Synthesis of the Enantiomers of 6-Deoxy-*myo*-Inositol 1,3,4,5-Tetrakisphosphate, Structural Analogues of *myo*-Inositol 1,3,4,5-Tetrakisphosphate

Graeme Horne and Barry V. L. Potter*[a]

Abstract: D-*myo*-Inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P_4] is produced rapidly from the established second messenger D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] in stimulated cells. Despite extensive investigations, in particular concerning its potential role in mediating cellular Ca^{2+} influx, no exact cellular function has been described for this inositol phosphate; however, binding sites have been identified in a number of tissues and it has been shown to act synergistically with Ins(1,4,5)P_3. To assist in the elucidation of the mechanism of action and structural requirements within the Ins(1,3,4,5)P_4 moiety that are necessary for recognition and activation of the receptor, structural analogues of this tetrakisphosphate are required. Routes for the synthesis of racemic 6-deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate [6-deoxy-DL-Ins(1,3,4,5)P_4] and the chiral antipodes D- and L-6-deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate are described here. The racemic tetrakisphosphate was synthesised from DL-1,2-*O*-isopropylidene-*myo*-inositol in eight steps. Deoxygenation at C-6 was achieved following the Barton – McCombie procedure. Both chiral tetrakisphosphates were synthesised through resolution of racemic *cis*-diol 6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol with the chiral auxiliary (*S*)-(+)-*O*-acetylmandelic acid. Absolute configuration was confirmed by synthesis of the known D-6-deoxy-*myo*-inositol. Both D-6-deoxy-Ins(1,3,4,5)P_4 and its enantiomer will be useful tools to unravel the enigmatic role of Ins(1,3,4,5)P_4 in the polyphosphoinositide pathway of signal transduction.

Keywords: signal transduction · chiral resolution · cyclitols · *myo*-inositol polyphosphates

Introduction

The involvement of *myo*-inositol polyphosphates in signal transduction through the phosphoinositide pathway has stimulated the need for the synthesis of molecules that will interfere with, or modulate, the process of cellular signalling.[1] The process of signal transduction via the second messenger D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3, **1**] (Figure 1) starts when a cell surface receptor activates the enzyme phospholipase C-β via a G-protein.[2] This enzyme hydrolyses the membrane phospholipid, phosphatidylinositol 4,5-bisphosphate to produce diacylglycerol and Ins(1,4,5)P_3 as signalling molecules. Ins(1,4,5)P_3 interacts specifically at an N-terminal binding site of a tetrameric Ins(1,4,5)P_3 receptor-operated Ca^{2+} channel in order to release Ca^{2+} from non-mitochondrial stores.[3] After this Ca^{2+} release the signal must be removed and this is accomplished by one or more metabolic pathways. An Ins(1,4,5)P_3 5-phosphatase removes the 5-phosphate group from Ins(1,4,5)P_3 to give D-*myo*-inositol 1,4-bisphosphate [Ins(1,4)P_2, **2**] which is inactive for Ca^{2+} release.[4] Ins(1,4,5)P_3 can also be phosphorylated by a cytosolic 3-kinase to give D-*myo*-inositol 1,3,4,5-tetrakisphos-

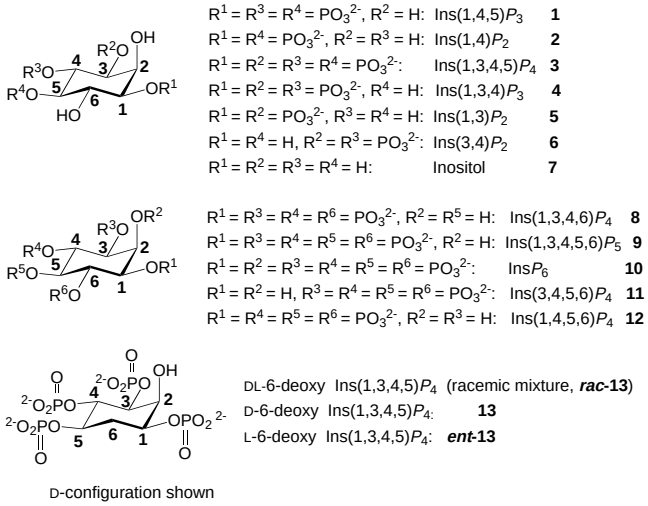

Figure 1. *myo*-Inositol phosphates.

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phate[5] [Ins(1,3,4,5)P_4, **3**] which is subsequently degraded to D-*myo*-inositol 1,3,4-trisphosphate [Ins(1,3,4)P_3, **4**]. Ins(1,3,4)P_3 is subsequently metabolised by one of two possible pathways. The products D-*myo*-inositol 1,3-bisphosphate [Ins(1,3)P_2, **5**] and/or D-*myo*-inositol 3,4-bisphosphate [Ins(3,4)P_2, **6**] are subsequently converted into monophosphates which are ultimately dephosphorylated to inositol **7**. It has now emerged that Ins(1,3,4)P_3 can be phosphorylated by a 6-kinase to D-*myo*-inositol 1,3,4,6-tetrakisphosphate [Ins(1,3,4,6)P_4, **8**][6] which can be further phosphorylated to D-*myo*-inositol 1,3,4,5,6-pentakisphosphate [Ins(1,3,4,5,6)P_5, **9**]. The latter higher polyphosphate is metabolised to three compounds, phytic acid [InsP_6, **10**], D-*myo*-inositol 3,4,5,6-tetrakisphosphate [Ins(3,4,5,6)P_4, **11**] and D-*myo*-inositol 1,4,5,6-tetrakisphosphate [Ins(1,4,5,6)P_4, **12**]. Such higher polyphosphates have long been known to provide phosphate storage and to modulate the oxygen affinity of haemoglobin in plants and avian erythrocytes, respectively.[7, 8] Recently, it was reported that these higher inositol polyphosphates have a direct role in the regulation of gene expression.[9, 10] Inositol phosphate signalling has also been implicated in the induction of genes whose proteins catabolise arginine with the effect being mediated through Ins(1,4,5,6)P_4. Ins(3,4,5,6)P_4 has been shown to inhibit Ca^{2+} dependent Cl^- currents in T84 colonic epithelial cells[11] as well as inhibiting receptor mediated Ca^{2+} dependent Cl^- currents in CFPAC-1 cells.[12] This latter effect identifies proteins that bind this particular polyphosphate as potentially important therapeutic targets for pathological conditions such as cystic fibrosis.

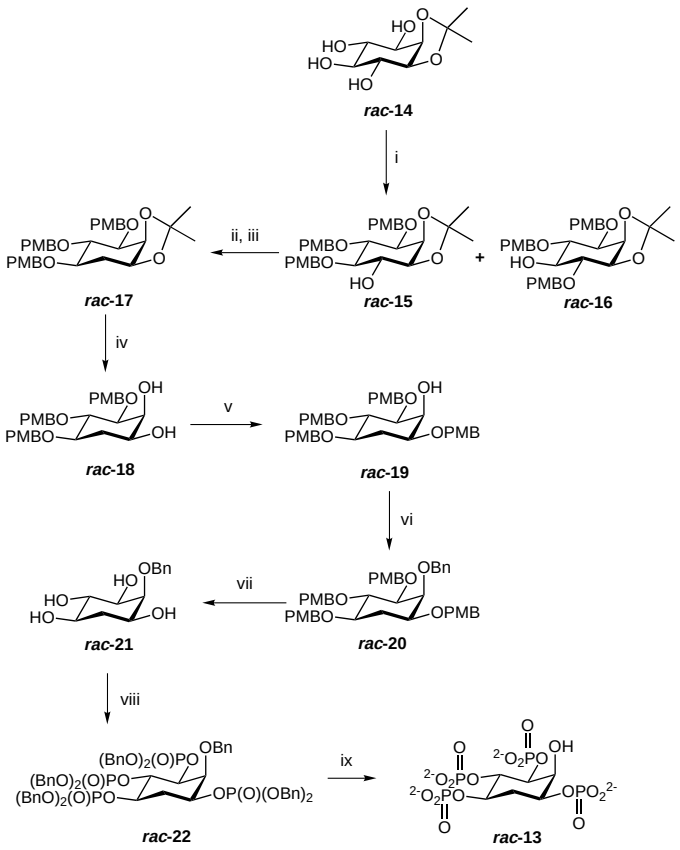
Release of Ca^{2+} from intracellular stores is one effect of the phosphoinositide pathway, but subsequent Ca^{2+} entry through plasma membrane channels is also crucial. Experiments have demonstrated a potential role for Ins(1,3,4,5)P_4 acting synergistically with Ins(1,4,5)P_3[13–16] and Ins(1,3,4,5)P_4 has been shown to independently mobilise intracellular Ca^{2+} through the Ins(1,4,5)P_3 receptor.[17]

The exact reasons for the rapid production of Ins(1,3,4,5)P_4 following receptor stimulation are currently unclear; however, essentially there are three possibilities: 1) the phosphorylation of Ins(1,4,5)P_3 to Ins(1,3,4,5)P_4 is considered to be an off signal terminating the release of Ca^{2+} by Ins(1,4,5)P_3; 2) Ins(1,3,4,5)P_4 is a metabolic intermediate with no other function; 3) Ins(1,3,4,5)P_4 has a second messenger function itself, initiated through binding to its own specific intracellular receptor. In particular, a role mediating Ca^{2+} entry through plasma membrane channels has been proposed. Despite proposals that option 2) may be correct[18] the function of Ins(1,3,4,5)P_4 as another potential second messenger involved in Ca^{2+} release has not been unambiguously resolved.[19] However, we have recently suggested a role for Ins(1,3,4,5)P_4 in facilitating store-operated Ca^{2+} influx in cells by inhibition of Ins(1,4,5)P_3-5-phosphatase[20] and this may ultimately prove to be the real function of Ins(1,3,4,5)P_4, with Ins(1,3,4,5)P_4 acting as a long-lived bi-modal "memory" molecule. An Ins(1,3,4,5)P_4-sensitive Ca^{2+}-permeable channel has been characterised from endothelial cells[21] and Ins(1,3,4,5)P_4 binding proteins have been identified from pig[22] and rat[23, 24] cerebellum and porcine platelets.[25] The latter example has been characterised and identified as a putative Ins(1,3,4,5)P_4 receptor and is a member of a family of GTPase activating proteins (GAP) designated as GAP^{IP4BP}. The highly specific nature of Ins(1,3,4,5)P_4 binding to GAP^{IP4BP} has been demonstrated[26] and it is apparent that phosphorylation of the 1, 3 and 5 positions is essential for high affinity binding and that there is some tolerance of phosphorylation of the 6-hydroxyl group, but none of phosphorylation of the 2-hydroxyl group.

Recently, it was reported that the interaction of Ins(1,3,4,5)P_4 with the pleckstrin homology (PH) domain of Bruton's tyrosine kinase (Btk) may be involved in B-cell activation and development;[27] mutations in the Btk PH domain causing human X-linked agammaglobulinaemia (XLA) and murine X-linked immunodeficiency (Xid) are associated with dramatically reduced Ins(1,3,4,5)P_4-binding activity. We also reported an X-ray crystal structure of synthetic Ins(1,3,4,5)P_4[28] bound to the PH domain of Btk[29] and determination of the phosphate pK_a values of Ins(1,3,4,5)P_4.[30] In order to investigate the possibility of a second messenger function for Ins(1,3,4,5)P_4 the synthesis of structural analogues of this molecule is of continuing interest. We have recently reported the synthesis of D-2-deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate from D-glucose.[31] To further enhance and elucidate these structure-activity studies on the Ins(1,3,4,5)P_4 specific GAP^{IP4BP} binding protein,[32–34] and for other applications[20] we required a synthesis of both enantiomers of 6-deoxy-Ins(1,3,4,5)P_4. Additionally, such structurally modified Ins(1,3,4,5)P_4 analogues are of considerable use as head-group surrogates for inositol phospholipids which themselves have been shown to have signalling roles.[35] We now report here the synthesis of 6-deoxy-Ins(1,3,4,5)P_4 in racemic and chiral form by resolution of partially blocked *myo*-inositol derivatives using the chiral auxiliary (*S*)-(+)-*O*-acetylmandelic acid.

Results and Discussion

Alkylation of tetraol ***rac*-14**,[36] obtained from *myo*-inositol, (Scheme 1) following the stannylene acetal procedure using *p*-methoxybenzyl chloride (PMBCl) in the presence of dibutyl tin oxide (Bu_2SnO) and tetrabutylammonium iodide (Bu_4NI), yielded two major products ***rac*-15** ($t_R = 0.19$) and ***rac*-16** ($t_R = 0.28$) [ether/hexane 2:1]. This selectivity can be explained by considering the stannylene acetals formed and the reactivity of the individual oxygen atoms involved. These acetals exist as dimers in which the tin atoms are at the centre of a trigonal bipyramid with the butyl groups occupying the equatorial positions. The more electronegative of the two oxygen atoms is co-ordinated with only one tin atom whereas the less electronegative oxygen atom is co-ordinated to two tin atoms. The regioselectivity observed in such reactions is a consequence of a cascade of effects beginning with the selection of a particular pair of hydroxyls for stannylene formation followed by orientation of the more electronegative oxygen in an apical position which is intrinsically the more reactive. The observed regioselectivity reported here can be rationalised by considering the stannylene acetals that are most likely to be formed and the reactivity of the individual oxygen atoms in each



Scheme 1. i) *p*-methoxybenzyl chloride, Bu_4NI, Bu_2SnO, toluene, 120 °C, 16 h (***rac*-15**, 32 %; ***rac*-16**, 41 %); ii) NaH, CS_2, THF, 1 h; then MeI, 1 h; then iii) Bu_3SnH, AIBN, toluene, 120 °C, 1 h (83 %); iv) 80 % AcOH, 100 °C, 1 h (77 %); v) PMB-Cl, Bu_4NI, Bu_2SnO, toluene, 120 °C, 16 h (76 %); vi) BnBr, NaH, DMF, room temperature, 4 h (84 %); vii) 10 % TFA (CH_2Cl_2), room temperature, 30 min (71 %); viii) dibenzyl diisopropylphosphoroamidate, 1*H*-tetrazole, CH_2Cl_2, room temperature, 1 h; then *m*-CPBA, −78 °C, 1 h (79 %); ix) Pd/C (10 %), MeOH/H_2O 9:1, H_2, 80 psi, 16 h, and purification by Q-Sepharose Fast Flow ion-exchange chromatography (87 %). All compounds are racemic.

cyclic system. It can be presumed that initially two acetals are formed (1,6 and 4,5) and in these the oxygen atoms at positions 1 and 4 will occupy the more reactive apical position and hence be preferentially alkylated. The stannylene acetal formed between the remaining *trans* diol (hydroxyl groups on positions 5 and 6) does not result in the preferential alkylation of one specific hydroxyl. However, the small difference noticed in the alkylation (32 % for alkylation of position 5 and 41 % for position 6) can be explained through the assumed higher electronegativity of the hydroxyl group at position 6. Differentiation between the two monols ***rac*-15** and ***rac*-16** was effected by NMR methods.

The next step of the synthesis required deoxygenation at position 6. Deoxygenation of sugar hydroxyls is readily performed by metal hydride reduction of halides, sulphonates and epoxides as well as radical deoxygenation of thiocarbonyl derivatives (Barton–McCombie reaction).[37]-[41] Of these methods available, radical deoxygenation was chosen because of its suitability for the deoxygenation of secondary alcohols and its compatibility with benzyl ethers and acetals/ketals. Treatment of ***rac*-15** with carbon disulfide (CS_2) in the presence of sodium hydride (NaH) in anhydrous THF followed by addition of methyl iodide (MeI) and work-up yielded the corresponding *S*-methyl xanthate as a non-isolated intermediate. The crude residue was then dissolved in anhydrous toluene with tributyl tin hydride (Bu_3SnH) and 2,2′-azobis(2-methylpropionitrile) (AIBN) being added. Reflux followed by work-up and purification yielded ***rac*-17**. Removal of the *cis*-isopropylidene group was accomplished by careful treatment of ***rac*-17** with 80 % aqueous acetic acid (AcOH) with the resulting *cis*-diol being selectively alkylated with PMBCl in the presence of Bu_2SnO and Bu_4NI in refluxing toluene, yielding monol ***rac*-19**. Benzylation of ***rac*-19** with benzyl bromide (BnBr) in DMF at ambient temperature with NaH as base yielded fully protected racemic 6-deoxy-*myo*-inositol derivative ***rac*-20**. The *p*-methoxybenzyl protecting groups were then removed selectively using 10 % trifluoroacetic acid (TFA) in dichloromethane[42] leaving tetraol ***rac*-21**. Initial attempts at the deprotection of the *p*-methoxybenzyl ethers employed 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant[43] but problems associated with isolation of the resulting tetraol from the aqueous work-up negated the use of this procedure.

For the introduction of phosphate groups into tetraol ***rac*-21** the phosphitylating reagent bis(benzyloxy) (diisopropylamino)phosphine[44, 45] was chosen. Treatment of tetraol ***rac*-21** with this phosphitylating reagent and 1*H*-tetrazole followed by oxidation of the tetrakisphosphite intermediate afforded fully protected DL-2-*O*-benzyl-1,3,4,5-tetrakis-*O*-[bis(benzyloxy)phospho]-6-deoxy-*myo*-inositol (***rac*-22**). All the benzyl protecting groups were removed from the fully blocked compound in one step by hydrogenation. The crude residue was purified by ion-exchange chromatography on Q-Sepharose Fast Flow and, after pooling and evaporation of fractions was accurately quantified by total phosphate assay.[46] The final racemic DL-6-deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate (***rac*-13**) eluted at 65–85 % 1M TEAB and was isolated as its triethylammonium salt. Removal of all phosphate benzyl groups was confirmed by ^{1}H-coupled ^{31}P NMR spectroscopy; the observed sextet for each dibenzylated phosphate changed to a doublet for each deprotected phosphate.

In order to synthesise the two diastereisomers of 6-deoxy-1,3,4,5-tetrakisphosphate-*myo*-inositol **13** and ***ent*-13** it was necessary to resolve a suitable racemic precursor. This is best achieved through the selective introduction of a chiral auxiliary with subsequent separation of the two resulting diastereoisomers. Racemic *cis*-diol ***rac*-18** provided an excellent precursor for resolution since equatorial hydroxyl groups can be acylated selectively. (*S*)-(+)-*O*-Acetylmandelic acid (**23**) was chosen for resolution of *cis*-diol ***rac*-18**; unlike the enantiomers of commonly used camphanic acid chloride, both *R* and *S* isomers are cheaply available. Additionally, (*S*)-(+)-*O*-acetylmandelic acid has previously been used successfully in this laboratory for the resolution of several blocked *myo*-inositol derivatives.[45, 47, 48]

Coupling of DL-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-18**) with (*S*)-(+)-*O*-acetylmandelic acid (**23**) at low temperature yielded the two diastereoisomers **24** and **25** (Scheme 2), (structures determined after the determination of the chirality of derived pentaols **26** and ***ent*-26**, respectively,

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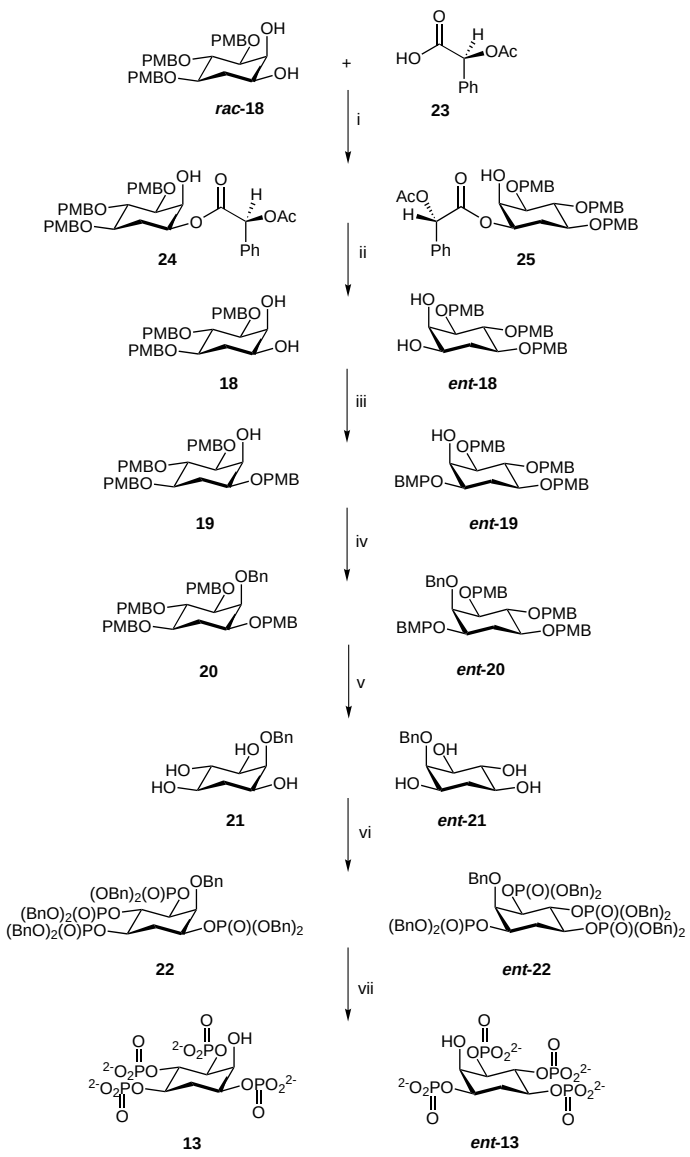
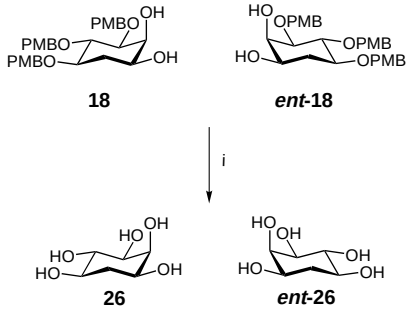


Scheme 2. i) DMAP, DCC, CH_2Cl_2, $-20\,^{\circ}C$ (38% for **24**, 40% for **25**); ii) NaOH, MeOH, reflux, 30 min (87% for **18**, 81% for ***ent*-18**); iii) PMB-Cl, Bu_2SnO, Bu_4NI, toluene, 120 °C, 16 h (72% for **19**, 77% for ***ent*-19**); iv) BnBr, NaH, DMF, room temperature, 4 h (67% for **20**, 81% for ***ent*-20**); v) 10% TFA (CH_2Cl_2), room temperature, 30 min (83% for **21**, 77% for ***ent*-21**); vi) dibenzyl diisopropylphosphoroamidate, 1*H*-tetrazole, CH_2Cl_2, room temperature, 1 h; then *m*-CPBA, $-78\,^{\circ}C$, 1 h (74% for **22**, 68% for ***ent*-22**); vii) Pd/C (10%), MeOH/H_2O 9:1, H_2, 80 psi, 16 h, and purification by Q-Sepharose Fast Flow ion-exchange chromatography (85% for **13** and 61% for ***ent*-13**). DMAP: 4-dimethylaminopyridine, DCC: dicyclohexylcarbodiimide.

the absolute configuration of each isomer. These values of $\delta = 4.10$ (**24**) and 4.37 (**25**) are in good agreement with H-2 chemical shifts for similar compounds previously synthesised and resolved using (*S*)-(+)-*O*-acetylmandelic acid as the chiral auxiliary.[47, 48] In all cases an H-2 chemical shift of approximately $\delta = 4.15$ has been observed for the D-isomer with an H-2 chemical shift value of approximately $\delta = 4.40$ being detected for the corresponding L-isomer. Similarly, the TLC mobilities of the diastereoisomers resulting from the use of (*S*)-(+)-*O*-acetylmandelic acid as chiral auxiliary also provide for a tentative determination of the absolute configuration of each isomer. In all cases the t_R value of the D-isomer has been lower than that of the L-isomer.

Deacylation of isomers **24** and **25** with methanolic sodium hydroxide solution yielded enantiomers **18** and ***ent*-18**, respectively. The equatorial hydroxyl group of each enantiomeric *cis*-diol was selectively alkylated with PMBCl yielding the respective monols **19** and ***ent*-19** which were subsequently benzylated, followed by the selective removal of the *p*-methoxybenzyl protecting groups affording tetraols **21** and ***ent*-21**. These chiral tetraols were then phosphitylated, oxidised, and the products deprotected and purified by ion-exchange chromatography followed by accurate quantification by total phosphate assay[46] yielding D- and L-6-deoxy-Ins(1,3,4,5)P_4 **13** and ***ent*-13**, respectively, as their triethylammonium salts.

To establish the absolute configuration of antipodes **18** and ***ent*-18** we used D-6-deoxy-*myo*-inositol[49] as a reference. This compound was readily accessible from **18**, with the L-isomer being easily obtained from ***ent*-18**. Thus, removal of the *p*-methoxybenzyl groups of both enantiomers by hydrogenation provided pentaols **26** and ***ent*-26**, respectively (Scheme 3). The



Scheme 3. i) Pd/C (10%), MeOH/H_2O 9:1, H_2, 80 psi, 16 h (quantitative yields for both **26** and ***ent*-26**).

see below). Selectivity for the equatorial hydroxyl group was achieved by keeping the initial temperature at $-20\,^{\circ}C$. No acylation of the axial hydroxyl group was detected (by ^1H NMR) with both **24** and **25** being separated by flash chromatography. The purity of the samples was gauged by ^1H NMR analysis which revealed two singlets (corresponding to $CH_3CO_2CH(Ph)CO_2$) at $\delta = 5.98$ for isomer **24** and 5.99 for isomer **25**. No impurities were detected in either sample. The distinctive chemical shift value for the H-2 proton for each diastereoisomer was also indicative of the high purity of each diastereoisomer and provided for a tentative determination of specific rotation of **26** was found to be $[\alpha]_D = +6.3$ and agreed well with the literature value of +7. The specific rotation of ***ent*-26** was found as expected to be equal and opposite to the literature value for **26**. 6-Deoxy-Ins(1,4,5)P_3 has been prepared by several routes[50, 51] and some of its biological properties studied.[50–52] Similarly, 3-deoxy[53] and 3-position modified analogues[54, 55] of Ins(1,4,5)P_3 have also been synthesised and some of their biological properties studied.[53, 54] Whilst this work was in progress a route to D-6-deoxy-Ins(1,3,4,5)P_4 (**13**) only, starting from D-galactose was reported.[56]

We anticipate that the present compounds will find considerable application in studies on the enigmatic nature of Ins(1,3,4,5)P_4 activity. Unlike the enantiomers of Ins(1,4,5)P_3, because of the regioisomeric arrangement of phosphate groups (Figure 2), L-6-deoxy-Ins(1,3,4,5)P_4 could also bind to Ins-

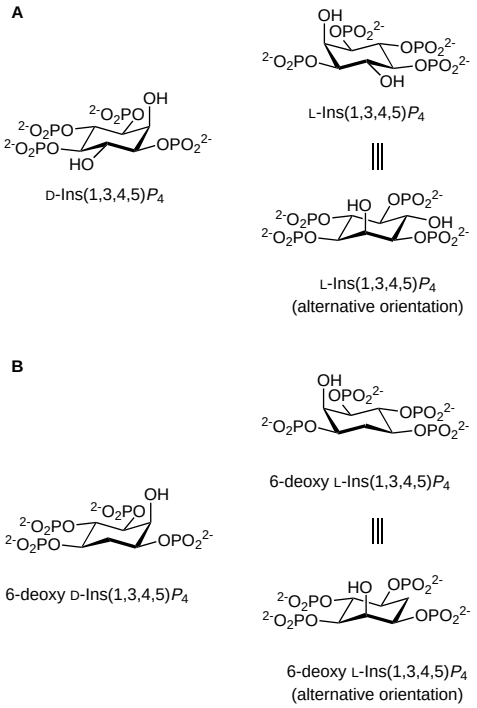


Figure 2. Regioisomeric arrangement of phosphate groups in Ins(1,3,4,5)P_4 and 6-deoxy-Ins(1,3,4,5)P_4. **A**: Superimposition of phosphate groups in both D- and L-Ins(1,3,4,5)P_4. **B**: Superimposition of phosphate groups of both D- and L-6-deoxy-Ins(1,3,4,5)P_4. As a consequence of this regioisomeric overlap of phosphate groups, L-6-deoxy-Ins(1,3,4,5)P_4 could also bind to Ins(1,3,4,5)P_4 receptors.

(1,3,4,5)P_4 receptors. We anticipate that L-6-deoxy-Ins(1,3,4,5)P_4 (***ent*-13**) may show unusual binding properties in its own right. Experimental data for 6-deoxy-DL-Ins(1,3,4,5)P_4 and the chiral antipodes 6-deoxy D- and L-Ins(1,3,4,5)P_4 regarding binding to the Ins(1,3,4,5)P_4 "receptor" and the Ins(1,4,5)P_3 receptor and interaction with metabolic enzymes will be published elsewhere. Preliminary data indicate that the D-isomer binds to GAP^{IP4BP}, interacts potently with Ins(1,4,5)P_3/Ins(1,3,4,5)P_4 5-phosphatase and facilitates Ins(1,4,5)P_3-mediated activation[20] of the store operated Ca^{2+} current I_{CRAC}, but to a lesser extent than Ins(1,3,4,5)P_4 itself.

Experimental Section

Dry toluene and dichloromethane were distilled from calcium hydride and stored over 4 Å molecular sieves; tetrahydrofuran was distilled from sodium/benzophenone. Molecular sieves (4 Å) were predried in an oven and activated for 1 h under vacuum at 250 °C. Ether is diethyl ether. All aqueous (aq) solutions were saturated unless otherwise stated. Reactions were carried out at room temperature under nitrogen in predried glassware unless otherwise stated. Sodium hydride (NaH) was a 60% dispersion in mineral oil. 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 staining with ethanolic phosphomolybdic acid, or with ethanolic sulphuric acid followed by charring. Column chromatography was carried out under pressure on Sorbsil C60 silica gel. NMR spectra (^{31}P, ^{1}H, ^{13}C, COSY, HETCOR) were recorded on a Varian Mercury 400 spectrometer with signals being assigned by 1D, DEPT, and 2D spectra (COSY, HETCOR). Chemical shifts were measured in parts per million (ppm) relative to tetramethylsilane (TMS), deuterium oxide (D_2O), D_6-dimethyl sulfoxide ([D_6]DMSO), or D_4-methanol (CD_3OD). Coupling constants are quoted in Hz and refer to $^{3}J_{H,H}$ unless stated otherwise. The ^{31}P NMR shifts were measured in ppm relative to external 85% phosphoric acid. Melting points (uncorrected) were determined using a Reichert–Jung Thermo Galen Kofler block. 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. High resolution mass spectrometry was carried out by the University of Bath Mass Spectrometry Service. Elemental analyses were carried out by the Micro-Analysis Department in the School of Chemistry at the University of Bath. Optical rotations were measured using an Optical Activity Ltd. AA-10 polarimeter; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and all rotations were measured at ambient temperature. Ion-exchange chromatography was performed on an LKB-Pharmacia medium pressure ion exchange chromatograph using Q-Sepharose and gradients of TEAB as eluent. Fractions containing phosphate were assayed by a modification of the Briggs phosphate test.[46]

DL-2,3-*O*-Isopropylidene-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (*rac*-15) and DL-2,3-*O*-isopropylidene-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (*rac*-16): A mixture of ***rac*-14**[36] (4.4 g, 10 mmol), Bu_2SnO (22.6 g, 90 mmol), Bu_4NI (18 g, 56 mmol) and *p*-methoxybenzyl chloride (18.48 g, 16 mL, 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 t_R values of 0.28 and 0.19. The solution was cooled and washed with H_2O (2 × 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude syrup was purified by flash chromatography (ether/hexane 2:1) to provide DL-2,3-*O*-isopropylidene-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-15**) as a white crystalline solid (3.7 g, 32%) and DL-2,3-*O*-isopropylidene-1,4,6-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-16**) as a colourless syrup (4.76 g, 41%). ***rac*-15:** TLC: $t_R = 0.19$ (ether/hexane 2:1); m.p. 89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.33–6.80 (m, 12H, ArH), 4.80–4.61 (m, 4H, CH_2), 4.78,4.64 (AB, 2H, CH_2), 4.25 (dd, 1H, $J = 3.9$, 5.1 Hz, H-2), 4.08 (t, 1H, $J = 6.6$ Hz, H-3), 3.99 (t, 1H, $J = 9.7$ Hz, H-6), 3.77 (s, 9H, OCH_3), 3.65 (dd, 1H, $J = 6.6$, 9.0 Hz, H-4), 3.51 (dd, 1H, $J = 3.9$, 9.8 Hz, H-1), 3.24 (t, $J = 9.0$ Hz, H-5), 1.47, 1.33 (2s, ×3H, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.49$, 159.35, 159.26 (p-C_q-Ar), 130.77, 130.68, 130.22 (C_q-Ar), 129.85, 129.81, 129.72 (*o*-CH-Ar), 114.06, 113.89 (*m*-CH-Ar), 110.00 ($C_{dioxolane}$), 82.39 (C-4), 81.71 (C-5), 79.67 (C-3), 76.71 (C-1), 74.98 (CH_2), 74.30 (C-2), 73.59 (CH_2), 72.51 (CH_2), 71.95 (C-6), 55.59 (OCH_3), 28.28 (CH_3), 26.27 (CH_3); MS (FAB$^+$, NBA): *m/z* (%): 579.3 (29) $[M-H]^+$; MS (FAB$^-$, NBA): *m/z* (%): 733.3 (100) $[M+NBA]^+$, 579.2 (15) $[M-H]^+$; HRMS-FAB (*m/z*): $[M]^+$ calcd for $C_{33}H_{40}O_9$, 580.26724; found, 580.26414; elemental analysis calcd (%) for $C_{33}H_{40}O_9$: C 68.26, H 6.94; found C 68.40, H 6.93. ***rac*-16:** TLC: $t_R = 0.28$ (ether/hexane 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30-6.84$ (m, 12H, ArH), 4.83–4.62 (m, 4H, CH_2), 4.82, 4.63 (AB, 2H, CH_2), 4.34 (dd, 1H, $J =$ 4.1, 5.6 Hz, H-2), 4.06 (dd, 1H, $J = 5.9$, 6.7 Hz, H-3), 3.76 (m, 10H, H-6, OCH_3), 3.63 (m, 2H, H-1, H-4), 3.44 (br t, 1H, $J = 9.1$ Hz, H-5), 1.51, 1.35 (2s, 2 × 3H, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.93$, 158.87, 158.83 (p-C_q-Ar), 130.12, 130.10, 129.80 (C_q-Ar), 129.33, 129.31 (*o*-CH-Ar), 113.58, 113.50, 113.49 (*m*-CH-Ar), 109.51 ($C_{dioxolane}$), 81.27 (C-4), 80.09 (C-6), 78.75 (C-3), 76.57 (C-1), 74.47 (C-2), 74.36 (CH_2), 73.16 (C-5), 72.80 (CH_2), 72.47 (CH_2), 55.12 (OCH_3), 27.68 (CH_3), 25.70 (CH_3); MS (FAB$^+$, NBA): *m/z* (%): 579.3 (11) $[M-H]^+$; MS (FAB$^-$, NBA): *m/z* (%): 733.2 (100) $[M+NBA]^+$; HRMS-FAB (*m/z*): $[M]^+$ calcd for $C_{33}H_{40}O_9$ 580.26724; found 580.26414; elemental analysis calcd (%) for $C_{33}H_{40}O_9$: C 68.26, H 6.94; found C 68.40, H 6.99.

DL-6-Deoxy-2,3-*O*-isopropylidene-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (*rac*-17): DL-2,3-*O*-Isopropylidene-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-15**, 5 g, 8.6 mmol) was dissolved in THF (50 mL) and stirred under nitrogen at 0 °C for 10 min. NaH (400 mg, 10 mmol) was added and the solution was stirred for an additional 10 min. CS_2 (723 mg, 570 µL, 9.5 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature for 30 min afterwhich MeI (1.35 g, 592 µL, 9.5 mmol)

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was added and the reaction mixture was stirred for an additional 30 min. TLC analysis (toluene/ethyl acetate 8:3) revealed all starting material had been consumed and the mixture was concentrated in vacuo to yield a yellow syrup. The crude residue was dissolved in CH_2Cl_2 and washed with H_2O (2×50 mL), dried ($MgSO_4$), and the solvent evaporated. The residue was dissolved in toluene (50 mL) and Bu_3SnH (5.82 g, 5.38 mL, 20 mmol) and AIBN (40 mg) were added. The mixture was refluxed for 1 h, cooled and concentrated in vacuo. The crude residue was purified by flash chromatography (ether/hexane 2:1) to yield DL-6-deoxy-2,3-*O*-isopropylidene-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-17**) as a colourless syrup (4.03 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.31-6.82$ (m, 12H, ArH), 4.79, 4.69, 4.60, 4.53, 4.58, 4.54 (3AB, 6H, CH_2), 4.27 (bdd, 1H, $J =$ 3.9, 5.1 Hz, H-2), 4.00 (dd, 1H, $J = 5.1$, 6.6 Hz, H-3), 3.58 (dd, 1H, $J = 6.6$, 9.4 Hz, H-4), 3.52 (dt, 1H, $J = 3.9$, 12.1 Hz, H-1), 3.24 (ddd, 1H, $J = 4.3$, 9.4, 11.7 Hz, H-5), 2.11 (br dt, 1H, $J = 4.3$, 12.1 Hz, H-6_{eq}), 1.88 (q, 1H, $J =$ 12.1 Hz, H-6_{ax}), 1.50, 1.49 (2s, 2×3H, $2 \times CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.48$, 159.30, 159.20 (p-C_q-Ar), 131.14, 130.82, 130.12 (C_q-Ar), 129.76, 129.70, 129.53 (*o*-CH-Ar), 114.07, 113.99, 113.84 (*m*-CH-Ar), 110.15 ($C_{dioxolane}$), 84.34 (C-4), 80.61 (C-3), 76.88 (C-5), 75.47 (C-2), 73.87 (CH_2), 72.33 (CH_2), 71.67 (C-1), 70.76 (CH_2), 55.60 (OCH_3), 30.17 (C-6), 28.44 (CH_3), 26.85 (CH_3); MS (FAB$^-$ NBA): *m/z* (%): 563.3 (34) $[M-H]^+$; HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{33}H_{40}O_8$ 564.27232; found 564.26707; elemental analysis calcd (%) for $C_{33}H_{40}O_8$: C 70.19, H 7.14; found C 70.00, H 7.01.

DL-6-Deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (*rac*-18): DL-6-Deoxy-2,3-*O*-isopropylidene-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-17**, 8.5 g, 15 mmol) was dissolved in 80% aqueous acetic acid (100 mL) and heated at 50 °C for 30 min. The solution was allowed to cool to room temperature before being poured into iced-water (100 mL). The aqueous layer was extracted with ethyl acetate (4×100 mL) and the combined organic layers were washed to neutrality with $NaHCO_3$ (6×150 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by flash chromatography (toluene/ethyl acetate 8:3) to yield DL-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-18**) (6.09 g, 77%): m.p. 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29-6.81$ (m, 12H, ArH), 4.87, 4.63, 4.59, 4.53, 4.50, 4.46 (3AB, 6H, CH_2), 4.16 (br t, 1H, $J = 2.3$ Hz, H-2), 3.79 (m, 10H, H-4, OCH_3), 3.40 (m, 3H, H-1, H-3, H-5), 2.08 (m, 2H, H-6_{eq}, H-6_{ax}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.50$, 159.35, 159.26 (p-C_q-Ar), 130.98, 130.61, 130.00 (C_q-Ar), 129.79, 129.51, 129.46 (*o*-CH-Ar), 114.10, 114.00 (*m*-CH-Ar), 81.58 (C-4), 77.47, 74.16, 72.45 (C-1, C-3, C-5), 74.99 (CH_2), 71.81 (CH_2), 70.68 (CH_2), 69.67 (C-2), 55.62 (OCH_3), 30.14 (C-6); MS (FAB$^+$, NBA): *m/z* (%): 523.3 (30) $[M-H]^+$; MS (FAB$^-$, NBA): *m/z* (%): 677.3 (82) $[M+NBA]^+$, 523.3 (100) $[M-H]^+$; HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{30}H_{36}O_8$ 524.24102; found 524.23801; elemental analysis calcd (%) for $C_{30}H_{36}O_8$: C 68.69, H 6.92; found C 68.90, H 6.98.

DL-6-Deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (*rac*-19): A mixture of DL-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-18**, 5.24 g, 10 mmol), Bu_2SnO (2.98 g, 12 mmol), Bu_4NI (4.8 g, 13 mmol), and *p*-methoxybenzyl chloride (2.03 g, 1.76 mL, 13 mmol) in toluene (100 mL) was heated under reflux with 4 Å molecular sieves in a Soxhlet apparatus for 16 h. The solution was cooled and washed with H_2O (2×50 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude syrup was purified by flash chromatography (ether/hexane 1:1 to 2:1) to provide DL-6-deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol as a white crystalline material (***rac*-19**) (4.90 g, 76%): m.p. 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29-6.81$ (m, 16H, ArH), 4.79, 4.77, 4.66, 4.62, 4.61, 4.58, 4.47, 4.44 (4AB, 8H, CH_2), 4.20 (br s, 1H, H-2), 3.84 (t, 1H, $J = 9.4$ Hz, H-4), 3.81–3.79 (3s, 12H, OMe), 3.33 (m, 3H, H-1, H-3, H-5), 2.14–2.09 (m, 1H, H-6_{eq}), 1.94 (q, 1H, $J = 12.1$ Hz, H-6_{ax}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 159.40, 159.34, 159.20, 159.16 (p-C_q-Ar), 131.49, 130.94, 130.49, 130.10 (C_q-Ar), 129.80, 129.63, 129.47, 129.41 (*o*-CH-Ar), 114.06, 113.98, 113.96, 113.88 (*m*-CH-Ar), 82.38 (C-4), 80.23, 77.60, 73.78 (C-1, C-3, C-5), 75.73 (CH_2), 72.54 (CH_2), 72.30 (CH_2), 70.48 (CH_2), 68.49 (C-2), 55.61 (OCH_3), 30.18 (C-6); MS (FAB$^+$, NBA): *m/z* (%): 643.3 (30) $[M-H]^+$; MS (FAB$^-$, NBA): *m/z* (%): 797.4 (100) $[M+NBA]^+$; HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{38}H_{44}O_8$ 644.29854; found 644.29747; elemental analysis calcd (%) for $C_{38}H_{44}O_8$: C 70.79, H 6.88; found C 70.60, H 6.85.

DL-2-*O*-Benzyl-6-deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (*rac*-20): DL-6-Deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-19**, 5 g, 7.7 mmol) was dissolved in DMF (70 mL) and stirred at 0 °C for 10 min. NaH (400 mg, 10 mmol) was added and the solution was stirred at 0 °C for a further 10 min afterwhich benzyl bromide (1.54 g, 1.07 mL, 9 mmol) was added and the solution was stirred for 2 h. The reaction was quenched by addition of MeOH and the solvent was evaporated. The crude residue was dissolved in ether and was washed with H_2O (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by flash chromatography (ether/hexane 1:1 to 2:1) to yield DL-2-*O*-benzyl-6-deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-20**) as a colourless syrup (4.78 g, 84%): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.42-6.82$ (m, 21H, ArH), 4.89, 4.84, 4.77, 4.74, 4.60, 4.55, 4.59, 4.58, 4.40, 4.37 (5AB, 10H, CH_2), 4.02 (br s, 1H, H-2), 3.94 (dd, 1H, $J = 9.1$, 9.7 Hz, H-4), 3.80–3.78 (3s, 12H, OCH_3), 3.35 (m, 1H, H-5), 3.23 (m, 2H, H-1, H-3), 2.11 (m, 2H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.25$, 159.18, 159.13 (p-C_q-Ar), 139.47, 131.62, 131.07, 130.96, 130.48 (C_q-Ar), 129.89, 129.45, 129.36, 129.18 (*o*-CH-Ar), 128.27 (*m*-CH-Ar), 127.89 (*o*-CH-Ar), 127.35 (*p*-CH-Ar), 114.00, 113.95, 113.93, 113.86 (*m*-CH-Ar), 82.90 (C-4), 81.32 (C-3), 78.13 (C-5), 75.70 (CH_2), 75.33 (C-1), 75.22 (C-2), 73.96 (CH_2), 72.67 (CH_2), 72.27 (CH_2), 70.67 (CH_2), 55.63 (OCH_3), 31.04 (C-6); MS (FAB$^+$, NBA): *m/z* (%): 733.4 (70) $[M-H]^+$; MS (FAB$^-$, NBA): *m/z* (%): 887.5 (100) $[M+NBA]^+$; HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{45}H_{50}O_9$ 734.34549; found 734.33974; elemental analysis calcd (%) for $C_{45}H_{50}O_9$: C 73.97, H 6.75; found C 73.50, H 6.88.

DL-2-*O*-Benzyl-6-deoxy-*myo*-inositol (*rac*-21): DL-2-*O*-Benzyl-6-deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-20**, 1.3 g, 1.7 mmol) was dissolved in CH_2Cl_2/TFA (9:1, 40 mL) and stirred at room temperature for 30 min. The reaction mixture was concentrated in vacuo and the crude residue was redissolved in toluene. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/acetone 1:0 to 0:1) to yield DL-2-*O*-benzyl-6-deoxy-*myo*-inositol (***rac*-21**, 461 mg, 71%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 7.41-7.19$ (m, 5H, ArH), 4.78, 4.76 (AB, 2H, CH_2), 4.65–4.55 (m, 4H, $4 \times$ OH), 3.65 (s, 1H, H-2), 3.52 (m, 1H, H-1), 3.32 (ddd, 1H, $J = 3.9$, 5.1, 12.9 Hz, H-4), 3.14 (m, 2H, H-3, H-5), 1.67 (t, 2H, $J = 8.6$ Hz, H-6_{eq}, H-6_{ax}); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 140.63$ (C_q-Ar), 128.48 (*m*-CH-Ar), 127.66 (*o*-CH-Ar), 127.44 (*p*-CH-Ar), 83.11 (C-2), 75.72 (C-4), 74.66 (CH_2), 73.24, 70.23 (C-3, C-5), 67.79 (C-1), 30.41 (C-6).

DL-2-*O*-Benzyl-1,3,4,5-tetrakis[bis(benzyloxy)phospho]-6-deoxy-*myo*-inositol (*rac*-22): A mixture of bis(benzyloxy)(diisopropylamino)phosphine (1.63 g, 1.13 mL, 4.8 mmol) and DL-2-*O*-benzyl-6-deoxy-*myo*-inositol (***rac*-21**, 150 mg, 0.6 mmol) in CH_2Cl_2 (3 mL) was stirred for 15 min at 0 °C. 1*H*-Tetrazole (350 mg, 5 mmol) in CH_2Cl_2 (2 mL) was added and the reaction was stirred for a further 1 h. The solution was cooled to −78 °C and *m*-CPBA (862 mg, 5 mmol) was added and the mixture was stirred for one further hour. The reaction mixture was diluted with CH_2Cl_2 (8 mL) and washed with water (20 mL), 10% sodium metabisulfite (20 mL) and $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting syrup was purified by flash chromatography (ether/hexane 1:1 to 2:1) to give DL-2-*O*-benzyl-1,3,4,5-tetrakis [bis(benzyloxy)phospho]-6-deoxy-*myo*-inositol (***rac*-22**) as a colourless syrup (613 mg, 79%): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33-7.14$ (m, 45H, ArH), 5.06–4.91 (m, 17H, H-4, CH_2), 4.70, 4.65 (AB, 2H, CH_2), 4.43 (br s, 1H, H-2), 4.18 (m, 2H, H-1, H-5), 4.09 (m, 1H, H-3), 2.52 (m, 1H, H-6_{eq}), 2.30 (q, 1H, $J = 12.1$ Hz, H-6_{ax}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 139.63$ (C_q-Ar), 127.46 (*m*-CH-Ar), 126.66 (*o*-CH-Ar), 126.43 (*p*-CH-Ar), 78.31 (C-2), 76.06 (C-3), 75.76 (CH_2), 73.67 (C-4), 72.40, 72.34 (C-1, C-5), 70.15–69.73 (CH_2), 32.24 (C-6); ^{31}P NMR (162 MHz, $CDCl_3$) [^{1}H decoupled] $\delta = -0.35$, −0.62, −1.05, −1.07 (4s, $4 \times$ P), [^{1}H coupled] $\delta = -0.32$, −0.59, −1.01, −1.04 (4 sextet, $^3J_{PH} = 7.9$ Hz, $4 \times$ P); MS (FAB$^+$, NBA): *m/z* (%): 1295 (100) $[M]^+$; MS (FAB$^-$, NBA): *m/z* (%): 1447.2 (70) $[M+NBA]^+$; HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{69}H_{70}O_{17}P_4$ 1295.35635; found 1295.36816; elemental analysis calcd (%) for $C_{69}H_{70}O_{17}P_4$: C 63.99, H 5.45; found C 64.00, H 5.51.

DL-6-Deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate (*rac*-13): DL-2-*O*-Benzyl-1,3,4,5-tetrakis[bis(benzyloxy)phospho]-6-deoxy-*myo*-inositol (***rac*-22**, 120 mg, 92 μmol) was dissolved in the minimum amount of MeOH/H_2O 9:1 and was hydrogenated for 16 h under 80 psi, in the presence of twice the amount of 10% Pd/C. The catalyst was removed by filtration and the filtrate was concentrated to give crude racemic tetrakisphosphate ***rac*-13**. The residue was then purified by ion-exchange chromatography using a gradient of 1M TEAB (0–100%). The title compound ***rac*-13** eluted between 65–85% TEAB and after pooling and evaporation of fractions was obtained as the triethylammonium salt (60 mg, 87%). ^{1}H NMR (400 MHz, CD_3OD): $\delta = 4.48$ (q, 1H, $J = 9.0$ Hz, H-4), 4.31 (br s, 1H, H-2),

4.14 (m, 2H, H-1, H-5), 4.05 (dt, 1H, $J=2.7$, 10.2 Hz, H-3), 2.37 (m, 1H, H-6_{eq}), 2.10 (q, 1H, $J=12.1$ Hz, H-6_{ax}); ^{31}P NMR (162 MHz, CD_3OD) [^{1}H decoupled]: $\delta=1.94$, 1.31, 1.27, 0.96, (4s, 4 × P); [^{1}H coupled]: $\delta=2.02$, 1.59, 1.52, 1.17 (4d, $^3J_{P,H}=9.1$ Hz, 4 × P).

D- and L-3-*O*-[*S*-(+)-*O*-Acetylmandelyl]-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (24 and 25): A mixture of DL-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (***rac*-15**) (4 g, 7 mmol), (*S*)-(+)-*O*-acetylmandelic acid (**23**) (1.55 g, 8 mmol), and DMAP (60 mg, 0.5 mmol) in CH_2Cl_2 (20 mL), was stirred at −20 °C. A solution of DCC (1.75 g, 8.5 mmol), in CH_2Cl_2 (10 mL), was added dropwise over 1 h at −20 °C and stirring continued overnight. TLC (ether/hexane 3:2) showed two major products of $t_R=0.28$ and 0.21. The reaction mixture was filtered through Celite, which was washed thoroughly with CH_2Cl_2 (2 × 100 mL). The solvent was evaporated to give a syrup which was purified by flash chromatography using ether/hexane (1:1 to 3:2) to provide D-3-*O*-[*S*-(+)-*O*-acetylmandelyl]-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (**24**) (2.03 g, 38%) and L-3-*O*-[*S*-(+)-*O*-acetylmandelyl]-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (**25**) (2.14 g, 40%). **24:** TLC: $t_R=0.21$ (ether/hexane 3:2); m.p. 112–113 °C; $[\alpha]_D=+25.7$ ($c=1$ in methanol); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.60-6.8$ (m, 17H, ArH), 5.98 (s, 1H, O_2CCH(OAc)Ph), 4.72 (dd, 1H, $J=2.3$, 9.8 Hz, H-3), 4.70, 4.63, 4.57, 4.53, 4.40, 4.38 (3 AB, 6H, CH_2), 4.10 (br s, 1H, H-2), 3.94 (t, 1H, $J=9.8$ Hz, H-4), 3.38–3.31 (m, 2H, H-1, H-5), 2.19 (s, 3H, OAc), 2.10 (dt, 1H, $J=4.7$, 12.1 Hz, H-6_{eq}), 1.89 (q, 1H, $J=12.1$ Hz, H-6_{ax}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.73$, 168.37 (CO), 159.47, 159.25, 159.17 (*p*-C_q-Ar), 133.73, 130.99, 130.75 (C_q-Ar), 129.85, 129.53, 129.46 (*o*-CH-Ar), 129.40 (*p*-CH-Ar), 128.99 (*o*-CH-Ar), 127.57 (*m*-CH-Ar), 114.12, 113.97, 113.83 (*m*-CH-Ar), 79.37 (C-4), 77.31 (C-5), 76.04 (C-3), 75.24 (CH_2), 75.05 (O_2CCH(OAc)Ph), 73.46 (C-1), 72.35 (CH_2), 70.70 (CH_2), 68.44 (C-2), 55.59 (OCH_3), 30.29 (C-6), 21.16 (OAc); MS (FAB$^+$, NBA): *m/z* (%): 699.3 (20) $[M-H]^+$; MS (FAB$^-$, NBA): *m/z* (%): 853.4 (85) $[M+NBA]^+$, 699.3 (100) $[M-H]^+$; HRMS-FAB (*m/z*): $[M]^+$ calcd for $C_{40}H_{44}O_{11}$ 700.28837; found 700.282715. **25:** TLC: $t_R=0.28$ (ether/hexane 3:2); $[\alpha]_D=+12.0$ ($c=1$ in methanol); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.53-6.67$ (m, 17H, ArH), 5.99 (s, 1H, O_2CCH(OAc)Ph), 4.72 (dd, 1H, $J=2.3$, 9.8 Hz, H-3), 4.56–4.27 (m, 6H, CH_2), 4.37 (br d, 1H, $J=2.3$ Hz, H-2), 3.89 (t, 1H, $J=9.8$ Hz, H-4), 3.39 (m, 1H, H-1), 3.31 (m, 1H, H-5), 2.18 (s, 3H, OAc), 2.10 (dt, 1H, $J=4.7$, 12.4 Hz, H-6_{eq}), 1.92 (q, 1H, $J=12.15$, H-6_{ax}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.10$, 168.41 (CO), 159.49, 159.20, 158.92 (*p*-C_q-Ar), 133.30, 130.82, 130.60 (C_q-Ar), 129.64, 129.52, 129.44 (*o*-CH-Ar), 129.26 (*p*-CH-Ar), 129.05 (*o*-CH-Ar), 128.17 (*m*-CH-Ar), 114.14, 113.902, 113.59 (*m*-CH-Ar), 79.14 (C-4), 76.92 (C-5), 76.04 (C-3), 74.92 (O_2CCH(OAc)Ph), 74.58 (CH_2), 73.11 (C-1), 72.05 (CH_2), 70.45 (CH_2), 68.11 (C-2), 55.24 (OCH_3), 29.95 (C-6), 20.66 (OAc); MS (FAB$^+$, NBA): *m/z* (%): 699.3 (35) $[M-H]^+$; MS (FAB$^-$, NBA): *m/z* (%): 853.3 (60) $[M+NBA]^+$, 699.3 (100) $[M-H]^+$; HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{40}H_{44}O_{11}$ 700.28837; found 700.28301.

D-6-Deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (18): A mixture of D-3-*O*-[*S*-(+)-*O*-acetylmandelyl]-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (**24**, 1.6 g, 2.3 mmol), sodium hydroxide (2 g, 50 mmol) and methanol (50 mL) was heated at reflux temperature for 30 min. The mixture was cooled to room temperature and neutralised by careful addition of carbon dioxide. The resulting solid was diluted with water (25 mL) and evaporated to dryness in vacuo. The crude product was extracted with CH_2Cl_2 (4 × 100 mL) which was then evaporated off leaving the title compound D-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (1.04 g, 87%); $[\alpha]_D=+7.2$ ($c=0.9$ in CH_2Cl_2); HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{30}H_{36}O_8$ 524.24102; found 524.23549; elemental analysis calcd (%) for $C_{30}H_{36}O_8$: C 68.69, H 6.92; found C 68.40, H 6.88. NMR and mass spectrum data as for ***rac*-18**.

L-6-Deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (*ent*-18): was obtained in an identical fashion to that described for **18** (600 mg, 81%). $[\alpha]_D=-8.1$ ($c=1$ in CH_2Cl_2); HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{30}H_{36}O_8$ 524.24102; found 524.23807; elemental analysis calcd (%) for $C_{30}H_{36}O_8$: C 68.69, H 6.92; found C68.40, H 6.85. NMR and mass spectrum data as for ***rac*-18**.

D-6-Deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (19): A mixture of D-6-deoxy-1,4,5-tri-*O*-*p*-methoxybenzyl-*myo*-inositol (**18**, 750 mg, 1.4 mmol), Bu_2SnO (400 mg, 1.6 mmol), Bu_4NI (591 mg, 1.6 mmol), and *p*-methoxybenzyl chloride (234 mg, 200 μL, 1.5 mmol) in toluene (30 mL) was heated under reflux with 4 Å molecular sieves in a Soxhlet apparatus for 16 h. The solution was cooled and washed with H_2O (2 × 50 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude syrup was purified by flash chromatography using ether/hexane 2:1 to provide D-6-deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (740 mg, 72%) as a colourless syrup; $[\alpha]_D=0-1$ ($c=1$ in dichloromethane); HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{38}H_{44}O_8$ 644.29854; found 644.29590; elemental analysis calcd (%) for $C_{38}H_{44}O_8$: C 70.79, H 6.88; found C 70.40, H 6.83. NMR and mass spectrum data as for ***rac*-19**.

L-6-Deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (*ent*-19) was obtained in an identical fashion to that described for **19** and isolated as a colourless syrup (791 mg, 77%). $[\alpha]_D=-1.4$ ($c=0.7$ in dichloromethane); HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{38}H_{44}O_8$ 644.29854; found 644.29319; elemental analysis calcd (%) for $C_{38}H_{44}O_8$: C 70.79, H 6.88; found C 70.20, H 6.88. NMR and mass spectrum data as for ***rac*-19**.

D-2-*O*-Benzyl-6-deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (20): D-6-Deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (**19**, 500 mg, 0.8 mmol) was dissolved in DMF (10 mL) and stirred at 0 °C for 10 min. NaH (50 mg, 1.2 mmol) was added and the solution was stirred at 0 °C for a further 10 min afterwhich benzyl bromide (171 mg, 118 μL, 1 mmol) was added and the solution was stirred for 2 h. The reaction was quenched by addition of MeOH and the solvent was evaporated. The crude residue was dissolved in ether and was washed with H_2O (2 × 20 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by flash chromatography using ether/hexane (1:1 to 2:1) to yield D-2-*O*-benzyl-6-deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (365 mg, 67%): $[\alpha]_D=+13.2$ ($c=1.1$ in acetone); HRMS-FAB (*m/z*): $[M]^+$ calcd for $C_{45}H_{50}O_9$ 734.34549; found 734.34021. NMR and mass spectrum data as for ***rac*-20**.

L-2-*O*-Benzyl-6-deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (*ent*-20) was obtained in an identical fashion as that described for **20** (475 mg, 81%): $[\alpha]_D=-7.0$ ($c=1$ in acetone); HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{45}H_{50}O_9$ 734.34549; found 734.34101. NMR and mass spectrum data as for ***rac*-20**.

D-2-*O*-Benzyl-6-deoxy-*myo*-inositol (21): D-2-*O*-Benzyl-6-deoxy-1,3,4,5-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol (**20**, 250 mg, 0.35 mmol) was dissolved in CH_2Cl_2/TFA (9:1, 15 mL) and stirred at room temperature for 30 min. The reaction mixture was concentrated in vacuo and the crude residue was redissolved in toluene. The solvent was evaporated and the crude residue was purified by flash chromatography ethyl acetate/acetone (1:0 to 0:1) to yield D-2-*O*-benzyl-6-deoxy-*myo*-inositol (71 mg, 83%): $[\alpha]_D=+3.8$ ($c=0.76$ in acetone). NMR data as for ***rac*-21**.

L-2-*O*-Benzyl-6-deoxy-*myo*-inositol (*ent*-21) was obtained in an identical fashion to that for **21** (93 mg, 77%): $[\alpha]_D=-3.0$ ($c=1$ in acetone). NMR data as for ***rac*-21**.

D-2-*O*-Benzyl-1,3,4,5-tetrakis[bis(benzyloxy)phospho]-6-deoxy-*myo*-inositol (22): A mixture of bis(benzyloxy)(diisopropylamino)phosphine (650 mg, 634 μL, 1.9 mmol) and D-2-*O*-benzyl-6-deoxy-*myo*-inositol (60 mg, 0.24 mmol) in CH_2Cl_2 (4 mL) was stirred for 15 min at 0 °C. 1*H*-Tetrazole (140 mg, 2 mmol) in CH_2Cl_2 (3 mL) was added and the reaction was stirred for a further 1 h. The solution was cooled to −78 °C and *m*-CPBA (345 mg, 2 mmol) was added and the mixture was stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 (8 mL) and washed with water (20 mL), 10% sodium metabisulfite (20 mL) and $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The remaining syrup was purified by flash chromatography (ether/hexane 1:1 to 2:1) to give D-2-*O*-benzyl-1,3,4,5-tetrakis[bis(benzyloxy)phospho]-6-deoxy-*myo*-inositol as a colourless syrup (230 mg, 74%): $[\alpha]_D=+9.0$ ($c=1$ in methanol); HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{69}H_{70}O_{17}P_4$ 1294.35635; found 1294.35745; elemental analysis calcd (%) for $C_{69}H_{70}O_{17}P_4$: C 63.99, H 5.45; found C 63.60, H 5.48. NMR and mass spectrum data as for ***rac*-22**.

L-2-*O*-Benzyl-1,3,4,5-tetrakis[bis(benzyloxy)phospho]-6-deoxy-*myo*-inositol (*ent*-22) was obtained in an identical fashion as to that for **22** and was isolated as a colourless syrup (281 mg, 68%): $[\alpha]_D=-8.3$ ($c=0.9$ in methanol); HRMS-FAB: (*m/z*): $[M]^+$ calcd for $C_{69}H_{70}O_{17}P_4$ 1294.35635; found 1294.35843; elemental analysis calcd (%) for $C_{69}H_{70}O_{17}P_4$: C 63.99 H 5.45; found C 63.50, H 5.52. NMR and mass spectrum data as for ***rac*-22**.

D-6-Deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate (13): D-2-*O*-Benzyl-1,3,4,5-tetrakis[bis(benzyloxy)phospho]-6-deoxy-*myo*-inositol (80 mg, 60 μmol) was dissolved in the minimum amount of MeOH/H_2O 9:1 and was hydrogenated for 16 h under 80 psi, in the presence of twice the amount of 10% Pd/C. The catalyst was removed by filtration and the

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filtrate was concentrated to give crude tetrakisphosphate **13**. The residue was then purified by ion-exchange chromatography using a gradient of 1M TEAB (0–100%). D-6-Deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate eluted at 65–85% TEAB and after pooling and evaporation of fractions was obtained as the triethylammonium salt (40 mg, 85%). $[\alpha]_D = +9.8$ ($c =$ 0.3 in water, pH approximately 4). NMR data as for ***rac*-13**.

L-6-Deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate (*ent*-13) was obtained in an identical fashion to that described for **13** (25 mg, 61%). $[\alpha]_D = -8.5$ ($c =$ 0.35 in water, pH approximately 4). NMR data as for ***rac*-13**.

D-6-Deoxy-*myo*-inositol (26): D-1,4,5-Tri-*O*-*p*-methoxybenzyl-*myo*-inositol (30 mg, 0.06 mmol) was dissolved in the minimum amount of MeOH/H_2O 9:1 and was hydrogenated for 16 h under 80 psi, in the presence of twice the amount of 10% Pd/C. The catalyst was removed by filtration and the filtrate was concentrated to give crude pentaol **26**. The residue was then purified by flash chromatography using ethyl acetate/acetone as the eluent (1:0 to 0:1) to yield title compound in quantitative yield. $[\alpha]_D = +6.3$ ($c =$ 1.37 in water) lit. $[\alpha] = +7.0$.[49]

L-6-Deoxy-*myo*-inositol (*ent*-26) was obtained in an identical fashion to that described for **26**. $[\alpha]_D = -7.0$ ($c = 1.37$ in water).

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