A Definitive Synthesis of D-*myo*-Inositol 1,4,5,6-Tetrakisphosphate and Its Enantiomer D-*myo*-Inositol 3,4,5,6-Tetrakisphosphate from a Novel Butane-2,3-diacetal-Protected Inositol

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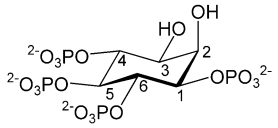
Abstract: New and rapid syntheses of the enantiomeric intracellular signalling molecules D-*myo*-inositol 1,4,5,6-tetrakisphosphate (**1a**) and D-*myo*-inositol 3,4,5,6-tetrakisphosphate (**1b**) are described. The synthetic strategy employs the novel butane-2,3-diacetal-protected (BDA-protected) *myo*-inositol (±)-**3ab**, directly accessible from *myo*-inositol on a large scale, and an optical resolution with diastereoisomeric (*R*)-(−)-acetylmandelate esters. The X-ray crystal structure of (±)-**4**, an unusual side product of acid-catalysed reaction of *myo*-inositol with butanedione is also presented, and the absolute configurations of **1a** and **1b** are definitively assigned by conversion of key precursors into (+)-bornesitol and L-iditol hexaacetate, respectively. Biological activity of synthetic **1b** was confirmed in comparison with the natural polyphosphate.

Keywords: butane-2,3-diacetal · chiral resolution · cyclitols · inositol · signal transduction

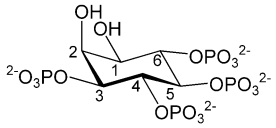
Introduction

Since the discovery in 1983 that D-*myo*-inositol 1,4,5-trisphosphate, Ins(1,4,5)P_3, acts as a Ca^{2+}-mobilising intracellular second messenger, many other inositol phosphates have been discovered, although it is only in recent years that their physiological functions are beginning to be understood.[1] D-*myo*-Inositol 1,3,4,5-tetrakisphosphate, Ins(1,3,4,5)P_4, for example, may act in a coordinated way to assist Ins(1,4,5)P_3-initiated Ca^{2+} mobilisation, and has recently been shown to have a physiological role, inhibiting Ins(1,4,5)P_3 5-phosphatase.[2]

Two other inositol tetrakisphosphates, D-*myo*-inositol 1,4,5,6-tetrakisphosphate, Ins(1,4,5,6)P_4, **1a**, and its enantiomer, D-*myo*-inositol 3,4,5,6-tetrakisphosphate, Ins(3,4,5,6)P_4, **1b**, are also attracting growing attention. Ins(1,4,5,6)P_4 levels in human colonic epithelial cells are dramatically increased in response to *Salmonella* invasion, leading to inhibition of the phosphatidylinositol 3,4,5-trisphosphate, PtdIns(3,4,5)P_3, signalling pathway,[3] and a role for Ins(1,4,5,6)P_4 in the regulation of transcription has also been proposed.[4] Recently, it was reported that the tumour suppressor protein PTEN, which is known to have PtdIns(3,4,5)P_3 3-phosphatase activity, can also hydrolyse the 3-phosphate group of Ins(1,3,4,5,6)P_5 to generate Ins(1,4,5,6)P_4 (**1a**),[5] thus raising the possibility that perturbations in the Ins(1,3,4,5,6)P_5/Ins(1,4,5,6)P_4 cycle may contribute to the neoplastic consequences of PTEN gene mutations.[5]



Ins(1,4,5,6)P_4 **1a**



Ins(3,4,5,6)P_4 **1b**

Ins(3,4,5,6)P_4 (**1b**) is now thought to behave as an intracellular signal that inhibits the conductance of Ca^{2+}-activated Cl^- channels in the plasma membrane,[6] thereby contributing to the control of salt and fluid secretion from epithelial cells. Recently, it has been shown that signalling by Ins(3,4,5,6)P_4 is regulated in vivo by inositol 1,3,4-trisphosphate, Ins(1,3,4)P_3,[7] which acts by activating an Ins(1,3,4,5,6)P_5 1-phosphatase.[8] In cystic fibrosis (CF),

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cyclic AMP-activated Cl^- channels are defective, leaving the Ca^{2+}-activated channels unimpaired. Thus, drugs that could antagonise the synthesis or actions of Ins(3,4,5,6)P_4 might have therapeutic value in CF by stimulating Cl^- secretion through Ca^{2+}-activated channels.[9]

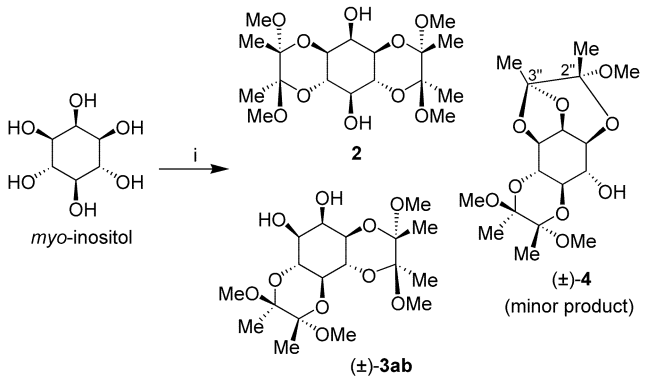
The fact that Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**) are enantiomeric, and yet appear to have distinct physiological roles, requires that homochiral materials of high purity and certain absolute configurations are available in sufficient quantities for biological studies. This demand cannot be met with material obtained from biological sources because the two enantiomers cannot be separated by standard HPLC techniques, nor can the absolute configurations of the tiny quantities involved be determined without difficulty. Thus, a simple synthetic route to both **1a** and **1b** is required, and the absolute configurations of the products must be established beyond doubt. Various syntheses of Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**) have been reported,[10] although there are contradictions in the chemical literature regarding the optical rotation of Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**), and also of key synthetic intermediates used in their synthesis.[10g] Thus, specific rotations opposite in sign but similar in magnitude have been reported for the same compounds. Ins(1,4,5,6)P_4 itself, for example, has been designated as either the levorotatory[10b,c,g] or the dextrorotatory[10e,f] enantiomer.

Here we present new syntheses of Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**) from a novel butane-2,3-diacetal-protected inositol. The absolute configurations of the two tetrakisphosphates were definitively assigned by reference to two independent standards. In the course of this study, we also identified an unusual side product of the inositol protection reaction and established its structure by a single-crystal X-ray study.

Results and Discussion

The major challenge in the synthesis of inositol polyphosphates is to obtain a chiral intermediate suitable for phosphorylation. This usually requires multiple regiospecific protection of the hydroxy groups in inositol with various permanent and temporary protecting groups, and an optical resolution of enantiomeric intermediates.[11] Rapid and simplified routes are therefore of great advantage. Recent years have seen an increasing use of 1,2-diacetals in organic synthesis,[12] and their application to the selective protection of diequatorial 1,2-diols gives them great potential in the synthesis of many inositol phosphates and analogues. The current route arises out of our recent studies[13] on the protection of inositols with the butane-2,3-diacetal (BDA) protecting group.

The application of the BDA group to the protection of *myo*-inositol was first demonstrated by Montchamp et al.,[14] who showed that the acid-catalysed reaction of 2,2,3,3-tetramethoxybutane (TMB) with *myo*-inositol on a small scale gave the symmetrical diol 1,6:3,4-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol (**2**, Scheme 1). It was later shown that the BDA group could be introduced into a variety of



Scheme 1. i) Butanedione, $(MeO)_3CH$, CSA, MeOH, reflux.

polyols by using cheap and commercially available butanedione instead of TMB.[15] We have recently applied the butanedione method to both *myo*- and *chiro*-inositol on a large scale in syntheses of the rare *neo* isomer of inositol[13a] and of novel *chiro*-inositol-based analogues[13b] of **1a** and **1b**.

Here we report that, in addition to the symmetrical diol **2**, a second major product also results from the acid-catalysed reaction of butanedione with *myo*-inositol: namely the asymmetrical diol DL-1,6:4,5-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol (±)-**3ab** (Scheme 1). When the cooled reaction mixture is filtered, compound **2** is obtained as a solid precipitate, while (±)-**3ab**, which is much more soluble in methanol, remains in the mother liquor and can be isolated by flash chromatography followed by recrystallisation. With reaction times of around 40 h, the asymmetrical diol [(±)-**3ab**] and the symmetrical diol **2** were both obtained from 25 g of inositol, in 20% and 26% yield, respectively. The pattern of protection in (±)-**3ab** clearly makes it an ideal precursor for the synthesis of the enantiomers Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**). Furthermore, the reaction gives rapid access to (±)-**3ab** on a multigram scale in a single step.

In our initial report[13a] we noted that prolonged reaction times gave a higher yield of the symmetrical diol **2**, but also that a less polar product steadily accumulated in the equilibrium mixture. By use of extended reaction times (up to 28 days on this scale) it was later possible to isolate this third product [(±)-**4**], in low yield, as a highly crystalline material. The ^{1}H NMR spectrum of (±)-**4** (see Experimental Section) was unusual for a *myo*-inositol derivative. It was immediately obvious that the compound was asymmetrical, and abnormal coupling constants between vicinal protons in the *myo*-inositol ring implied that the inositol ring did not take on the usual chair conformation in (±)-**4**. It was also clear that only three *O*-methyl groups were present in the molecule, and derivatisation to give a monoacetate confirmed that (±)-**4** contained only one hydroxy group. Finally, a significant downfield shift for a quaternary carbon atom in the ^{13}C NMR spectrum of (±)-**4** [$\delta = 107.62$ ppm, compared to $\delta = 99.15$, 99.33, 99.88 and 100.39 ppm for the acetal carbon atoms in (±)-**3ab**] suggested the presence of a five-membered dioxolane ring.[16,17] A single-crystal X-ray

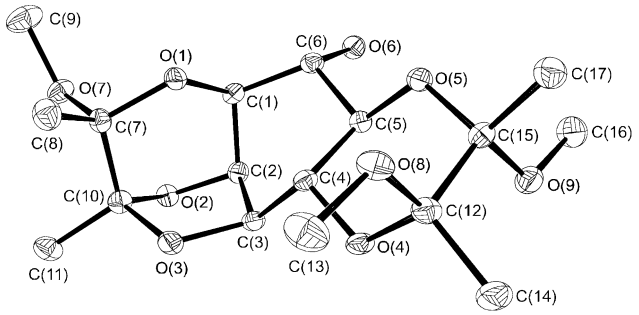
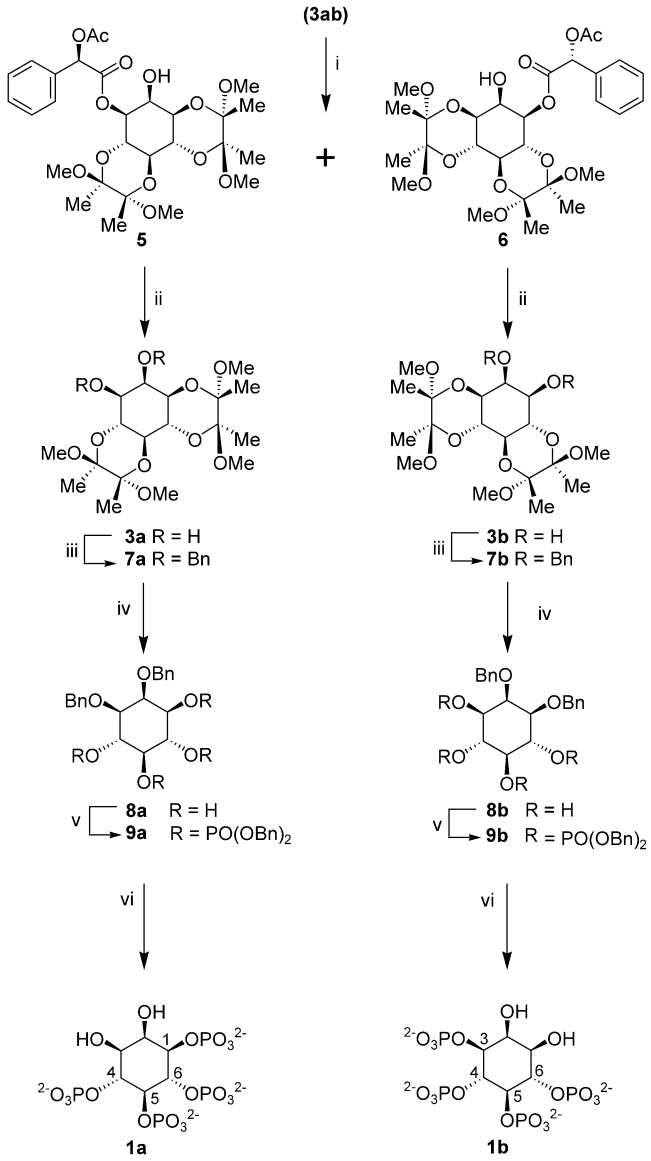


Figure 1. X-ray crystal structure of (±)-**4** (ellipsoids are represented at the 30% level).

study established the structure of (±)-**4** to be as shown in Figure 1. It is hard to define a unique mechanism to account for the origin of (±)-**4**, but a feasible route involves the elimination of a molecule of methanol from an unstable bis(butane-2,3-diacetal) intermediate with the 1,2:4,5 protection pattern, presumably formed as part of competing acid-catalysed equilibria. It seems likely that the formation of (±)-**4**, in which the inositol ring is held in a twist-boat conformation by the formation of a rigid cage involving O-1, O-2 and O-3, is favoured by stabilizing anomeric effects, together with the avoidance of steric clashes.[16] Thus, both dioxane rings in (±)-**4** adopt chair conformations with axial *O*-methyl groups. While this work was nearing completion, a similar side product of acid-catalysed reaction of *myo*-inositol with butanedione was reported,[18] although that structure, inferred from the X-ray crystal structure of its benzyl ether, apparently has the opposite relative stereochemistry at C-2″ to that found in (±)-**4** in the present work. To the best of our knowledge, no crystal structure of the benzyl ether derivative[18] has yet been published to allow formal direct comparison with ours.

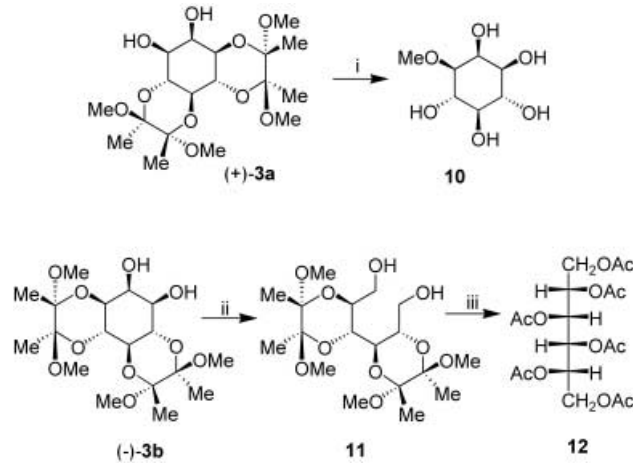
Because the asymmetrical diol (±)-**3ab** is racemic at this stage, a resolution step is required (Scheme 2). It was found that DCC-promoted regioselective esterification of (±)-**3ab** with (*R*)-(−)-acetylmandelic acid (1.06 equivalents) gave diastereoisomeric acetylmandelate esters **5** and **6**, which were conveniently separated by flash chromatography. The individual diastereoisomers were then saponified in refluxing methanolic sodium hydroxide to give the individual homochiral diols (+)-**3a** and (−)-**3b** in good yield. Their specific rotations (+270 and −270 respectively) were unusually large for *myo*-inositol derivatives.



Scheme 2. i) (*R*)-(−)-acetylmandelic acid, DCC, DMAP, CH_2Cl_2, 36.5% (**5**), 36.5% (**6**); ii) NaOH in MeOH, reflux, 30 min, 91% for **3a** and **3b**; iii) BnBr, NaH, DMF, RT 2 h, 84% for **7a** and 86% for **7b**; iv) 95% aqueous trifluoroacetic acid in CH_2Cl_2 (1:1), 82% for **8a**, 75% for **8b**; v) bis(benzyloxy)diisopropylaminophosphine, 1*H*-tetrazole, CH_2Cl_2, then **8a** or **8b**, then *m*CPBA, −78°C, 88% for **9a**, 54% for **9b**; vi) 20% $Pd(OH)_2$ on carbon, H_2 (50 psi), MeOH/H_2O (5:1), 20 h. DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, *m*CPBA = 3-chloroperoxybenzoic acid.

As noted above, there are contradictions in the literature regarding the specific rotations of synthetic Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**). While it is likely that the specific rotations of these tetrakisphosphates will be dependent on salt form and pH, the specific rotations reported for key intermediates used in some syntheses of Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**) have also been reported with opposite signs for the same material. It was therefore vital, in the present case, to establish the absolute configurations of intermediates, and thereby those of our synthetic Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**) by reliable means. Accordingly, (+)-**3a** was subjected to regioselective stannylene-mediated methylation of the equatorial hydroxy group, followed by hydrolysis of BDA acetals with TFA to give pentaol **10** (Scheme 3). The ^1H and ^{13}C NMR spectra of **10** were identical to those reported for 1-*O*-methyl-*myo*-inositol [(−)-bornesitol],[19] although the specific rotation of **10** was opposite in sign, identifying it as (+)-bornesitol (3-*O*-methyl-*myo*-inositol).[20] This identified (+)-**3a** as the 1,6:4,5-protected compound, and enabled the absolute configurations of all chiral intermediates and products to be assigned.

For additional confirmation, the enantiomeric diol (−)-**3b** was subjected to oxidative glycol cleavage with silica-supported sodium metaperiodate[21] followed by reduction of



Scheme 3. i) a) Bu_2SnO, CH_3CN, CH_3I, tetrabutylammonium bromide; b) 95% aqueous trifluoroacetic acid in CH_2Cl_2 (1:1), 81%; ii) a) $NaIO_4/SiO_2$,[21] CH_2Cl_2; b) $NaBH_4$, EtOH, 87%; iii) a) 50% aqueous trifluoroacetic acid; b) Ac_2O, pyridine, 46%.

the resulting dialdehyde with sodium borohydride to give the highly crystalline C_2-symmetric iditol derivative **11** (Scheme 3). Treatment of **11** with 50% aqueous trifluoroacetic acid for 2 h, followed by peracetylation of the product, gave **12** in modest (46%) yield. NMR spectra, melting point and specific rotation of **12** identified it as L-iditol hexaacetate,[22] thus identifying (−)-**3b** as the 3,4:5,6-protected diacetal, and confirming the configurational assignments made above.

The diols **3a** and **3b** were then benzylated (Scheme 2) with benzyl bromide and sodium hydride in DMF to give the fully blocked dibenzyl derivatives **7a** and **7b** in good yield. Treatment of **7a** and of **7b** with aqueous trifluoroacetic acid in dichloromethane at room temperature removed the BDA protecting groups to give the previously unknown crystalline 1,4,5,6- and 3,4,5,6-tetraols **8a** and **8b** respectively. Phosphitylation of the individual tetraols was achieved by treatment of **8a** and **8b** with the tetrazolide formed by treatment of bis(benzyloxy)diisopropylaminophosphine with 1*H*-tetrazole. At this stage, the ^{31}P NMR spectrum (Figure 2) of each resulting tetrakisphosphite (not isolated) showed two doublets (corresponding to P-1 and P-4, $^5J_{P,P} \approx 6$ Hz) and two apparent triplets (for P-5 and P-6, $^5J_{P,P} \approx 6$ Hz); the same pattern of signals was obtained for the enantiomer. This further exemplifies our original observation of $^5J_{P,P}$ couplings in such species.[23] The spectrum obtained in Figure 2 can only arise from the presence of four adjacent equatorial phosphites in an asymmetrical structure, thus confirming the required substitution pattern of the *myo*-inositol ring.

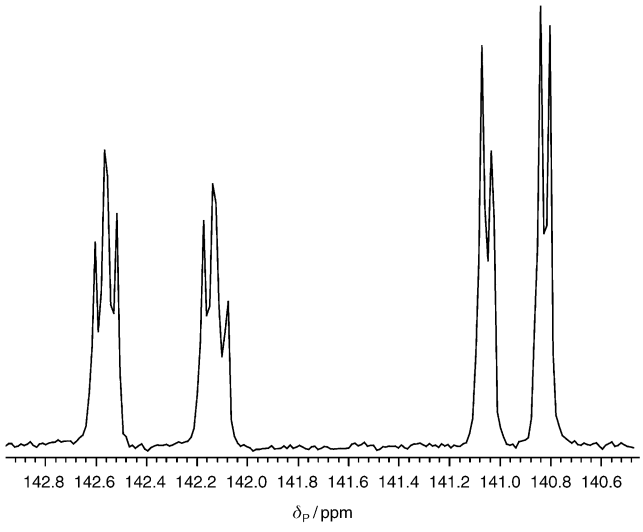


Figure 2. ^{31}P NMR spectrum (162 MHz in $CDCl_3$) of D-2,3-di-*O*-benzyl-1,4,5,6-*myo*-inositol-tetrakis[di(benzyloxy)phosphite] (intermediate not isolated).

Oxidation of the tetrakisphosphite intermediates with 3-chloroperoxybenzoic acid gave the protected tetrakisphosphates **9a** and **9b**, respectively. Deprotection of **9a** and of **9b** was accomplished by hydrogenolysis over 20% $Pd(OH)_2$/C, at 50 psi, to provide Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**), respectively. For biological evaluation, **1a** and **1b** were further purified by ion-exchange chromatography on Q-Sepharose Fast Flow resin, with elution with a gradient of triethylammonium hydrogen carbonate buffer, to give the pure triethylammonium salts of Ins(1,4,5,6)P_4 (**1a**) or Ins(3,4,5,6)P_4 (**1b**). Measurement of the specific rotations of **1a** and **1b** showed that Ins(1,4,5,6)P_4 (**1a**) was the levorotatory enantiomer. Accurate quantification of each tetrakisphosphate was carried out by a modification of the Briggs phosphate assay.[24]

Synthetic Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**) were evaluated biologically in a preliminary fashion by using a single CFPAC-1 cell in whole-cell mode, with 500 nM Ca^{2+} as the stimulus for activation. While **1b** was able to inhibit the conductance of the Ca^{2+}-activated Cl^- channels to the same degree as seen with Ins(3,4,5,6)P_4 from other sources, **1a** was, as expected, without effect.

Conclusions

In summary, we have described short and practical syntheses of Ins(1,4,5,6)P_4 (**1a**) and Ins(3,4,5,6)P_4 (**1b**) starting from a novel BDA-protected *myo*-inositol. To resolve any uncertainty concerning the absolute configurations of the tetrakisphosphates produced by some earlier reported syntheses, the absolute configurations of the products were established unambiguously by correlation with (+)-bornesitol and L-iditol. Also **1b** was biologically active. These tetrakisphosphates, accessible in large quantities by this route, should be useful in further evaluation of the disparate biological roles of these two enantiomers in cellular signalling pathways.

Experimental Section

General: Chemicals were purchased from Aldrich and Fluka. Dichloromethane, pyridine and dimethylformamide (DMF) were purchased in anhydrous form. TLC was performed on precoated plates (Merck TLC aluminium sheets silica $60F_{254}$. Art. No. 5554). Products were viewed under UV light at 254 nm or with phosphomolybdic acid in methanol followed by heating. Flash chromatography was carried out with Sorbsil C60 silica

gel. NMR spectra were recorded on either JEOL EX-270 or Varian Mercury EX-400 NMR spectrometers. ^{1}H chemical shifts were measured in ppm relative to tetramethylsilane (TMS). ^{31}P chemical shifts were measured in ppm relative to external 85% H_3PO_4 and are positive when downfield from this reference. Melting points (uncorrected) were determined with a Reichert–Jung Thermo Galen Kofler Block. Microanalysis was carried out by the University of Bath microanalysis service. Optical rotations were measured with an Optical Activity Ltd. AA-10 polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Fast atom bombardment (FAB) mass spectra were recorded at the Mass Spectrometry Service of the University of Bath, with 3-nitrobenzyl alcohol (NBA) as matrix. Ion-exchange chromatography was performed on a LKB-Pharmacia medium-pressure ion-exchange chromatograph on Q Sepharose Fast Flow with gradients of triethylammonium hydrogen carbonate (TEAB) as eluent. Column fractions containing inositol polyphosphates were assayed for total phosphate by a modification of the Briggs test.[24]

X-ray crystallography of (±)-4: A crystal of approximate dimensions $0.03\times0.01\times0.075$ mm was used for data collection. Crystal data: $C_{34}H_{56}O_{18}$, M_r = 752.79, monoclinic, a = 11.840(2), b = 12.176(2), c = 13.606(2) Å, β = 113.63(2)°, U = 1797.0(5) Å^3, space group $P2_1/c$, Z = 2, ρ_{calcd} = 1.391 g cm^{-3}, $\mu(Mo_{K\alpha})$ = 0.113 mm^{-1}, $F(000)$ = 808. Crystallographic measurements were made at 293(2) K on a Nonius Kappa CCD diffractometer in the range $1.88<\theta<27.49^o$. Data (23153 reflections) were corrected for Lorentz and polarisation and also for absorption. [SORTAV program].

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant. Analysis of the gross structure revealed that molecules interact through hydrogen bonding between the alcoholic proton H6 of one molecule and the proximate O3 of a lattice neighbour, to generate one-dimensional polymers.

The solution of the structure (SHELXS-86)[25] and the refinement (SHELXL-97)[26] converged to a conventional [that is, based on 2580 F^2 data with $F_o>4\sigma(F_o)$] $R1$ = 0.0469 and $wR2$ = 0.1059. Goodness of fit = 0.938. The maximum and minimum residual densities were 0.281 and −0.308 e Å^{-3}, respectively. The asymmetric unit (shown in Figure 1) along with the labelling scheme used was produced by using ORTEX.[27]

CCDC-199689 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

DL-1,6:4,5-Bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol [(±)-3ab]: A mixture of methanol (400 mL), camphorsulfonic acid (1 g) and trimethyl orthoformate (100 mL) was stirred vigorously at room temperature. *myo*-Inositol (25 g, 138.5 mmol) was added to the stirred solution, followed by butanedione (25 mL, 285 mmol), and the mixture was heated under reflux for 41 h. The cherry red suspension was allowed to cool and was then filtered through a large sinter funnel. The precipitate was washed with methanol and then with diethyl ether to leave the symmetrical bis(butane-2,3-diacetal) **2** [(14.75 g, 26%) R_f = 0.37, (CH_2Cl_2/acetone 3:1)] as a white solid. The red mother liquor and combined washings were concentrated and then purified by flash chromatography (CH_2Cl_2/acetone 3:1) to give a second product (R_f = 0.34) as a foam. Addition of ether to the foam gave a white solid, which was recrystallised from acetone/hexane to give pure DL-1,6:4,5-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol [(±)-**3ab**] (11.15 g, 20%) from acetone/hexane; m.p. 215–218 °C.

^{1}H–^{1}H COSY (400 MHz, $CDCl_3$): δ = 1.29, 1.30, 1.32, 1.33 (4×s, 12H; 4×CH_3), 2.70 (br, D_2O exch, 1H; OH-3), 2.94 (br, D_2O exch, 1H; OH-2), 3.24 (s, 3H; OCH_3), 3.27 (s, 6H; 2×OCH_3), 3.29 (s, 3H; OCH_3), 3.51 (dd, J = 2.6, 9.9 Hz, 1H; H-3), 3.61 (dd, J = 9.9, 9.9 Hz, 1H; H-5), 3.64 (br, D_2O exch. gives dd, J = 9.9, 2.7 Hz, 1H; H-3), 3.92 (dd, J = 9.9, 9.9 Hz, 1H; H-4 or H-6), 4.06 (dd, J = 9.9, 9.9 Hz, 1H; H-4 or H-6), 4.11 (br, exch. gives dd, J = 2.7, 2.7 Hz, 1H; H-2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.07, 18.12, 18.17 (4×CH_3), 48.20, 48.27, 48.41 (4×OCH_3), 65.93, 68.21, 69.35, 70.13, 70.28, 70.64 (6×CH), 99.15, 99.33, 99.88, 100.39 (4×C_q of BDA) ppm; elemental analysis calcd (%) for $C_{18}H_{32}O_{10}$ (408.45): C 52.93, H 7.90; found: C 52.5, H 7.95.

Isolation of DL-(2′*S,3′*S**,2″*R**,3″*S**)-4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1,2,3-*O*-(2″-methoxybutane-2″-yl-3″-ylidene)-*myo*-inositol [(±)-4]**: Trimethyl orthoformate (200 mL), butanedione (50 mL, 570 mmol) and (±)-camphorsulphonic acid (1 g) were added to a stirred suspension of *myo*-inositol (50.0 g, 277 mmol) in MeOH (500 mL). The mixture was heated at reflux for 28 days and then allowed to cool. The suspension was filtered, and the filtrate was washed with MeOH (200 mL) and allowed to dry. The resulting white solid (50 g) was suspended in propan-2-ol (600 mL) and the mixture was heated at reflux for 2 h with vigorous stirring. The hot suspension was filtered, and as the filtrate cooled to room temperature, a white solid (5 g) precipitated. This was found to consist of a 4:1 mixture of (±)-**4** and **2**, as judged by ^{1}H NMR spectroscopy. Crystallisation of this solid from boiling acetonitrile (250 mL) gave alcohol (±)-**4** (3.42 g, 3.4%) as colourless needles: R_f 0.60 (CH_2Cl_2/acetone 2:1); the needles undergo a phase change above 165 °C to plates, which then sublime, with softening, above 270 °C.

^{1}H–^{1}H COSY (400 MHz, [D_5]pyridine, TMS): δ = 1.37, 1.45, 1.47, 1.57 (4×s, 12H; 4×CH_3), 3.20, 3.33, 3.40 (3×s, 9H; 3×OCH_3), 4.06 (dd, J = 12.0, 7.0 Hz, 1H; H-5), 4.26 (m, D_2O exch. gives dd, J = 7.0, 1.5 Hz, 1H; H-6), 4.43 (brs, 1H; H-1), 4.60 (ddd, J = 5.5, 4.7, 0.8 Hz, 1H; H-3), 4.78 (dd, J = 12.1, 4.7 Hz, 1H; H-4), 5.02 (brs, D_2O exch; 1H; OH-6), 5.08 (dd, J = 5.5, 1.6 Hz, 1H; H-2) ppm; ^{13}C NMR (100 MHz, [D_5]pyridine): δ = 18.07, 18.14, 18.91, 18.94 (4×CH_3), 47.64, 47.77, 48.30 (3×OCH_3), 71.08 (CH), 72.36 (2×CH), 74.24, 74.69, 78.56 (3×CH), 99.40, 99.45, 99.79 (3×C_q), 107.62 (C-3″); MS (+ve ion FAB) 345 (70%) $[M-OCH_3]^+$, 255 (40%), 173 (50%), 101 (100%); elemental analysis calcd (%) for $C_{17}H_{28}O_9$ (376.40): C 54.25, H 7.50; found: C 54.3, H 7.48.

1D-3-*O*-[(*R*)-(−)-Acetylmandelyl]-1,6:4,5-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol (5) and 1D-1-*O*-[(*R*)-(−)-acetylmandelyl]-3,4:5,6-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol (6): A solution of DCC (5.16 g, 25.0 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise at −78 °C over 3 h with stirring to a mixture of (±)-**3ab** (9.62 g, 23.5 mmol), DMAP (50 mg, 0.41 mmol) and (*R*)-(−)-acetylmandelic acid (4.85 g, 25.0 mmol) in dry CH_2Cl_2 (200 mL). The resulting mixture was stirred overnight at room temperature and then filtered through a bed of Celite, which was then washed thoroughly with CH_2Cl_2 (2×50 mL). The combined filtrate and washings were evaporated under reduced pressure to give a foam. The individual diastereoisomers were separated by flash chromatography on silica ($CHCl_3$/acetone 15:1 and then EtOAc/toluene 2:3) to give the less polar diastereoisomer **5** (5.04 g, 36.5%) and then the more polar diastereoisomer **6** (5.03 g, 36.5%) as waxy solids. Both diastereoisomers were recrystallised from hexane. Compound **5** (m.p. 101–103 °C), **6** (m.p. 119–122 °C).

Compound 5: R_f = 0.22 ($CHCl_3$/acetone 15:1); $[\alpha]_D^{20}$ = +174 (c = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3H; CH_3), 1.29 (s, 3H; CH_3), 1.30 (s, 6H; 2×CH_3), 2.17 (s, 3H; $COCH_3$), 3.22, 3.25, 3.26, 3.27 (4×s, 12H; 4×OCH_3), 3.51 (dd, J = 2.5, 9.9 Hz, 1H; H-1), 3.67 (dd, J = 9.8, 9.8 Hz, 1H; H-5), 4.06 (dd, J = 10.1, 10.1 Hz; 1H; H-4 or H-6), 4.12–4.20 [m, 2H; H-2 and (H-4 or H-6)], 4.84 (dd, J = 2.7, 9.7 Hz, 1H; H-3), 5.89 (s, 1H; acetylmandelyl CH), 7.35–7.40 (m, 3H; ArH), 7.47–7.52 (m, 2H; ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.01, 18.07, 18.12 (4×CH_3), 21.10 (CH_3CO), 48.00, 48.42, 48.47 (4×OCH_3), 65.46, 67.16, 68.25, 68.42, 68.60, 72.87, 75.47 (6×*myo*-inositol ring carbons and 1×CH acetylmandelate), 99.09, 99.33, 99.89, 100.37 (4×C_q), 127.88, 129.00, 129.63 (3×CH, Ar), 133.60 (C_q, Ar), 167.81, 171.24 (2×C_q carbonyl) ppm; elemental analysis calcd (%) for $C_{28}H_{40}O_{13}$ (584.62): C 57.53, H 6.90; found: C 57.9, H 7.13.

Compound 6: R_f = 0.12 ($CHCl_3$/acetone 15:1); $[\alpha]_D^{20}$ = −210 (c = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01, 1.22, 1.26, 1.30 (4×s, 12H; 4×CH_3), 2.17 (s, 3H; $COCH_3$), 2.72, 3.22, 3.23, 3.25 (4×s, 12H; 4×OCH_3), 3.53 (dd, J = 2.4, 10.1 Hz, 1H; H-3), 3.61 (dd, J = 9.8, 9.8 Hz, 1H; H-5), 4.05 (dd, J = 9.8, 9.8 Hz, 1H; H-4 or H-6), 4.06 (dd, J = 9.8, 9.8 Hz, 1H; H-4 or H-6), 4.23 (dd, J = 2.4, 2.4 Hz, 1H; H-2), 4.91 (dd, J = 3.0, 10.7 Hz, 1H; H-1), 5.97 (s, 1H; acetylmandelyl CH), 7.34–7.39 (m, 3H; ArH), 7.46–7.51 (m, 2H; ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.87, 17.96, 18.05, 18.12 (4×CH_3), 21.10 (CH_3CO), 47.79, 48.40, 48.42, 48.48 (4×OCH_3), 65.45, 66.96, 68.34, 68.94, 68.98, 72.44, 74.91 (6×*myo*-inositol ring carbons and 1×CH acetylmandelate), 99.13, 99.25, 99.59, 100.40 (4×C_q), 128.43, 128.83, 129.47 (CH, Ar), 133.62 (C_q, Ar), 168.42, 170.56 (C_q, carbonyl) ppm; elemental analysis calcd (%) for $C_{28}H_{40}O_{13}$ (584.62): C 57.53, H 6.90; found: C 57.9, H 7.05.

D-1,6:4,5-Bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol (3a): A mixture of compound **5** (3.10 g, 5.3 mmol), sodium hydroxide (1.20 g 30 mmol) and methanol (150 mL) was heated at reflux for 30 min. The mixture was cooled and then neutralised with carbon dioxide. The remaining solid was dissolved in water (50 mL), and evaporated to dryness in vacuo. The crude product was extracted with CH_2Cl_2 (4×100 mL), and purification by flash chromatography (CH_2Cl_2/acetone 2:1) gave **3a** as a solid (1.96 g, 91%). R_f = 0.32 (CH_2Cl_2/acetone 2:1); m.p. 235–237°C (from acetone/hexane); $[\alpha]_D^{20}$ = +270 (c = 0.5 in $CHCl_3$); $(FAB)^+$ acc. mass found 377.1812 $[M-OMe]^+$; $C_{17}H_{29}O_9$ calcd 377.1811; elemental analysis calcd (%) for $C_{18}H_{32}O_{10}$ (408.45): C 52.93, H 7.90; found: C 52.5, H 7.94.

The NMR data were the same as for the racemic compound.

D-3,4:5,6-Bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol (3b): A mixture of compound **6** (3.00 g, 5.13 mmol), sodium hydroxide (1.20 g 30 mmol) and methanol (150 mL) was heated at reflux for 30 min. Workup and purification as for compound **3a** gave **3b** (1.91 g, 91%). R_f = 0.32 (CH_2Cl_2/acetone 2:1); m.p. 236–238°C (from acetone/hexane); $[\alpha]_D^{20}$ = −270 (c = 0.5 in $CHCl_3$); $(FAB)^+$ acc. mass found 377.1816 $[M-OMe]^+$; $C_{17}H_{29}O_9$ calcd 377.1811; elemental analysis calcd (%) for $C_{18}H_{32}O_{10}$ (408.45): C 52.93, H 7.90; found: C 52.4, H 7.86.

The NMR data were the same as for the racemic compound.

D-2,3-Di-*O*-benzyl-1,6:4,5-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol (7a): A mixture of compound **3a** (1.73 g, 4.25 mmol), DMF (40 mL), benzyl bromide (2.0 mL, 20 mmol) and sodium hydride (0.8 g, 20 mmol) was stirred at room temperature for 2 h. TLC (ether/hexane 1:1) showed a new product (R_f = 0.36), and no starting material. The excess sodium hydride was destroyed with methanol (5 mL) and the solvents were evaporated in vacuo. The remaining syrup was partitioned between water and ether (100 mL of each) and washed with 0.1 M aqueous hydrochloric acid, a saturated solution of sodium hydrogen carbonate and water (100 mL of each). The organic layer was dried ($MgSO_4$) and the remaining syrup was purified by flash chromatography (ether/hexane 1:1) to give a white foam (2.11 g, 84%). R_f = 0.36 (Et_2O/hexane 1:1); $[\alpha]_D^{20}$ = +182 (c = 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27, 1.29, 1.31, 1.33 (4×s, 12H; 4×CH_3), 3.21, 3.27, 3.28 (4×s, 12H; 4×OCH_3), 3.45 (dd, J = 2.3, 10.1 Hz, 1H; H-1 or H-3), 3.46 (dd, J = 2.7, 10.1 Hz, 1H; H-1 or H-3), 3.65 (dd, J = 9.8, 10.1 Hz, 1H; H-5), 3.91 (dd, J = 2.3, 2.3 Hz, 1H; H-2), 4.18 (dd, J = 10.15, 10.15 Hz, 1H; H-4 or H-6), 4.19 (dd, J = 9.8, 10.15 Hz, 1H; H-4 or H-6), 4.63, 4.82 (AB, J = 11.7 Hz, 2H; CH_2Ph), 4.85, 4.76 (AB, J = 11.7 Hz, 2H; CH_2Ph), 7.22–7.52 (m, 10H; CH_2Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.77, 17.86, 17.89, 18.01 (4×CH_3), 47.81, 47.88, 48.03, 48.08 (4×OCH_3), 72.78, 74.20 (2×CH_2Ph), 65.78, 68.77, 69.95, 70.32, 76.33, 77.66 (6×*myo*-inositol ring carbons), 98.52, 98.97, 99.42, 99.55 (4×C_q of BDA), 126.92, 127.10, 127.73, 127.87, 128.05 (CH, Ar), 138.96, 139.10 (C_q, Ar) ppm; elemental analysis calcd (%) for $C_{32}H_{44}O_{10}$ (588.70): C 65.29, H 7.53; found: C 65.4, H 7.41.

D-1,2-Di-*O*-benzyl-3,4:5,6-bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-*myo*-inositol (7b): A mixture of compound **3b** (1.43 g, 3.51 mmol), DMF (40 mL), benzyl bromide (2.0 mL, 20 mmol) and sodium hydride (0.8 g, 20 mmol) was stirred at room temperature for 2 h. TLC (ether/hexane 1:1) showed a new product (R_f = 0.36), and no starting material. Workup and purification as for the enantiomer **7a** gave the title compound (1.78 g, 86%), as a white foam.R_f = 0.36 (Et_2O/hexane 1:1); $[\alpha]_D^{20}$ = −182 (c = 0.5 in $CHCl_3$); elemental analysis calcd (%) for $C_{32}H_{44}O_{10}$ (588.70): C 65.29, H 7.53; found: C 65.3, H 7.54.

The NMR data were the same as for compound **7a**.

D-2,3-Di-*O*-benzyl-*myo*-inositol (8a): A mixture of compound **7a** (1.94 g, 3.30 mmol) and 95% aqueous trifluoroacetic acid (10 mL) was stirred in CH_2Cl_2 (10 mL) at room temperature for 30 minutes. The solvents were evaporated under reduced pressure and co-evaporated with chloroform (2×25 mL). The solid was suspended in cold MeOH (50 mL) and filtered off to give a white powder, which was recrystallised from acetonitrile (0.975 g, 82%). R_f = 0.24 ($CHCl_3$/MeOH 6:1); m.p. 197–198°C; $[\alpha]_D^{20}$ = +47 (c = 0.5 in DMF); ^1H NMR (400 MHz, $(CD_3)_2SO$): δ = 2.97 (ddd, J = 4.7, 9.0, 9.4 Hz, D_2O exch. gives dd, J = 9.0, 9.4 Hz, 1H; H-5), 3.21 (dd, J = 2.3, 10.15 Hz, 1H; H-3), 3.26 (ddd, J = 2.3, 4.7, 9.8 Hz, H-1, D_2O exch. gives dd, J = 2.0, 9.8 Hz, 1H; H-1), 3.44 (ddd, J = 4.7, 9.4, 9.4, D_2O exch. gives dd, J = 9.4, 9.4 Hz, 1H; H-4 or H-6), 3.59 (ddd, J = 4.7, 9.0, 9.4, D_2O exch. gives dd, J = 9.4, 9.4 Hz, 1H; H-4 or H-6), 3.94 (dd, J = 2.3, 2.3 Hz; 1H; H-2), 4.62 (s, 2H; CH_2Ph), 4.69–4.72 (br m, D_2O exch. gives AB, J = 11.7 Hz, 3H; CH_2Ph and OH), 4.75 (d, J = 4.7 Hz, D_2O exch., 1H; OH), 4.81 (d, J = 4.7 Hz, D_2O exch., 2H; 2× OH), 7.21–7.41 (m, 10H; CH_2Ph) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ = 71.26, 73.87 (2×CH_2Ph), 71.93, 72.38, 72.73, 75.28, 78.54, 80.19 (6×*myo*-inositol ring carbons), 126.77, 126.86, 126.94, 127.16, 127.72, 127.86 (CH, Ar), 138.94, 139.48 (C_q, Ar) ppm; elemental analysis calcd (%) for $C_{20}H_{24}O_6$ (360.41): C 66.65, H 6.71; found: C 66.3, H 6.77.

D-1,2-Di-*O*-benzyl-*myo*-inositol (8b): A mixture of compound **7b** (1.64 g, 2.78 mmol) and 95% aqueous trifluoroacetic acid (10 mL) was stirred in CH_2Cl_2 (10 mL) at room temperature for 30 minutes. Workup and purification as for compound **8a** gave the title compound (0.747 g, 75%). R_f = 0.24 ($CHCl_3$/MeOH 6:1); m.p. 197–198°C; $[\alpha]_D^{20}$ = −47 (c = 0.5 in DMF); elemental analysis calcd (%) for $C_{20}H_{24}O_6$ (360.41): C 66.65, H 6.71; found: C 67.0, H 6.71.

The NMR data were the same as for compound **8a**.

D-2,3-Di-*O*-benzyl-1,4,5,6-tetrakis[di(benzyloxy)phospho]-*myo*-inositol (9a): A mixture of bis(benzyloxy)diisopropylaminophosphine (1.035 g, 3.00 mmol) and 1*H*-tetrazole (0.35 g, 5 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 minutes in order to give the tetrazolide intermediate (δ_P 127 ppm). The tetraol **8a** (216 mg, 0.6 mmol) was then added, and the solution was stirred for a further 30 minutes. The reaction mixture was cooled to −78°C, and MCPBA (1.60 g, 4.6 mmol) was added. The cooling bath was removed and stirring was continued at room temperature for a further 30 minutes. The solvent was evaporated to give a white solid, which was dissolved in EtOAc (50 mL) and washed successively with 10% aqueous sodium metabisulfite and a saturated aqueous solution of sodium hydrogen carbonate (50 mL of each). The organic layer was separated and dried ($MgSO_4$), and the organic solvent was evaporated to give a syrup. The product was purified by flash chromatography, first with $CHCl_3$/acetone (5:1) and then with EtOAc/hexane (2:1), to provide the title compound as a syrup (740 mg, 88%). R_f = 0.12 ($CHCl_3$/acetone 5:1); $[\alpha]_D^{20}$ = 0 (c = 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.51 (dd, J = 9.8 Hz, 1H; H-1), 4.30 (ddd, J = 2.7, 7.4, 9.8 Hz, 1H; H-3), 4.44 (br s, 1H; H-2), 4.43, 4.52 (AB, J = 11.3 Hz, 2H; CH_2Ph), 4.59 (ddd, J = 9.4, 9.4, 9.8 Hz, 1H; H-5), 4.64, 4.79 (AB, J = 11.3 Hz, 2H; CH_2Ph), 4.82–5.10 (m, 18H; 8×CH_2Ph, H-4 and H-6), 7.06–7.33 (m, 50H; Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.14, 69.38, 69.51, 69.62, 69.77 (CH_2Ph of benzyl phosphate), 72.25, 75.25 (CH_2Ph), 74.54, 75.75, 76.80, 77.30, 77.59 (6×*myo*-inositol ring carbons), 127.35, 127.43, 127.56, 127.58, 127.62, 127.72, 127.81, 127.85, 127.90, 128.00, 128.04, 128.09, 128.12, 128.14, 128.16, 128.38 (CH, Ar), 132.61, 134.16, 135.35, 135.45, 135.75, 135.82, 137.04, 137.86 (C_q, Ar) ppm; $(FAB)^+$ acc. mass found 1401.4119; $C_{76}H_{77}O_{18}P_4$ calcd 1401.4060; elemental analysis calcd (%) for $C_{76}H_{77}O_{18}P_4$ (1401.32): C 65.14, H 5.47; found: C 64.8, H 5.45.

D-1,2-Di-*O*-benzyl-3,4,5,6-tetrakis[di(benzyloxy)phospho]-*myo*-inositol (9b): A mixture of bis(benzyloxy)diisopropylaminophosphine (1.035 g, 3.00 mmol) and 1*H*-tetrazole (0.35 g, 5.00 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 minutes in order to give the tetrazolide intermediate (δ_P 127 ppm). The tetraol **8b** (216 mg, 0.60 mmol) was added, and the solution was stirred for a further 30 minutes. Workup and purification as for the enantiomer **9a** gave the title compound as a syrup (457 mg, 54%). R_f = 0.12 ($CHCl_3$/acetone 5:1); $[\alpha]_D^{20}$ = 0 (c = 0.5 in $CHCl_3$); $(FAB)^+$ acc. mass found 1401.4123; $C_{76}H_{77}O_{18}P_4$ calcd 1401.4060; elemental analysis calcd (%) for $C_{76}H_{77}O_{18}P_4$ (1401.32): C 65.14, H 5.47; found: C 65.0, H 5.49.

The NMR data were identical to those for compound **9a**.

1D-*myo*-Inositol 1,4,5,6-tetrakisphosphate (1a): Compound **9a** (473 mg, 338 μmol) was hydrogenolysed in a mixed solvent containing methanol and water (60 mL, 5:1) in the presence of palladium hydroxide (1.0 g, 20% on carbon) at 50 psi for 20 h. The reaction mixture was filtered through a PTFE syringe filter to remove the catalyst, and the solvents were evaporated in vacuo to give a glassy residue. The compound was then subjected to ion-exchange chromatography on Q-Sepharose Fast Flow with a triethylammonium hydrogen carbonate buffer gradient of 0.40 M to 1.0 M over 80 tubes and 1.0 M to 2.0 M buffer over 15 tubes. The compound eluted between 0.8 M to 1.0 M buffer, and was detected by the Briggs test[24] for the detection of inorganic phosphate. The required frac-

tions were pooled and further quantified by the Briggs test[24] to give the pure title compound (178 μmol, 53%). $[\alpha]_D^{20} = -7.9$ (c = 1.4 in MeOH) [lit.[10a] −6.2 (c = 2.15 in H_2O, pH 9.5); lit.[10b] −6.9 (c = 0.65 in H_2O, 8 K^+ salt); lit.[10c] −10.2 (c = 2.46 in H_2O, pH 10.7); lit.[10e] +8.0 (c = 1.05 in H_2O, pH 7); lit.[10f] +8.0 (c = 1.1 in H_2O, pH 7); lit.[10g] −4.8 (c = 2.7 in H_2O, free acid)]; ^{1}H NMR (400 MHz, D_2O): δ = 3.56 (dd, J = 2.7, 9.7 Hz, 1H; H-3), 4.08 (ddd, J = 2.7, 9.7, 9.7 Hz, 1H; H-1), 4.16 (br, 1H; H-2), 4.17 (ddd, J = 9.5, 9.5, 9.5 Hz, 1H; CH), 4.41 (ddd, J = 9.4, 9.4, 9.4 Hz, 1H; CH), 4.60 (ddd, J = 9.8, 9.8, 9.8 Hz, 1H; CH) ppm; ^{31}P NMR (160 MHz, D_2O ^{1}H-decoupled): δ = 3.26 (s, 1P), 2.39 (s, 1P), 2.14 (s, 1P), 2.03 (s, 1P) ppm; m/z (−ve ion FAB): 498.9 (100%) $[M-H]^-$; $(FAB)^-$ acc. mass found: 498.9209; $C_6H_{15}O_{18}P_4$ calcd 498.9209.

1D-*myo*-Inositol 3,4,5,6-tetrakisphosphate (1b): Deprotection of compound **9b** as described for **9a**, and purification as described for enantiomer **1a** gave tetrakisphosphate **1b** (72 μmol, 37%); $[\alpha]_D^{20} = +8.1$ (c = 1.72 in MeOH) [lit.[10a] +6.2 (c = 2.15 in H_2O, pH 9.5); lit.[10b] +7.2 (c = 2.3 in H_2O, 8 K^+ salt); lit.[10c] +9.8 (c = 1.43 in H_2O, pH 11.1); lit.[10d] −3.0 (c = 1 in H_2O, free acid); lit.[10f] −2.9 (c = 0.3, H_2O, pH 1.6); lit.[10f] −5.6 (c = 0.2 in H_2O, pH 7); lit.[10g] + 4.1 (c = 2.7 in H_2O, free acid)].

NMR spectra and mass spectra were as for **1a**.

1D-3-*O*-methyl-*myo*-inositol [(+)-bornesitol, 10]: Methyl iodide (2.5 mL, 40 mmol) was added to a mixture of diol (+)-**3a** (408 mg, 1.00 mmol), dibutyl tin oxide (274 mg, 1.1 mmol) and tetrabutylammonium bromide (355 mg, 1.1 mmol) in acetonitrile (40 mL). The mixture was heated at reflux for 17 h under a Soxhlet apparatus containing 3 Å sieves, allowed to cool, and then concentrated by evaporation under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 2:1) to give a white solid (411 mg). Aqueous TFA (90%, 4 mL) was added to this solid and the solution was stirred at room temperature for 1.5 h, after which time TLC showed a single product (R_f = 0.22, acetone/water 5:1). The solution was concentrated by evaporation under reduced pressure, and then under high vacuum to remove traces of TFA and butanedione, giving pentaol **10** (157 mg, 81%) as a crystalline solid. R_f = 0.22 (acetone/water 5:1); m.p. 202–205°C (from MeOH/EtOH) (lit.[20] 205–207°C); $[\alpha]_D^{20} = +34$ (c = 0.6 in H_2O) [lit.[20] +31.9 (c = 1 in H_2O)].

NMR data agreed with those reported for the enantiomer.[19]

L-2,3:4,5-Bis-*O*-(2,3-dimethoxybutane-2,3-diyl)-iditol (11): A solution of the diol (−)-**3b** (320 mg, 0.783 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of $SiO_2/NaIO_4$[21] (2.0 g) in CH_2Cl_2 (5 mL). The suspension was stirred vigorously at room temperature for 16 h and was then filtered through a pad of Celite. The Celite was washed well with $CHCl_3$ (4× 20 mL) and the combined washings were concentrated by evaporation under reduced pressure to leave a colourless oil. The oil was taken up in ethanol (10 mL), and $NaBH_4$ (78 mg, 2.0 mmol) was added. The mixture was stirred at room temperature for 30 min, water (2 mL) was added, and after a further 30 min the mixture was concentrated by evaporation under reduced pressure. The residue was taken up in water (20 mL) and extracted with CH_2Cl_2 (5×20 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated by evaporation under reduced pressure to give the diol **11** (281 mg, 87%) as a white crystalline solid. R_f = 0.24 (ethyl acetate); m.p. 205–207°C, with sublimation (from EtOAc/hexane); $[\alpha]_D^{20} = -190$ (c = 1 in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.27 (s, 6H; 2×CH_3), 1.29 (s, 6H; 2×CH_3), 3.25 (s, 12H; 4×OCH_3), 3.49 (dd, J = 10.4, 4.8 Hz, D_2O exch., 2H; 1-OH and 6-OH), 3.62 (ddd, J = 10.4, 10.4, 3.0 Hz, 2H; H-1a and H-6a), 3.75–3.85 (m, 4H; H-1b, H-6b and 2×CH), 3.95–4.05 (m, 2H; 2×CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.60 (2×CH_3), 17.70 (2×CH_3), 48.36 (2×OCH_3), 48.43 (2×OCH_3), 63.85 (C-1 and C-6), 70.03 (2×CH), 72.43 (2×CH), 99.03 (2×C_q of BDA), 99.44 (2×C_q of BDA) ppm; m/z (+ve ion FAB): 347.3 (10), 315.2 (50), 116.2 (50), 101.1 (100), 73.1 (75); elemental analysis calcd (%) for $C_{18}H_{34}O_{10}$ (410.46): C 52.67, H 8.35; found: C 52.6, H 8.3.

L-Iditol hexaacetate (12): A mixture of trifluoroacetic acid and water (2 mL of each) was added to compound **11** (100 mg, 0.244 mmol). The solution was stirred at room temperature for 2 h and was then concentrated by evaporation under reduced pressure. Pyridine (2 mL) and acetic anhydride (1 mL) were added to the residue and the solution was stirred at room temperature for 16 h. The solution was concentrated by evaporation under reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc 3:2 to 1:1) to give **12** (49 mg, 0.113 mmol, 46%) as a colourless, crystalline solid. R_f = 0.16 (ethyl acetate/hexane 1:1); m.p. 122–124°C (from ethanol) (lit.[22] 119–120°C); $[\alpha]_D^{20} = -23$ (c = 0.95 in $CHCl_3$) [lit.[22] −22.7 (c = 1.27 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (6H; 2×CH_3), 2.10 (6H; 2×CH_3), 2.11 (6H; 2×CH_3), 4.04 (J = 12.1, 5.9 Hz, 2H; H-1a and H-6a), 4.31 (J = 12.1, 4.7 Hz, 2H; H-1b and H-6b), 5.24–5.31 (m, 2H; 2×CH), 5.34–5.39 (m, 2H; 2×CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.65 (2×CH_3), 20.72 (2×CH_3), 20.76 (2×CH_3), 61.67 (C-1 and C-6), 68.65 (2×CH), 69.10 (2×CH), 169.47 (2×C=O), 169.68 (2×C=O), 170.07 (2×C=O) ppm.

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