

THE TOTAL SYNTHESIS OF *myo*-INOSITOL POLYPHOSPHATES

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Abstract

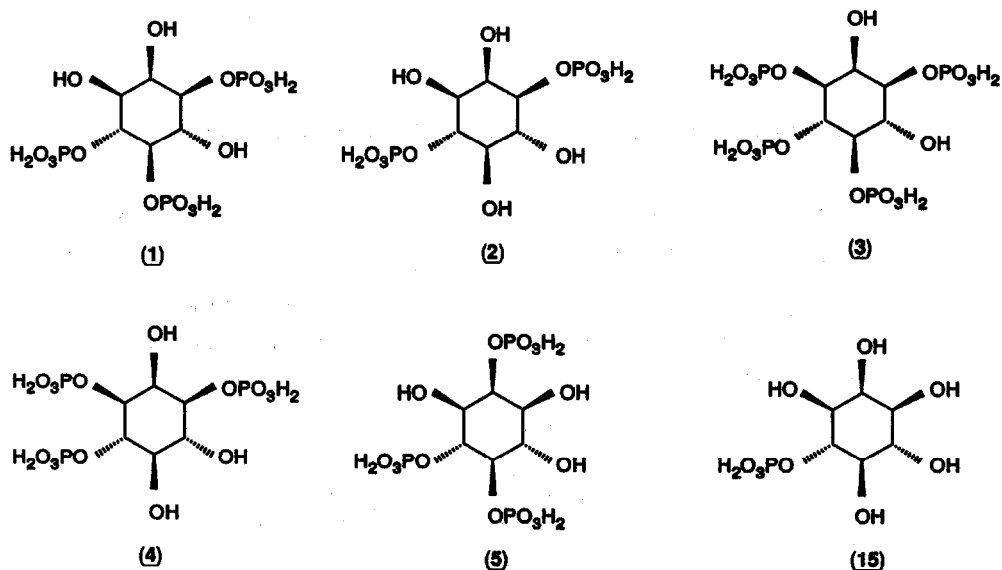
Total synthesis of the individual enantiomers of *myo*-inositol 4-phosphate (**15**), *myo*-inositol 1,4-bisphosphate (**2**) and *myo*-inositol 1,4,5-trisphosphate (**1**), together with syntheses of racemic *myo*-inositol 1,3,4-trisphosphate (**4**) and *myo*-inositol 2,4,5-trisphosphate (**5**) are reported. The syntheses feature the use of camphanic acid esters for resolution of protected inositols, and the use of tetrabenzylpyrophosphate as an efficient phosphorylating agent for polyhydroxy alcohols.

Recently it has been found that agonist stimulation of a number of receptors results in the hydrolysis of phosphatidylinositol-4,5-bisphosphate [(Ptd)Ins(4,5)P₂] to give diacylglycerol¹ and D-*myo*-inositol-1,4,5-trisphosphate [1,4,5-IP₃, (**1**) Fig 1].^{2,3} 1,4,5-IP₃ acts as a second messenger and directly mediates the release of calcium from intracellular stores.² The major pathway for terminating the action of 1,4,5-IP₃ is believed to occur through removal of the 5-phosphate group by a specific 5-phosphatase present in the plasma membranes.³ The 1,4-bisphosphate formed, [1,4-IP₂, (**2**)], is further degraded by other phosphatases first to give 1- and 4-monophosphates and ultimately free inositol which is recycled in the brain to provide more (Ptd)Ins(4,5)P₂.^{4,5} An alternate pathway for 1,4,5-IP₃ degradation has been identified⁵ which involves phosphorylation of the 3-hydroxyl group of 1,4,5-IP₃ to give 1,3,4,5-IP₄ (**3**). This is dephosphorylated to 1,3,4-IP₃ (**4**) which is further metabolized to bisphosphates that are then recycled in the IP pathway. In addition to the naturally occurring inositol phosphates, D-*myo*-2,4,5-trisphosphate [2,4,5-IP₃, (**5**)], which has been isolated as a by-product^{2,7} in the preparation of 1,4,5-IP₃, has also been shown to release calcium.²

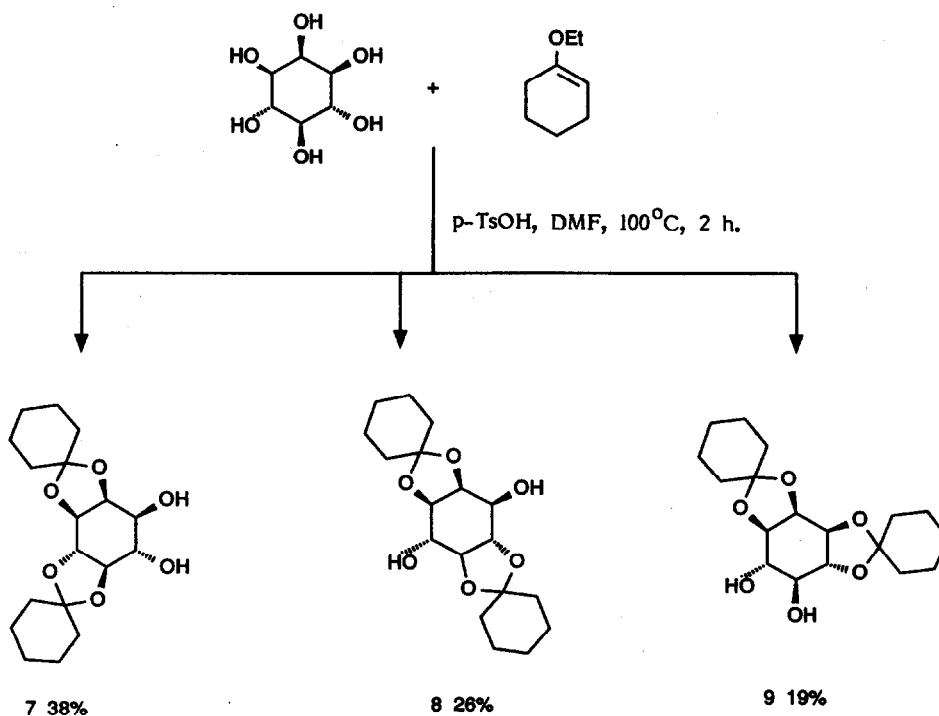
In order to study the fundamental biochemical processes related to the inositol pathway, an adequate supply of the natural products, as well as derivatives which are not readily available from natural sources was needed. This need led us to develop a general and efficient method for synthesizing inositol phosphates which we have communicated in preliminary form.^{8,9}

A key problem encountered in the synthesis of inositol phosphates is the synthesis and resolution of suitably protected inositol derivatives. A popular solution to this problem involves treating *myo*-inositol (**6**) with ethoxycyclohexene^{10a} and a catalytic amount of acid, giving all three of the bicyclic ketals of *myo*-inositol **7**, **8**, and **9** in large quantities^{10b} (Scheme 1). The following paper will deal with the subsequent manipulation of protecting groups of ketals **7** and **8** and their conversion to the natural products **1**, **2**, **4**, **5** and **15**.

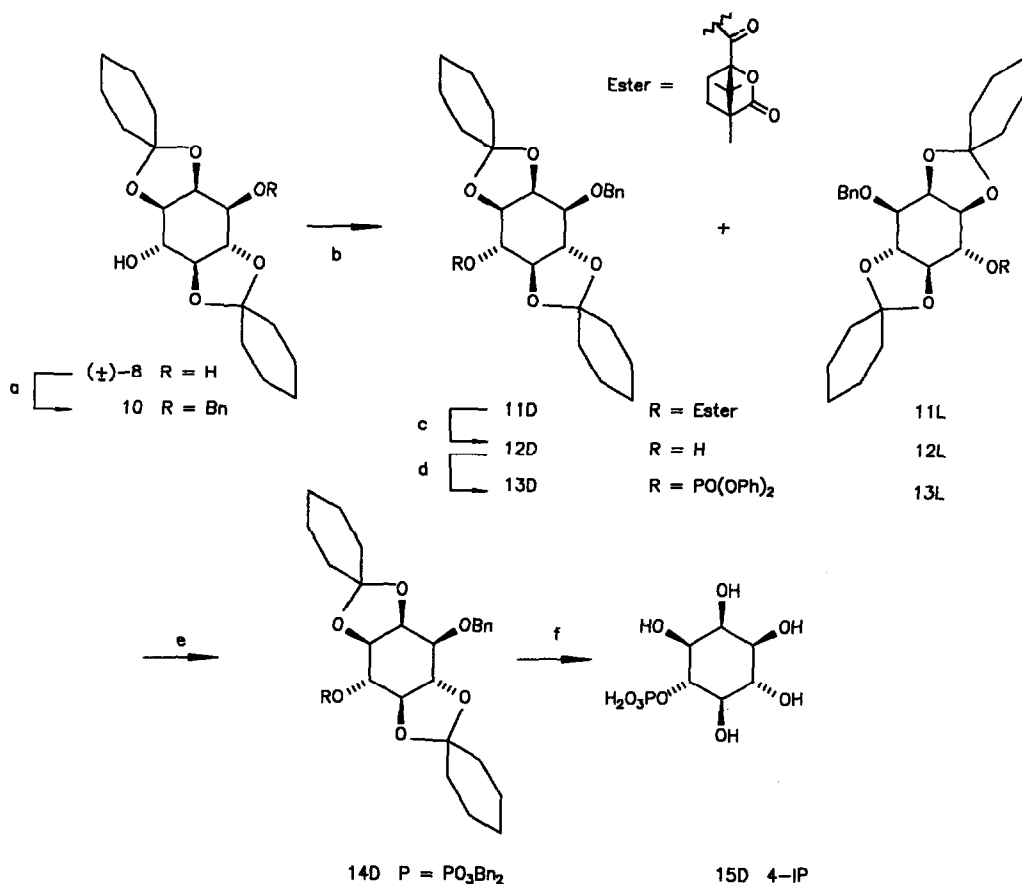
FIGURE 1



SCHEME 1



SCHEME 2



Scheme 2

(a) NaH, PhCH₂Br, PhMe, reflux; (b) S(-)-camphanic acid chloride, CH₂Cl₂, (Et)₃N, DMAP, 25°C; (c) KOH, EtOH, 25°C; (d) (PhO)₂POCl, CH₂Cl₂, (Et)₃N, DMAP, 25°C; (e) PhCH₂OH, NaH, THF, 25°C; (f) 10% Pd/C, EtOH-H₂O (80:20), H₂, 50 psig, 25°C.

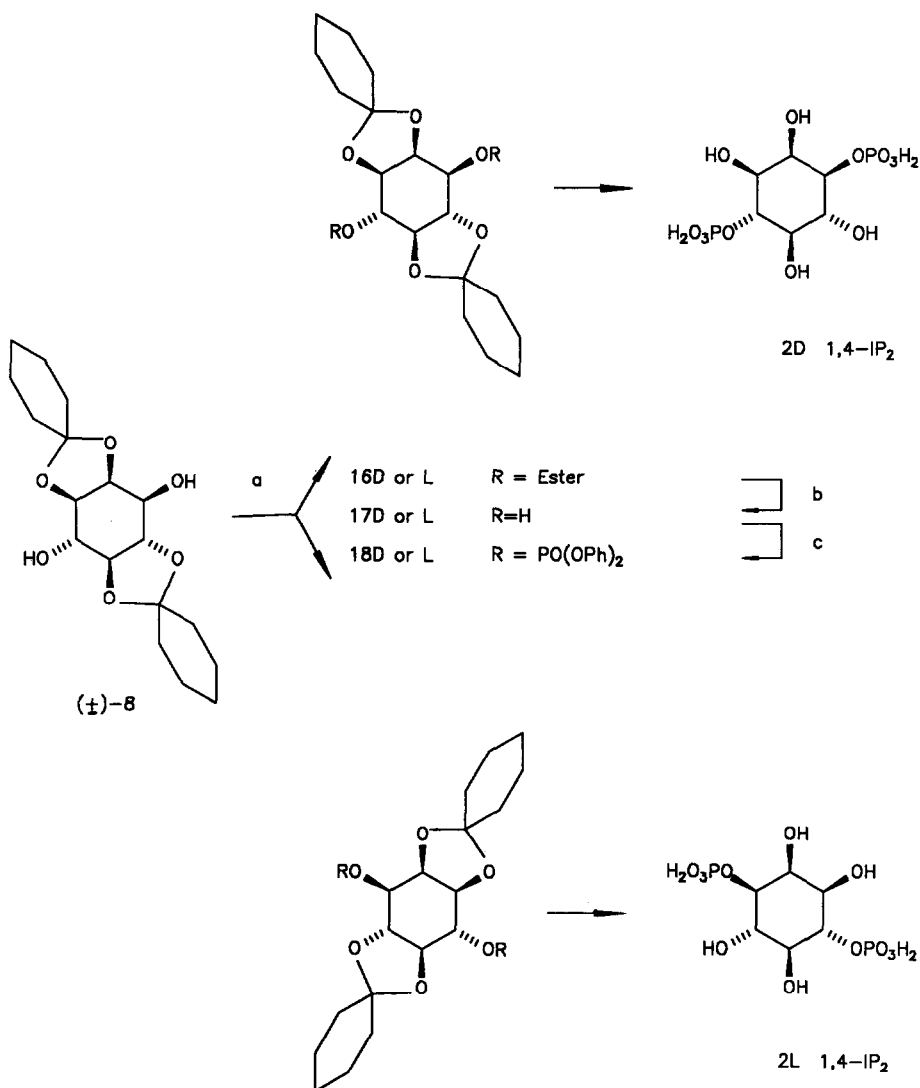
Results

D- and L-*myo*-inositol 4-phosphate: (Scheme 2) Racemic 1,2:4,5-di-O-cyclohexylidene *myo*-inositol (**8**) was alkylated selectively in the 3-position in 60% yield. The resultant alcohol **10** was acylated with S-(-)-camphanic acid chloride to give the diastereomeric camphanate esters **11D** and **11L** in quantitative yield. The more polar diastereomer was obtained by crystallization from the mixture followed by two more recrystallizations (EtOAc/petrol, 1:2). The second diastereomer was recovered from the mother liquors by MPLC (Lichoprep Silica 60). Both diastereomers showed >99% purity by HPLC and ^1H NMR. The use of camphanic acid esters provides a more convenient method for resolving *myo*-inositol derivatives than that of mono-glycosides which was first pioneered by Stepanov.¹¹ Basic hydrolysis of the camphanate esters afforded the enantiomeric alcohols **12D** ($[\alpha]_{\text{D}} = -26.1^\circ$) and **12L** ($[\alpha]_{\text{D}} = 25.9^\circ$). The alcohol **12D** was phosphorylated in the normal manner to yield the diphenyl protected inositol phosphate, **13D**. This was transesterified using the anion of benzyl alcohol in tetrahydrofuran (THF) to give the dibenzyl phosphate **14D**. Hydrogenolysis of **14D** resulted in deprotection of the benzyl groups followed by concomitant cleavage of the ketals, to yield (-)-*myo*-inositol 4-phosphate **15D**, which was isolated as its cyclohexylammonium salt, ($[\alpha]_{\text{D}} = -1.3^\circ$). No isomeric inositol phosphates were evident by HPLC or ^1H NMR. Starting with alcohol **12L** and employing the same methodology yielded (+)-*myo*-inositol 4-phosphate, **15L** ($[\alpha]_{\text{D}} = 1.1^\circ$).

D- and L-*myo*-inositol 1,4-bisphosphates (Scheme 3) D-*myo*-inositol 1,4-bisphosphate (**2**) has been synthesized from resolved 1,2:4,5-di-O-cyclohexylidene *myo*-inositol (**8**) by Shvets.¹² The resolution of diol **8** involved forming an orthoacetate of the 1-alcohol followed by tedious separation of the diastereomers.¹¹ In theory, ester **11D** could be fully deprotected to give the resolved diol. However, we found that it was more convenient to treat diol **8** with two equivalents of S-(-)-camphanic acid chloride to form diastereomeric biscamphanate esters **16**. These were separated using MPLC (Lichoprep Silica 60) to yield the two camphanate esters **16D** and **16L** in 60% overall yield. Attempts to prepare the mono-camphanate ester gave a mixture of mono and bisesters, and the diastereomeric monoesters were not readily separable by flash chromatography. Basic hydrolysis of the esters afforded the two enantiomeric diols **17D** ($[\alpha]_{\text{D}} = 15.7^\circ$) and **17L** ($[\alpha]_{\text{D}} = 16.0^\circ$) in near quantitative yield. Phosphorylation of each enantiomer with diphenylphosphoryl chloride gave a 90% yield of the bisphosphate esters **18**. Hydrogeneolysis of each protected bisphosphate resulted in deprotection of the phenyl protecting groups as well as cleavage of the cyclohexylidene ketals to yield (+)-*myo*-inositol 1,4-bisphosphate¹¹ ($[\alpha]_{\text{D}} = 0.12^\circ$) and (-)-*myo*-inositol 1,4-bisphosphate ($[\alpha]_{\text{D}} = -0.12^\circ$).

D- and L-*myo*-inositol 1,4,5-trisphosphates. (Scheme 4) In order to synthesize 1,4,5-IP₃, it was necessary to develop an efficient method for phosphorylating a protected triol such as **20**. Gigg was the first to report a syntheses of racemic triol **20** from (+)-1,2:4,5-bis-cyclohexylidene *myo*-inositol **8**.¹³ Ozaki¹⁴ has also published a similar synthesis of enantiomerically pure **20** that involved a resolution of an inositol intermediate. We found that the requisite enantiomeric 1,4,5-triol could be most expeditiously obtained in four steps from 1,2:5,6-di-O-cyclohexylidene *myo*-inositol¹⁰ (**7**), the major product of the ketalization of *myo*-inositol (Scheme 1). Benzylolation of **7** following Garegg's

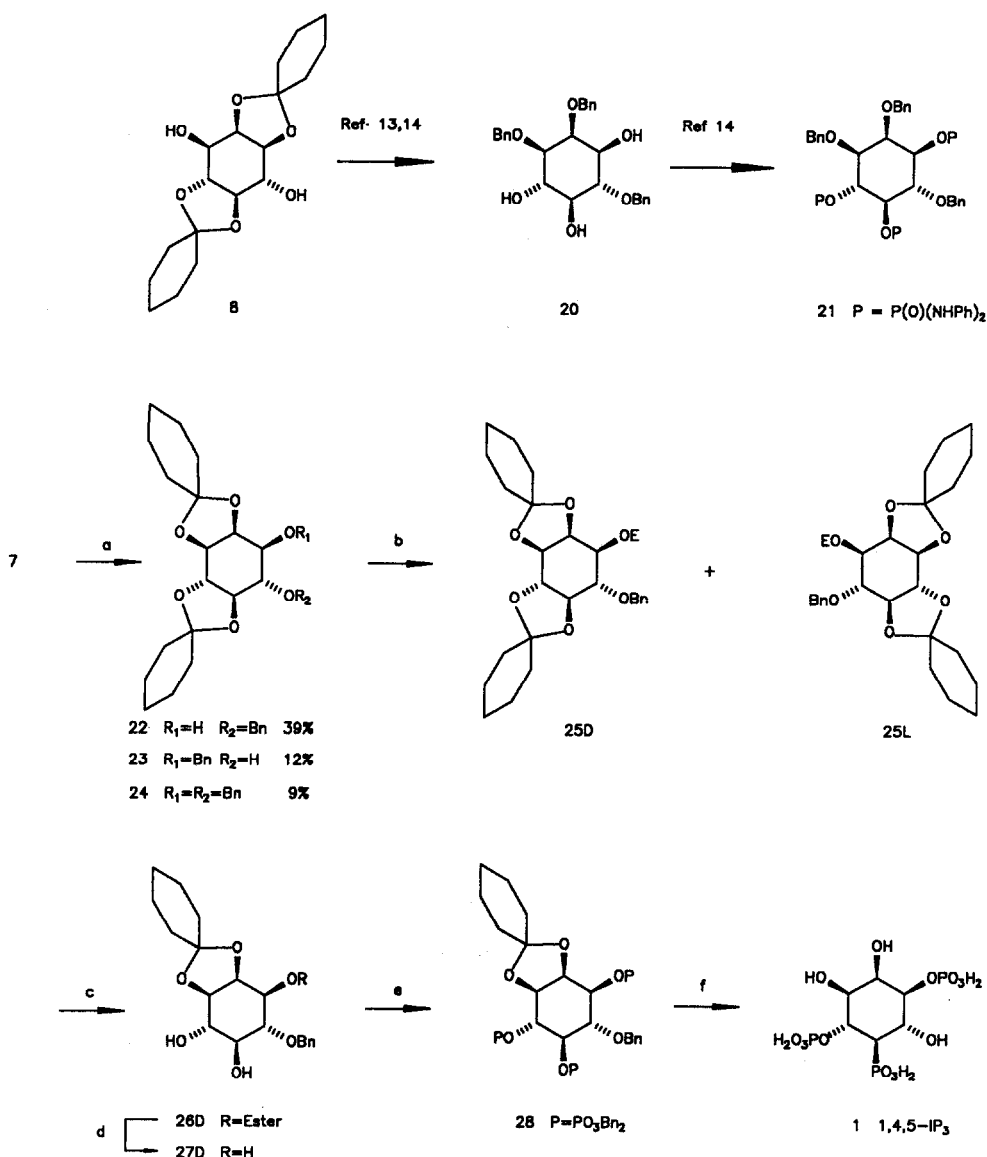
SCHEME 3



Scheme 3

(a) *S*(-)-camphanic acid chloride, CH₂Cl₂, (Et)₃N, DMAP, 25°C; (b) KOH, EtOH, 25°C; (c) (PhO)₂POCl, CH₂Cl₂, (Et)₃N, DMAP, 25°C; (d) PtO₂, EtOH, 1 atm, 25°C.

SCHEME 4



Scheme 4

(a) $PhCH_2Br$, Bu_4NHSO_4 , CH_2Cl_2 , 5% NaOH, reflux, 6 h; (b) *S*(-)-camphanic acid chloride, CH_2Cl_2 , $(Et)_3N$, DMAP, 25°C; (c) Acetyl chloride, $MeOH/CH_2Cl_2$ (1:5 v/v), 25°C, 3 h; (d) LiOH, DME/ H_2O (1:1), 25°C, 2 h; (e) NaH, $((BnO)_2P(O))_2O$, DMF, 0°C; (f) H_2 , 50 psig, 10% Pd/C, 95% EtOH, 25°C, 3 h then $AcOH/H_2O$, 25°C, 18 h.

procedure^{10b} provided the 3-hydroxyl-4-benzyl derivative 22 in 39% yield along with formation of the 3-benzyl-4-hydroxyl and bis-benzyl derivatives 23 and 24 in 19% and 9% yields, respectively. All three compounds were readily separated by chromatography. Recently Fraser-Reid¹⁵ has developed a chemoselective alkylation of diol 8 which gives exclusively the 3-hydroxyl compound 22. Esterification of the free hydroxyl substituent of 22 with S-(-)-camphanic acid chloride yielded a mixture of diastereomers which were chromatographically separated to give 25D and 25L. The diastereomeric purity of each compound exceeded 98% as determined both by HPLC and ¹H NMR. All three methyl groups in the ester were singlets, two of which were nonequivalent in the diastereomers. Selective hydrolysis of the trans ketal of each diastereomer gave diols 26D and 26L. Basic hydrolysis of the ester group afforded enantiomerically pure triols 27D and 27L.

With an efficient route to 1,4,5-triol in hand, it was critical to develop a procedure for phosphorylating the three hydroxyl groups of 27 in high yield. It was also important that the phosphate protecting groups be readily removed to facilitate purification of the final products. Diphenylphosphoryl chloride, which was successfully employed in the synthesis of 4-IP and 1,4-IP₂, has been shown to phosphorylate the vicinal diols of ketals 8 and 9 in low yields¹². We found that use of this reagent with more functionalized inositol derivatives as well as triol 27D gave a mixture of bisphosphates and 4,5-cyclized phosphates due to the lability of the phosphate protecting group. A reagent which has also found modest success in phosphorylating myo-inositols with vicinal diols is dianilidophosphoryl chloride.^{16,17} Ozaki found that this reagent reacted with triol 20 in 44% yield to give hexaanilido trisphosphate 21.¹⁴ Removal of the blocking groups led to low yield of 1,4,5-IP₃ after tedious ion exchange chromatography to separate isomers and by-products. We experienced these poor results with triol 27. An answer to the phosphorylation problem was recently reported by Bartlett.¹⁸ He showed that tetrabenzylpyrophosphate (TBPP)¹⁹ reacted in high yield with an alkoxide salt to give a dibenzyl-phosphate which was easily deprotected in high yield. The question remaining was whether or not this method would be applicable to phosphorylating vicinally disposed alcohols. Triol 27D was treated with three equivalents of potassium hydride in THF (60°C, 30 min) followed by TBPP to yield the protected trisphosphate 28D in low (25-40%) yield. The yield of phosphate was increased by simply preforming the tri-alkoxide salt at elevated temperatures and then adding the TBPP at ambient temperature. Under these conditions, trisphosphate 28D was obtained in 65% yield with no evidence of cyclized products. Even higher yields (>80%) of phosphate 28D were realized when the tri-sodium salt of 27D was formed at 0°C in DMF in the presence of TBPP. Hydrogenation of 28D rapidly removed the benzyl groups and mild acid hydrolysis cleaved the cyclohexylidene group to give D-(+)-myo-inositol 1,4,5-trisphosphate^{20,21} (1D). In a similar manner L-(-)-myo-inositol 1,4,5-trisphosphate (1L) was synthesized using triol 27L.

Since our preliminary communication reporting the synthesis of 1, other groups have disclosed methods for phosphorylating vicinal diols using either TBPP^{15,22} or phosphite triesters.^{14,23-26}

(+)-myo-inositol 1,3,4-trisphosphate (Scheme 5) Manipulation of the ketal, benzyl and alkyl protecting groups on the various hydroxyls of myo-inositol using similar methodology to that described by Gigg¹³ et al allows for the preparation of any triol from any of the three biscyclohexylidene ketals. In

(±)8 $\xrightarrow{\text{Ref 13}}$ $\xrightarrow{\text{c}}$ 32

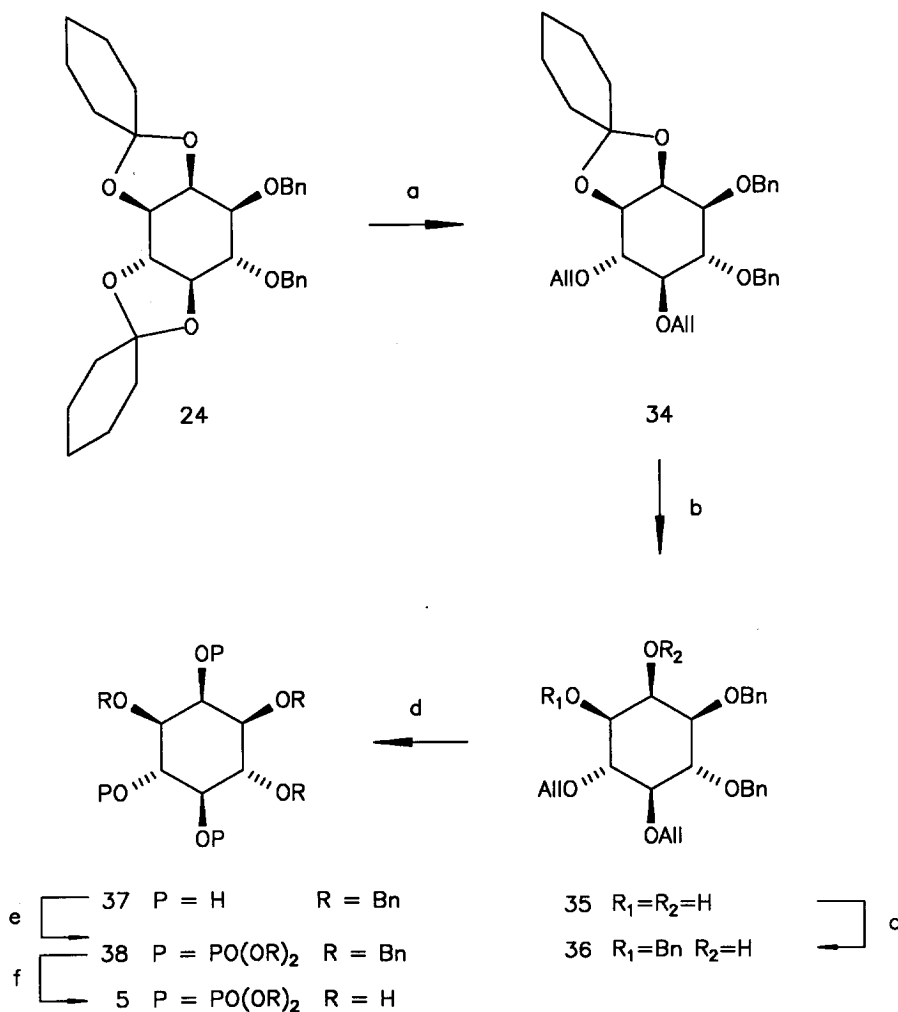
29 $\text{R}_1=\text{R}_2=\text{H}$ a
 30 $\text{R}_1=\text{AlI} \text{ R}_2=\text{H}$ b
 31 $\text{R}_1=\text{AlI} \text{ R}_2=\text{Bn}$ c

32 $\xrightarrow{\text{d}}$ 33

33 $\xrightarrow{\text{e}}$ 4 1,3,4-IP₃

(a) AllylBr, NaOH, PhH, 80°C; (b) NaH, PhCH₂Br, DMF; (c) 10% Pd/C, p-TsOH, MeOH, H₂O; (d) NaH, ((BnO)₂P(O))₂O, DMF, 0°C; (e) H₂, 50 psig, 10% Pd/C, 95% EtOH, 25°C, 3 h.

SCHEME 6



Scheme 6

(a) CHCl₃, MeOH, acetyl chloride, 25°C, 1 h; NaH, AllylBr, DMF; (b) HOAc, H₂O, 80°C, 1 h; (c) NaOH, PhCH₂Cl, PhH, 80°C, 18 h; (d) 10% Pd/C, p-TsOH, MeOH, H₂O; (e) NaH, ((BnO)₂P(O))₂O, DMF, 0°C; (f) H₂, 50 psig, 10% Pd/C, 95% EtOH, 25°C, 3 h.

the present case, 2,5,6-tri-*O*-cyclo-hexylidene-myo-inositol (32) was prepared from 1,2:4,5-di-*O*-cyclo-hexylidene-myo-inositol (8). Exhaustive allylation of 8 gave the fully protected inositol. Selective removal of the trans ketal, followed by benzylation and removal of the cis ketal provided 1,4-di-*O*-allyl-5,6-di-*O*-benzyl-myo-inositol (29) previously prepared by Gigg¹³ *et al* through the isopropylidene ketals. The equatorial alcohol of this racemic diol was selectively alkylated with allyl bromide to give 1,3,4-tri-*O*-allyl-5,6-di-*O*-benzyl-myo-inositol (30) in 88% yield. This selectivity for equatorial over axial alkylation is well precedented in the myo-inositol literature.²⁷ Benzylation of the axial alcohol gave the fully protected myo-inositol (31) in 93% yield. Removal of the allyl groups was accomplished using palladium on carbon, *p*-toluenesulfonic acid in methanol²⁸ to give 2,5,6-tri-*O*-benzyl-myo-inositol 32 (65%). In contrast to the 1,4,5-IP₃ phosphorylation, treatment of the tripotassium alkoxide of triol 32 with TBPP in THF at room temperature gave poor yields of tris-dibenzylphosphate 33. When the trisodium salt of the triol 32 was formed in the presence of TBPP in DMF at <0°C, the tris-dibenzylphosphate 33 was obtained in 70% yield. Subsequent deprotection led to racemic myo-inositol-1,3,4-trisphosphate²⁹ (4).

(+)-myo-inositol-2,4,5-trisphosphate (Scheme 6) In our previous communication,⁸ the triol 37 needed for the synthesis of myo-inositol 2,4,5-trisphosphate was derived from 1,2:4,5-di-*O*-cyclohexylidene-myo-inositol (8) by protecting group manipulation similar to that described above. In an effort to improve this sequence, we elected to prepare 37 from 3,4-di-*O*-cyclohexylidene-myo-inositol 24, a byproduct in the 1,4,5-IP₃ sequence. This fully protected inositol was treated with mild acid to remove selectively the trans ketal, and then diallylated to give 34. Acid hydrolysis of the cis-ketal gave racemic diol 35 which was identical with a sample prepared from compound 8. Selective benzylation of the equatorial alcohol provided 36 and subsequent diallylation gave 1,3,4-tri-*O*-benzyl-myo-inositol (37).¹³ As in the 1,3,4-IP₃ case, good phosphorylation yields were obtained if the trisodium alkoxide was formed at <0°C in the presence of TBPP (64%). The nine benzyl groups of 38 were removed by catalytic hydrogenation in 75% to give racemic myo-inositol-2,4,5-trisphosphate (5) isolated as its pentasodium salt.

Although both the 1,3,4-IP₃ and 2,4,5-IP₃ trisphosphates were obtained in racemic form, it should be possible to use the resolved diols 12D or 12L to prepare either compound in enantiomerically pure form.

Conclusion

We have described methodology for preparing a number of inositol phosphates. In the course of our investigations, a new procedure for resolving inositol derivative was found. Also, a method for efficiently phosphorylating vicinal diols was developed. This method has also found use in the preparation of myo-inositol 1,3,4,5-tetrakisphosphate and other inositol phosphates starting from a common orthoacetal intermediate,^{9b} the details of which will be reported elsewhere.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. Tetrahydrofuran was distilled from the sodium ketyl of benzophenone. Triethylamine was dried by refluxing and distilling from calcium hydride. N,N-dimethylformamide (DMF) was dried by storing over 4A molecular sieves. Petrol refers to the fraction boiling between 60°C–80°C unless otherwise indicated.

Melting points were determined in open capillary tubes and are uncorrected. ^1H NMR and ^{31}P NMR were recorded on a Varian XL-300, Bruker AM360 or a Nicolet NT-360 spectrometer. Chemical shifts are reported as values relative to Me_4Si as internal standard unless otherwise indicated. HPLC were obtained on a Waters HPLC using Porasil (3.9mm x 30cm) or Bondapak-NH₂ (3.9mm x 30cm) columns with UV (A_{254}) or RI detection. Thin-layer chromatography (TLC) was carried out on E. Merck 60F-254 precoated silica plates. Visualization was done with UV light, iodine or a by dipping plates in a solution of 5% vanillin/90% EtOH/5% sulfuric acid followed by charring on a hot plate. All combined organic extracts were dried over anhydrous magnesium sulphate or sodium sulphate before evaporation on a Buchi rotary evaporator with bath temperature of 50°C or below. Chromatography refers to flash chromatography.²⁰ Optical rotations were recorded on a Perkin Elmer 241 polarimeter. Mass spectra were recorded with a VG70-250.

(+)-1,2:4,5-Dicyclohexylidene-my α -inositol (**8**), (+)-1,2:5,6-dicyclohexylidene-my α -inositol (**7**) and (+)-1,2:3,4-dicyclohexylidene-my α -inositol (**9**):^{10b} A mixture of my α -inositol (33 g, 180 mmol), 1-ethoxycyclohexene^{10a} (60 g, 430 mmol) and p-toluenesulphonic acid monohydrate (1 g, 5.2 mmol) in dry DMF (500 ml) was heated at 100°C for 2 h. The solution was cooled to room temperature, diluted with CH_2Cl_2 (750 ml) and washed sequentially with 5% aqueous NaHCO_3 (500 ml), H_2O (500 ml) and saturated aqueous NaCl (500 ml). The organic phase was dried and evaporated to an oil. The oil was dissolved in the minimum amount of acetone to which was added petroleum ether (40–69°C) to induce crystallization of the 1,2:4,5-bis-ketal. The solid obtained was filtered and recrystallized from acetone/petroleum ether to afford compound **8**, (15.5 g, 25%) mp 171–173°C (lit.¹⁰ 174°C); ^1H NMR (CDCl_3) 1.39–1.83 (m, 20H), 2.58 (d, 1H, J = 9 Hz), 2.92 (s, 1H), 3.30 (t, 1H, J = 9.5 Hz), 3.81 (t, 1H, J = 9.9 Hz), 3.86–3.89 (m, 1H), 3.98–4.04 (m, 1H), 4.07 (t, 1H, J = 5.2 Hz), 4.47 (t, 1H, J = 4.8 Hz); MS (EI), m/e 340 (M^+). Anal. Calcd. for $\text{C}_{18}\text{H}_{28}\text{O}_6$: C, 63.51, H, 8.29. Found: C, 63.48, H, 8.32.

The mother liquors were evaporated to an oil and subjected to chromatography on a Waters Prep 500 (Porasil cartridge, 30% EtOAc/ CH_2Cl_2) to yield the remaining two bis-ketals.

(+)-1,2:5,6-Dicyclohexylidene-my α -inositol, **7** (21.8 g, 35%) mp 134–135°C from acetone/petroleum ether (lit.¹⁰ 133°C); ^1H NMR (CDCl_3) 1.30–1.77 (m, 20H), 2.59 (d, 1H, J = 4.9 Hz), 2.71 (s, 1H), 3.39 (t, 1H, J = 8.9 Hz), 3.85 (q, 1H, J = 4.6 Hz), 3.94 (t, 1H, J = 8.1 Hz), 4.03–4.07 (m, 1H), 4.32 (t, 1H, J = 6.4 Hz), 4.46–4.49 (m, 1H); MS (EI), m/e 340 (M^+). Anal. Calcd. for $\text{C}_{18}\text{H}_{28}\text{O}_6$: C, 63.51, H, 8.29. Found: C, 63.43, H, 8.29.

(+)-1,2,3,4-Dicyclohexylidene-myio-inositol, 9 (13 g, 21%) mp 157–158°C from acetone/petroleum ether (lit¹⁰ 157°C); ¹H NMR (CDCl₃): 1.30–1.78 (m, 20H), 2.88 (s, 2H), 3.68–3.79 (m, 3H), 3.97 (t, 1H, J = 9.5 Hz), 4.19 (t, 1H, J = 5.5 Hz), 4.62–4.64 (m, 1H); MS (EI), m/e 340 (M⁺). Anal. Calcd. for C₁₈H₂₈O₆: C, 63.51, H, 8.29. Found: C, 63.39, H, 8.27.

(+)-Benzyl-1,2:4,5-dicyclohexylidene-myio-inositol (10): To a solution of 8 (12 g, 35.4 mmol) in toluene (200 mL) was added NaH (80% in oil, 1.17 g, 39 mmol) followed by benzyl bromide (4.6 mL, 39 mmol). The reaction was heated at reflux for 6 h followed by stirring at room temperature overnight. The reaction mixture was washed with H₂O (2 x 150 mL) and saturated aqueous NaCl (150 mL). The organic phase was dried and evaporated to an oil. This was subjected to flash chromatography (silica gel, 25% EtOAc/petroleum ether) using a slow flow rate which enabled separation of the faster running 3,6-bis-benzylated and 6-benzylated compounds yielding pure 10 (9 g, 60%) as a glass. ¹H NMR (CDCl₃): δ 1.30–1.70 (m, 20H), 2.64 (d, 1H, J = 2.8 Hz), 3.26 (t, 1H, J = 9.9 Hz), 3.77 (dd, 1H, J = 4.2, 10.1 Hz), 3.88 (dt, 1H, J = 2.8, 8.6 Hz), 3.93 (t, 1H, J = 5.6 Hz), 4.03 (t, 1H, J = 9.7 Hz), 4.35 (t, 1H, J = 4.5 Hz), 4.82 (d, 1H, J = 12.5 Hz), 4.90 (d, 1H, J = 12.5 Hz), 7.25–7.43 (m, 5H); HPLC (μPorasil 25% EtOAc/hexane, 2 mL/min). MS (CI) m/e calcd. for C₂₅H₃₄O₆(M⁺): 430.2355; Found 430.2315.

Resolution of (+)-3-Benzyl-1,2:4,5-dicyclohexylidene-myio-inositol: To a solution of 10 (8 g, 18.6 mmol) in CH₂Cl₂ (250 mL) was added 4-dimethylaminopyridine (DMAP) (250 mg, 2 mmol), triethylamine (7.7 mL, 55 mmol) and (–)-camphanic acid chloride (4.9 g, 22.3 mmol) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was washed with H₂O (2 x 100 mL) and saturated NaCl solution (100 mL). The organic phase was dried and evaporated to give a mixture of the diastereomeric camphanate esters. Three recrystallizations from petroleum ether EtOAc (1:2) yielded the more polar diastereomer 11D (4 g, 36%). mp 231–233°C; ¹H NMR (CDCl₃) δ 1.00 (s, 3H), 1.05 (s, 3H), 1.11 (s, 3H), 1.26 – 1.76 (m, 20H), 1.80 – 1.84 (m, 1H), 1.86 – 1.98 (m, 1H), 2.04 – 2.14 (m, 1H), 2.42 – 2.50 (m, 1H), 3.38 (t, 1H, J = 10.2 Hz), 3.77 (dd, 1H, J = 4.1, 10.2 Hz), 4.03 (t, 1H, 4.6 Hz), 4.15 (t, 1H, J = 9.7 Hz), 4.33 (t, 1H, J = 4.4 Hz), 4.80 (d, 1H, J = 12.5 Hz), 4.90 (d, 1H, J = 2.5 Hz), 5.38 (dd, 1H, J = 7.1, 11.2 Hz), 7.25 – 7.43 (m, 5H); MS (FAB) m/e 610 (M⁺); HPLC (μPorasil, 25% EtOAc/hexane, 2 mL/min); [α]_D²⁰ –30° ± 0.6° (C = 0.45, CHCl₃). Anal. Calcd. for C₃₅H₄₆O₉: C, 68.83, H, 7.59. Found: C, 69.09, H, 7.63.

MPLC of the mother liquors on silica gel [Lichroprep 69 (Merck), 25% EtOAc/petroleum ether, 5 mL/min] yielded the less polar camphanate 11L (3.5 g, 31%). mp 228–230°C; ¹H NMR (CDCl₃) δ 1.00 (s, 3H), 1.04 (s, 3H), 1.11 (s, 3H), 1.26 – 1.76 (m, 20H), 1.79 – 1.84 (m, 1H), 1.86 – 1.97 (m, 1H), 2.04 – 2.12 (m, 1H), 2.44 – 2.53 (m, 1H), 3.38 (t, 1H, J = 9.4 Hz), 3.77 (dd, 1H, J = 4.1, 10.1 Hz), 4.09 – 4.18 (m, 2H), 4.35 (t, 1H, J = 4.4 Hz), 4.81 (d, 1H, J = 12.5 Hz), 4.89 (d, 1H, J = 12.5 Hz), 5.36 (dd, 1H, J = 7.0, 11.2 Hz), 7.26 – 7.43 (m, 5H); MS (FAB) m/e 611 (M + 1)⁺; HPLC (μPorasil, 25% EtOAc/hexane, 2 mL/min); [α]_D²⁰ 20.4° ± 0.3° (C = 1.2, CHCl₃). Anal. Calcd. for C₃₅H₄₆O₉: C, 68.83, H, 7.59; Found: C, 68.95, H, 7.58.

(-)-3-Benzyl-1,2:4,5-diclohexylidene-my α -inositol (12D): To a solution of KOH (1.4 g, 25 mmol) in EtOH (250 mL) was added the more polar camphanate ester (11D) (1.5 g, 2.45 mmol) and the reaction was stirred overnight. The solvent was evaporated and the residue partitioned between water (50 mL) and Et₂O (75 mL). The aqueous phase was further extracted with Et₂O (75 mL) and the combined organic extracts were washed with saturated NaCl solution (75 mL). The ethereal solution was dried and evaporated to afford 12D as a foam (1.05 g, 98%). ¹H NMR (CDCl₃) δ 1.30 - 1.80 (m, 20H), 2.42 (s, 1H), 3.26 (t, 1H, J = 9.9 Hz), 3.77 (dd, 1H, J = 4.2, 10.1 Hz), 3.86 - 3.95 (m, 2H), 4.03 (t, 1H, J = 9.7 Hz), 4.35 (t, 1H, J = 4.5 Hz), 4.82 (d, 1H, J = 12.5 Hz), 4.90 (d, 1H, J = 12.5 Hz), 7.26 - 7.44 (m, 5H); HPLC (μ Porasil, 25% EtOAc/hexane, 2 mL/min); [α]_D -26.1° $\pm$ 0.1° (C = 1.1, CHCl₃), MS (CI) m/e Calcd. for C₂₅H₃₃O₆ (M-H)⁺ 429.2277; Found: 429.2255.

(+)-3-Benzyl-1,2:4,5-dicyclohexylidene-my α -inositol (12L): Repetition of the above procedure, using the less polar camphanate ester 11L, yielded 12L as a foam (90% yield). ¹H NMR (CDCl₃) δ 1.30 - 1.80 (m, 20H), 2.42 (s, 1H), 3.26 (t, 1H, J = 9.9 Hz), 3.77 (dd, 1H, J = 4.2, 10.1 Hz), 3.86 - 3.94 (m, 2H), 4.03 (t, 1H, J = 9.7 Hz), 4.35 (t, 1H, J = 4.5 Hz), 4.82 (d, 1H, J = 12.5 Hz), 4.90 (d, 1H, J = 12.9 Hz), 7.26 - 7.44 (m, 5H). HPLC (μ Porasil, 25% EtOAc/hexane, 2 mL/min); [α]_D 25.9° $\pm$ 0.1° (C = 1.1, CHCl₃); MS (CI) m/e Calcd. for C₂₅H₃₃O₆ (M - H)⁺ 429.2277; Found: 429.2235.

(-)-1-(3)-Benzyl-2,3:5,6-(1,2:4,5)-dicyclohexylidene-my α -inositol 4-(6)-diphenylphosphate (13D): To a solution of the resolved alcohol 9 (1 g, 2.3 mmol) in CH₂Cl₂ (50 mL) was added DMAP (25 mg, 0.25 mmol), triethylamine (1 mL, 6.9 mmol) and diphenyl chlorophosphate (0.8 mL, 3.5 mmol), and the solution stirred at room temperature overnight. The reaction mixture was washed with H₂O (50 mL), followed by extraction of the aqueous phase with CH₂Cl₂ (2 x 50 mL). The combined organic solutions were washed with saturated NaCl solution (75 mL) dried and evaporated to an oil. This was chromatographed [silica gel, EtOAc/petroleum ether (1:2)] to yield the title compound 13D, as an oil (1.15 g, 75%). ¹H NMR CDCl₃ δ 1.24 - 1.82 (m, 20H), 3.40 (t, 1H, J = 10.1 Hz), 3.75 (dd, 1H, J = 4.1 Hz, 10.2 Hz), 4.05 - 4.13 (m, 2H), 4.33 (t, 1H, J = 4.4 Hz), 4.76 - 4.81 (m, 2H), 4.89 (d, 1H, J = 12 Hz), 7.16 - 7.42 (m, 15H); HPLC (μ Porasil, 25% EtOAc/hexane, 2 mL/min); [α]_D -24.9° (C = 0.69, CHCl₃).

(+)-1-(3)-Benzyl-2,3:5,6-(1,2:4,5)-dicyclohexylidene-my α -inositol 4-(6)-diphenylphosphate (13L): Repetition of the above procedure using resolved alcohol 10 afforded the title compound (13L) (75% yield) as an oil. ¹H NMR (CDCl₃) δ 1.24 - 1.84 (m, 20H), 3.40 (t, 1H, J = 10.1 Hz), 3.75 (dd, 1H, J = 4.1, 10.2 Hz), 4.05 - 4.13 (m, 2H), 4.33 (t, 1H, J = 4.4 Hz), 4.75 - 4.91 (m, 3H), 7.11 - 7.42 (m, 15H); HPLC (μ Porasil, 25% EtOAc/hexane, 2 mL/min); [α]_D + 25.0° $\pm$ 0.2° (c = 0.73, CHCl₃).

(-)-1-Benzyl-2,3:5,6-diclohexylidene-my α -inositol 4-dibenzylphosphate (14D): To a solution of the diphenylphosphate (13D) (1 g, 1.5 mmol) in THF (25 mL) was added NaH (80% in oil, 99 mg, 3.3 mmol) followed by benzyl alcohol (0.35 mL, 3.3 mmol). The reaction was stirred at room temperature for 3 h before being quenched with 10% NH₄Cl solution (2 mL). The solvent was evaporated and the

residue partitioned between water (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic solutions were washed with saturated NaCl solution (40 mL), dried and evaporated to an oil. This was chromatographed [silica gel, EtOAc/petroleum ether (1:2)] to yield first the monophenyl monobenzyl ester (250 mg, 25%) and then the desired dibenzylphosphate ester (**14D**) (500 mg, 50%) as an oil. ^1H NMR (CDCl_3) δ 1.24 - 1.80 (m, 20H), 3.39 (t, 1H, J = 10.1 Hz), 3.75 (dd, 1H, J = 4.1, 10.2 Hz), 4.05 - 4.13 (m, 2H), 4.33 (t, 1H, J = 4.4 Hz), 4.65 - 4.72 (m, 1H), 4.80 (d, 1H, J = 12.5 Hz), 4.89 (d, 1H, J = 12 Hz), 5.10 - 5.20 (m, 4H), 7.26 - 7.43 (m, 15H); MS (FAB) m/e 599 ($\text{M} - \text{Bn}^+$); HPLC (μ Porasil, 25% EtOAc/hexane, 2 mL/min), $[\alpha]_D = 27.0^\circ + 0.1^\circ$ (C = 1, CHCl_3). Anal. Calcd. for $\text{C}_{39}\text{H}_{47}\text{O}_9\text{P}$: C, 67.81, H, 6.86; Found: C, 67.77, H, 6.99.

(+)-1-Benzyl-2,3:5,6-diclohexylidene-myco-inositol 4-dibenzylphosphate (14L): Repetition of the above procedure using the diphenylphosphate **13L** yielded the title compound **14L** (55% yield) as an oil. ^1H NMR (CDCl_3) δ 1.24 - 1.80 (m, 20H), 3.39 (t, 1H, J = 9.5 Hz), 3.76 (dd, 1H, J = 4.1, 10.2 Hz), 4.05 - 4.14 (m, 2H), 4.33 (t, 1H, J = 4.4 Hz), 4.64 - 4.72 (m, 1H), 4.80 (d, 1H, J = 12.5 Hz), 4.89 (d, 1H, J = 12.5 Hz), 5.09 - 5.19 (m, 4H), 7.26 - 7.43 (m, 15H), MS (FAB) m/e 599 ($\text{M} - \text{Bn}^+$); HPLC (μ Porasil, 25% EtOAc/hexane, 2 mL/min); $[\alpha]_D +26.5^\circ \pm 0.3^\circ$ (C = 1, CHCl_3). Calcd. for $\text{C}_{39}\text{H}_{47}\text{O}_9\text{P}$: C, 67.81, H, 6.86; Found: C, 67.80, H, 6.80.

(-)-Inositol 4-phosphate (15D): A solution of the fully protected inositol phosphate **14D** (300 mg, 0.4 mmol) in 10% aqueous EtOH (100 mL) was hydrogenolyzed over 10% Pd on carbon (150 mg) at 50 psi overnight. The catalyst was removed by filtration through a pad of Celite, washing the Celite with 50% aqueous EtOH (100 mL). The solvent was evaporated and the residue dissolved in H_2O (20 mL) to which was added cyclohexylamine (5 mL). The solution was stirred for 4 h, after which the excess cyclohexylamine was extracted into Et_2O (2 x 15 mL). The aqueous phase was lyophilized to yield (-)-biscyclohexylammonium myco-inositol 4-phosphate (**15D**) (100 mg, 50%) as a tan powder. mp. 180 - 200°C with dec.; ^1H NMR (D_2O) δ 1.10 - 1.40 (m, 10H), 1.60 - 2.00 (m, 10H), 3.02 - 3.12 (m, 2H), 3.42 (t, 1H, J = 9.2 Hz), 3.55 (dd, 1H, J = 2.9, 10 Hz), 3.63 (dd, 1H, J = 2.8, 9.7 Hz), 3.71 (t, 1H, J = 9.7 Hz), 4.05 - 4.14 (m, 2H); $[\alpha]_D -1.3^\circ \pm 0.2^\circ$ (C = 5, H_2O); HPLC (μ Bondapak NH_2 , 75 mM ammonium formate pH 4, 1 mL/min); MS (FAB) m/e 360 ($\text{M} + \text{CHA} + 1$).⁺ Anal. Calcd. for $\text{C}_6\text{H}_{13}\text{O}_6\text{P}$, 2 x $\text{C}_6\text{H}_{13}\text{N}$, 1.5 H_2O : C, 44.53, H, 8.72, N, 5.77; Found: C, 44.53, H, 8.31, N, 5.65.

(+)-Inositol 4-phosphate (15L): Repetition of the above procedure using the fully protected inositol phosphate **14L** yielded (+)-biscyclohexylammonium myco-inositol 4-phosphate **15L** (60% yield). mp. 180 - 200°C with dec.; ^1H NMR (D_2O): δ 1.10 - 1.40 (m, 10H), 1.60 - 2.00 (m, 10H), 3.02 - 3.12 (m, 2H), 3.42 (t, 1H, J = 9.2 Hz), 3.56 (dd, 1H, J = 2.9, 10 Hz), 3.63 (dd, 1H, J = 2.8, 9.7 Hz), 3.71 (t, 1H, J = 9.7 Hz), 4.05 - 4.13 (m, 2H); $[\alpha]_D 1.1^\circ \pm 0.3^\circ$ (C = 5, H_2O). HPLC: (μ Bondapak NH_2 , 75 mM ammonium formate pH 4, 1 mL/min) MS (FAB) m/e 360 ($\text{M} + \text{CHA} + 1$).⁺ Anal. Calcd. for $\text{C}_6\text{H}_{13}\text{O}_6\text{P}$, 2 x $\text{C}_6\text{H}_{13}\text{N}$, H_2O : C, 45.37, H, 8.67, N, 5.88; Found: C, 45.20, H, 8.47, N, 5.70.

Resolution of (+)-1,2:4,5-dicyclohexylidene-my α -inositol: To a solution of **8** (6 g, 17.6 mmol) in CH₂Cl₂ (200 mL) was added DMAP (250 mgs, 2 mmol), triethylamine (35 mL, 250 mmol) and (-)-camphanic acid chloride (19.1 g, 88.2 mmol), and the reaction was stirred for 24 h. The reaction mixture was washed with water (2 x 150 mL) and saturated NaCl solution (200 mL), dried and evaporated to a beige solid (11 g, 90%). The two diastereomers were separated using MPLC (Lichoprep 60 (Merck), 5% Et₂O/CH₂Cl₂, 5 mL/min) applying 3 g of the above solid in 500 mg batches, to yield the pure esters.

2,3:5,6-(1,2:4,5)-Dicyclohexylidene-my α -inositol 1,4-(3,6)-biscamphanate (16D**, more polar isomer, 1g, 30%).** mp. 250 - 330° sub, 338 - 339°C; ¹H NMR (CDCl₃): 1.00 (s, 3H), 1.02 (s, 3H), 1.06 (s, 3H), 1.09 (s, 3H), 1.13 (s, 3H), 1.37 - 1.74 (m, 20H), 1.77 - 1.80 (m, 2H), 1.91 - 1.99 (m, 2H), 2.07 - 2.13 (m, 2H), 2.43 - 2.53 (m, 2H), 3.52 (t, 1H, J = 9.4 Hz), 3.50 - 3.55 (m, 2H), 4.62 (t, 1H, J = 4.5 Hz), 5.23 (dd, 1H, J = 4.3, 10.5 Hz), 5.39 (dd, 1H, J = 7.0, 11.2 Hz); MS (FAB), m/e 723 (M = Na)⁺; [α]_D 9.0° ± 0.5° (C = 0.2, CHCl₃); Anal. Calcd. for C₃₈H₅₂O₁₂: C, 65.13, H, 7.48; Found: C, 64.90, H, 7.45.

2,3:5,6-(1,2:4,5)-Dicyclohexylidene-my α -inositol 1,4-(3,6)-biscamphanate (16L**, less polar isomer, 1g, 30%).** mp. 280 - 320° sub, 328 - 329°C; ¹H NMR (CDCl₃): 0.99 (s, 3H), 1.00 (s, 3H), 1.06 (s, 3H), 1.12 (s, 3H), 1.13 (s, 3H), 1.14 (s, 3H) 1.38 - 1.80 (m, 20H), 1.92 - 1.97 (m, 2H), 2.04 - 2.16 (m, 2H), 2.46 - 2.53 (m, 2H), 3.52 (t, 1H, J = 9.4 Hz), 4.14 (t, 1H, J = 9.9 Hz), 4.26 (t, 1H, J = 4.9 Hz), 4.67 (t, 1H, J = 4.6 Hz), 5.20 (dd, 1H, J = 4.3, 10.5 Hz), 5.38 (dd, 1H, J = 7, 11.2 Hz); MS (FAB), m/e 723 (M = Na)⁺; [α]_D -31.0° ± 0.5° (C = 0.2, CHCl₃); Anal. Calcd. for C₃₈H₅₂O₁₂: C, 65.13, H, 7.48; Found: C, 65.10, H, 7.35.

(+)-1,2:4,5-Dicyclohexylidene-my α -inositol (17D**):** To a solution of KOH (1.1 g, 20 mmol) in absolute ethanol (200 mL) was added **16D** (750 mg, 1.1 mmol) and the mixture was stirred overnight. The solvent was evaporated and the residue partitioned between water (50 mL) and EtOAc (50 mL). The aqueous phase was further extracted with EtOAc (2 x 50 mL) and the combined organic solutions were dried and evaporated to yield the title compound **17D** (315 mgs, 86%) as a white foam. ¹H NMR (CDCl₃) 1.40 - 1.86 (m, 20H), 2.32 - 2.56 (m, 2H), 3.31 (t, 1H, J = 10 Hz), 3.81 (t, 1H, J = 9.7 Hz), 3.85 - 3.90 (m, 1H), 3.98 - 4.04 (m, 1H), 4.07 (t, 1H, J = 5.3 Hz), 4.47 (t, 1H, J = 4.8 Hz); MS (EI), m/e 340 (M⁺); [α]_D 15.7° ± 0.1° (C = 3.65, CHCl₃).

(-)-1,2:4,5-Dicyclohexylidene-my α -inositol (17L**):** Repetition of the above procedure, but starting with the less polar diastereomer **16L** (750 mgs, 1.1 mmol) afforded the title compound **17L** (365 mgs, 100%) as a white foam. ¹H NMR (CDCl₃) 1.40 - 1.86 (m, 20H), 2.32 - 2.56 (m, 2H), 3.31 (t, 1H, J = 10 Hz), 3.81 (t, 1H, J = 9.7 Hz), 3.85 - 3.90 (m, 1H), 3.98 - 4.04 (m, 1H), 4.07 (t, 1H, J = 5.3 Hz), 4.47 (t, 1H, J = 4.8 Hz); MS (EI), m/e 340 (M⁺); [α]_D -16.0° ± 0.2° (C = 3.15, CHCl₃).

(+)-2,3:5,6-(1,2:4,5)-Dicyclohexylidene-my α -inositol 1,4-(3,6)-bis(diphenylphosphate) (18D**):** To a solution of **17D** (2.5 g, 7.35 mmol) in CH₂Cl₂ (100 mL) was added (DMAP, (90 mgs, 0.73 mmol), triethylamine

(6 ml, 44 mmol) and diphenyl chlorophosphate (4.6 mL, 22 mmol) and the solution stirred overnight. The reaction mixture was washed with H₂O (100 mL), followed by extraction of the aqueous phase with CH₂Cl₂ (3 x 50 mL). The combined organic solutions were washed with saturated NaCl solution (100 mL), dried and evaporated to an oil. This was chromatographed (silica gel, 40% EtOAc/petroleum ether) to afford 18 (5.25 g, 89%). mp 181 - 182°C.; ¹H NMR (CDCl₃) 1.30 - 1.76 (m, 20H), 3.49 (t, 1H, J = 10 Hz), 4.12 - 4.17 (m, 2H), 4.54 (t, 1H, J = 4.5 Hz), 4.79 - 4.83 (m, 1H), 4.87 - 4.92 (m, 1H), 7.10 - 7.33 (m, 20H). MS (FAB), m/e 806 (M = 2H)⁺; [α]_D 5.6° ± 0.2° (C = 0.52, CHCl₃); Anal. Calcd. for C₄₂H₄₆O₁₂P₂: C, 62.68, H, 5.76; Found: C, 62.44, H, 5.82.

(-)-2,3,5,6-(1,2,4,5)-Dicyclohexylidene-myo-inositol 1,4-(3,6)-bis(diphenylphosphate) (18L): Repetition of the above procedure but starting with 17L afforded the title compound 18L. mp 181-182°C.; ¹H NMR (CDCl₃) 1.30 - 1.76 (m, 20H), 3.49 (t, 1H, J = 10 Hz), 4.12 - 4.17 (m, 2H), 4.54 (t, 1H, J = 4.5 Hz), 4.79 - 4.83 (m, 1H), 4.87 - 4.92 (m, 1H), 7.10 - 7.33 (m, 20H). MS (FAB), m/e 806 (M = 2H)⁺; [α]_D -5.7° ± 0.1° (C = 0.52, CHCl₃); Anal. Calcd. for C₄₂H₄₆O₁₂P₂: C, 62.68, H, 5.76; Found: C, 62.45, H, 5.80.

(+)-myo-Inositol 1,4-bisphosphate (2D): The fully protected inositol 18D (500 mgs, 0.6 mmol) was suspended in EtOH (250 mL) and hydrogenolysed over platinum oxide (250 mgs) at atmospheric pressure. When hydrogen uptake had stopped the catalyst was removed by filtration through a pad of Celite and the Celite pad was washed with 50% aqueous ethanol (100 mL). The filtrate was evaporated and the residue dissolved in water (20 mL) to which was added cyclohexylamine (5 mL). After stirring at room temperature for 4 h the excess cyclohexylamine was extracted into Et₂O (2 x 15 mL) and the aqueous phase lyophilized to a white powder. Recrystallization from water/acetone afforded (+)-tetracyclohexylammonium myo-inositol 1,4-bisphosphate, 2D (300 mgs, 66%). mp 184 - 194°C with dec.; ¹H NMR (D₂O) 1.15 - 1.98 (m, 40H), 3.11 - 3.13 (m, 4H), 3.46 (t, 1H, J = 10 Hz), 3.66 (dd, 1H, J = 3, 10 Hz), 3.82 (t, 1H, J = 9.5 Hz), 3.90 (dt, 1H, J = 3, 10 Hz), 4.12 (q, 1H, J = 3, 8 Hz), 4.22 (t, 1H, J = 2.8 Hz); MS (FAB), m/e 339 (M-H)⁺; [α]_D 0.12° ± 0.05° (C = 4, H₂O). Anal. Calcd. for C₆H₁₄O₁₂P₂, 4 x C₆H₁₃N: C, 48.9, H, 9.03, N, 7.6. Found: C, 48.63, H, 8.95, N, 7.55.

(-)-myo-Inositol 1,4-bisphosphate (2L): Repetition of the above procedure with 18L afforded compound 2L. mp 184 - 194°C with dec.; ¹H NMR (D₂O) 1.15 - 1.98 (m, 40H), 3.11 - 3.13 (m, 4H), 3.46 (t, 1H, J = 10 Hz), 3.66 (dd, 1H, J = 3, 10 Hz), 3.82 (t, 1H, J = 9.5 Hz), 3.90 (dt, 1H, J = 3, 10 Hz), 4.12 (q, 1H, J = 3, 8 Hz), 4.22 (t, 1H, J = 2.8 Hz); MS (FAB), m/e 339 (M-H)⁺; [α]_D -0.12° ± 0.05° (C = 4, H₂O); Anal. Calcd. for C₆H₁₄O₁₂P₂, 4 x C₆H₁₃N: C, 48.9, H, 9.03, N, 7.6. Found: C, 48.6, H, 8.8, N, 7.51.

(+)-1(3)-0-Benzyl-2,3,4,5-di-0-cyclohexylidene-myo-inositol (23), (+)-4-0-Benzyl-1,2,5,6-di-0-cyclohexylidene-myo-inositol (22) and (+)-1(3),6(4)-di-0-Benzyl-2,3,4,5-di-0-cyclohexylidene-myo-inositol (24). Bis-ketal 7 (5.0 g, 15 mmol) was heated at reflux with benzyl bromide (2.78 mL, 24 mmol) and tetrabutylammonium hydrogen sulfate (5.0 g, 15 mmol) in a mixture of CH₂Cl₂ (250 mL) and 5% aq

NaOH (250 ml) for 6 h. The two layers were separated, the organic phase washed with H_2O , dried and concentrated to an oil which was chromatographed (SiO_2 , hexane:EtOAc, 7:1) to give the 4-O-benzyl derivative 22, 2.43 g (38%), mp 87 - 9°C, the 3,4-dibenzyl derivative 24, 0.75 g (10%) as an oil, and the 3-benzyl derivative 23, 0.75 g (12%). Compound 22: ^1H NMR (CDCl_3) 1.4 - 1.5 (4H, m), 1.5 - 1.8 (16H, m), 2.60 (1H, s), 3.56 (1H, dd, $J = 9, 12$ Hz), 3.88 (1H, dd, $J = 2, 6$ Hz), 4.04 (1H, m), 4.19 (1H, dd, $J = 9, 12$ Hz), 4.35 (1H, t, $J = 8$ Hz), 4.46 (1H, dd, $J = 4, 8$ Hz), 4.73 (2H, abq), 7.3 - 7.5 (5H, m); MS (FAB) m/e 431 ($M+1$); Anal. Calcd. for $\text{C}_{25}\text{H}_{34}\text{O}_6$ C, 69.74; H, 7.96. Found C, 70.02; H, 8.28. Compound 23: ^1H NMR (CDCl_3) 1.3 - 1.8 (20H, m); 2.57 (1H, d, $J = 2.2$ Hz); 3.32 (1H, t, $J = 5$ Hz); 3.58 (1H, dd, $J = 4, 3$ Hz); 3.78 (1H, dd, $J = 5, 6$ Hz); 4.1 - 4.3 (2H, m); 4.40 (1H, t, 4.6 Hz); 4.75 (2H, abq); 7.3 - 7.5 (5H, m). Compound 24: ^1H NMR (CDCl_3) 1.35 - 1.5 (4H, m), 1.5 - 1.8 (16H, m), 3.51 (1H, dd, $J = 8, 10$ Hz), 3.76 (1H, t, $J = 2$ Hz), 3.88 (1H, dd, $J = 3, 9$ Hz), 4.14 (1H, dd, $J = 8, 10$ Hz), 4.3 - 4.4 (2H, m), 4.63 (2H, abq), 4.67 (2H, abq), 7.2 - 7.4 (10H, m)

Resolution of (+)-4-O-benzyl-1,2:5,6-di-O-cyclohexylidene-myoinositol: To a solution of 22 (2.39 g, 5.6 mmol), triethylamine (2.34 ml, 16.8 mmol) and DMAP (0.068 g, 0.56 mmol) in CH_2Cl_2 (100 ml) was added S-(-)-camphanic acid chloride (1.46 g, 6.7 mmol). The reaction mixture was stirred at ambient temperature for 2 h, then washed with H_2O , brine, dried, filtered, and concentrated to an oil which was chromatographed with 2% $\text{Et}_2\text{O}:\text{CH}_2\text{Cl}_2$ to afford two diastereomers, L-camphanate ester 25L: 0.99 g after crystallization from petroleum ether (29% yield), mp 121 - 3°C, $[\alpha]_{\text{D}}^{+23}$ (C = 1 mg/ml CHCl_3); ^1H NMR (CDCl_3) 0.93 (3H, s), 1.02 (3H, s), 1.12 (3H, s), 1.32 - 1.76 (21H, m), 1.88 - 2.08 (2H, m), 2.4 - 2.5 (1H, m), 3.50 (1H, dd, $J = 9, 10$ Hz), 3.8 - 3.9 (2H, m), 4.34 (1H, dd, $J = 5, 7$ Hz), 4.61 (1H, dd, $J = 6, 7$ Hz), 4.83 (2H, abq, $J = 18, 24$ Hz), 5.28 (1H, s, $J = 4$ Hz), 7.3 - 7.4 (5H, m); MS (FAB) m/e 611 ($M+1$). Anal. Calcd. for $\text{C}_{35}\text{H}_{46}\text{O}_9$ C, 68.83; H, 7.59. Found: C, 68.54; H, 7.83.

D-camphanate ester 25D: 1.19 g (35% yield), mp 152 - 3°C, $[\alpha]_{\text{D}}^{-37}$ (C = 1 mg/ml CHCl_3) after crystallization from petroleum ether; ^1H NMR (CDCl_3): 0.93 (3H, s), 1.07 (3H, s), 1.13 (3H, s), 1.34 - 1.81 (21H, m), 1.88 - 2.08 (2H, m), 2.36 - 2.48 (1H, m), 4.54 (1H, dd, $J = 9, 10$ Hz), 3.87 - 3.92 (2H, m), 4.35 (1H, dd, $J = 6, 7$ Hz), 4.63 (1H, dd, $J = 6, 7$ Hz), 4.81 (2H, abq, $J = 12, 32$ Hz), 7.30 - 7.38 (5H, m); MS (FAB) m/e 611 ($M+1$); Anal. Calcd. for $\text{C}_{35}\text{H}_{46}\text{O}_9$ C, 68.83; H, 7.59. Found: C, 69.12, H, 7.93.

(D)-Camphanate Ester Diol (26D). Camphanate ester 25D (0.59 g, 0.967 mmol) was dissolved in a mixture of 50 mL of CH_2Cl_2 and 10 mL MeOH and 100 μL of acetyl chloride was added. The progress of the reaction was checked by TLC (70% EtOAc/hexane, R_f of starting material = 0.9, R_f of product = 0.2). After 3 h at 23°C the reaction was concentrated and the residue chromatographed to give 0.389 g of 26D as a white solid. mp 176 - 7°C, $[\alpha]_{\text{D}} = -32^\circ$ (CHCl_3 , C = 1 mg/mL); ^1H NMR (CDCl_3) 0.96 (3H, s), 1.12 (3H, s), 1.14 (3H, s), 1.3 - 1.8 (12 H, m), 1.85 - 2.05 (2H, m), 2.32 - 2.36 (1H, m), 2.86 (1H, br s), 2.91 (1H, br s), 3.46 (1 H, dd, $J = 10, 2$ Hz), 3.75 (1H, dd, $J = 9, 2$ Hz), 3.84 (1 H, t, $J = 9$ Hz), 4.08 (1H, dd, $J = 6, 5$ Hz), 4.56 (1H, t, $J = 5$ Hz), 4.79 (2H, abq, $J = 15, 11$ Hz), 5.22 (1H, dd, $J = 10, 4$ Hz), 7.25 - 7.34 (5H, m).

(L)-Camphanate Ester Diol (26L). In the same manner as described above, 25L (1.0 g, 1.64 mmol) was dissolved in 30 mL of CHCl_3 and 30 mL of MeOH and treated with 0.10 mL of acetyl chloride. After 1 h at 23° the reaction was quenched with saturated NaHCO_3 soln, concentrated, and the residue partitioned between CH_2Cl_2 and H_2O . The organic layer was separated, washed with brine and dried. Chromatography (SiO_2 , EtOAc: hexane, 1:3) provided 0.66 g of 26L (76%), mp $145 - 9^\circ\text{C}$. $[\alpha]_D^{26} = 26^\circ$ (CHCl_3 , $C = 1$ mg/mL) ^1H NMR (CDCl_3) 1.06 (3H, s), 1.15 (3H, s), 1.3 - 1.8 (1H, m), 1.9 - 2.0 (2H, m), 2.44 - 2.56 (1H, m), 2.78 (2H, br s), 3.44 (1H, dd, $J = 9, 2$ Hz), 3.76 (1H, dd, $J = 9, 2$ Hz), 3.88 (1H, t, $J = 9$ Hz), 4.08 (1H, dd, $J = 5, 6$ Hz), 4.58 (1H, t, $J = 5$ Hz), 4.87 (2H, abq, $J = 15, 11$ Hz), 5.19 (1H, dd, $J = 6, 9$ Hz), 7.3 - 7.4 (5H, m); MS (FAB) m/e 531 (M+1), 553 (M+Na); Anal. Calcd. for $\text{C}_{29}\text{H}_{38}\text{O}_9$ C, 65.64; H, 7.22. Found: C, 65.36; H, 7.48.

(D)-4-0-benzyl-2,3-0-cyclohexylidene-myo-inositol (27D). Ester 26D (0.34 g, 0.64 mmol) was dissolved in a mixture of H_2O and 1,2-dimethoxyethane (DME) (1/1, 10 mL each) and treated with LiOH (0.16 g, 6.75 mmol). The reaction was stirred at 23°C until TLC indicated complete reaction (2h) (EtOAc, rf starting material = 0.8, rf product = 0.7). The reaction was concentrated, the residue was diluted with CH_2Cl_2 and washed with H_2O (2 x 50 mL). The organic layer was dried and concentrated to give triol 27D (0.197 g, 88%). The compound was sufficiently pure for use in the next reaction. The analytical sample was obtained by recrystallization from pet. ether. $[\alpha]_D^{21} = +21^\circ$ (CHCl_3 , $C = 1$ mg/mL); mp $135-8^\circ$; ^1H NMR 1.4 - 1.5 (2H, m), 1.55 - 1.8 (8H, m), 2.54 (1H, d, $J = 6$ Hz), 2.7 (1H, brs), 2.9 (1H, brs), 3.44 (1H, ddd, $J = 12, 9, 3$ Hz), 3.69 (1H, t, $J = 7.5$ Hz), 3.84 (1H, ddd, $J = 12, 9, 3$ Hz), 3.97 (1H, m), 4.07 (1H, dd, $J = 6$ Hz), 4.45 (1H, dd, $J = 8, 6$ Hz), 4.87 (2H, abq, $J = 10$ Hz), 7.3 - 7.5 (5H, m). Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_6$ C, 65.12; H, 7.48. Found: C, 64.82; H, 7.39.

(L)-4-0-benzyl-2,3-0-cyclohexylidene-myo-inositol (27L): In the same manner as described for 27D, ester 26D (0.66 g, 1.25 mmol) gave 0.42 g (95%) of 27L, mp $138-9^\circ\text{C}$; $[\alpha]_D^{20} = -22^\circ$ (CHCl_3 , $C = 1$ mg/mL); ^1H NMR (CDCl_3) 1.4 - 1.5 (2H, m), 1.55 - 1.8 (8H, m), 2.56 (1H, d, $J = 5$ Hz), 2.83 (1H, br s), 2.95 (1H, br s), 3.44 (1H, ddd, $J = 12, 9, 3$ Hz), 3.67 (1H, t, $J = 7.5$ Hz), 3.84 (1H, ddd, $J = 12, 9, 3$ Hz), 3.95 (1H, m), 4.05 (1H, dd, $J = 6$ Hz), 4.44 (1H, dd, $J = 8, 6$ Hz), 4.85 (2H, abq, $J = 10$ Hz), 7.2 - 7.4 (5H, m); MS (FAB) m/e 351 (M+1), 373 (M+Na); Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_6$ C, 65.12; H, 7.48. Found: C, 65.19; H, 7.88.

(D)-4-0-benzyl-2,3-0-cyclohexylidene-myo-inositol 1,4,5-(hexabenzyl)trisphosphate (28D). Method A: 0.5 g of KH (25% in oil) was washed free of oil with hexane and to this was added 25 mL of THF followed by 0.18 g (0.514 mmol) of triol (27D). The reaction mixture was heated to 60°C for 15 min, cooled to 23°C and then tetrabenzyl pyrophosphate (TBPP) (0.165 g, 3.08 mmol) was added in one portion. After 3 h, TLC (60% EtOAc/hexane, rf sm = 0.2, rf product = 0.35) showed the reaction was complete. The reaction was filtered through a pad of celite to remove precipitated sodium dibenzylphosphate, the filtrate was evaporated and chromatographed on silicAR-CC4 neutral silica gel (25% EtOAc/hexane) to give 0.378 g (65%) of trisphosphate as an oil. $[\alpha]^{25} = -4.2^\circ$ (CHCl_3 , $C = 1$ mg/mL); MS (FAB) m/e 1131 (M+H), 1153 (M+Na); ^1H NMR 1.2 - 1.9 (10H, m), 4.17 (1H, dd, $J = 6$,

6 Hz), 4.27 (1H, t, $J = 6.5$ Hz), 4.6 - 4.68 (2H, m), 4.75 - 5.25 (16H, m), 7.1 - 7.35 (35H, m); ^{31}P NMR (121.4 MHz, CDCl_3 , $(\text{MeO})_3\text{PO}$ as external reference, 1H decoupled) -2.01 (s), -2.218 (s), -2.405 (s).

Method B: The triol 27D (0.197 g, 0.56 mmol) was dissolved in 25 mL of DMF and TBPP (1.51 g, 2.8 mmol) was added. The reaction was cooled to 0°C and NaH (0.27 g, 50% in oil) was added. A precipitate was observed after approximately 30 min and the reaction was complete within 1 h. The reaction mixture was concentrated under high-vacuum. The residue was stirred in CH_2Cl_2 and after 20 min the suspension was filtered. The filtrate was concentrated and chromatographed (SiO_2 , 70% EtOAc/hexane) to give the product 28D as an oil. (80%, $[\alpha]_{\text{D}} = -4.5^\circ$).

(L)-4-0-benzyl-2,3-0-cyclohexylidene-myoinositol 1,4,5-(hexabenzyl)trisphosphate (28L): Using Method A described above for the phosphorylation of D-triol, the L-triol 27L (0.25 g, 0.714 mmol) gave 0.545 g (68%) of 28L as an oil, $[\alpha]_{\text{D}} +6.5$ ($C = 2.8$ mg/mL CHCl_3). MS (FAB) m/e 1131 (M+1), 1153 (M+Na).

(D)-myoinositol 1,4,5-trisphosphate (1D): Trisphosphate 28D (0.49 g, 0.434 mmol) was dissolved in 50 mL of 90% EtOH and 0.5 g of 10% Pd/C was added. This was shaken on a mini-Parr apparatus under an atmosphere of H_2 (50 psig) for 3 hrs, filtered and concentrated. A crude ^1H NMR as well as a mass spectrum indicated that all of the benzyl groups were removed but the cyclohexylidene ketal still remained. The residue was dissolved in 3 mL of acetic acid and 3 mL of water and stirred for 18 h. The reaction was concentrated to dryness, the residue triturated with CH_2Cl_2 , and the remaining residue dissolved in a minimum amount of H_2O to which 6-7 eq of 10% NaOH soln was added. The solution was diluted with MeOH to precipitate the product as a hexa-sodium salt tri-hydrate. $[\alpha]_{\text{D}} = -30^\circ$ (H_2O , $C = 1$ mg/mL, pH = 10 (cyclohexylamine added to insure basicity) Lit⁷ $[\alpha]_{\text{D}} = -27^\circ$ (H_2O , pH = 9); ^1H NMR (D_2O , pH = 9) 3.64 (1H, dd, $J = 10$, 3 Hz), 3.83 (3H, brn), 4.08 (1H, q, $J = 9$ Hz), 4.26 (1H, brd, $J = 1.5$ Hz); ^{31}P NMR (121.7 MHz, D_2O , pH = 9, 1H decoupled) 5.67 (s), 7.32 (s), 7.47 (s); (1H coupled) 5.64 (d, $J = 3.5$ Hz), 7.29 (d, $J = 7$ Hz), 7.39 (d, $J = 7$ Hz); MS (FAB) m/e 421 (M+H), 443 (M+Na). Anal. Calcd. for $\text{C}_6\text{H}_9\text{O}_{15}\text{Na}_6\text{P}_3 \cdot 3\text{H}_2\text{O}$ C, 11.89; H, 2.50. Found: C, 12.28; H, 2.74.

(L)-myoinositol 1,4,5-trisphosphate (1L): Trisphosphate 28L (0.4 g, 0.35 mmol) was treated in the manner described above for 28D to give 0.14 g of 1L isolated as a hexa-sodium salt penta-hydrate. $[\alpha]_{\text{D}} + 35^\circ$ (H_2O , $C = 1$ mg/mL, pH = 10), MS (FAB) m/e 421 (M+1), 443 (M+Na). Anal. Calcd. for $\text{C}_6\text{H}_9\text{O}_{15}\text{Na}_6\text{P}_3 \cdot 5\text{H}_2\text{O}$ C, 11.22; H, 2.98. Found: C, 10.87; H, 2.70.

(+)-1,3,4-tri-0-allyl-5,6-di-0-benzyl-myoinositol (30): A mixture of 29 (0.93 g, 2.1 mmol), allyl bromide (0.216 mL, 2.5 mmol) and powdered NaOH (0.12 g, 3 mmol) in benzene (50 mL) was heated at reflux for 48 h. The residue was partitioned between benzene and H_2O , the organic layer washed with H_2O and brine, then dried and concentrated to dryness to give 0.89 g (88%) of 30. ^1H NMR (CDCl_3) 3.25 - 3.35 (2H, m), 3.39 (1H, t, $J = 9.5$ Hz), 3.81 (1H, t, $J = 9.5$ Hz), 3.91 (1H, t, $J = 9.5$ Hz), 4.1

- 4.25 (4H, m), 4.25 - 4.4 (2H, m), 4.8 - 4.9 (4H, m), 5.1 - 5.4 (6H, m), 5.9 - 6.05 (3H, m), 7.2 - 7.4 (10H, m), MS (FAB) m/e 481 (M+1). Anal. Calcd. for $C_{29}H_{36}O_6$ C, 72.48; H, 7.55. Found: C, 71.74; H, 7.62.

(+)-1,3,4-tri-*O*-allyl-2,5,6-tri-*O*-benzyl-myoinositol (31): NaH (0.598 g, 12.5 mmol) was added to a solution of **(30)** (2.0 g, 4.16 mmol) in DMF (50 mL) at ambient temperature with magnetic stirring. After 1 h benzyl bromide (1.50 mL, 12.5 mmol) was added and stirring was continued for 18 h. The reaction mixture was added to crushed ice and extracted with CH_2Cl_2 . The organic layer was washed with H_2O and brine, then dried and concentrated to dryness. Flash chromatography on SiO_2 (hexane:EtOAc, 6:1) provided 2.22 g (93%) of **31** as a colorless oil. 1H NMR ($CDCl_3$) 3.2 - 3.3 (2H, m), 3.39 (1H, t, $J = 9.5$ Hz), 3.88 (1H, t, $J = 9.5$ Hz), 4.0 - 4.1 (6H, m), 4.3 - 4.4 (2H, m), 4.8 - 4.9 (6H, m), 5.1 - 5.45 (6H, m), 5.85 - 6.05 (3H, m), 7.2 - 7.45 (15H, m). MS (FAB) m/e 571 (M+1). Anal. Calcd. for $C_{32}H_{42}O_6$ C, 75.75; H, 7.42. Found: C, 75.10; H, 7.51.

(+)-2,4,5-tri-*O*-benzyl-myoinositol (32): A mixture of **31** (0.5 g, 0.88 mmol), 10% Pd on C (0.5 g) and *p*-toluenesulfonic acid monohydrate (0.5 g) in MeOH (100 mL)- H_2O (20 mL) was heated at reflux for 72 h. The reaction mixture was filtered through filter cel, washed with MeOH and the filtrate was concentrated. The mixture was partitioned between CH_2Cl_2 and H_2O . The organic layer was washed with brine, dried and concentrated. Flash chromatography provided 0.31 g (78%) of **32**, mp 126 - 128°C. 1H NMR ($CDCl_3$) 2.36 (1H, d, $J = 7$ Hz), 2.33 (1H, d, $J = 5.5$ Hz), 2.45 (1H, d, $J = 2$ Hz), 3.35 (1H, t, $J = 9$ Hz), 3.4 - 3.5 (1H, m), 3.6 - 3.65 (1H, m), 3.79 (1H, t, $J = 9.5$ Hz), 3.85 (1H, td, $J = 2, 9$ Hz), 4.03 (1H, s, $J = 3$ Hz), 4.75 - 4.95 (6H, m), 7.3 - 7.4 (15H, m). Anal. Calcd. for $C_{27}H_{30}O_6$ C, 71.98; H, 6.71. Found: C, 72.35; H, 6.90.

(+)-nona-benzyl-1,3,4-myoinositol-trisphosphate (33): Compound **32** (150 mg, 0.34 mmol) was phosphorylated using method B. Flash chromatography (SiO_2 , EtOAc: hexane, 1:1) gave 0.338 g (80%) of **33**. 1H NMR ($CDCl_3$) 3.47 (1H, t, $J = 9.5$ Hz), 4.05 (1H, t, $J = 9.5$ Hz), 4.2 - 4.35 (2H, m), 4.6 - 5.0 (20H, m), 7.0 - 7.4 (45H, m). ^{31}P NMR ($CDCl_3$) -1.31, -1.45, -1.89 MS (FAB) m/e 1232 (M+1).

(+)-1,3,4-myoinositol-trisphosphate (4): A mixture of **33** (0.22 g, 0.18 mmol) and 10% Pd on C (0.22 g) in 95% EtOH (15 mL) was hydrogenated on a Parr apparatus for 6 h at ambient temperature. The reaction mixture was filtered through filter cel and concentrated to dryness at $<30^\circ C$. The residue was dissolved in H_2O , treated with 6 eq of 1N NaOH (1.07 mL), filtered, then concentrated to dryness. The residue was dissolved in a minimum amount of H_2O then treated with MeOH to precipitate 0.065 g (64%) of **4** as its penta-Na salt. 1H NMR (D_2O) (360 MHz) 3.55 (1H, t, $J = 9$ Hz), 3.83 (1H, t, $J = 9.7$ Hz), 3.97 (2H, m), 4.18 (1H, dt, $J = 7.62, 9.21, 9.31$ Hz), 4.46 (1H, t, $J = 2.44, 2.52$ Hz). ^{31}P NMR (121.4 MHz, D_2O , 83% H_3PO_4 as external reference, 1H decoupled) 3.87, .85, 5.42. Anal. Calcd. for $C_6H_{10}O_{15}P_3 \cdot 5Na \cdot 2H_2O$ C, 12.73; H, 2.49. Found: C, 12.66; H, 2.69.

(+)-5,6-di-O-allyl-1,4-di-O-benzyl-myio-inositol (34). Step 1. A solution of **24** (2.21 g, 4.24 mmol) in CHCl_3 (50 mL) was added to MeOH (50 mL) containing 3 drops of acetyl chloride with stirring at room temperature. After 1 h the reaction mixture was neutralized with aq. NaHCO_3 solution, concentrated to dryness, and the residue partitioned between CH_2Cl_2 and H_2O . The organic layer was separated, washed with brine, dried and then concentrated to give 1.27 g (68%) of (+) 3,4-di-O-benzyl-1,2-cyclohexylidene-myio-inositol, mp 114–116°C after trituration with pet ether. ^1H NMR (CDCl_3) 1.4 – 1.8 (10H, m); 2.62 (2H, dd, $J = 2.2, 6$ Hz); 3.30 (1H, t, $J = 9$ Hz); 3.7 – 3.8 (3H, m); 3.92 (1H, dd, $J = 7.5, 5$ Hz); 4.31 (1H, t, $J = 4.5$ Hz); 4.76 (2H, s); 4.84 (2H, abq); 7.25 – 7.4 (10H, m). MS (FAB) m/e 441 (M+); 463 (M+Na). Anal. Calcd. for C, 70.89; H, 7.32. Found: C, 70.58; H, 7.47.

Step 2. NaH (0.835 g, 17.4 mmol) was added to a solution of (+) 3,4-di-O-benzyl-1,2-cyclohexylidene-myio-inositol (1.27 g, 2.9 mmol) in DMF (50 mL) with stirring at room temperature. After 1.5 h allyl bromide (1.5 mL, 17.4 mmol) in DMF (5 mL) was added dropwise. The reaction mixture was left to stir for 18 h, then added to ice:water and extracted with CH_2Cl_2 . The organic layer was washed with H_2O , brine, dried and concentrated to give 1.2 g (79%) of **34** after flash chromatography (SiO_2 , EtOAc:hexane 1:3). ^1H NMR (CDCl_3) 1.3 – 1.8 (10H, m); 3.21 (1H, t, $J = 9.4$ Hz); 3.6 – 3.7 (2H, m); 3.86 (1H, t, $J = 8.5$ Hz); 3.96 (1H, dd, $J = 5.4, 7.2$ Hz); 4.2 – 4.4 (5H, m); 4.7 – 4.85 (4H, m); 5.1 – 5.35 (4H, m); 5.9 – 6.05 (2H, m); 7.25 – 7.4 (10H, m). MS (FAB) m/e 521 (M+).

(+)-3,4-di-O-benzyl-5,6-di-O-allyl-myio-inositol (35): Compound **34** (1.2 g, 2.3 mmol), glacial HOAc (15 mL) and H_2O (15 mL) were heated at reflux for 1 h, cooled to room temperature, then added to ice:water to precipitate 0.817 g (81%) of **35**, mp 88–90°C (hexane). ^1H NMR (CDCl_3) 2.5 – 2.55 (2H, m); 3.28 (1H, t, $J = 9.5$ Hz); 3.41 (2H, dd, $J = 3, 6.5$ Hz); 3.67 (1H, t, $J = 9.5$ Hz); 3.88 (1H, t, $J = 9.5$ Hz); 4.21 (1H, t, $J = 3$ Hz); 4.25 – 4.5 (4H, m); 4.72 (2H, abq); 4.85 (2H, abq); 5.15 – 5.35 (4H, m); 5.9 – 6.05 (2H, m); 7.25 – 7.4 (10H, m). MS (FAB) m/e 441 ((M+)); 463 (M+Na). Anal. Calcd. for $\text{C}_{26}\text{H}_{32}\text{O}_6$ C, 70.89; H, 7.32. Found: C, 70.92; H, 7.51.

(+)-5,6-di-O-allyl-1,3,4-tri-O-benzyl-myio-inositol (36): A mixture of 5,6-di-O-allyl-1,4-di-O-benzyl-myio-inositol (**35**) (0.77 g, 1.7 mmol), powdered NaOH (0.176 g, 4.4 mmol) and benzyl chloride (0.46 mL, 4 mmol) in benzene (50 mL) was heated at reflux with stirring for 18 h. The mixture was partitioned between benzene and water and the organic layer was washed with brine, dried and concentration to provide 0.80 g (89%) of **36** as a pale yellow oil. ^1H NMR (CDCl_3) 2.43 (1H, s), 3.2 – 3.5 (3H, m), 3.79 (1H, t, $J = 9.5$ Hz), 3.90 (1H, t, $J = 9.5$ Hz), 4.18 (1H, d, $J = 2$ Hz), 4.3 – 4.85 (10H, m), 5.1 – 5.35 (4H, m), 5.9 – 6.1, (2H, m), 7.2 – 7.4 (15 H, m). MS (FAB) m/e 531 (M+), 553 (M+Na).

(+)-1,3,4-tri-O-benzyl-myio-inositol (37): A mixture of **36** (0.8 g), 10% Pd on C (0.08 g and p-toluenesulfonic acid monohydrate (80 mg) in MeOH (200 mL)- H_2O (40 mL) was heated at reflux 72 h, then filtered through filter cel, washed with MeOH and the filtrate concentrated. The mixture

was partitioned between H_2O and Et_2O and the organic layer was washed with saturated NaHCO_3 solution, brine, and dried and concentrated to provide **37**, 0.33 g (49%), which solidified upon trituration with Et_2O -hexane, mp 102-104°C. ^1H NMR (CDCl_3) 2.33 (1H, d, J = 5.5 Hz), 2.36 (1H, d, J = 7 Hz), 2.47 (1H, s), 2.6 (1H, s), 3.25 (1H, dd, J = 2.7, 9.2 Hz), 3.4-3.5 (2H, m), 3.84 (1H, t, J = 9.5 Hz), 3.98 (1H, td, J = 2.3, 9.5 Hz), 4.26 (1H, t, J = 2.6 Hz), 4.6-5.0 (6H, m), 7.3-7.5 (15H, m). MS (FAB) m/e 473 ($\text{M}+\text{Na}$); Anal. Calcd. for $\text{C}_{27}\text{H}_{30}\text{O}_6$ C, 71.98; H, 6.71. Found: C, 72.23; H, 6.76.

(+)-nona-0-benzyl-2,4,5-myo-inositol triphosphate (39): NaH (0.102 g, 2.1 mmol) was added to a mixture of **37** (0.16 g, 0.36 mmol) and TBPP (1.15 g, 2.1 mmol) in DMF (10 mL) with stirring at -20°C. After stirring at -20°C for 4 h the reaction mixture was treated with 3 drops of 6N HCl and concentrated at <30°C. The residue was triturated with CH_2Cl_2 , and the resulting solid filtered off. The filtrate was concentrated and chromatographed (Flash, SiO_2 EtOAc: hexane, 1:1) to give 0.283 g (64%) of **38**. ^1H NMR (CDCl_3) 3.51 (2H, br t, J = 5Hz), 3.90 (1H, t, J = 5Hz), 4.55 (1H, t, J = 5Hz), 4.6-5.15 (19H, m), 5.37 (1H, br d, J = 5Hz), 7.0-7.5 (45H, m). ^{31}P NMR (CDCl_3) -1.526, -1.572, -1.761. MS (FAB) m/e 1231 ($\text{M}+\text{I}$). Anal. Calcd. for $\text{C}_{69}\text{H}_{69}\text{O}_{15}\text{P}_3$ C, 67.31; H, 5.65. Found: C, 67.63; H, 6.17.

(+)-2,4,5-myo-inositol-triphosphate (5): A mixture of **38** (0.19 g, 0.15 mmol) and 10% Pd on C (0.19 g) in 95% EtOH was hydrogenated in a mini-Parr apparatus for 5 h at ambient temperature. The reaction was filtered through filter-cel and concentrated to dryness at <30°C. The residue was dissolved in distilled H_2O , treated with 0.926 mL of 1N NaOH soln (0.924 mmol), filtered and concentrated to dryness. Trituration with MeOH gave 0.032 g (34%) of **5** as its hexasodium salt. ^1H NMR (D_2O) (360 MHz) 3.48 (1H, dd, J = 2.1, 9.9 Hz), 3.72 (1H, dt, J = 2.5, 2.5, 9.7 Hz), 3.84 (1H, q, J = 7.5, 9.9 Hz), 3.95 (1H, t, J = 9, 10 Hz), 4.23 (1H, q, J = 7.5, 9.5 Hz), 4.45 (1H, dt, J = 2, 2.5, 7.2 Hz). ^{31}P NMR (121.4 MHz) (D_2O) (85% H_3PO_4 ext. ref.) 5.38, p-2, 7 Hz; 5.50, p-4, 7 and 2 Hz; 5.23, p-5, 7 Hz. MS (FAB) $m/3$ 417 ($\text{M}+\text{I}$). Anal. Calcd. for $\text{C}_6\text{H}_9\text{O}_{15}\text{P}_3 \cdot 6\text{Na} \cdot 3\text{H}_2\text{O}$ C, 11.89; H, 2.50. Found: C, 11.87; H, 2.17.

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