $3\times CH_2C_6H_4OMe$), 4.83–4.62 (m, 4H, $2\times CH_2C_6H_4OMe$), 4.82, 4.63 (AB, 2H, $CH_2C_6H_4OMe$), 4.34 (dd, 1H, $J_{2,3}$ 5.6 Hz, H-2), 4.06 (dd, 1H, $J_{3,4}$ 6.7 Hz, H-3), 3.76 (m, 10H, H-6, $3\times CH_2C_6H_4OMe$), 3.63 (m, 2H, H-1, H-4), 3.44 (br t, 1H, H-5), 1.51, 1.35 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 158.93, 158.87, 158.83 (C_q, CH_2PhOMe), 130.12, 130.10, 129.80 (C_q, CH_2PhOMe), 129.33, 129.31 (CH_2PhOMe), 113.58, 113.50, 113.49 (CH_2PhOMe), 109.51 ($C(CH_3)_2$), 81.27, 80.09, 78.75, 76.57, 74.47, 73.16 (6×*myo*-inositol ring carbons), 74.36, 72.80, 72.47 (CH_2PhOMe), 55.12 ($CH_2C_6H_4OMe$), 27.68, 25.70 ($C(CH_3)_2$); MS: (FAB^+) *m*/*z* 603.3, 579.3, 459.2, 121.1; (HRMS, FAB^+) *m*/*z* Calcd for $C_{33}H_{41}O_9$, $[M+H]^+$ 581.2750. Found: 581.2690. Anal. Calcd for $C_{33}H_{40}O_9$: C, 68.26; H, 6.94. Found: C, 68.4; H 6.99.

3.3. DL-5-*O*-Benzyl-2,3-*O*-isopropylidene-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (15)

To a solution of compound **14** (1.16 g, 2 mmol) in DMF (40 mL) was added NaH (120 mg, 3 mmol), which was stirred at room temperature for 10 min. Benzyl bromide (0.36 mL, 3 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. TLC revealed the disappearance of the starting material and the appearance of a less polar product. The reaction was quenched by careful addition of MeOH and diluted with an ice and water mixture. The product was then extracted with ether and the organic layers were washed with brine, dried ($MgSO_4$), then filtered and the solvent removed. The crude residue was purified by silica gel chromatography (ether–hexane, 1:1 to 2:1) to give compound **15** as a colourless syrup (1.23 g, 92%). ^{1}H NMR ($CDCl_3$): δ 7.35–6.81 (m, 17H, $3\times CH_2C_6H_4OMe$, CH_2Ph), 4.80–4.61 (m, 8H, $3\times CH_2C_6H_4OMe$, CH_2Ph), 4.21 (dd, 1H, $J_{2,3}$ 5.8 Hz, H-2), 4.06 (dd, 1H, $J_{3,4}$ 6.7 Hz, H-3), 3.90 (t, 1H, $J_{1,6}$ 8.8 Hz, H-6), 3.78–3.74 (m, 10H, $3\times CH_2C_6H_4OMe$, H-4), 3.65 (dd, 1H, $J_{1,2}$ 3.8 Hz, H-1), 3.37 (t, 1H, $J_{5,6}$ 8.8 Hz, H-5), 1.52, 1.35 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 158.90, 158.77, 158.71 (C_q, CH_2PhOMe), 138.31, 130.46, 130.33 (C_q, CH_2PhOMe, CH_2Ph), 129.94, 129.36, 129.30, 129.27, 129.22, 128.14, 128.02, 127.98, 127.60, 127.22, 126.56 (CH_2PhOMe, CH_2Ph), 113.46, 113.34 (C_q, CH_2PhOMe), 109.43 ($C(CH_3)_2$), 82.07, 81.91, 80.36,

78.96, 76.54, 74.42 (6×*myo*-inositol ring carbons), 75.08, 74.83, 73.39, 72.71 (*C*H_2PhOMe, *C*H_2Ph), 55.06 ($CH_2C_6H_4O$*Me*), 27.71, 25.74 (C(*C*H_3)$_2$); MS: (FAB$^+$) *m*/*z* 669.3, 549.3, 121.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{40}H_{47}O_9$, [M+H]$^+$ 671.3220. Found: 671.3131.

3.4. DL-5-*O*-Benzyl-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (16)

Compound **15** (670 mg, 1 mmol) was dissolved in THF–1 M aq HCl (50 mL, 1:1 v/v) and refluxed for 1 h. TLC revealed the disappearance of the starting material and the presence of a more polar product. The reaction was cooled to room temperature and poured into an ice and water mixture and the product was extracted into ether. The organic solution was washed with an aqueous solution of $NaHCO_3$ then dried ($MgSO_4$) and the solvent was then evaporated to give the impure product. The crude residue was purified by silica gel chromatography (ether–hexane, 1:1 to 1:0) to give compound **16** as a colourless syrup (587 mg, 93%). ^{1}H NMR ($CDCl_3$): δ 7.36–6.80 (m, 17H, 3×CH_2C_6*H*$_4$OMe, CH_2*Ph*), 4.93–4.60 (m, 8H, 3×C*H*$_2C_6H_4$OMe, C*H*$_2$Ph), 4.14 (m, 1H, H-2), 3.92 (t, 1H, $J_{1,6}$ 11.4 Hz H-6), 3.83–3.76 (m, 10H, 3×$CH_2C_6H_4O$*Me*, H-4), 3.45–3.39 (m, 3H, H-1, H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 159.47, 159.43, 159.26 (*C*$_q$, CH_2*Ph*OMe), 138.78, 130.99, 130.77, 130.08 (*C*$_q$, CH_2*Ph*OMe, CH_2*Ph*), 129.84, 129.80, 129.69, 128.58, 127.88, 127.77 (CH_2*Ph*OMe, CH_2*Ph*), 114.19, 114.10, 113.97 (CH_2*Ph*OMe), 83.54, 81.69, 81.21, 80.02, 71.98, 69.46 (6×*myo*-inositol ring carbons), 75.92, 75.56, 72.71 (*C*H_2Ph), 55.61 ($CH_2C_6H_4O$*Me*); MS: (FAB$^+$) *m*/*z* 629.2, 509.2, 121.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{37}H_{43}O_9$, [M+H]$^+$ 631.2907. Found: 631.2847.

3.5. DL-5-*O*-Benzyl-1,4,6-tri-*O*-*p*-methoxybenzyl-3-*O*-tosyl-*myo*-inositol (17)

Compound **16** (1.26 g, 2 mmol) was dissolved in acetonitrile (60 mL) and stirred at room temperature for 10 min. Dibutyltin oxide (740 mg, 3 mmol) was added and the reaction mixture was stirred at room temperature for an additional 30 min, after which, tosyl chloride (762 mg, 4 mmol) and benzyltriethylammonium bromide (1.36 g, 5 mmol) were added. The reaction mixture was stirred at room temperature for 24 h then TLC revealed the presence of a less polar product. The solution was filtered through Celite and the remaining solid was washed with acetonitrile. The combined organic layers were washed with aqueous solutions of $NaHCO_3$ and brine, dried ($MgSO_4$), then filtered and concentrated. The crude product was purified by silica gel chromatography (diethyl ether–hexane, 1:1 to 2:1) to give compound **17** as an amorphous solid (1.19 g, 76%). ^{1}H NMR ($CDCl_3$): δ 7.80–6.75 (m, 21H, 3×CH_2C_6*H*$_4$OMe, CH_2*Ph*, SO_2*Ph*Me), 4.84, 4.79 (AB, 2H, C*H*$_2$PhOMe or C*H*$_2$Ph), 4.80, 4.74 (AB, 2H, C*H*$_2$PhOMe or C*H*$_2$Ph), 4.62 (AB, 2H, C*H*$_2$PhOMe or C*H*$_2$Ph), 4.61, 4.52 (AB, 2H, C*H*$_2$PhOMe or C*H*$_2$Ph), 4.49 (dd, 1H, $J_{3,4}$ 9.7 Hz, H-3), 4.42 (br d, 1H, $J_{2,3}$ 2.3 Hz, H-2), 4.03 (t, 1H, $J_{4,5}$ 9.7 Hz, H-4), 3.92 (dd, 1H, $J_{1,6}$ 9.4 Hz, H-6), 3.82, 3.80 (2s, 9H, 3×$CH_2C_6H_4O$*Me*), 3.44 (dd, 1H, $J_{1,2}$ 3.1 Hz, H-1), 3.43 (t, 1H, $J_{5,6}$ 9.7 Hz, H-5) 2.40 (s, 3H, SO_2Ph*Me*); ^{13}C NMR ($CDCl_3$): δ 159.20, 158.92, 158.75 (*C*$_q$, CH_2*Ph*OMe), 144.75, 138.26, 133.76, 130.56, 130.13 (*C*$_q$, CH_2*Ph*OMe, CH_2*Ph*, SO_2*Ph*Me), 129.57, 129.38, 129.06, 128.13, 127.56, 127.46, 127.36 (CH_2*Ph*OMe, CH_2*Ph*, SO_2*Ph*Me), 113.79, 113.60, 113.36 (CH_2*Ph*OMe), 82.69, 81.31, 80.41, 79.01, 78.23, 68.61 (6×*myo*-inositol ring carbons), 75.84, 75.54, 75.15, 72.48 (*C*H_2Ph and *C*H_2PhOMe), 55.27, 55.24, 55.22 ($CH_2C_6H_4O$*Me*), 21.71 (SO_2Ph*Me*); MS: (FAB$^+$) *m*/*z* 783.2, 663.1, 121.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{44}H_{49}O_{11}S$, [M+H]$^+$ 785.2995. Found: 785.2922.

3.6. DL-5-*O*-Benzyl-3-deoxy-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (18)

Compound **17** (784 mg, 1 mmol) was dissolved in THF (30 mL) then Super Hydride (lithium triethylborohyride, 1 M solution in THF, 1.2 mmol) was added dropwise and the mixture was refluxed for 1 h. TLC revealed the disappearance of the starting material and the presence of a slightly more polar product. The reaction was cooled to 0 °C and water was added with caution to destroy excess reagent. The solution was then concentrated and the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and the solvent was removed. The crude residue was purified by silica gel chromatography (ether–hexane, 1:1 to 3:1) to give the title compound **18** (411 mg, 67%) as a colourless syrup. ^{1}H NMR ($CDCl_3$): δ 7.38–6.83 (m, 17H, CH_2C_6*H*$_4$OMe, CH_2*Ph*), 4.93, 4.86 (AB, 2H, C*H*$_2C_6H_4$OMe or C*H*$_2$Ph), 4.80, 4.76 (AB, 2H, C*H*$_2C_6H_4$OMe or C*H*$_2$Ph), 4.68, 4.61 (AB, 2H, C*H*$_2C_6H_4$OMe or C*H*$_2$Ph), 4.64, 4.59 (AB, 2H, C*H*$_2C_6H_4$OMe or C*H*$_2$Ph), 4.08 (br s, 1H, H-2), 3.94–3.84 (m, 1H, H-4), 3.82, 3.80, 3.79 (3s, 9H, 3×$CH_2C_6H_4O$*Me*), 3.81–3.76 (m, 1H, H-6), 3.47–3.43 (m, 2H, H-1, H-5), 2.36–2.32 (m, 1H, H-3$_{eq}$), 1.37 (m, 1H, H-3$_{ax}$); ^{13}C NMR ($CDCl_3$): δ 159.52, 159.26 (*C*$_q$, CH_2*Ph*OMe), 139.24, 131.26, 131.06, 130.37 (*C*$_q$, CH_2*Ph*OMe, CH_2*Ph*), 129.83, 129.64, 129.57, 128.51, 128.05, 127.64 (CH_2*Ph*OMe, CH_2*Ph*), 114.14, 114.01, 113.99 (CH_2*Ph*OMe), 86.08, 82.90, 81.67, 76.01, 66.37 (5×*myo*-inositol ring carbons), 75.96, 72.93, 72.87 (*C*H_2PhOMe, *C*H_2*Ph*), 55.64 ($CH_2C_6H_4O$*Me*), 32.95 (C-3, deoxy-*myo*-inositol ring carbon); MS: (FAB$^+$) *m*/*z* 613.4, 493.3, 121.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{37}H_{43}O_8$, [M+H]$^+$ 615.2957. Found: 615.2846.

3.7. DL-2,5-Di-*O*-benzyl-3-deoxy-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (19)

Compound **18** (1.28 g, 2 mmol) was dissolved in DMF (50 mL) and stirred at room temperature for 10 min. NaH (120 mg, 3 mmol) was then added and the reaction was stirred for an additional 10 min. Benzyl bromide (0.36 mL, 3 mmol) was added and the reaction was stirred for 4 h then quenched with methanol and poured into an ice and water slurry. The product was extracted with ether and the organic layers were washed with brine and dried ($MgSO_4$). The crude product was purified by silica gel chromatography (ether–hexane, 1:1 to 2:1) to give compound **19** as a colourless syrup (1.37 g, 93%). ^{1}H NMR ($CDCl_3$): δ 7.60–6.85 (m, 22H, 3×$CH_2C_6H_4$OMe, 2×CH_2Ph), 4.96, 4.91 (AB, 2H, CH_2Ph), 4.89, 4.80 (AB, 2H, CH_2Ph or C$H_2C_6H_4$OMe), 4.66, 4.61 (AB, 2H, CH_2Ph or C$H_2C_6H_4$OMe), 4.66, 4.56 (AB, 2H, CH_2Ph or C$H_2C_6H_4$OMe), 4.63, 4.51 (AB, 2H, CH_2Ph or C$H_2C_6H_4$OMe), 3.99 (dd, 1H, $J_{1,6}$ 9.7 Hz, H-6), 3.90–3.85 (m, 2H, H-4, H-2), 3.83, 3.82, 3.81 (3s, 9H, 3×$CH_2C_6H_4$O*Me*), 3.49 (t, 1H, $J_{5,6}$ 9.4 Hz, H-5), 3.42 (dd, 1H, $J_{1,2}$ 2.7 Hz, H-1), 2.07 (m, 1H, H-3$_{eq}$), 1.32–1.28 (m, 1H, H-3$_{ax}$); ^{13}C NMR ($CDCl_3$): δ 159.34, 159.28, 159.25 (C_q, CH_2*Ph*OMe), 139.35, 138.90, 131.50, 131.05, 130.97 (C_q, CH_2*Ph*OMe, CH_2Ph), 129.97, 129.79, 129.51, 128.75, 128.56, 128.53, 128.12, 127.88, 127.80, 127.74, 127.67, 127.16 (CH_2*Ph*OMe, CH_2*Ph*), 114.03, 113.99 (CH_2*Ph*OMe), 86.43, 83.19, 82.09, 77.04, 72.99 (5×*myo*-inositol ring carbons), 76.07, 76.03, 72.95, 72.72, 71.92 (*C*H_2PhOMe and *C*H_2Ph), 55.64 (CH_2PhO*Me*), 31.63 (C-3, deoxy-*myo*-inositol ring carbon); MS: (FAB$^+$) *m*/*z* 703.3, 583.2, 121.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{44}H_{49}O_8$, $[M+H]^+$ 705.3427. Found: 705.3352.

3.8. DL-5-*O*-Benzyl-3-deoxy-2-*O*-methyl-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (20)

Compound **18** (614 mg, 1 mmol) was dissolved in DMF (30 mL) and stirred at room temperature for 10 min. NaH (60 mg, 1.5 mmol) was added and the reaction was stirred for an additional 10 min. Methyl iodide (212 mg, 1.5 mmol) was added and the reaction was stirred for 4 h then quenched with methanol and poured into an ice and water slurry. The product was then extracted with ether and the organic layers were washed with brine and dried ($MgSO_4$). The solvent was evaporated to give the crude product, which was purified by silica gel chromatography (ether–hexane, 1:1 to 2:1) to give compound **20** as a colourless syrup (446 mg, 71%). ^{1}H NMR ($CDCl_3$): δ 7.76–6.81 (m, 17H, $CH_2C_6H_4$OMe, CH_2*Ph*), 4.96, 4.92 (AB, 2H, C$H_2C_6H_4$OMe or CH_2Ph), 4.88, 4.80 (AB, 2H, C$H_2C_6H_4$OMe or CH_2Ph), 4.72, 4.67 (AB, 2H, C$H_2C_6H_4$OMe or CH_2Ph), 4.68, 4.59 (AB, 2H, C$H_2C_6H_4$OMe or CH_2Ph), 3.91 (m, 1H, H-6), 3.82, 3.81, 3.80 (3s, 9H, 3×$CH_2C_6H_4$O*Me*), 3.81–3.78 (m, 1H, H-4), 3.58–3.38 (m, 3H, H-1, H-2, H-5), 3.37 (s, 3H, O*Me*), 2.29 (m, 1H, H-3$_{eq}$), 1.20 (m, 1H, H-3$_{ax}$); ^{13}C NMR ($CDCl_3$): δ 158.82, 158.81, 158.75 (C_q, CH_2*Ph*OMe), 138.85, 130.93, 130.52, 130.35 (C_q, CH_2*Ph*OMe, CH_2*Ph*), 129.49, 129.27, 129.18, 129.08, 128.04, 127.77, 127.65, 127.53, 127.15 (CH_2*Ph*OMe, CH_2*Ph*), 113.47 (CH_2*Ph*OMe), 85.83, 82.24, 81.52, 76.46, 75.02 (5×*myo*-inositol ring carbons), 75.58, 75.51, 72.54, 72.32 (*C*H_2PhOMe and *C*H_2Ph), 57.11 (O*Me*), 55.14, 55.13 ($CH_2C_6H_4$O*Me*), 30.02 (C-3, deoxy-*myo*-inositol ring carbon); MS: (FAB$^+$) *m*/*z* 627.4, 507.3, 121.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{38}H_{45}O_8$, $[M+H]^+$ 629.3114. Found: 629.3059.

3.9. DL-2,5-Di-*O*-benzyl-3-deoxy-*myo*-inositol (21)

Compound **19** (704 mg, 1 mmol) was dissolved in a mixture of trifluoroacetic acid in dichloromethane (1:9, 20 mL) and stirred at room temperature for 30 min. The reaction was quenched by the addition of water and diluted with dichloromethane then separated. The product was extracted with ethyl acetate and the combined organic layers were washed with an aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and the solvent evaporated. The crude residue was purified by silica gel chromatography (ether–acetone, 1:0 to 1:1) to give compound **21** as an amorphous solid (277 mg, 80%). ^{1}H NMR (Me_2SO-d_6): δ 7.41–7.19 (m, 10H, 2CH_2Ph), 4.81–4.75 (br m, 3H, CH_2Ph, O*H*), 4.72 (d, 1H, O*H*), 4.69 (d, 1H, O*H*), 4.62, 4.57 (AB, 2H, CH_2Ph), 3.67–3.62 (br m, 2H, H-2, H-4), 3.58–3.51 (m, 1H, H-6), 3.24–3.27 (m, 1H, H-1), 3.01 (t, 1H, $J_{5,6}$ 8.9 Hz, H-5), 2.03–2.00 (m, 1H, H-3$_{eq}$), 1.29 (m, 1H, H-3$_{ax}$); MS: (FAB$^+$) *m*/*z* 343.2, 91.0; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{20}H_{25}O_5$, $[M+H]^+$ 345.1701. Found: 345.1694.

3.10. DL-5-*O*-Benzyl-3-deoxy-2-*O*-methyl-*myo*-inositol (22)

Compound **22** was prepared in an identical fashion to that described for **21**. Yield (217 mg, 81%). ^{1}H NMR (Me_2SO-d_6): δ 7.42–7.19 (m, 5H, CH_2Ph), 4.79, 4.76 (AB, 2H, CH_2Ph), 4.65 (br s, 1H, O*H*), 4.64 (br s, 1H, O*H*), 4.47 (br s, 1H, O*H*), 3.58–3.38 (m, 3H, H-2, H-4, H-6), 3.30 (s, 3H, OMe), 3.31–3.23 (m, 1H, H-1), 2.99 (t, 1H, $J_{5,6}$ 8.9 Hz, H-5), 2.10–2.00 (m, 1H, H-3$_{eq}$), 1.24 (m, 1H, H-3$_{ax}$); ^{13}C NMR ($CDCl_3$): δ 139.95 (C_q, CH_2Ph), 128.04, 127.68, 127.11 (CH_2Ph), 86.72, 78.40, 74.64, 73.99, 68.03 (5×*myo*-inositol ring carbons), 73.20 (*C*H_2Ph), 57.49 (O*Me*), 33.38 (C-3, deoxy-*myo*-inositol ring carbon).

3.11. DL-2,5-Di-*O*-benzyl-3-deoxy-1,4,6-tris-(dibenzyloxyphosphoryl)-*myo*-inositol (23)

Compound **21** (100 mg, 0.3 mmol) was dissolved in dichloromethane and stirred under nitrogen for 10 min. 1*H*-Tetrazole (126 mg, 1.8 mmol) was added and the

solution was stirred for an additional 30 min then bis(benzyloxy)(diisopropylamino)phosphine (625 mg, 1.8 mmol) was added and the mixture was stirred for an additional 1 h. TLC indicated the conversion of the starting material into a single product. The reaction mixture was cooled to −78 °C and 40% MCPBA (776 mg, 1.8 mmol) was added. After 1 h TLC indicated the disappearance of the intermediate and the appearance of a more polar product. The solution was warmed to room temperature and diluted with dichloromethane then poured into water. The product was extracted with ethyl acetate and the combined organic layers were washed with 10% aqueous sodium sulfite solution, aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and the solvent evaporated. The remaining residue was purified by silica gel chromatography (ether–acetone, 1:0 to 1:1) to give compound **23** as a colourless syrup (206 mg, 61%). ^{1}H NMR ($CDCl_3$): δ 7.46–7.02 (m, 40H, 8×CH_2*Ph*), 5.02–4.66 (m, 16H, 7×C*H*$_2$Ph, H-4, H-6), 4.50, 4.42 (AB, 2H, C*H*$_2$Ph), 4.28 (m, 1H, H-1), 4.13 (br s, 1H, H-2), 3.52 (m, 1H, H-5), 2.53–2.50 (m, 1H, H-3$_{eq}$), 1.46–1.39 (m, 1H, H-3$_{ax}$); ^{13}C NMR ($CDCl_3$): δ 137.80, 135.54 (C_q, CH_2*Ph*), 128.36, 128.34, 128.28, 128.18, 128.16, 127.97, 127.93, 127.83, 127.66, 127.64, 127.52, 127.45, 127.17, 124.24 (CH_2*Ph*), 81.9, 78.17, 77.76, 76.69, 73.05 (5×*myo*-inositol ring carbons), 74.53, 73.05, 72.02, 69.68, 69.63, 69.49, 69.43, 69.36, 69.30, 69.27, 69.21, 69.16 (*C*H$_2$Ph), 31.30 (C-3, deoxy-*myo*-inositol ring carbon); ^{31}P NMR ($CDCl_3$): δ −0.41, −0.74, −0.90 (^{31}P–^{1}H decoupled); MS: (FAB$^+$) *m*/*z* 1125.2, 91.0; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{62}H_{64}O_{14}P_3$, $[M+H]^+$ 1125.3483. Found: 1125.3508.

3.12. DL-5-*O*-Benzyl-3-deoxy-2-*O*-methyl-1,4,6-tris-(dibenzyloxyphosphoryl)-*myo*-inositol (24)

Compound **24** was prepared in an identical fashion to that described for **23** and was isolated as a colourless syrup (119 mg, 57%). ^{1}H NMR ($CDCl_3$): δ 7.38–7.02 (m, 35H, 7×CH_2*Ph*), 5.03–4.72 (m, 15H, 7×C*H*$_2$Ph, H-6), 4.63–4.56 (m, 1H, H-4), 4.25 (m, 1H, H-1), 3.91 (br s, 1H, H-2), 3.50 (m, 1H, H-5), 3.22 (s, 3H, OMe), 2.53 (m, 1H, H-3$_{eq}$), 1.38 (br m, 1H, H-3$_{ax}$); ^{31}P NMR ($CDCl_3$): δ 2.12, 1.70, 1.35 (^{31}P–^{1}H decoupled).

3.13. DL-3-Deoxy-*myo*-inositol 1,4,6-trisphosphate (6)

Compound **23** (112 mg, 0.1 mmol) was dissolved in the minimum amount of water and methanol (MeOH/H_2O, 9:1) and hydrogenolysed for 16 h at 20 psi, in the presence of twice the amount of 20% $Pd(OH)_2$. The catalyst was filtered off and the filtrate was concentrated to give crude trisphosphate **6**. The residue was then purified by ion exchange chromatography using a gradient of 1 M TEAB (0–100%). The title compound **6** eluted between 55% and 75% TEAB and obtained as the triethylammonium salt in quantitative yield. ^{1}H NMR (CD_3OD): δ 4.47–4.34 (m, 2H, H-4, H-6), 4.20 (br s, 1H, H-2), 4.02 (m, 1H, H-1), 3.64–3.54 (m, 1H, H-5), 2.31 (m, 1H, H-3$_{eq}$), 1.57 (m, 1H, H-3$_{ax}$); ^{31}P NMR (CD_3OD): δ 2.84 (d, 1P, $J_{P,H}$ 8.7 Hz), 2.09 (d, 1P, $J_{P,H}$ 7.9 Hz), 1.76 (d, 1P, $J_{P,H}$ 8.7 Hz); (HRMS, FAB$^-$) *m*/*z* Calcd for $C_6H_{14}O_{14}P_3$, $[M-H]^-$ 402.9596. Found: 402.9594.

3.14. DL-3-Deoxy-2-*O*-methyl-*myo*-inositol 1,4,6-trisphosphate (7)

Compound **7** was prepared in an identical fashion to that described for **6** and was isolated as the triethylammonium salt in quantitative yield. ^{1}H NMR (CD_3OD): δ 4.05–3.87 (m, 3H, H-1, H-4, H-6), 3.67 (br s, 1H, H-2), 3.38 (m, 1H, H-5), 3.23 (s, 3H, OCH_3), 2.36 (m, 1H, H-3$_{eq}$), 1.32 (m, 1H, H-3$_{ax}$); ^{31}P NMR (CD_3OD): δ 2.16 (d, 1P, $J_{P,H}$ 8.3 Hz), 1.45 (d, 1P, $J_{P,H}$ 9.1 Hz), 1.10 (d, 1P, $J_{P,H}$ 7.9 Hz).

3.15. DL-1,4,6-Tri-*O*-allyl-2,3-*O*-isopropylidene-*myo*-inositol (26) and DL-1,4,5-tri-*O*-allyl-2,3-*O*-isopropylidene-*myo*-inositol (25)

A mixture of compound **12** (22 g, 100 mmol), acetonitrile (1000 mL), dibutyltin oxide (87.5 g, 350 mmol), tetrabutylammonium iodide (129.15 g, 350 mmol) and allyl bromide (34.6 mL, 400 mmol) was heated under reflux in a Soxhlet apparatus for 48 h. The reaction mixture was cooled, the solvent was evaporated, and the residue was partitioned between Et_2O and water. The product was extracted with more Et_2O from the aqueous layer and the combined Et_2O solutions were stirred with an aqueous solution of $NaHCO_3$ for 1 h. The solution was filtered through a pad of Celite, washed with Et_2O and dried ($MgSO_4$). TLC (Et_2O–pentane, 1:1) showed two main products (R_f 0.42) and (R_f 0.24), for the 1,4,6-tri-*O*-allyl derivative **22** and 1,4,5-tri-*O*-allyl derivative **23**, respectively. The two compounds were separated by flash chromatography (Et_2O–pentane, 1:1) to give **26** (8.12 g, 24%) and **25** (7.30 g, 21%), which were isolated as syrups. **26**: ^{1}H NMR ($CDCl_3$): δ 5.89–6.02 (m, 3H, 3×OCH_2CH=CH_2), 5.17–5.34 (m, 6H, 3×OCH_2-CH=C*H*$_2$), 4.18–4.40 (m, 7H, H-2 and 3×OCH_2CH=CH_2), 4.07 (dd, 1H, $J_{2,3}$ 5.7 Hz, $J_{3,4}$ 6.6 Hz, H-3), 3.52–3.68 (m, 3H, H-1, H-4 and H-6), 3.40 (ddd, 1H, $J_{5,OH}$ 2.0, $J_{4,5}$ 9.7 Hz, D_2O ex, dd, $J_{5,6}$ 8.1 Hz, H-5), 2.76 (d, 1H, exchangeable, HO-5), 1.37, 1.54 (2s, 6H, CMe_2); ^{13}C NMR ($CDCl_3$): δ 134.88, 134.78 (OCH_2*C*H=CH_2), 117.56, 117.25, 117.06 (OCH_2CH=*C*H$_2$), 109.87 (C_q, *C*Me$_2$), 81.40, 79.92, 78.93, 77.03, 74.66, 73.16 (6×*myo*-inositol ring carbons), 73.50, 72.30, 72.27 (O*C*H$_2$CH=CH_2), 27.73, 25.79 ($C(CH_3)_2$). Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.6; H, 8.28.

25: ^{1}H NMR ($CDCl_3$): δ 5.89–6.03 (m, 3H, 3×OCH_2CH=CH_2), 5.16–5.35 (m, 6H, 3×OCH_2CH=

CH_2), 4.42 (dd, 1H, $J_{2,3}$ 4.2 Hz, H-2), 4.20–4.34 (m, 6H, 3×OCH_2CH=CH_2), 4.08 (dd, 1H, $J_{3,4}$ 5.9 Hz, H-3), 3.92 (dd, 1H, $J_{1,6}$ 9.5 Hz, H-6), 3.53 (dd, 1H, $J_{4,5}$ 9.0 Hz, H-4), 3.50 (dd, 1H, $J_{1,2}$ 6.8 Hz, H-1), 3.14 (dd, 1H, $J_{5,6}$ 9.2 Hz, H-5), 2.79 (s, 1H, exchangeable, HO-6), 1.37, 1.53 (2s, 6H, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 134.86, 134.64, 132.61 (OCH$_2$*C*H=CH$_2$), 117.82, 116.96, 116.75 (OCH$_2$CH=*C*H$_2$), 109.72 (*C*$_q$, *C*Me$_2$), 81.91, 81.18, 79.01, 72.59, 71.18 (6×*myo*-inositol ring carbons), 73.71, 71.71, 71.63 (O*C*H$_2$CH=CH$_2$), 27.75, 25.72 (C*Me*$_2$); Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.5; H, 8.17.

3.16. DL-1,4,6-Tri-*O*-allyl-5-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol (27)

A mixture of compound **26** (4.35 g, 12.8 mmol) and NaH (0.96 g, 40 mmol) was stirred in dry DMF (50 mL). Benzyl bromide (2.38 mL, 20 mmol) was added and the solution was stirred for 2 h at room temperature. TLC (Et_2O–pentane, 1:2) showed a new product. The remaining NaH was destroyed with MeOH (5 mL) and the solution was evaporated in vacuo to give a syrup. The organic residue was partitioned between water and Et_2O and washed with brine and water. The organic solution was dried ($MgSO_4$) and the solvent was evaporated to give a syrup. The product was purified by flash chromatography (Et_2O–pentane, 1:2) to give the title compound **27** as a syrup (4.49 g, 82%). ^{1}H NMR ($CDCl_3$): δ 7.26–7.39 (m, 5H, CH$_2$*Ph*), 5.89–6.03 (m, 3H, 3×OCH$_2$C*H*=CH$_2$), 5.15–5.34 (m, 6H, 3×OCH$_2$CH=CH_2), 4.78 (s, 2H, CH_2Ph), 4.24–4.38 (m, 7H, H-2 and 3×OCH_2CH=CH$_2$), 4.07 (dd, 1H, $J_{2,3}$ 5.7 Hz, $J_{3,4}$ 6.6 Hz, H-3), 3.74 (dd, 1H, $J_{4,5}$ 8.8 Hz, H-4), 3.62 (dd, 1H, $J_{1,6}$ 7.0 Hz, H-6), 3.57 (dd, 1H, $J_{1,2}$ 3.85 Hz, H-1), 3.31 (dd, 1H, $J_{5,6}$ 9.3 Hz, H-5), 1.37, 1.53 (2s, 6H, CMe$_2$); ^{13}C NMR ($CDCl_3$): δ 138.50 (*C*$_q$, CH$_2$*Ph*), 135.16, 134.95 (OCH$_2$*C*H=CH$_2$), 128.33, 128.18, 127.65 (CH$_2$*Ph*), 117.50, 116.82, 116.73 (OCH$_2$CH=*C*H$_2$), 109.83 (*C*$_q$, *C*Me$_2$), 82.22, 82.11, 80.33, 79.04, 76.85, 74.67 (6×*myo*-inositol ring carbons), 75.43, 73.92, 72.98, 72.57 (O*C*H$_2$CH=CH$_2$ and *C*H$_2$Ph), 27.78, 25.85 (C(*C*H$_3$)$_2$); Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.9; H, 7.96.

3.17. DL-1,4,6-Tri-*O*-allyl-5-*O*-benzyl-*myo*-inositol (28)

Compound **27** (4.35 g, 10.1 mmol), was dissolved in a mixture of MeOH and 1 M aq HCl (100 mL, 9:1) and the solution was heated under reflux for 1 h. After this time, TLC (Et_2O) showed a single product and the solvents were evaporated and the remaining syrup was partitioned between CH_2Cl_2 and water then washed with an aqueous solution of $NaHCO_3$, and water. The organic solution was dried ($MgSO_4$) and evaporated to give a syrup **28** (3.85 g, 98%), which did not require purification by chromatography. ^{1}H NMR ($CDCl_3$): δ 7.26–7.36 (m, 5H, CH$_2$*Ph*), 5.88–6.02 (m, 3H, 3×OCH$_2$C*H*=CH$_2$), 5.13–5.34 (m, 6H, OCH$_2$CH=CH_2), 4.77, 4.86 (AB, 2H, J_{AB} 10.6 Hz, CH_2Ph), 4.17–4.40 (m, 7H, H-2 and 3×OCH_2CH=CH$_2$), 3.72 (dd, 1H, $J_{1,6}$ 9.5 Hz, H-6), 3.65 (dd, 1H, $J_{4,5}$ 9.5 Hz, H-4), 3.45 (dd, 1H, $J_{2,3}$ 2.75 Hz, $J_{3,4}$ 9.7 Hz, H-3), 3.34 (dd, 1H, $J_{5,6}$ 9.0 Hz, H-5), 3.29 (dd, 1H, $J_{1,2}$ 2.75 Hz, H-1), 2.68 (br s, 2H, exchangeable HO-2 and HO-3); Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.3; H, 7.72.

3.18. DL-1,4,6-Tri-*O*-allyl-3,5-di-*O*-benzyl-*myo*-inositol (29)

A mixture of compound **28** (3.70 g, 9.48 mmol), tetrabutylammonium bromide (3.36 g, 10.40 mmol), dibutyltin oxide (2.60 g, 10.44 mmol) and benzyl bromide (1.78 mL, 15 mmol) in acetonitrile (200 mL) was heated under reflux in a Soxhlet apparatus containing 4 Å sieves for 24 h. The reaction mixture was cooled, the solvent was evaporated and the remaining syrup was partitioned between water and Et_2O. The organic layer was separated and stirred with an aqueous solution of $NaHCO_3$ for 1 h. The remaining solid was filtered off over a bed of Celite and washed with Et_2O and the organic solution was dried ($MgSO_4$). The title compound was purified by flash chromatography (pentane–EtOAc, 4:1 to 1:3), to give the product (3.64 g, 80%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 7.24–7.37 (m, 10H, 2×CH$_2$*Ph*), 5.85–6.04 (m, 3H, 3×OCH$_2$C*H*=CH$_2$), 5.12–5.32 (m, 6H, 3×OCH$_2$CH=CH_2), 4.82 (s, 2H, CH_2Ph), 4.74, 4.71 (AB, 2H, J_{AB} 11.7 Hz, CH_2Ph), 4.15–4.37 (m, 7H, H-2 and 3×OCH_2CH=CH$_2$), 3.79 (dd, 1H, $J_{1,6}$ 9.5 Hz, H-6), 3.75 (dd, 1H, $J_{4,5}$ 9.5 Hz, H-4), 3.33 (dd, 1H, $J_{5,6}$ 9.0 Hz, H-5), 3.31 (dd, 1H, $J_{2,3}$ 2.7 Hz, $J_{3,4}$ 9.5 Hz, H-3), 3.21 (dd, 1H, $J_{1,2}$ 2.7 Hz, H-1), 2.42 (s, 1H, exchangeable HO-2); ^{13}C NMR ($CDCl_3$): δ 138.72, 138.06 (*C*$_q$, CH$_2$*Ph*), 135.30, 134.70 (OCH$_2$*C*H=CH$_2$), 128.43, 128.31, 128.07, 127.58 (CH$_2$*Ph*), 117.25, 116.56 (OCH$_2$CH=*C*H$_2$), 83.05, 80.73, 79.61, 79.35, 67.87 (6×*myo*-inositol ring carbons), 75.95, 74.52, 72.78, 71.86 (O*C*H$_2$CH=CH$_2$ and *C*H$_2$Ph); Anal. Calcd for $C_{29}H_{36}O_6$: C, 72.48; H, 7.55. Found: C, 72.6; H, 7.61.

3.19. DL-1,4,6-Tri-*O*-allyl-3,5-di-*O*-benzyl-2-*O*-methyl-*myo*-inositol (30)

A mixture of compound **29** (2.14 g, 4.45 mmol) and NaH (406 mg, 10.15 mmol) was stirred in dry DMF (20 mL). Methyl iodide (1.0 mL, 16 mmol) was added dropwise and the solution was stirred for a further 2 h. TLC (pentane–EtOAc, 3:1) showed a new product. The excess NaH was destroyed with MeOH and the solvents were evaporated in vacuo to give a syrup. The crude product was partitioned between water and Et_2O and

the organic layer was dried ($MgSO_4$). The solvent was evaporated to give the title compound as a syrup that was purified by flash chromatography (3:1, pentane–EtOAc, 2.0 g, 91%). ^{1}H NMR ($CDCl_3$): δ 7.24–7.39 (m, 10H, 2×CH_2*Ph*), 5.84–6.05 (m, 3H, 3×OCH_2CH=CH_2), 5.12–5.31 (m, 6H, 3×OCH_2CH=CH_2), 4.82 (s, 2H, CH_2Ph), 4.68, 4.74 (AB, 2H, J_{AB} 11.7 Hz, CH_2Ph), 3.69–3.81 (m, 3H, H-4, H-6, H-2), 3.59 (d, 3H, $J_{2,Me}$ 0.55 Hz, CH_3), 3.31 (dd, 1H, $J_{5,6}$ 9.2 Hz, H-5), 3.28 (dd, 1H, $J_{2,3}$ 1.5 Hz, $J_{3,4}$ 9.9 Hz, H-3), 3.15 (dd, 1H, $J_{1,2}$ 1.5 Hz, $J_{1,6}$ 9.9 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 138.84, 138.38 (C_q, CH_2*Ph*), 135.37, 134.88 (OCH_2*C*H=CH_2), 128.31, 128.23, 127.97, 127.60, 127.45 (CH_2*Ph*), 116.72, 116.36 (OCH_2CH=*C*H_2), 83.52, 81.17, 80.55, 80.21, 77.63 (6×*myo*-inositol ring carbons), 75.86, 74.45, 72.98, 71.83 (O*C*H_2CH=CH_2 and *C*H_2Ph), 60.98 (O*C*H_3); Anal. Calcd for $C_{30}H_{38}O_6$: C, 72.85; H, 7.74. Found: C, 73.0; H, 7.86.

3.20. DL-1,5-Di-*O*-benzyl-2-*O*-methyl-*myo*-inositol (31)

Compound **30** (2.0 g, 4.04 mmol), and freshly sublimed potassium *tert*-butoxide (4.43 g, 36.36 mmol) in dry Me_2SO (30 mL), was kept at 60 °C for 6 h. The organic mixture was poured into a solution of brine (200 mL) and the product was extracted from the mixture with Et_2O and purified by flash chromatography using EtOAc–pentane (1:3). The solvent was evaporated and the product was heated in a mixture of 1 M aqueous HCl–MeOH (100 mL, 1:9) for 30 min. The solution was cooled and powdered sodium carbonate was added and the solvents were evaporated. The remaining residue was partitioned between CH_2Cl_2 and water and the organic solvent was evaporated to give the crude product. The pure title compound was obtained after flash chromatography (chloroform–EtOAc 1:1; 1.03 g, 68%); mp 123–125 and 134–135 °C, from EtOAc–hexane. ^{1}H NMR ($CDCl_3$): δ 7.25–7.37 (m, 10H, 2×CH_2*Ph*), 4.79, 4.93 (AB, 2H, J_{AB} 11.7 Hz, CH_2Ph), 4.63, 4.74 (AB, 2H, J_{AB} 11.35 Hz, CH_2Ph), 4.01 (dd, 1H, $J_{1,6}$ 9.5 Hz, H-6), 4.01 (dd, 1H, $J_{2,3}$ 2.2 Hz, H-2), 3.74 (dd, 1H, $J_{4,5}$ 9.3 Hz, H-4), 3.60 (s, 3H, O*C*H_3), 3.35 (dd, 1H, $J_{3,4}$ 9.7 Hz, H-3), 3.25 (dd, 1H, $J_{1,2}$ 2.9 Hz, H-1), 3.19 (dd, 1H, $J_{5,6}$ 9.2 Hz, H-5), 2.62 (s, 3H, exchangeable, HO-1, HO-4, HO-6); ^{13}C NMR ($CDCl_3$): δ 138.87, 137.86 (C_q, CH_2*Ph*), 128.59, 128.48, 128.00, 127.93, 127.84, 127.73 (CH_2*Ph*), 82.71, 80.89, 78.54, 73.34, 72.61, 72.39 (6×*myo*-inositol ring carbons), 74.57, 72.77 (CH_2Ph), 61.34 (O*C*H_3); Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.3; H, 6.95.

3.21. DL-3,5-Di-*O*-benzyl-2-*O*-methyl-1,4,6-tris-(dibenzyloxyphosphoryl)-*myo*-inositol (32)

A mixture of bis(benzyloxy)diisopropylaminophosphine (0.69 g, 2 mmol) and 1*H*-tetrazole (0.42 g, 6 mmol) in dry CH_2Cl_2 (10 mL) was stirred for 15 min at room temperature. Compound **31** (187 mg, 0.5 mmol) was added and the reaction was stirred for a further 30 min. The solution was diluted with EtOAc (50 mL) and washed with 10% aqueous sodium metabisulfite solution, brine and water (50 mL of each). The organic layer was dried ($MgSO_4$) and the product was purified by flash chromatography (chloroform–acetone, 5:1) to give the trisphosphate (544 mg, 96%) as a solid; mp 100–102 °C, from EtOAc–hexane. ^{1}H NMR ($CDCl_3$): δ 7.02–7.43 (40H, 8×CH_2*Ph*), 4.18–5.03 (20H, 8×CH_2Ph, H-2, H-1, H-4 and H-6), 3.54 (dd, 1H, $J_{5,6}$ 9.3 Hz, H-5), 3.51 (s, 3H, O*C*H_3), 3.39 (dd, 1H, $J_{2,3}$ 2.2 Hz, $J_{3,4}$ 9.7 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 138.06, 137.31, 136.05, 135.94, 135.68, 135.61 (C_q, CH_2*Ph*), 128.61, 128.56, 128.30, 128.07, 128.07, 127.78, 127.62, 127.52, 127.13 (CH_2*Ph*), 79.58, 78.35, 78.27, 77.26, 76.38, 76.12 (6×*myo*-inositol ring carbons), 73.11, 72.25, 69.83, 69.75, 69.62, 69.54, 69.28, 69.28, 69.20 (*C*H_2Ph), 61.38 (O*C*H_3); ^{31}P NMR ($CDCl_3$): δ −1.20, −0.80, −0.50 (^{31}P–^{1}H decoupled); Anal. Calcd for $C_{63}H_{65}O_{15}P_3$: C, 65.51; H, 5.67. Found: C, 65.2; H, 5.62.

3.22. DL-2-*O*-Methyl-*myo*-inositol-1,4,6-trisphosphate (8)

Compound **32** (200 mg, 0.173 mmol) was dissolved in a mixed solvent of MeOH and water (50 mL, 4:1) in a hydrogenator bomb. Palladium on charcoal (Aldrich, 10%, 200 mg) was added and the mixture was shaken in the hydrogenator under hydrogen (30 psi) for 20 h. The catalyst was removed by passing the solution through a PTFE syringe filter and the solvents were evaporated in vacuo. The remaining glassy compound was purified by ion exchange chromatography on Q-Sepharose Fast Flow resin using a gradient of 1 M triethylammonium hydrogen carbonate (0–100%). The compound eluted between 50% and 70% buffer and these fractions were pooled and the solvent was evaporated in vacuo to give the title compound **8**. ^{1}H NMR (D_2O): δ 4.08 (ddd, 1H, $J_{H,P}$ 9.5 Hz, $J_{1,6}$ 9.2 Hz, H-6), 3.90 (ddd, 1H, $J_{H,P}$ 8.2 Hz, $J_{4,5}$ 9.15 Hz, H-4), 3.88 (ddd, 1H, $J_{1,2}$ 2.75 Hz, $J_{H,P}$ 9.8 Hz, H-1), 3.71 (dd, 1H, $J_{2,3}$ 2.4 Hz, H-2), 3.51 (dd, 1H, $J_{3,4}$ 9.8 Hz, H-3), 3.43 (s, 3H, O*C*H_3), 3.36 (dd, 1H, $J_{5,6}$ 9.2 Hz, H-5). ^{31}P NMR (D_2O): δ 1.70 (1P, d, *J* 8.1 Hz), 0.80 (1P, d, *J* 8.6 Hz), 0.25 (1P, d, *J* 9.7 Hz). MS: (HRMS, FAB$^-$) *m*/*z* Calcd for $C_7H_{16}O_{15}P_3$, $[M-H]^-$ 432.9702. Found: 432.9695.

3.23. DL-5-*O*-Benzyl-3-*O*-(2-benzyloxy-ethyl)-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (33)

A mixture of compound **16** (630 mg, 1 mmol), Bu_2SnO (373 mg, 1.5 mmol), Bu_4NBr (477 mg, 1.5 mmol) and benzyl-2-bromoethyl ether (322 mg, 1.5 mmol) in toluene (40 mL) was refluxed for 16 h with a Soxhlet apparatus containing 4 Å molecular sieves. The solution was cooled and washed with an aqueous solution of $NaHCO_3$, water

and brine, then dried ($MgSO_4$) and concentrated in vacuo. The crude syrup was purified by silica gel chromatography (ether–hexane, 1:1 to 2:1) to give compound **33** (550 mg, 72%) as a colourless syrup. ^{1}H NMR ($CDCl_3$): δ 7.37–6.82 (m, 22H, 2×CH_2Ph and 3×$CH_2C_6H_4$OMe), 4.88, 4.86 (AB, 2H, $CH_2C_6H_4$OMe or CH_2Ph), 4.83, 4.58 (m, 8H, 4×CH_2Ph and $CH_2C_6H_4$OMe), 4.23 (br dd, 1H, $J_{2,3}$ 2.7 Hz, H-2), 3.96 (dd, 1H, $J_{4,5}$ 9.7 Hz, H-4), 3.89 (dd, 1H, $J_{1,6}$ 9.7 Hz, H-6), 3.81, 3.76, 3.75 (3s, 9H, 3×$CH_2C_6H_4OMe$), 3.67–3.57 (m, 4H, OCH_2CH_2OBn), 3.41 (dd, 1H, $J_{5,6}$ 9.4 Hz, H-5), 3.38 (dd, 1H, $J_{3,4}$ 9.4 Hz, H-3), 3.21 (dd, 1H, $J_{1,2}$ 2.3 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 159.08, 158.90 (C_q, CH_2PhOMe) 138.71 (C_q, CH_2Ph), 130.87, 130.82, 130.01 (C_q, CH_2PhOMe, CH_2Ph), 129.53, 129.29, 128.31, 128.17, 127.63, 127.53, 127.29 (CH_2PhOMe, CH_2Ph), 113.71, 113.61 (CH_2PhOMe), 83.09, 80.93, 80.80, 80.53, 79.69, 67.31 (6×*myo*-inositol ring carbons), 75.80, 75.64, 75.53, 72.40, 70.71 (CH_2Ph, OCH_2CH_2OBn), 55.27 (CH_2PhOMe); MS: (FAB$^+$) m/z 763.5, 643.4, 121.1; (HRMS, FAB) m/z Calcd for $C_{46}H_{53}O_{10}$, $[M+H]^+$ 765.3638. Found: 765.3610.

3.24. DL-5-*O*-Benzyl-3-*O*-(3-benzyloxy-propyl)-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (34)

Compound **34** was prepared in an identical manner to that described for compound **33** using benzyl-3-bromopropyl ether as alkylating agent and the product was isolated as a colourless syrup (490 mg, 63%). ^{1}H NMR ($CDCl_3$): δ 7.53–6.79 (m, 22H, 2×CH_2Ph and 3×$CH_2C_6H_4$OMe), 4.91–4.45 (m, 10H, 2×CH_2Ph and 3×$CH_2C_6H_4$OMe), 4.24 (br dd, 1H, $J_{2,3}$ 2.7 Hz, H-2), 3.95 (dd, 1H, $J_{4,5}$ 9.7 Hz, H-4), 3.89 (dd, 1H, $J_{1,6}$ 9.7 Hz, H-6), 3.81, 3.80, 3.77 (3s, 9H, 3×$CH_2C_6H_4OMe$), 3.82–3.56 (m, 4H, $OCH_2CH_2CH_2$OBn), 3.41 (dd, 1H, $J_{5,6}$ 9.3 Hz, H-5), 3.37 (dd, 1H, $J_{3,4}$ 9.3 Hz, H-3), 3.21 (dd, 1H, $J_{1,2}$ 2.4 Hz, H-1), 1.96 (m, 2H, $OCH_2CH_2CH_2$OBn); ^{13}C NMR ($CDCl_3$): δ 159.41, 159.23, 159.20 (C_q, CH_2PhOMe), 139.02, 138.54, 131.15, 130.55, 130.31 (C_q, CH_2PhOMe, CH_2Ph), 129.85, 129.73, 129.62, 129.45, 128.54, 128.50, 127.99, 127.87, 127.78, 127.75, 127.63 (CH_2PhOMe, CH_2Ph), 114.05, 113.94 (CH_2PhOMe), 83.41, 81.24, 81.08, 80.94, 79.93, 67.53 (6×*myo*-inositol ring carbons), 76.12, 75.92, 75.80, 73.27, 72.68, 68.05 (CH_2Ph, CH_2PhOMe, $OCH_2CH_2CH_2OBn$), 55.61 ($CH_2C_6H_4OMe$), 30.86 ($OCH_2CH_2CH_2OBn$); MS: (FAB$^+$) m/z 777.5, 657.5, 121.1; (HRMS, FAB$^+$) m/z Calcd for $C_{47}H_{55}O_{10}$, $[M+H]^+$ 779.3795. Found: 779.3699.

3.25. DL-5-*O*-Benzyl-3-*O*-(4-benzyloxy-butyl)-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (35)

Compound **35** was prepared in an identical manner to that described for compound **33** using benzyl 4-bromobutyl ether as alkylating agent and the product was isolated as a colourless syrup (641 mg, 81%). ^{1}H NMR ($CDCl_3$): δ 7.38–6.80 (m, 22H, 2×CH_2Ph and 3×$CH_2C_6H_4$OMe), 4.97–4.61 (m, 10H, 2×CH_2Ph and 3×$CH_2C_6H_4$OMe), 4.19 (br s, 1H, H-2), 4.00–3.92 (m, 2H, H-4, H-6), 3.82–3.72 (m, 13H, 3×$CH_2C_6H_4OMe$, $OCH_2CH_2CH_2CH_2$OBn), 3.49–3.33 (m, 3H, H-1, H-3, H-5), 2.20–2.11 (m, 4H, $OCH_2CH_2CH_2CH_2$OBn); ^{13}C NMR ($CDCl_3$): δ 159.06, 158.88 (C_q, CH_2PhOMe), 138.61, 137.82 130.74, 130.71 (C_q, CH_2PhOMe, CH_2Ph), 129.88, 129.53, 129.50, 129.31, 128.28, 128.19, 127.65, 127.52, 127.45, 127.33 (CH_2PhOMe, CH_2Ph), 113.69, 113.60 (CH_2PhOMe), 83.12, 80.88, 79.78, 79.47, 67.52 (6×*myo*-inositol ring carbons), 75.82, 75.61, 72.68, 72.35 (CH_2Ph, CH_2PhOMe, $OCH_2CH_2CH_2CH_2OBn$), 55.25 ($CH_2C_6H_4OMe$), 31.01 ($OCH_2CH_2CH_2CH_2OBn$); MS: (FAB$^+$) m/z 791.6, 121.1; (HRMS, FAB$^+$) m/z Calcd for $C_{48}H_{57}O_{10}$, $[M+H]^+$ 793.3951. Found: 793.3943.

3.26. DL-2,5-Di-*O*-benzyl-3-*O*-(2-benzyloxy-ethyl)-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (36)

Compound **33** (382 mg, 0.5 mmol) was dissolved in DMF (15 mL) and stirred at room temperature for 10 min. NaH (40 mg, 1 mmol) was added and the solution was stirred for an additional 10 min. Benzyl bromide (0.12 mL, 1 mmol) was added and the solution was stirred for 4 h at room temperature. TLC revealed the disappearance of the starting material and the presence of a less polar product. The reaction was quenched by the addition of methanol and the solution was poured into an ice and water slurry then extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent was evaporated. The crude residue was purified by silica gel chromatography (ether–hexane, 1:1 to 2:1) to give compound **36** (380 mg, 89%). ^{1}H NMR ($CDCl_3$): δ 7.43–6.77 (m, 27H, 3×CH_2Ph and 3×$CH_2C_6H_4$OMe), 4.92–4.71 (m, 8H, 4×CH_2Ph and $CH_2C_6H_4$OMe), 4.55, 4.52 (AB, 2H, CH_2Ph or $CH_2C_6H_4$OMe), 4.52, 4.49 (AB, 2H, CH_2Ph or $CH_2C_6H_4$OMe), 4.07 (t, 1H, $J_{2,3}$ 2.3 Hz, H-2), 4.03 (dd, 1H, $J_{1,6}$ 9.7 Hz, H-6), 3.99 (t, 1H, $J_{4,5}$ 9.4 Hz, H-4), 3.81, 3.79, 3.78 (3s, 9H, 3×$CH_2C_6H_4OMe$), 3.83–3.65 (m, 4H, OCH_2CH_2OBn), 3.42 (t, 1H, $J_{5,6}$ 9.4 Hz, H-5), 3.31 (dd, 1H, $J_{3,4}$ 9.7 Hz, H-3), 3.27 (dd, 1H, $J_{1,2}$ 2.3 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 158.86, 158.83 (C_q, CH_2PhOMe), 139.02, 138.89, 138.10, 131.18, 130.98, 130.51 (C_q, CH_2PhOMe, CH_2Ph), 129.61, 129.56, 128.93, 128.23, 128.16, 127.93, 127.64, 127.53, 127.44, 127.24, 127.07 (CH_2PhOMe, CH_2Ph), 113.61, 113.59 (CH_2PhOMe), 83.63, 82.15, 81.40, 81.36, 80.73, 74.49 (6×*myo*-inositol ring carbons), 75.77, 75.47, 75.34, 74.11, 73.25, 72.30, 70.50, 70.26 (CH_2Ph, CH_2PhOMe, OCH_2CH_2OBn), 55.28 ($CH_2C_6H_4OMe$); MS: (FAB$^+$) m/z 853.6, 733.5, 121.1; (HRMS, FAB$^+$) m/z Calcd for $C_{53}H_{59}O_{10}$, $[M+H]^+$ 855.4108. Found: 855.4069.

3.27. DL-2,5-Di-*O*-benzyl-3-*O*-(3-benzyloxy-propyl)-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (37)

Compound **37** was prepared in an identical manner to that described for **36** and was isolated as a colourless syrup (360 mg, 83%). ^{1}H NMR ($CDCl_3$): δ 7.44–6.79 (m, 27H, 3×CH_2*Ph* and 3×$CH_2C_6H_4$OMe), 4.89–4.43 (m, 12H, 3×C*H*$_2$Ph and 3×C*H*$_2C_6H_4$OMe), 4.07–3.96 (m, 3H, H-2, H-4, H-6), 3.82, 3.80, 3.78 (3s, 9H, 3×$CH_2C_6H_4O$*Me*), 3.72–3.57 (m, 4H, OC*H*$_2CH_2$C*H*$_2$OBn), 3.43 (t, 1H, $J_{5,6}$ 9.4 Hz, H-5), 3.35 (dd, 1H, $J_{3,4}$ 9.7 Hz, H-3), 3.19 (dd, 1H, $J_{1,2}$ 2.3 Hz, $J_{1,6}$ 9.7 Hz, H-1), 1.94 (m, 2H, OCH_2C*H*$_2CH_2$OBn); ^{13}C NMR ($CDCl_3$): δ 158.90, 158.85 (C_q, CH_2*Ph*OMe), 138.93, 138.26, 130.99, 130.92, 130.45 (C_q, CH_2*Ph*OMe, CH_2*Ph*), 129.59, 129.44, 129.05, 128.94, 128.38, 128.20, 128.14, 127.95, 127.63, 127.52, 127.50, 127.42, 127.39, 127.24, 127.12, 126.80 (CH_2*Ph*OMe, CH_2*Ph*), 113.63, 113.58 (CH_2*Ph*OMe), 83.62, 81.56, 81.38, 81.23, 80.76, 74.36 (6×*myo*-inositol ring carbons), 75.77, 75.47, 75.33, 74.17, 72.92, 72.41, 67.75, 67.31 (*C*H_2Ph, O*C*H_2CH_2*C*H_2OBn), 55.26 (CH_2PhO*Me*), 30.74 (OCH_2*C*H_2CH_2OBn); MS: (FAB$^+$) *m*/*z* 867.6, 747.5, 121.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{54}H_{61}O_{10}$, [M+H]$^+$ 869.4264. Found: 869.4209.

3.28. DL-2,5-Di-*O*-benzyl-3-*O*-(4-benzyloxy-butyl)-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (38)

Compound **38** was prepared in an identical manner to that described for compound **36** and was isolated to give the title compound as a colourless syrup (410 mg, 93%). ^{1}H NMR ($CDCl_3$): δ 7.43–6.78 (m, 27H, 3×CH_2*Ph* and 3×$CH_2C_6H_4$OMe), 4.89–4.47 (m, 12H, 3×C*H*$_2$Ph and 3×C*H*$_2C_6H_4$OMe), 4.09–3.97 (m, 3H, H-2, H-4, H-6), 3.83–3.77 (m, 13H, 3×$CH_2C_6H_4O$*Me*, OC*H*$_2CH_2CH_2$-C*H*$_2$OBn), 3.64–3.31 (m, 3H, H-1, H-3, H-5), 2.23–2.18 and 1.73–1.71 (2m, 4H, OCH_2C*H*$_2$C*H*$_2CH_2$OBn); ^{13}C NMR ($CDCl_3$): δ 158.86 (C_q, CH_2*Ph*OMe), 138.84, 138.29, 130.92, 130.38 (C_q, CH_2*Ph*OMe, CH_2*Ph*), 129.61, 129.00, 128.21, 128.18, 127.98, 127.62, 127.52, 127.42, 127.36, 127.27, 127.16 (CH_2*Ph*OMe, CH_2*Ph*), 113.64, 113.59 (CH_2*Ph*OMe), 83.71, 81.58, 80.95, 80.69, 74.43 (6×*myo*-inositol ring carbons), 75.82, 75.51, 74.07, 72.74, 72.43 (*C*H_2PhOMe, *C*H_2Ph, O*C*H_2CH_2-CH_2*C*H_2OBn), 53.29 (CH_2PhO*Me*), 30.09 (OCH_2*C*H_2-*C*H_2CH_2OBn); MS: (FAB$^+$) *m*/*z* 881.6, 121.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{55}H_{63}O_{10}$, 883.4421. Found: 883.4472.

3.29. DL-2,5-Di-*O*-benzyl-3-*O*-(2-benzyloxy-ethyl)-*myo*-inositol (39)

Compound **36** (425 mg, 0.5 mmol) was dissolved in a 10% solution of TFA in dichloromethane (20 mL) and stirred at room temperature for 30 min. The reaction was quenched by the addition of water and the resulting solution was diluted with dichloromethane and separated. The product was extracted with ethyl acetate and the combined organic layers were washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and the solvent was evaporated. The crude residue was purified by silica gel chromatography (ether–acetone, 1:0 to 1:1) to give the title compound **39** (180 mg, 71%). ^{1}H NMR ($CDCl_3$): δ 7.49–7.02 (m, 15H, 3×CH_2*Ph*), 4.79, 4.76 (AB, 2H, C*H*$_2$Ph), 4.76, 4.72 (AB, 2H, C*H*$_2$Ph), 4.51, 4.47 (AB, 2H, C*H*$_2$Ph), 3.91 (br d, 1H, $J_{2,3}$ 1.9 Hz, H-2), 3.84–3.50 (m, 6H, OC*H*$_2$C*H*$_2$OBn, H-4, H-6), 3.30 (dd, 1H, $J_{1,2}$ 1.9 Hz, H-1), 3.18 (dd, 1H, $J_{3,4}$ 9.7 Hz, H-3), 3.04 (t, 1H, $J_{5,6}$ 8.9 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 139.53, 139.48, 138.25 (C_q, CH_2*Ph*), 127.93, 127.65, 127.61, 127.22, 127.08, 126.74, 126.66 (CH_2*Ph*), 83.97, 81.00, 78.18, 72.60, 72.07, 71.75 (6×*myo*-inositol ring carbons), 73.73, 73.65, 69.46, 69.27 (*C*H_2Ph, O*C*H_2*C*H_2OBn); MS: (FAB$^+$) *m*/*z* 495.4, 91.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{29}H_{35}O_7$, [M+H]$^+$ 495.2382. Found: 495.2392.

3.30. DL-2,5-Di-*O*-benzyl-3-*O*-(3-benzyloxy-propyl)-*myo*-inositol (40)

Compound **40** was prepared in an identical manner to that described for compound **39** and was isolated as a colourless syrup (176 mg, 67%). ^{1}H NMR (Me_2SO-d_6): δ 7.58–7.20 (m, 15H, 3×CH_2*Ph*), 4.86–4.63 (m, 7H, 2×C*H*$_2$Ph, 3×O*H*), 4.41, 4.38 (AB, 2H, C*H*$_2$Ph), 3.86 (br d, 1H, $J_{2,3}$ 2.3 Hz, H-2), 3.73–3.49 (m, 6H, OC*H*$_2CH_2$C*H*$_2$OBn, H-4, H-6), 3.33–3.28 (m, 1H, H-1), 3.09 (dd, 1H, $J_{3,4}$ 9.7 Hz, H-3), 3.03 (t, 1H, $J_{5,6}$ 9.4 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 139.54, 139.42, 138.39 (C_q, CH_2*Ph*), 127.96, 127.82, 127.69, 127.59, 127.22, 127.12, 127.06, 126.73, 126.66 (CH_2*Ph*), 83.97, 80.54, 78.06, 72.59, 72.01, 71.84 (6×*myo*-inositol ring carbons), 73.77, 73.64, 71.77, 66.83, 66.72 (*C*H_2Ph, O*C*H_2CH_2*C*H_2OBn), 30.04 (OCH_2*C*H_2CH_2OBn); MS: (FAB$^+$) *m*/*z* 509.4, 91.1; (HRMS, FAB$^+$) *m*/*z* Calcd for $C_{30}H_{37}O_7$, [M+H]$^+$ 509.2539. Found: 509.2542.

3.31. DL-2,5-Di-*O*-benzyl-3-*O*-(4-benzyloxy-butyl)-*myo*-inositol (41)

Compound **41** was prepared in an identical manner to that described for compound **39** and was isolated as a colourless syrup (201 mg, 75%). ^{1}H NMR (Me_2SO-d_6): δ 7.42–6.86 (m, 15H, 3×CH_2*Ph*), 5.04–4.85 (m, 3H, 3×O*H*), 4.81–4.63 (m, 6H, 3×CH_2*Ph*), 3.94 (br s, 1H, H-2), 3.76 (m, 1H, H-6), 3.60 (m, 1H, H-4), 3.37–3.25 (m, 6H, OC*H*$_2CH_2CH_2$C*H*$_2$OBn, H-1, H-3), 3.05 (m, 1H, H-5), 2.49–2.47 and 1.61–1.52 (2m, 4H, OCH_2C*H*$_2$C*H*$_2CH_2$OBn); ^{13}C NMR ($CDCl_3$): δ 139.54, 139.41, 138.86 (C_q, CH_2*Ph*), 127.87, 127.73, 127.62, 127.26, 127.20, 126.98, 126.79, 126.70 (CH_2*Ph*), 84.05, 80.19, 78.18, 72.61, 72.18, 71.92 (6×*myo*-inositol ring carbons), 73.79, 71.29 (*C*H_2Ph,

$OCH_2CH_2CH_2CH_2OBn$), 31.48 ($OCH_2CH_2CH_2$-CH_2OBn); MS: (FAB^+) m/z 523.4, 91.1; (HRMS, FAB^+) m/z Calcd for $C_{31}H_{39}O_7$, $[M+H]^+$ 523.2695. Found: 523.2698.

3.32. DL-2,5-Di-*O*-benzyl-3-*O*-(2-benzyloxy-ethyl)-1,4,6-tris(dibenzyloxyphosphoryl)-*myo*-inositol (42)

Compound **39** (50 mg, 0.1 mmol) was dissolved in dichloromethane (3 mL) and stirred under nitrogen for 10 min. 1*H*-Tetrazole (42 mg, 0.6 mmol) was added and the solution was stirred for an additional 30 min then bis(benzyloxy)(diisopropylamino)phosphine (208 mg, 0.6 mmol) was added and the mixture was stirred for an additional 1 h. TLC showed the conversion of the starting material into a less polar compound. The reaction mixture was cooled to −78 °C then 40% MCPBA (258 mg, 0.6 mmol) was added. After 1 h, TLC indicated the disappearance of the trisphosphite intermediate and the appearance of a more polar product. The solution was warmed to room temperature then diluted with dichloromethane and poured into water. The product was extracted with ethyl acetate and the combined organic layers were washed with solutions of 10% sodium sulfite, $NaHCO_3$ and brine, the organic layer was dried ($MgSO_4$) and the solvent was evaporated. The crude residue was purified by silica gel chromatography (ether–acetone, 1:0 to 1:1) to give the title compound **42** as a colourless syrup (90 mg, 71%). ^1H NMR ($CDCl_3$): δ 7.43–6.96 (m, 45H, 9×CH_2Ph), 5.10–4.68 (m, 18H, 8×CH_2Ph, H-4, H-6), 4.48 (br s, 1H, H-2), 4.43, 4.39 (AB, 2H, CH_2Ph), 4.28–4.23 (m, 1H, H-1), 3.65–3.45 (m, 5H, OCH_2CH_2OBn, H-5), 3.40 (m, 2H, H-1, H-3); ^{13}C NMR ($CDCl_3$): δ 138.19, 137.91, 137.73, 135.93, 135.83, 135.75, 135.42 (C_q, CH_2Ph), 128.36, 128.34, 128.18, 128.16, 127.96, 127.84, 127.62, 127.59, 127.48, 127.33, 127.30, 127.12, 126.98 (CH_2Ph), 79.49, 79.28, 79.00, 77.55, 76.21, 74.91 (6×*myo*-inositol ring carbons), 75.04, 73.50, 73.11, 70.04, 69.76, 69.70, 69.48, 69.33, 69.27, 69.04, 68.99 (CH_2Ph, OCH_2CH_2OBn); ^{31}P NMR ($CDCl_3$): δ −0.36 (sextet, 1P, $J_{P,H}$ 8.1 Hz), −0.79 to −1.10 (m, 2P); MS: (FAB^+) m/z 1275.7, $[M+H]^+$ 91.1; MS: (FAB^-) m/z 1428.3, $[M+NBA]^-$ 121.1.

3.33. DL-2,5-Di-*O*-benzyl-3-*O*-(3-benzyloxy-propyl)-1,4,6-tris(dibenzyloxyphosphoryl)-*myo*-inositol (43)

Compound **43** was prepared in an identical manner to that described for compound **42** and was isolated as a colourless syrup (73 mg, 57%). ^1H NMR ($CDCl_3$): δ 7.42–6.99 (m, 45H, 9×CH_2Ph), 5.08–4.64 (m, 18H, 8×CH_2Ph, H-4, H-6), 4.40–4.34 (m, 3H, CH_2Ph, H-2), 4.23 (m, 1H, H-1), 3.57–3.37 (m, 5H, $OCH_2CH_2CH_2$OBn, H-5), 3.25 (m, 1H, H-3), 1.80 (m, 2H, $OCH_2CH_2CH_2$OBn); ^{13}C NMR ($CDCl_3$): δ 138.25, 138.06, 137.78, 135.84, 135.76, 135.70, 135.56 (C_q, CH_2Ph), 128.40, 128.37, 128.21, 128.18, 128.12, 128.04, 127.99, 127.95, 127.90, 127.84, 127.61, 127.58, 127.54, 127.44, 127.34, 127.31, 127.27, 126.99 (CH_2Ph), 79.51, 78.93, 77.35, 76.34, 74.84 (6×*myo*-inositol ring carbons), 75.14, 73.57, 72.83, 69.81, 69.75, 69.58, 69.52, 69.35, 69.29, 69.24, 69.09, 69.04, 67.99, 66.94 (CH_2Ph, $OCH_2CH_2CH_2$OBn), 30.16 (OCH_2CH_2-CH_2OBn); ^{31}P NMR ($CDCl_3$): δ −0.39, −0.89, −0.94 (3s, 3P) (^{31}P–^1H decoupled); MS: (FAB^-) m/z 1441.3, 277.1; (FAB^+) m/z 1289.8, 91.1; (HRMS, FAB^+) m/z Calcd for $C_{72}H_{76}O_{16}P_3$, $[M+H]^+$ 1289.4346. Found: 1289.4343.

3.34. DL-2,5-Di-*O*-benzyl-3-*O*-(4-benzyloxy-butyl)-1,4,6-tris(dibenzyloxyphosphoryl)-*myo*-inositol (44)

Compound **44** was prepared in an identical manner to that described for compound **42** and was isolated as a colourless syrup (88 mg, 68%). ^1H NMR ($CDCl_3$): δ 7.83–6.97 (m, 45H, 9×CH_2Ph), 5.09–4.42 (m, 25H, 9×CH_2Ph, H-2, H-4, H-6, $OCH_2CH_2CH_2CH_2$OBn), 4.21 (m, 1H, H-1), 3.56 (m, 1H, H-5), 3.41 (m, 1H, H-3), 1.61 (br s, 4H, $OCH_2CH_2CH_2CH_2$OBn); ^{31}P NMR ($CDCl_3$): δ −0.40, −0.69, −0.84 (3s, 3P) (^{31}P–^1H decoupled); MS: (FAB^+) m/z 91.1; (FAB^-) m/z 277.1.

3.35. DL-3-*O*-(2-Hydroxy-ethyl)-*myo*-inositol 1,4,6-trisphosphate (9)

Compound **42** (128 mg, 0.1 mmol) was dissolved in the minimum amount of MeOH–H_2O (9:1) and was hydrogenated for 24 h under 20 psi hydrogen, in the presence of excess 20% $Pd(OH)_2$ on carbon. The catalyst was filtered off and the residue was concentrated to give crude tetrakisphosphate then purified by ion-exchange chromatography using a gradient of 1 M TEAB (0–100%), which eluted at 45–60% TEAB to give compound **9** as its triethylammonium salt in quantitative yield. ^1H NMR (CD_3OD): δ 4.46–4.42 (m, 2H, H-4, H-6), 4.37 (br s, 1H, H-2), 4.01 (m, 1H, H-1), 3.76–3.57 (m, 5H, OCH_2CH_2OH, H-5), 3.33–3.29 (m, 1H, H-3); ^{31}P NMR (CD_3OD): δ 3.04 (d, $J_{P,H}$ 9.5 Hz, 1P), 2.55 (d, $J_{P,H}$ 7.9 Hz, 1P), 2.02 (d, $J_{P,H}$ 11.0 Hz, 1P); (HRMS, FAB^-) m/z Calcd for $C_8H_{18}O_{16}P_3$, $[M-H]^-$ 462.9807. Found: 462.9801.

3.36. DL-3-*O*-(3-Hydroxy-propyl)-*myo*-inositol 1,4,6-trisphosphate (10)

Compound **10** was prepared in an identical manner to that described for **9** and was isolated as the triethylammonium salt in quantitative yield. ^1H NMR (CD_3OD): δ 4.46–4.36 (m, 3H, H-2, H-4, H-6), 3.99 (m, 1H, H-1), 3.85–3.59 (m, 6H, $OCH_2CH_2CH_2OH$, H-3, H-5), 1.78 (m, 2H, $OCH_2CH_2CH_2OH$); ^{31}P NMR (CD_3OD) δ 2.94

(d, 1P, $J_{P,H}$ 7.9 Hz), 2.83 (d, 1P, $J_{P,H}$ 8.7 Hz), 2.13 (d, 1P, $J_{P,H}$ 9.5 Hz); (HRMS, FAB$^-$) m/z Calcd for $C_9H_{20}O_{16}P_3$, $[M-H]^-$ 476.9964. Found: 476.9961.

3.37. DL-3-*O*-(4-Hydroxy-butyl)-*myo*-inositol 1,4,6-trisphosphate (11)

Compound **11** was prepared in an identical manner to that described for **9** and was isolated as the triethylammonium salt in quantitative yield. ^{1}H NMR (CD_3OD): δ 4.45–4.31 (m, 2H, H-4, H-6), 4.18 (br s, 1H, H-2), 4.08–4.01 (m, 1H, H-1), 3.57–3.50 (m, 2H, H-3, H-5), 3.36–3.29 (m, 4H, $OCH_2CH_2CH_2CH_2OH$), 1.92–1.90 (m, 4H, $OCH_2CH_2CH_2CH_2OH$); ^{31}P NMR (CD_3OD): δ 3.90, 3.43, 2.05 (3s, 3P) (^{31}P–^{1}H decoupled); (HRMS, FAB$^-$) m/z Calcd for $C_{10}H_{22}O_{16}P_3$, $[M-H]^-$ 491.0107. Found: 491.0126.

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