General synthesis of 3-phosphorylated *myo*-inositol phospholipids and derivatives

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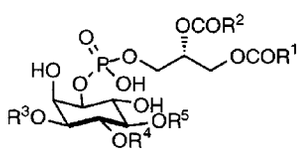
The D-3-phosphorylated *myo*-inositol phospholipids PtdIns(3)P, PtdIns(3,4)P_2, PtdIns(3,4,5)P_3 and PtdIns(3,5)P_2 were synthesised from *myo*-inositol orthoformate **8**. Key transformations included the regioselective DIBAL- and trimethylaluminium-mediated cleavages of *myo*-inositol orthoformate intermediates and a resolution–protection protocol using the camphor acetals **17**. The final reductive debenzylation was effected with Pearlman's catalyst [$Pd(OH)_2$] in the presence of sodium hydrogen carbonate. The biological properties of the phospholipids were evaluated against various protein kinases (PKB and PDK-1) in which they played an important activation role.

Introduction

It is now accepted that phosphatidylinositol 3-phosphate (PtdIns(3)P **1**), PtdIns(3,4)P_2 **2**, PtdIns(3,4,5)P_3 **3** and possibly



1 $R^1 = C_{17}H_{35}$, $R^2 = C_{19}H_{31}$, $R^3 = P(O)(OH)_2$, $R^4 = R^5 = H$
2 $R^1 = C_{17}H_{35}$, $R^2 = C_{19}H_{31}$, $R^3 = R^4 = P(O)(OH)_2$, $R^5 = H$
3 $R^1 = C_{17}H_{35}$, $R^2 = C_{19}H_{31}$, $R^3 = R^4 = R^5 = P(O)(OH)_2$
4 $R^1 = R^2 = C_{15}H_{31}$, $R^3 = R^5 = P(O)(OH)_2$, $R^4 = H$
5 $R^1 = R^2 = C_{15}H_{31}$, $R^3 = R^4 = P(O)(OH)_2$, $R^5 = H$
6 $R^1 = R^2 = C_{15}H_{31}$, $R^3 = R^4 = R^5 = P(O)(OH)_2$
7 $R^1 = R^2 = C_{15}H_{31}$, $R^3 = P(O)(OH)_2$, $R^4 = R^5 = H$

PtdIns(3,5)P_2 **4** are intracellular signals in mammalian cells.[1] Phospholipids **2** and **3** act acutely downstream of various cell-surface receptors with appropriate receptor activation driving the accumulation of PtdIns(3,4,5)P_3 and/or PtdIns(3,4)P_2. PtdIns(3,4,5)P_3 is the lipid product of phosphoinositide 3-kinase (PI3K),[2] which phosphorylates the D-3-hydroxy group of a relatively abundant lipid, PtdIns(4,5)P_2, found in unstimulated cells. PtdIns and PtdIns(4)P also appear to be substrates for PI3K *in vitro*, but *in vivo* results are more complex. More recently PtdIns(3,5)P_2 **4** was isolated from mammalian cells[3] and was subsequently shown to be produced in yeast when hyperosmotically stressed.[4]

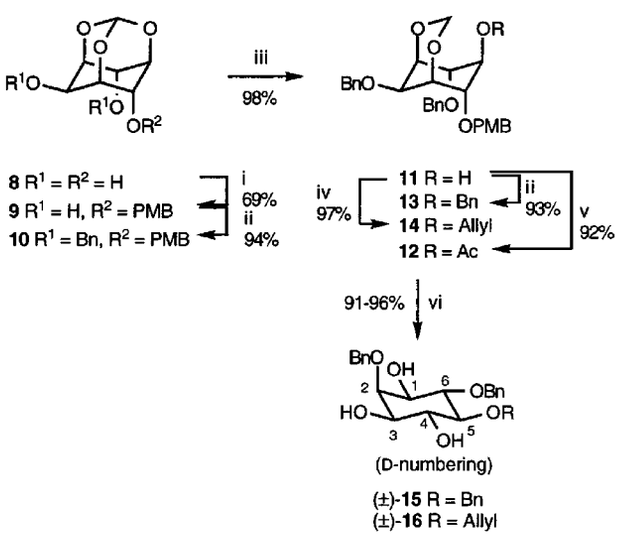
In order to probe the biological function of the various D-3-phosphorylated *myo*-inositol phospholipids and any potential inter-play there may be within this group by kinase or phosphatase action we now report the concise syntheses of dipalmitoyl lipids **1**–**4**. The method also provided for the preparation of the corresponding enantiomers in each case.

Results and discussion

Synthesis of PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3

The chemical synthesis of *myo*-inositol phospholipids has received extensive attention in recent years.[5–19] However, in many cases only limited experimental data is given and/or only the synthesis of one or two of the biologically relevant isomers is reported. We now report the synthesis of the complete set, to date, of the biologically relevant D-3-phosphorylated *myo*-inositol phospholipids together with full experimental details on the final lipid products.

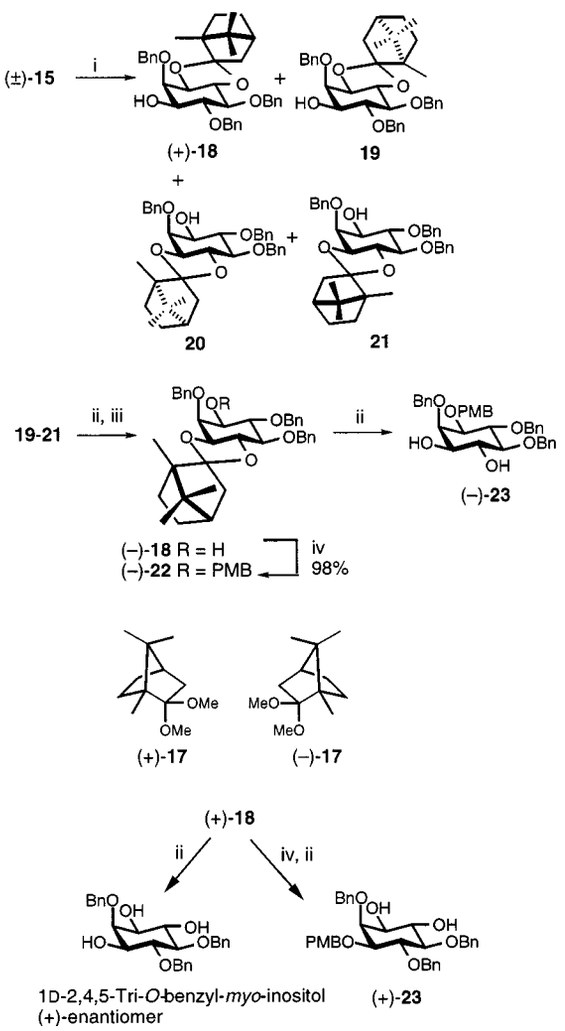
The common starting material in our strategy for the synthesis of the phospholipids **5** and **6** and further derivatives was the readily available triol **8** (Scheme 1).[20] Chemical manipula-



Scheme 1 *Reagents and conditions*: i, NaH, *p*-$MeOC_6H_4CH_2Cl$ (PMBCl), DMF, 0 °C to RT; ii, NaH, BnBr, DMF, 0 °C to RT; iii, DIBAL-H (2.5 equiv.), CH_2Cl_2–hexanes, 0 °C to RT; iv, NaH, allyl bromide, DMF, 0 °C to RT; v, Ac_2O, DMAP, pyridine, RT; vi, HCl, MeOH, reflux.

tion of the triol **8**, including a regioselective DIBAL-H reduction[21,22] and chemoselective *p*-methoxybenzylation[9] involving the intermediates **9**–**14**, afforded the racemic triols **15**[23] and **16** which are suitable precursors for the synthesis of **5** and **6** respectively.

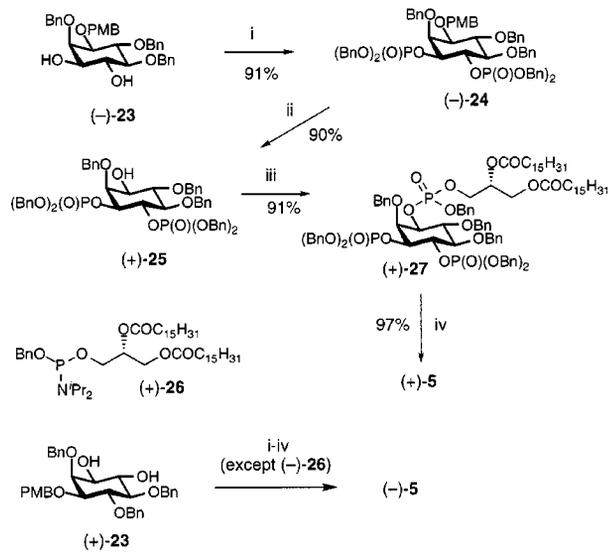
It was attractive to employ a resolution procedure which selectively protected the vicinal 3,4-diol system. The camphor acetal method introduced by Bruzik[24] was particularly attractive for this purpose. Treatment of the racemic benzyl-protected triol **15** with the camphor dimethyl acetal (+)-**17**[24] afforded a mixture of diastereoisomers from which (+)-**18** could be isolated by flash chromatography in 31% yield (Scheme 2). The



Scheme 2 *Reagents and conditions*: i, (+)-**17** (2.3 equiv.), toluene-4-sulfonic acid (TsOH) (cat.), CH_2Cl_2, reflux; ii, AcCl, CH_2Cl_2–MeOH (2:1); iii, (−)-**17** (2.3 equiv.), TsOH (cat.), CH_2Cl_2, reflux; iv, NaH, PMBCl, DMF, 0 °C to RT.

stereochemistry of (+)-**18** was determined by chemical correlation.[25] Acid hydrolysis of (+)-**18** (MeOH–AcCl) afforded 1D-2,4,5-tri-*O*-benzyl-*myo*-inositol. The stereochemistry of this tribenzylinositol was determined by comparison of its optical rotation {$[\alpha]_D^{22}$ + 26.1 (*c* 1.2 in $CHCl_3$)} with that reported by Desai *et al.*[26] {$[\alpha]_D$ + 25 (*c* 1 in $CHCl_3$)}, and corresponds to the enantiomeric series in the ring configuration required for the synthesis of naturally occurring PtdIns(3,4)P_2. Hydrolysis of the inseparable mixture of acetals **19**–**21**, followed by treatment with the *enantiomeric* camphor acetal (−)-**17**, afforded (−)-**18** in 41% yield (23% from racemic **18**). Protection of the final hydroxy group in **18** as the PMB ether **22**, followed by removal of the acetal afforded the diol (−)-**23**, {$[\alpha]_D^{22}$ − 14.7 (*c* 1.2 in $CHCl_3$); lit.,[26] $[\alpha]_D$ − 14.0 (*c* 1 in $CHCl_3$)}, a key precursor for the synthesis of PtdIns(3,4)P_2 **2**.

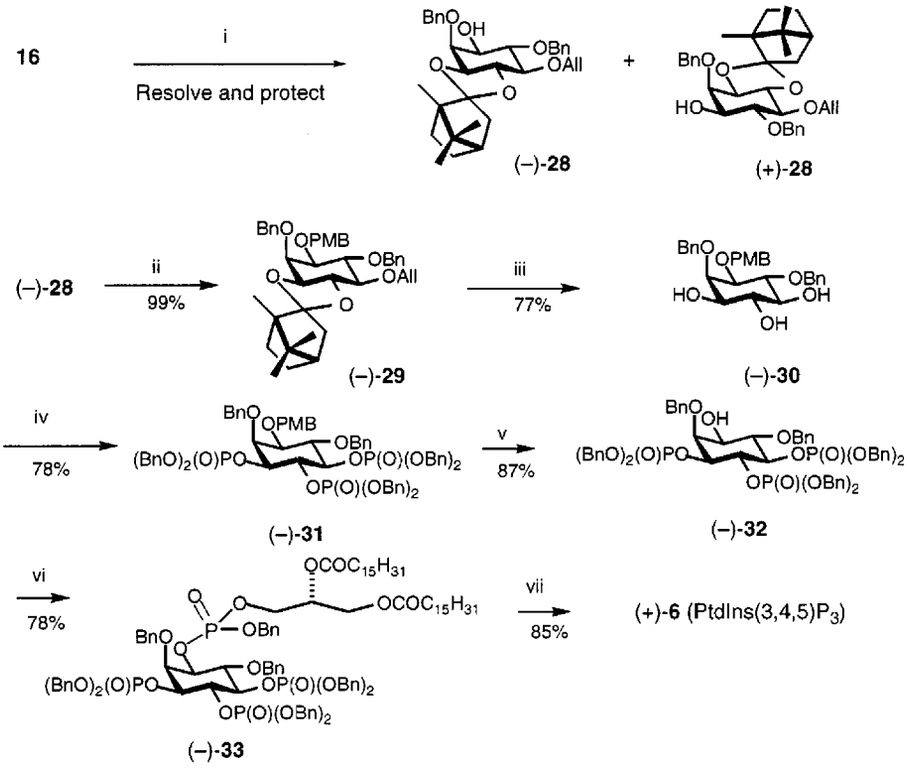
Elaboration of the diol (−)-**23** afforded dipalmitoyl PtdIns(3,4)P_2 (+)-**5** (Scheme 3). The 3,4-bis-phosphorylated



Scheme 3 i, $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_2Cl_2, then mCPBA; ii, $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O (4:1); iii, (+)-**26**, 1*H*-tetrazole, CH_2Cl_2, then mCPBA; iv, $Pd(OH)_2$–C, H_2 (50 psi), Bu^{t}OH.

derivative (−)-**24**[17,27] was prepared *via* phosphorylation of (−)-**23** with bis(benzyloxy) (diisopropylamino)phosphine[28] and 1*H*-tetrazole followed by *in situ* oxidation with MCPBA. After removal of the *p*-methoxybenzyl ether with ceric ammonium nitrate the remaining hydroxy group in (+)-**25** was coupled with the phosphoramidite (+)-**26**.[29] *In situ* oxidation of the phosphorus(III) species afforded the fully protected phospholipid (+)-**27**.[17] Reductive debenzylation was readily effected using the conditions reported by Kozikowski,[30] furnishing dipalmitoyl PtdIns(3,4)P_2 (+)-**5**.[12,14,17] The key transformation in this sequence was the final global deprotection. Debenzylation of protected phospholipids has been reported[30] sometimes to be problematical owing to the increased acidity of the reaction mixture as the reaction proceeds,[13] which may lead to transesterification between the *sn*-2-glycerylacyl and inositol hydroxy groups. We have found that hydrogenolysis utilising Pearlman's catalyst in Bu^{t}OH is generally satisfactory for the preparation of the free acid [20% $Pd(OH)_2$–C, H_2 (50 psi), Bu^{t}OH, 30 °C]. However, we also note that the preparation of the sodium salts [for PtdIns(3,4)P_2, PtdIns(3,5)P_2 and PtdIns(3,4,5)P_3] using Pd-black, Bu^{t}OH–H_2O (6:1) as the solvent, H_2 (50 psi) and $NaHCO_3$ is a most convenient method for the preparation of samples for biological evaluation. In particular, the ^{31}P NMR spectra of the sodium salts recorded in D_2O gave sharp well resolved signals. In comparison, ^{31}P NMR spectra of the free acids recorded in d_6-DMSO tended to give broad although usually discrete signals. In spite of the differing spectroscopic properties, lipids prepared by either method had almost identical biological responses. For example, protein kinase B (PKB) was phosphorylated (at Thr^{308}) to the same extent in an assay containing phosphoinositide dependent kinase (PDK-1), [^{32}P]ATP and either the sodium salt or the free acid of PtdIns(3,4,5)P_3 at the same concentration (5 μM).

One of the major uncertainties in evaluating the biological function of the PtdIns phosphates is the inherent surfactant activity which is quite non-specific. We believed that the enantiomers of the natural substrates would serve as the perfect control substances to evaluate this non-specific surfactant effect,[31] and we therefore embarked on a synthesis of the enantiomeric phospholipids. Elaboration of the alcohol (+)-**18** through a similar reaction sequence as outlined for (−)-**18** but using (−)-**26** afforded (−)-**5** (Schemes 2 and 3).



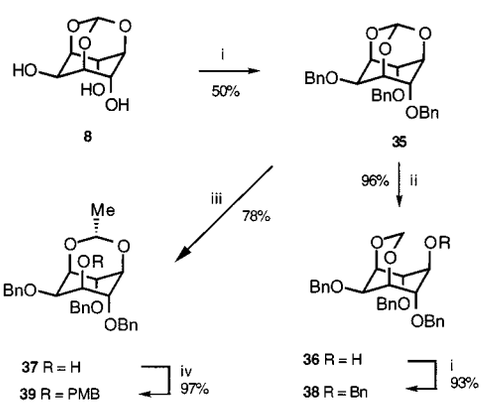
Scheme 4 i, (−)-**17** (2.3 equiv.), TsOH (cat.), CH_2Cl_2, reflux, separate, then AcCl, CH_2Cl_2–MeOH (2:1), followed by (+)-**17** (2.3 equiv.), TsOH (cat.), CH_2Cl_2, reflux, separate; ii, NaH, PMBCl, DMF, 0 °C to RT; iii, $(Ph_3P)_3RhCl$, DABCO, EtOH–toluene–H_2O (7:3:1), reflux, then AcCl, CH_2Cl_2–MeOH (2:1); iv, $(BnO)_2PN^iPr_2$, 1*H*-tetrazole, CH_2Cl_2, then MCPBA; v, $(NH_4)_2Ce(NO_3)_6$, acetonitrile-H_2O (4:1); vi, (+)-**26**, 1*H*-tetrazole, CH_2Cl_2, then MCPBA; vii, $Pd(OH)_2$–C, H_2 (60 psi), ^{t}BuOH.

The allyl-protected triol (±)-**16** was resolved first using the laevorotary camphor acetal (−)-**17**, separation, and hydrolysis followed by a second resolution with (+)-**17** in a similar manner as described for **15** to give eventually the separate enantiomers (−)-**28** and (+)-**28** (Scheme 4). After protection of the D-1-hydroxy group of (−)-**28** as the PMB-ether, the allyl group was isomerised to the enol ether with Wilkinson's catalyst.[32] Hydrolysis now afforded the D-3,4,5-triol (−)-**30**.[17,27] Phosphorylation of (−)-**30** with bis(benzyloxy) (diisopropylamino)phosphine and 1*H*-tetrazole, as before, followed by *in situ* oxidation with MCPBA afforded (−)-**31**,[27] $[a]_D^{21}$ −9.5 (*c* 1.5 in $CHCl_3$) {lit.,[27] $[a]_D$ −10.2 (*c* 1.3 in $CHCl_3$}. The PMB group was removed and the free hydroxy group was coupled with (+)-**26**. Hydrogenolysis of the fully protected material, (−)-**33**, $[a]_D^{22}$ −3.2 (*c* 1.6 in $CHCl_3$) {lit.,[17] $[a]_D^{23}$ −2 (*c* 0.8 in $CHCl_3$)} with a palladium catalyst afforded PtdIns(3,4,5)P_3 (+)-**6**.[12,14,17] The enantiomeric lipid, (−)-**6**, was prepared from (+)-**28** in a similar manner using (−)-**26** in the side chain coupling step.

Synthesis of PtdIns(3)P and PtdIns(3,5)P_2

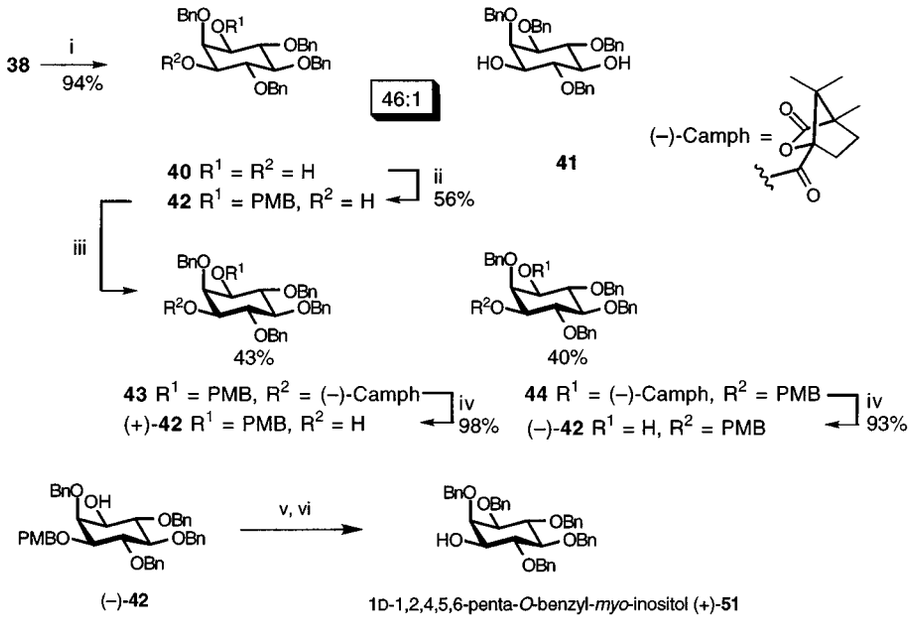
For the synthesis of dipalmitoyl PtdIns(3)P **7** and dipalmitoyl PtdIns(3,5)P_2 **4** the starting material was again the *meso*-triol **8** (Scheme 5). Exhaustive benzylation afforded the tribenzyl ether **35**[9] which was regioselectively cleaved with DIBAL-H as already discussed to give the acetal **36** whereas the use of trimethylaluminium gave the regioisomer **37** in excellent yield.[22] Benzylation of the *meso*-alcohol **36** afforded the intermediate **38** and *p*-methoxybenzylation of the alcohol **37** gave the ether **39**. We note in passing that the cleavage of analogues of the orthoformate **35** has recently been adopted by Potter in *myo*-inositol phospholipid synthesis.[6] We will report our earlier studies on the Lewis-acid mediated cleavage of *myo*-inositol orthoformate and ortho-acetate derivatives in full in a later paper.

Acidic hydrolysis of the acetal **38** gave the known[26] *meso*-



Scheme 5 *Reagents and conditions*: i, NaH, BnBr, DMF, 0 °C to RT; ii, DIBAL-H (2.5 equiv.), CH_2Cl_2–hexanes, 0 °C to RT; iii, Me_3Al (2.5 equiv.), CH_2Cl_2–hexanes, 0 °C to RT; iv, NaH, PMBCl, DMF, 0 °C to RT.

diol, 2,4,5,6-tetra-*O*-benzyl-*myo*-inositol **40** (Scheme 6). This hydrolysis also gave a small proportion of the diol **41**[33] which arose by the alternative mode of reductive cleavage of the orthoester **35**. The isomeric diols **40** and **41** were readily separated by flash chromatography and the mass recovery of each allowed the regioselectivity of the orthoformate reduction to be determined as 46:1. Mono-*p*-methoxybenzylation of **40** afforded the required racemic alcohol **42**[27] which was needed for the synthesis of PtdIns(3)P **7**. Resolution of **42** was readily effected by the formation of the (1*S*)-(−)-camphanate esters **43** and **44** which were separated by flash chromatography in 43 and 40% respectively. The diastereoisomeric purity was established by examination of the ^{1}H NMR spectra which displayed separate methyl resonances for each diastereoisomer. The absolute configuration of the less polar camphanate ester **43** was assigned from the relative stereochemistry of the ring substituents as determined by X-ray



Scheme 6 *Reagents and conditions*: i, conc. HCl, MeOH, reflux; ii, NaH, PMBCl, THF, RT; iii, (1*S*)-(−)-camphanic chloride, Et_3N, CH_2Cl_2, RT; iv, LiOH, THF–H_2O (10:1), RT; v, NaH, BnBr, DMF, 0 °C to RT; vi, $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O (4:1), 0 °C.

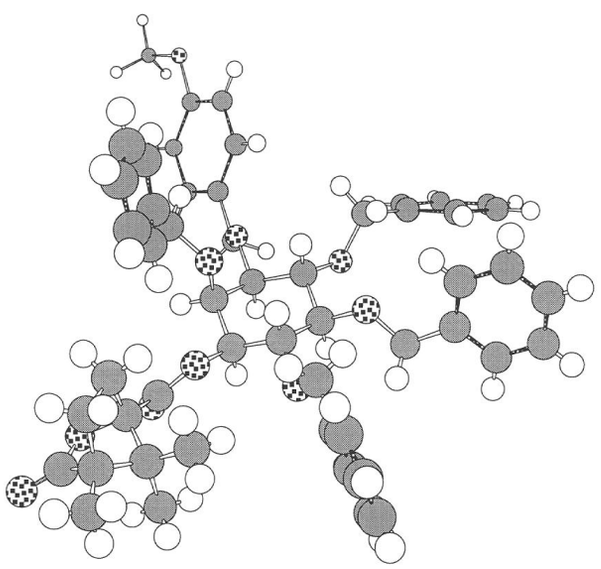
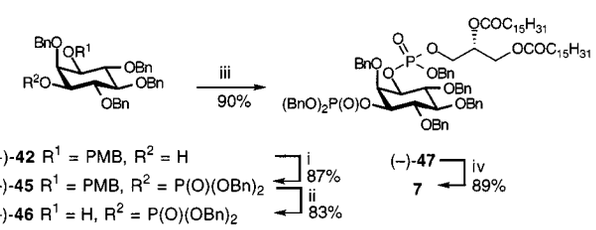


Fig. 1 Chem 3D representation of the X-ray structure of the camphanate ester **43**.†

analysis (Fig. 1)† and the known absolute configuration of (1*S*)-(−)-camphanic acid chloride.

Saponification of **44** afforded (−)-**42**[27] and, after benzylation, the PMB group was removed to afford the known 1D-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol (+)-**51**.[34,35] These results support the clarification of some earlier inconsistencies in the literature which had previously been noted first by Gigg[35] and later by Aneja *et. al.*[34]

Phosphorylation of the alcohol (+)-**42** with bis(benzyloxy)(diisopropylamino)phosphine[28] in the presence of 1*H*-tetrazole followed by *in situ* oxidation with MCPBA afforded the dibenzyl phosphate (−)-**45**[17] $[a]_D^{22}$ −7.7 (*c* 0.82 in $CHCl_3$) {lit.,[17] $[a]_D^{23}$ −6.3 (*c* 0.2 in $CHCl_3$)} (Scheme 7). Removal of the

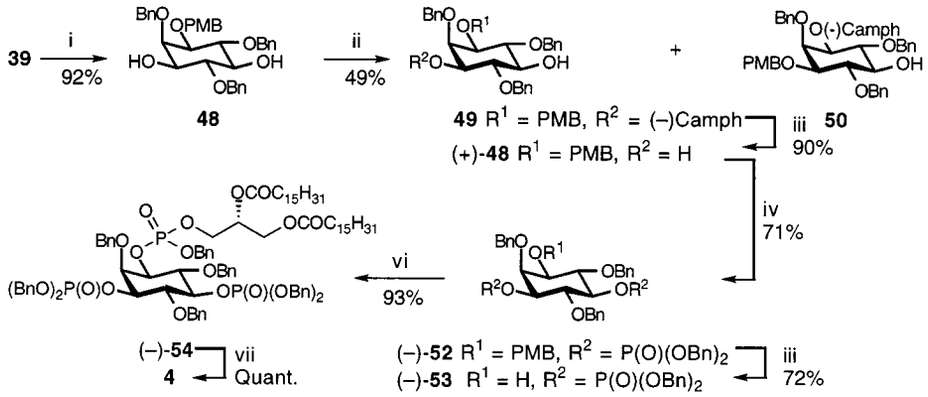


Scheme 7 *Reagents and conditions*: i, $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_2Cl_2, RT then MCPBA, −78 to 0 °C; ii, $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O (4:1), 0 °C; iii, (+)-**26**, 1*H*-tetrazole, CH_2Cl_2, RT then MCPBA, −78 to 0 °C; iv, H_2 (50 psi), $Pd(OH)_2$–C, Bu^{t}OH, 30 °C, 2 days.

p-methoxybenzyl ether group was accomplished with ceric ammonium nitrate (CAN) furnishing the alcohol (−)-**46**. Phosphorylation of (−)-**46** with the phosphoramidite (+)-**26** in the presence of 1*H*-tetrazole followed by *in situ* oxidation with MCPBA afforded the fully protected lipid (−)-**47**. The deprotection of (−)-**47** was readily effected by hydrogenation over Pearlman's catalyst to give dipalmitoyl PtdIns(3)P **7**.[14,17,18] The ^{31}P NMR spectrum of **7** recorded in d_6-DMSO displayed two resonances (δ_P 1.28 and −0.09 ppm) and positive FAB mass spectroscopy revealed a $(M + H)^+$ ion of 891.5024 ($C_{41}H_{81}O_{16}P_2$ requires *M*, 891.5000).

Dipalmitoyl PtdIns(3,5)P_2 **4** was prepared from the acetal **39** (Scheme 8). Mild acidic hydrolysis removed the acetal to afford the diol **48**. A small amount of the triol resulting from loss of the *p*-methoxybenzyl group was also isolated (8%). Resolution was effected by chemoselective[33] esterification of the D-1- and -3-hydroxy groups with (1*S*)-(−)-camphanic chloride to give the diastereoisomeric monocamphanate esters **49** and **50** which were separated by flash chromatography. Saponification of the less polar monocamphanate ester **49** gave (+)-**48**. The absolute configuration of the diol (+)-**48** was determined by benzylation

† Crystal data analysis and refinement for the camphanate ester **43**. Crystals were grown from dichloromethane. Empirical formula $C_{52}H_{56}O_{10}$; formula weight (*M*) 840.97, *T* 180(2) K, λ 0.71073 Å, crystal system triclinic, space group *P*1, unit cell dimensions $a = 6.164(9)$ Å, $b = 14.114(5)$ Å, $c = 14.378(5)$ Å, $\alpha = 64.94(4)°$, $\beta = 86.34(4)°$, $\gamma = 80.33(4)°$; volume 1117.0(17) Å^3; $Z = 1$, Density (calculated) 1.250 Mg m^{-3}; Absorption coefficient 0.086 mm^{-1}; $F(000)$ 448, crystal size 0.30 × 0.20 × 0.10 mm, θ range for data collection 3.55 to 25.2°, index ranges $0 \le h \le 7$, $-16 \le k \le 16$, $-16 \le l \le 17$, reflections collected 6913, independent reflections 3875 ($R_{int} = 0.0700$), refinement method: full-matrix least-squares on F^2; data/restraints/parameters 3875/3/564, Goodness-of-fit on F^2 1.012, Final *R* indices ($I > 2\sigma(I)$ $R1 = 0.0553$, w$R2 = 0.1078$; *R* indices (all data) $R1 = 0.0736$, w$R2 = 0.1163$, absolute structure parameter −1.5(13), extinction coefficient: 0.282(14), largest diff. peak and hole 0.329 and −0.301 e Å^{-3}. CCDC reference number 207/311. See http://www.rsc.org/suppdata/p1/1999/923 for crystallographic files in .cif format.



Scheme 8 *Reagents and conditions*: i, conc. HCl, MeOH–$CHCl_3$ (2:1), RT; ii, (1*S*)-(−)-camphanic chloride, Py, CH_2Cl_2, 0 °C; iii, LiOH, THF–H_2O (10:1), RT; iv, $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_2Cl_2, RT then MCPBA, −78 to 0 °C; v, $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O (4:1), 0 °C; vi, (+)-**26**, 1*H*-tetrazole, CH_2Cl_2, RT then MCPBA, −78 to 0 °C; vii, H_2 (50 psi), $Pd(OH)_2$–C, Bu^tOH, 30 °C, 2 days.

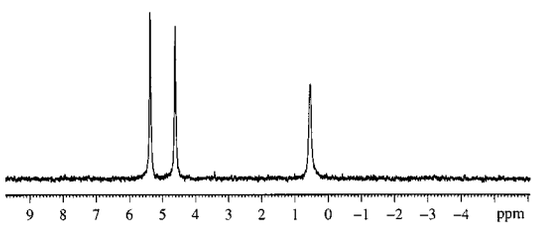
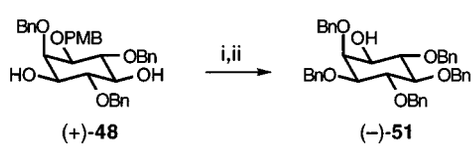


Fig. 2 ^{31}P NMR spectrum of the sodium salt of PtdIns(3,5)P_2 **4** recorded in D_2O.

and de-*p*-methoxybenzylation to give the known[36] alcohol 1D-2,3,4,5,6-penta-*O*-benzyl-*myo*-inositol (−)-**51** $[a]_D^{18}$ −10.0 (*c* 2.3 in $CHCl_3$) {lit.,[36] $[a]_D^{18}$ − 9.0 (*c* 1 in $CHCl_3$)} (Scheme 9).



Scheme 9 *Reagents and conditions*: i, NaH, DMF, BnBr; ii, $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O (4:1), 0 °C.

Phosphorylation of (+)-**48** with bis(benzyloxy) (diisopropylamino)phosphine followed by oxidation afforded the bis(dibenzyl phosphate) (−)-**52**. Removal of the *p*-methoxybenzyl ether group gave (−)-**53** and introduction of the 1,2-di-*O*-palmitoylglycerol moiety using the phosphoramidite (+)-**26** furnished the protected derivative (−)-**54**.[6] Debenzylation, as before, was effected by catalytic hydrogenation over palladium hydroxide to give dipalmitoyl PtdIns(3,5)P_2 **4**[5,6] (Scheme 8 and Fig. 2).

In conclusion, we have now reported in full the synthesis of dipalmitoyl PtdIns(3)P, PtdIns(3,4)P_2, PtdIns(3,4,5)P_3 and PtdIns(3,5)P_2 from *myo*-inositol. The methodology is considered to be versatile as it uses common reactions and reagents, and it also involves the use of common intermediates. Having the full set of D-3-phosphorylated *myo*-inositol lipids has been crucial in the biological evaluation and application of these compounds in cell signal transduction.[31,37,38]

Experimental

^1H NMR spectra were recorded on Bruker, WM-250 (250 MHz), WM-300 (300 MHz) and WM-400 (400 MHz) instruments, using deuterochloroform (or other indicated solvent) as reference or internal deuterium lock. The chemical shift data for each signal are given in units of δ relative to tetramethylsilane where δ (tetramethylsilane) = 0. The multiplicity of the signal is indicated as: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet, dd - doublet of doublets, dt - doublet of triplets, *etc.* ^{13}C NMR spectra were recorded on either a Bruker WM-250 (63.5 MHz) or WM-400 (100 MHz) instrument using an internal deuterium lock and proton decoupling. The chemical shift data for each signal are given in units of δ relative to tetramethylsilane (TMS; $\delta = 0$). The multiplicity of the signal was determined by an applied proton test experiment. ^{31}P Spectra were recorded on a Bruker WM-250 (101.3 MHz) instrument with proton decoupling. ^{31}P NMR chemical shifts were measured in δ relative to external 85% H_3PO_4. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrometer. The sample was prepared as a solution in the indicated solvent. Calibration in each case was made relative to polystyrene at 1603^{-1}. Mass spectra were recorded at both the SERC mass spectrometry centre, University of Swansea and the University Chemical Laboratory. Microanalyses were carried out by the staff of the University Chemical Laboratory Microanalytical Department. Melting points were determined using a Buchi 510 melting point apparatus and are uncorrected. HPLC analysis was carried out using a Gilson model 303 pump, Gilson model 803c manomeric module, Gilson Holochrome UV detector at 254 nm and Dynamax™ macro HPLC column. Optical rotations were measured using a Perkin-Elmer 241 polarimeter, in a cell of 1 dm path length. The concentration (*c*) is expressed in g per 100 cm^3 (equivalent to g per 0.1 dm^3) and $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Analytical thin layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick Merck 60 F_{254} silica gel plates. Visualisation was by absorption of UV light, or by thermal development after spraying with basic potassium permanganate solution or an ethanolic solution of phosphomolybdic acid. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) under a pressure of compressed air. Reagents were purified and dried where necessary by standard techniques.[40] Tetrahydrofuran (THF) was dried from potassium in a recycling still, using benzophenone ketyl as an indicator. Ether refers to diethyl ether, *n*-hexane is referred to as hexane, and light petroleum refers to the fraction bp 40–60 °C. Where appropriate and if not stated reactions were carried out under an argon atmosphere.

(1*R**,3*S**5*R**,7*S**,8*R**,9*R**)-6-[(4′-Methoxyphenyl)methoxy]-2,4,10-trioxatricyclo[3.3.1.1^{3,7}]decane-8,9-diol 9[9]

To a stirred solution of the triol **8** (11.0 g, 57.8 mmol) in dry DMF (400 cm^3) under argon at 5 °C, sodium hydride (2.33 g, 60% dispersion in mineral oil, 58.2 mmol) was added portionwise. Vigorous effervescence occurred and the suspension was stirred at 5 °C for 10 min then at room temperature for 30 min. To the resulting yellow–brown solution was added 4-methoxybenzyl chloride (8.60 cm^3, 63.4 mmol) dropwise and the solution was stirred for a further 4 h. The reaction was quenched by the addition of ethanol (5 cm^3) followed by water (5 cm^3) and

the solvent removed *in vacuo*. The residue was partitioned between ethyl acetate (500 cm^3) and water (200 cm^3) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 × 100 cm^3) and the combined organic extracts washed with brine (100 cm^3) and dried ($MgSO_4$). Evaporation and flash chromatography eluting with 50–100% ethyl acetate in hexane (twice) afforded the diol **9** (12.4 g, 40.0 mmol, 69%) as a gum (Found: C, 57.9; H, 5.9. $C_{15}H_{18}O_7$ requires C, 58.05; H, 5.9%); δ_H(400 MHz; $CDCl_3$) 7.25–7.20 (2 H, m, $OCH_2C_6H_4OMe$), 6.90–6.87 (2 H, m, $OCH_2C_6H_4OMe$), 5.45 (1 H, d, *J* 1.1, 3-H), 4.60 (1 H, d, J_{AB} 11.3, OCH_AH_B), 4.55 (1 H, d, J_{AB} 11.3, OCH_AH_B), 4.44–4.37 (2 H, m), 4.24–4.17 (3 H, m), 4.05 (1 H, d, *J* 9.8), 3.80 (3 H, s, OCH_3), 3.78 (1 H, d, *J* 10.3), 3.38 (1 H, br d, *J* 9.1, OH); δ_C(100 MHz; $CDCl_3$) 160.01 (CH_3C), 129.85 ($OCH_2C_6H_4OMe$), 127.91 (OCH_2C), 114.26 ($OCH_2C_6H_4OMe$), 102.58 (CO_3), 74.70, 73.75 (2 × inositol ring C), 72.72 (OCH_2), 72.26, 67.85, 67.24, 60.62 (4 × inositol ring C), 55.31 (OCH_3).

(1*R**,3*S**,5*R**,6*R**,7*S**,8*R**,9*R**)-8,9-Bis(benzyloxy)-6-[(4′-methoxyphenyl)methoxy]-2,4,10-trioxatricyclo[3.3.1.1^{3,7}]-decane 10

Sodium hydride (4.75 g, 60% dispersion in mineral oil, 120 mmol) was washed with dry hexane (20 cm^3) under argon. After removal of the solvent *via* cannulation the residual solid was suspended in dry DMF (100 cm^3) and cooled to 0 °C. A solution of the diol **9** (11.8 g, 38.0 mmol) in dry DMF (200 cm^3) was added with stirring. The suspension was stirred at room temperature for 1 h then recooled to 0 °C and benzyl bromide (11.3 cm^3, 95.0 mmol) was added dropwise and the suspension stirred for 11 h at room temperature. The reaction was quenched with the addition of ethanol (5 cm^3) followed by water (5 cm^3) and the solvent was removed *in vacuo*. The residue was partitioned between ether (500 cm^3) and water (200 cm^3) and the organic layer was separated. The aqueous layer was extracted with ether (2 × 100 cm^3) and the combined organic extracts washed with brine (100 cm^3) and dried ($MgSO_4$). Evaporation and flash chromatography eluting with 40–50% ether in hexane afforded the orthoformate **10** (17.3 g, 35.3 mmol, 93%) as a gum (Found: C, 71.1; H, 6.1. $C_{29}H_{30}O_7$ requires C, 71.0; H, 6.2%); δ_H(200 MHz; $CDCl_3$) 7.37–7.10 (12 H, m, Ph and $OCH_2C_6H_4OMe$), 6.82–6.78 (2 H, m $OCH_2C_6H_4OMe$), 5.52 (1 H, d, *J* 1.3, 3-H), 4.64–4.26 (11 H, m, OCH_2 and 5 × inositol ring H), 4.04 (1 H, q, *J* 1.5, 9-H), 3.80 (3 H, s, OCH_3); δ_C(62.9 MHz; $CDCl_3$) 159.35 (CH_3OC), 137.87, 137.63, 129.70 (OCH_2C), 129.29, 128.44, 128.40, 128.08, 127.82, 127.77, 127.63 (CH of Ph and $OCH_2C_6H_4OMe$), 113.81 ($OCH_2C_6H_4OMe$), 103.81 (CO_3), 74.07, 73.81 (2 × inositol ring C), 71.54, 71.33 (OCH_2), 70.67, 70.56, 68.20, 67.37 (4 × inositol ring C), 55.27 (OCH_3); *m*/*z* (CI, NH_3) [Found: $(M + NH_4)^+$ 508.2335. $C_{29}H_{34}NO_7$ requires *M*, 508.2335].

(1*R**,5*R**,6*R**,7*S**,8*S**,9*R**)-8,9-Bis(benzyloxy)-6-[(4′-methoxyphenyl)methoxy]-2,4-dioxabicyclo[3.3.1]nonan-7-ol 11

To a stirred solution of the orthoformate **10** (10.9 g, 22.2 mmol) in dry dichloromethane (140 cm^3) under argon at 0 °C was added DIBAL-H (56.0 cm^3, 1.00 mol dm^{-3} solution in hexanes, 56.0 mmol) over 5 min. The solution was stirred at 0 °C for 15 min then at room temperature for 7 h. The solution was cannulated onto a vigorously stirred solution of sodium potassium tartrate in water (100 cm^3, 1 mol dm^{-3}) and saturated ammonium chloride (100 cm^3) at 0 °C and stirring was continued overnight at room temperature to destroy the aluminium salts. Ethyl acetate (200 cm^3) was added and the organic layer was separated and the aqueous layer extracted with ethyl acetate (100 cm^3 then 2 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated. Flash chromatography eluting with 20–50% ethyl acetate in hexane afforded the alcohol **11** (10.3 g, 94%) as a gum (Found: C, 70.75; H, 6.5. $C_{29}H_{32}O_6$ requires C, 70.7; H, 6.6%); δ_H(400 MHz; $CDCl_3$) 7.34–7.17 (12 H, m, Ph and $OCH_2C_6H_4OMe$), 6.84–6.80 (2 H, m, $OCH_2C_6H_4OMe$), 5.55 (1 H, d, *J* 4.9, 3-H), 4.68–4.48 (7 H, m, OCH_2 and 3-H), 4.44–4.39 (2 H, m, 2 × inositol ring H), 4.28 (1 H, t, *J* 1.3, 9-H), 4.02–3.98 (2 H, m, 2 × inositol ring H), 3.94 (1 H, br d, *J* 10.2, 7-H), 3.79 (3 H, s, OCH_3), 2.96 (1 H, d, *J* 10.3, OH); δ_C(100 MHz; $CDCl_3$) 159.26 (CH_3OC), 137.94, 137.66, 129.99 (OCH_2C), 129.18, 128.43, 128.37, 127.81, 127.70, 127.53 (CH of Ph and $OCH_2C_6H_4OMe$), 113.78 ($OCH_2C_6H_4OMe$), 85.62 (CO_2), 81.14, 80.78, 72.73, 72.63 (4 × inositol ring C), 72.01, 71.70, 70.70 (3 × OCH_2), 70.25, 69.49 (2 × inositol ring C), 55.25 (OCH_3); *m*/*z* (CI, NH_3) [Found: $(M + NH_4)^+$ 510.2492. $C_{29}H_{36}NO_7$ requires *M*, 510.2492].

(1*R**,5*S**,6*R**,7*R**,8*S**,9*S**)-8,9-Bis(Benzyloxy)-6-[(4′-methoxyphenyl)methoxy]-2,4-dioxabicyclo[3.3.1]nonan-7-yl ethanoate 12

A sample of the alcohol **11** (31.1 mg, 63.1 μmol) was acetylated (Ac_2O–Py–DMAP) to give a product of R_f 0.28 (30% ethyl acetate in hexane). Aqueous work-up and flash chromatography eluting with 20% ethyl acetate in hexane gave the acetate **12** (31.1 mg, 92%) as a gum; δ_H(400 MHz; C_6D_6) 7.21–7.09 (12 H, m, Ph and $OCH_2C_6H_4OMe$), 6.79–6.76 (2 H, m, $OCH_2C_6H_4OMe$), 5.81 (1 H, d, *J* 4.3, 3-H), 5.55 (1 H, t, *J* 1.9, 7-H), 4.86 (1 H, *J* 4.3, 3-H), 4.66–4.54 (4 H, m, OCH_2 and 2 × inositol ring H), 4.47–4.43 (3 H, m, OCH_2 and inositol ring H), 4.36 (2 H, s, OCH_2), 4.15–4.11 (2 H, m, 2 × inositol ring H), 3.33 (3 H, s, OCH_3), 1.81 (3 H, s, $COCH_3$); *m*/*z* (CI, NH_3) [Found: $(M + NH_4)^+$ 552.2599. $C_{31}H_{38}NO_8$ requires *M*, 552.2597].

(1*R**,5*R**,6*R**,7*S**,8*S**,9*R**)-7,8,9-Tris(benzyloxy)-6-[(4′-methoxyphenyl)methoxy]-2,4-dioxabicyclo[3.3.1]nonane 13

To a solution of the alcohol **11** (2.70 g, 5.48 mmol) in dry DMF (100 cm^3) at 0 °C under argon was added sodium hydride (454 mg, 60% dispersion in mineral oil, 11.4 mmol) followed by imidazole (cat.). The suspension was stirred for 30 min at room temperature then benzyl bromide (1.00 cm^3, 8.41 mmol) was added dropwise and the suspension was stirred for 24 h. The reaction was quenched by the addition of methanol (5 cm^3) and the solvent removed *in vacuo*. The residue was partitioned between ethyl acetate (200 cm^3) and water (50 cm^3). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 50 cm^3) and the combined organic layers dried ($MgSO_4$). Evaporation of the solvent and flash chromatography eluting with 20% ethyl acetate in hexane afforded the acetal **13** (2.79 g, 87%) as a gum (Found: C, 74.1; H, 6.6. $C_{36}H_{38}O_7$ requires C, 74.2; 6.6%); δ_H(400 MHz; $CDCl_3$) 7.40–7.20 (17 H, m, Ph and $OCH_2C_6H_4OMe$), 6.87–6.83 (2 H, m, $OCH_2C_6H_4OMe$), 5.20 (1 H, d, *J* 5.6, 3-H), 4.86 (1 H, d, *J* 5.6, 3-H), 4.66 (2 H, s, OCH_2), 4.65 (2 H, s, OCH_2), 4.62 (1 H, d, J_{AB} 11.8, OCH_AH_B), 4.56 (1 H, d, J_{AB} 11.6, OCH_AH_B), 4.54 (1 H, d, J_{AB} 5.1, OCH_AH_B), 4.48 (1 H, d, J_{AB} 11.4, OCH_AH_B), 4.27–4.25 (2 H, m, 2 × inositol ring H), 3.98–3.94 (2 H, m, 2 × inositol ring H), 3.84 (1 H, t, *J* 1.9, 9-H), 3.80 (3 H, s, OCH_3), 3.61 (1 H, t, *J* 5.7, 7-H); δ_C(100 MHz; $CDCl_3$) 159.40 (CH_3OC), 137.41, 137.76, 137.74, 129.81 (OCH_2C), 129.56, 128.51, 128.45, 128.35, 127.90, 127.85, 127.66 (CH of Ph and $OCH_2C_6H_4OMe$), 113.89 ($OCH_2C_6H_4OMe$), 85.55 (CO_2), 82.16, 81.74, 82.27 (3 × inositol ring C), 73.50 (OCH_2), 72.11, 72.04 (2 × inositol ring C), 71.76, 71.44, 71.03 (3 × OCH_2), 70.33 (inositol ring C), 55.30 (OCH_3); *m*/*z* (CI, NH_3) [Found: $(M + NH_4)^+$ 600.2962. $C_{36}H_{42}NO_7$ requires *M*, 600.2961].

(1*R,5*R**,6*S**,7*S**,8*R**,8*R**)-6,9-Bis(benzyloxy)-8-[(4′-methoxyphenyl)methoxy]-7-(prop-2′-enyl)-2,4-dioxabicyclo-[3.3.1]nonane 14**

Allylation of the alcohol **11** (3.55 g, 7.21 mmol) as described for the benzylation of **11** gave a product of R_f 0.32 (30% ethyl acetate in hexane). Work-up and isolation as described before afforded the allyl ether **14** (3.63 g, 6.82 mmol, 94%) as a gum (Found: C, 72.0; H, 6.75. $C_{32}H_{36}O_7$ requires C, 72.15; H, 6.8%); δ_H(400 MHz; $CDCl_3$) 7.39–7.24 (12 H, m, Ph and $OCH_2C_6H_4OMe$), 6.88–6.86 (2 H, m, $OCH_2C_6H_4OMe$), 5.92–5.84 (1 H, m, $OCH_2CH{=}CH_2$), 5.24 (1 H, dq, *J* 17.2, 1.6, CH=CHH), 5.19 (1 H, d, *J* 5.5, 3-H), 5.16 (1 H, dq, *J* 10.5, 1.4, CH=CHH), 4.83 (1 H, d, *J* 5.5, 3-H), 4.68–4.51 (6 H, m, OCH_2), 4.26–4.24 (2 H, m, 2 inositol ring H), 4.13 (2 H, dt, *J* 5.6, 1.7, OCH_2CH), 3.91–3.88 (2 H, m, 2 × inositol ring H), 3.82 (1 H, t, *J* 1.9, 7-H), 3.80 (3 H, s, OCH_3), 3.53 (1 H, t, *J* 5.7, 9-H); δ_C(100 MHz; $CDCl_3$) 159.40 (CH_3OC), 137.83, 137.74 (OCH_2C of Ph), 135.01 ($CH{=}CH_2$), 129.87 (OCH_2C of PMP), 129.49, 128.50, 128.45, 128.45, 128.34, 127.88, 127.84, 127.81 (CH of Ph and $OCH_2C_6H_4OMe$), 116.96 ($CH{=}CH_2$), 113.89 ($OCH_2C_6H_4OMe$), 85.52 (CO_2), 82.11, 81.72, 80.17 (3 × inositol ring C), 72.54 (OCH_2), 72.12, 72.05 (2 × inositol ring C), 71.85, 71.55, 70.99 (3 × OCH_2), 70.31 (inositol ring C), 55.31 (OCH_3); *m*/*z* (CI, NH_3) [Found: $(M + NH_4)^+$ 550.2806. $C_{32}H_{40}NO_7$ requires *M*, 550.2805].

(±)-2,5,6-Tri-*O*-benzyl-*myo*-inositol 15[23]

To a solution of **13** (2.55 g, 4.37 mmol) in methanol (50 cm^3) under air was added concentrated hydrochloric acid (5 cm^3). The solution was refluxed for 2 h then cooled to room temperature. The reaction was quenched by the addition of solid sodium hydrogen carbonate, filtered and the filtrate evaporated. Flash chromatography eluting with 50–100% ethyl acetate in hexane afforded the triol (±)-**15** (1.80 g, 4.00 mmol, 92%) as a white solid, mp 134.0–134.5 °C (from ethyl acetate–hexane) [lit.,[23] 135–137 °C (from ethyl acetate–light petroleum)] (Found: C, 71.6; H, 6.65. $C_{27}H_{30}O_6$ requires C, 72.0; H, 6.7%); δ_H(250 MHz; $CDCl_3$) 7.38–7.22 (15 H, m, Ph), 4.98 (6 H, m, CH_2Ph), 4.00 (1 H, t, *J* 2.8, 2-H), 3.84 (1 H, br t, *J* 9.4, 6-H), 3.78 (1 H, t, *J* 9.4, inositol ring H), 3.63–3.56 (1 H, m, inositol ring H), 3.51–3.43 (1 H, m, inositol ring H), 3.34 (1 H, t, *J* 9.1, inositol ring H), 2.50 (1 H, br s, OH), 2.38 (1 H, br d, *J* 6.9, OH), 2.34 (1 H, d, *J* 5.2, OH); δ_C(100 MHz; $CDCl_3$) 138.51, 138.39 (OCH*C*), 128.61, 128.52, 128.10, 127.95, 127.89, 127.86, 127.81(CH of Ph), 82.98, 81.84, 78.85 (3 × inositol ring C), 75.48, 75.31, 75.23 (3 × OCH_2), 74.27, 72.90, 72.53 (3 × inositol ring C).

(±)-5-*O*-Allyl-2,6-di-*O*-benzyl-*myo*-inositol 16

The acetal **14** (6.07 g, 11.4 mmol) was hydrolysed as described above for the acetal **13** to give the triol (±)-**16** (4.37 g, 10.9 mmol, 96%) as a white solid, mp 111–112 °C (from ether) (Found: C, 69.0; H, 7.1. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.1%); δ_H(400 MHz; $CDCl_3$) 7.37–7.28 (10 H, m, Ph), 6.00–5.92 (1 H, m, $CH{=}CH_2$), 5.30 (1 H, dq, *J* 17.2, 1.6, CH=CHH), 5.18 (1 H, dd, *J* 10.4, 1.4, CH=CHH), 4.91 (1 H, J_{AB} 11.1, OCH_AH_BPh), 4.87 (1 H, J_{AB} 11.5, OCH_AH_BPh), 4.77 (1 H, J_{AB} 12.9, OCH_AH_BPh), 4.74 (1 H, J_{AB} 11.2, OCH_AH_BPh), 4.37 (1 H, ddt, *J* 12.5, 5.6, 1.1, OCHHCH), 4.31 (1 H, ddt, *J* 12.5, 5.6, 1.1, OCHHCH), 3.99 (1 H, t, *J* 2.8, 2-H), 3.80 (1 H, t, *J* 9.5, inositol ring H), 3.72 (1 H, t, *J* 9.4, inositol ring H), 3.55 (1 H, br d, *J* 9.7, inositol ring H), 3.44 (1 H, br d, *J* 8.7, inositol ring H), 3.20 (1 H, t, *J* 9.2, inositol ring H), 2.76 (1 H, br s, OH), 2.52 (1 H, br s, OH), 2.39 (1 H, br s, OH); δ_C(100 MHz; $CDCl_3$) 138.54, 138.42 (OCH_2C), 135.03 ($CH{=}CH_2$), 128.60, 128.51, 128.11, 127.95, 127.83, 127.79 (CH of Ph), 117.08 ($CH{=}CH_2$), 82.70, 81.68, 78.91 (3 × inositol ring C), 75.42, 75.29 (2 × OCH_2), 74.18 (inositol ring C), 74.05 (OCH_2), 72.78, 72.47 (2 × inositol ring C); *m*/*z* (CI, NH_3) [Found: $(M + NH_4)^+$ 418.2231. $C_{23}H_{32}NO_6$ requires *M*, 418.2229].

1D-2,4,5-Tri-*O*-benzyl-1-*O*-*endo*,6-*O*-*exo*-(D-1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylidene)-*myo*-inositol (+)-18, 1D-2,4,5-tri-*O*-benzyl-1-*exo*,6-*O*-*endo*-(D-1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylidene)-*myo*-inositol 19, 1D-2,5,6-tri-*O*-benzyl-3-*O*-*exo*,4-*O*-*endo*-(D-1′,7′,7′-trimethylbicyclo[2.2.1]-hept-2′-ylidene)-*myo*-inositol 20 and 1D-2,5,6-tri-*O*-benzyl-3-*O*-*endo*,4-*O*-*exo*-(D-1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylidene)-*myo*-inositol 21

To a solution of the triol **15** (289 mg, 0.642 mmol) in dry dichloromethane (10 cm^3) under argon was added the dimethyl acetal (+)-**17** (0.280 cm^3, 1.46 mmol) and *p*TsOH·H_2O (cat.). The solution was refluxed for 1.5 h then cooled to room temperature. TLC analysis indicated conversion of the starting material to two products of R_f 0.31 and 0.23 (20% ethyl acetate in hexane). The reaction was quenched by the addition of triethylamine (0.5 cm^3) and the solvent removed *in vacuo*. Flash chromatography eluting with 15–30% ethyl acetate in hexane gave the *less polar acetal isomers* **19**, **20** and **21** (223 mg, 59%), as a gum. Further elution gave the more polar acetal (+)-**18** (116 mg, 31%) as a gum; $[a]_D^{26}$ +6.3 (*c* 2.6 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 7.39–7.25 (15 H, m, Ph), 5.02 (1 H, d, J_{AB} 11.5, OCH_ACH_BPh), 4.94 (1 H, d, J_{AB} 11.7, OCH_ACH_BPh), 4.93 (1 H, d, J_{AB} 11.0, OCH_ACH_BPh), 4.79 (1 H, d, J_{AB} 11.7, OCH_ACH_BPh), 4.73 (1 H, d, J_{AB} 11.7, OCH_ACH_BPh), 4.68 (1 H, d, J_{AB} 11.5, OCH_ACH_BPh), 4.21 (1 H, dd, *J* 2.6, 2.0, 2-H), 4.05 (1 H, t, *J* 9.5, inositol ring H), 3.70–3.57 (3 H, m, 3 × inositol ring H), 3.31 (1 H, dd, *J* 9.8, 1.7, 1-H or 3-H), 2.46 (1 H, d, *J* 7.6, OH), 2.18 (1 H, dt, *J* 13.4, 3.8, CH of camphor), 1.96–1.90 (1 H, m, CH of camphor), 1.78–1.70 (2 H, m, CH of camphor), 1.48 (1 H, d, *J* 13.5, CH of camphor), 1.41 (1 H, td, *J* 13.0, 5.0, CH of camphor), 1.26–1.20 (1 H, m, CH of camphor), 1.08 (3 H, s, CH_3), 0.89 (3 H, s, CH_3), 0.88 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 138.82, 138.68, 138.08 (OCH_2C), 128.46, 128.36, 128.33, 128.02, 127.83, 127.63, 127.53 (CH of Ph), 120.55 (CO_2 of camphor), 84.02, 80.63, 77.48, 76.86 (4 × inositol ring C), 75.99, 74.27 (2 × OCH_2), 74.19, 73.68 (2 × inositol ring C), 72.69 (OCH_2), 52.95, 48.34 (2 × quaternary C of camphor), 46.20 (CH_2 of camphor), 44.99 (CH of camphor), 28.99, 26.73 (2 × CH_2 of camphor), 20.33, 20.25, 9.76 (3 × CH_3 of camphor); *m*/*z* (CI, NH_3) [Found: $(M + NH_4)^+$, 602.3483. $C_{37}H_{48}NO_6$ requires *M*, 602.3482].

Assignment of absolute stereochemistry to (+)-18. Conversion into 1D-2,4,5-tri-*O*-benzyl-*myo*-inositol

To a stirred solution of the acetal (+)-**18** (105.3 mg, 0.180 mmol) in dichloromethane (4 cm^3) and methanol (2 cm^3) under air in a septum sealed flask was added acetyl chloride (1×10^{-2} cm^3, 0.14 mmol) and the solution stirred for 3.5 h when TLC analysis indicated the complete consumption of the starting material. The reaction was quenched by the addition of triethylamine (0.5 cm^3) and the solvent removed *in vacuo*. Flash chromatography eluting with 50–100% ethyl acetate in hexane afforded 1D-2,4,5-tri-*O*-benzyl-*myo*-inositol (78.4 mg, 97%) as a solid, mp 101–103 °C (from ethyl acetate–light petroleum) (lit.,[26] 104–106 °C); $[a]_D^{26}$ +26.1 (*c* 1.2 in $CHCl_3$) [lit.,[26] $[a]_D$ +25 (*c* 1 in $CHCl_3$)] (Found: C, 71.6; H, 6.65. $C_{27}H_{30}O_6$ requires C, 72.0; H, 6.7%); δ_H(250 MHz; $CDCl_3$) 7.38–7.22 (15 H, m, Ph), 4.98 (6 H, m, CH_2Ph), 4.00 (1 H, t, *J* 2.8, 2-H), 3.84 (1 H, br t, *J* 9.4, 6-H), 3.78 (1 H, t, *J* 9.4, inositol ring H), 3.63–3.56 (1 H, m, inositol ring H), 3.51–3.43 (1 H, m, inositol ring H), 3.34 (1 H, t, *J* 9.1, inositol ring H), 2.50 (1 H, br s, OH), 2.38 (1 H, br d, *J* 6.9, OH), 2.34 (1 H, d, *J* 5.2, OH); δ_C(100 MHz; $CDCl_3$) 138.51, 138.39 (OCH*C*), 128.61, 128.52, 128.10, 127.95, 127.89, 127.86, 127.81 (CH of Ph), 82.98, 81.84, 78.85 (3 × inositol ring C), 75.48, 75.31, 75.23 (3 × OCH_2), 74.27, 72.90, 72.53 (3 × inositol ring C).

2,5,6-Tri-*O*-benzyl-*myo*-inositol 15 enriched with 1D-2,5,6-tri-*O*-benzyl-*myo*-inositol

To a solution of the acetals **19**, **20** and **21** (contaminated by a small amount of the more polar acetal (+)-**18**) in methanol (50 cm^3) under air was added *p*TsOH·H_2O (340 mg) and the solution stirred overnight. TLC analysis indicated the complete conversion of the starting material to the product which co-eluted with an authentic sample of the triol **15**. Removal of the solvent *in vacuo* and flash chromatography eluting with 50–100% ethyl acetate in hexane gave enantiomerically enriched triol **15** (1.030 g, 57% from the racemic **15**); identical to an authentic sample of racemic **15** by 250 MHz ^{1}H NMR analysis.

1D-2,5,6-Tri-*O*-benzyl-3-*O*-*endo*,4-*O*-*exo*-(L-1′,7′,7′-trimethylbicyclo[2.2.1] hept-2′-ylidene)-*myo*-inositol (−)-18, 1D-2,5,6-tri-*O*-benzyl-3-*O*-*exo*,4-*O*-*endo*-(L-1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylidene)-*myo*-inositol 19, 1D-2,4,5-tri-*O*-benzyl-1-*O*-*endo*,6-*O*-*exo*-(L-1′,7′,7′-trimethylbicyclo[2.2.1]-hept-2′-ylidene)-*myo*-inositol 20 and 1D-2,4,5-tri-*O*-benzyl-1-*O*-*exo*,6-*O*-*endo*-(L-1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylidene)-*myo*-inositol 21

To a solution of the enantiomerically enriched triol **15** (1.03 g, 245 mmol) in dry dichloromethane (30 cm^3) under argon was added *p*TsOH·H_2O (cat.) and the *opposite* camphor acetal (−)-**17** (1.30 cm^3, 6.80 mmol). The solution was heated to reflux for 2 h then cooled to room temperature. A significant amount of starting material remained as indicated by TLC analysis. A further portion of (−)-**17** (1.30 cm^3, 6.8 mmol) was added and the solution was refluxed for a further 45 min then cooled to room temperature. TLC analysis indicated the complete consumption of the starting material. The reaction mixture was quenched by the addition of triethylamine (2 cm^3) and the solvent was removed *in vacuo*. Flash chromatography eluting with 1–5% ethyl acetate in dichloromethane followed by 10–30% ethyl acetate in hexane gave the less polar acetal fractions presumed to comprise **19**, **20** and **21** (708 mg, 53% from the enriched triol) which were not examined further. Further elution gave the acetal (−)-**18** (591.4 mg, 41% from the enriched triol) as a gum; $[\alpha]_D^{26}$ −6.1 (*c* 1.4 in $CHCl_3$); identical to the enantiomer (+)-**18** by 400 MHz ^{1}H NMR.

1D-1-(1′,2′-Di-*O*-hexadecanoyl-*sn*-glycero(3′)phospho)-*myo*-inositol 3,4-bis(phosphate) (+)-5[14,17]

Palladium hydroxide on carbon (57 mg) was suspended in *tert*-butanol (2-methylpropan-2-ol) (7.5 cm^3) and the catalyst hydrogenated at 60 psi for 3 h then degassed and a solution of (+)-**27** (129 mg, 76.4 μmol) in *tert*-butanol (7.5 cm^3) was added. The suspension was hydrogenated at 60 psi and 30 °C for 2 days. The catalyst was removed by centrifugation and then re-washed with *tert*-butanol (15 cm^3). The combined solvent was then passed through a plug of Celite and washed with further *tert*-butanol (10 cm^3). After centrifugation the solvent was removed *in vacuo*. The residual solid was freeze-dried to give dipalmitoyl PtdIns(3,4)P_2 (+)-**5** (72.3 mg, 97%) as a white solid, mp 62–65 °C; $[\alpha]_D^{22}$ +6.8 [*c* 0.22 in H_2O (Na salt)] [lit.,[17] $[\alpha]_D^{23}$ +1.9 (*c* 0.5 in $CHCl_3$)]; δ_H(400 MHz; d_6-DMSO) 5.18–5.11 (1 H, m, 2′-H), 4.35–4.28 (2 H, m), 4.14–4.02 (5 H, m), 3.90 (2 H, br t, *J* 9.1), 3.60 (1 H, t, *J* 9.3, inositol ring H), 3.25 (1 H, t, *J* 9.0, inositol ring H), 2.33–2.24 (4 H, m, $OCOCH_2$), 1.55–1.44 (4 H, m, $OCOCH_2CH_2$), 1.28–1.19 (48 H, m, methylene envelope), 0.85 (6 H, t, *J* 6.7, CH_3); δ_P(101 MHz; d_6-DMSO) 1.64, 1.00, −0.16; *m/z* (FAB, glycerol) 971.8 [$(M + 2H)^+$, 0.5%], 863.7 (0.3), 771.8 (0.7), 755.8 (1.6), 733.8 (2.3), 553.6 (3), 461.5 (6), 403.1 (0.8), 277.2 (66), 239.1 (43), 207.1 (30), 185.1 (100) [Found: $(M + 2H)^+$ 972.4794. $C_{41}H_{83}O_{19}P_3$ requires *M*, 972.4741].

1D-5-*O*-Allyl-2,6-di-*O*-benzyl-3-*O*-*endo*,4-*O*-*exo*-(L-1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylidene)-*myo*-inositol (−)-28

To a solution of (±)-**16** (1.94 g, 4.86 mmol) in dry dichloromethane (50 cm^3) under argon was added *p*TsOH·H_2O (cat., *ca*. 18 mg) and (−)-**17** (2.30 cm^3, 12.1 mmol). The solution was refluxed for 1 h then cooled to room temperature. TLC analysis indicated the complete consumption of starting material to give at least two products of R_f 0.46 and 0.36 (5% ethyl acetate in dichloromethane). The reaction mixture was quenched by the addition of triethylamine (2 cm^3) and the solvent was removed *in vacuo*. Flash chromatography (vacuum packed column) eluting with 2–5% ethyl acetate in dichloromethane (twice) gave a mixture of diastereoisomers (1.82 g, 3.40 mmol, 70%) as a gum (R_f 0.46), presumed to consist of the other possible combinations arising from (±)-**16** with (−)-**17**. This mixture was not analysed, but hydrolysed as described in the next section to give the enantiomerically enriched triol **16**. Further elution gave the more polar acetal (−)-**28** (714 mg, 1.34 mmol, 27%) as a gum, R_f 0.36; $[\alpha]_D^{22}$ −11.7 (*c* 1.3 in $CHCl_3$) (Found: C, 74.0; H, 7.9. $C_{33}H_{42}O_6$ requires C, 74.1; H, 7.9%); δ_H(400 MHz; $CDCl_3$) 7.42–7.25 (10 H, m, Ph), 5.99–5.90 (1 H, m, CH=CH_2), 5.31 (1 H, dt, *J* 17.2, 1.7, CH=C*H*H), 5.16 (1 H, dd, *J* 10.3, 1.5, CH=CH*H*), 5.00 (1 H, J_{AB} 11.5, OCH_AH_BPh), 4.92 (1 H, J_{AB} 11.0, OCH_AH_BPh), 4.77 (1 H, J_{AB} 11.0, OCH_AH_BPh), 4.67 (1 H, J_{AB} 11.5, OCH_AH_BPh), 4.39 (1 H, ddt, *J* 12.9, 5.4, 1.5, OC*H*-HCH), 4.21–4.16 (2 H, m, OCH*H*CH and 2-H), 3.96 (1 H, t, *J* 9.6, 4-H), 3.66 (1 H, td, *J* 8.5, 3.3, 3-H), 3.59 (1 H, t, *J* 8.6, 6-H), 3.51 (1 H, dd, *J* 9.2, 8.5, 5-H), 3.29 (1 H, dd, *J* 9.8, 1.7, 3-H), 2.14 (1 H, dt, *J* 13.5, 3.8, CH of camphor), 1.94–1.87 (1 H, m, CH of camphor), 1.75–1.67 (2 H, m, CH of camphor), 1.45 (1 H, d, *J* 13.5, 3′-H_{endo}), 1.43–1.35 (1 H, m, CH of camphor), 1.27–1.18 (1 H, m, CH of camphor), 1.02 (3 H, s, CH_3), 0.86 (3 H, s, CH_3), 0.85 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 138.86, 138.10 (OCH_2C), 135.27 (CH=CH_2), 128.44, 128.36, 128.03, 127.82, 127.63 (CH of Ph), 120.45 (CO_2 of camphor), 116.62 (CH=CH_2), 83.99, 80.84, 77.35, 76.82 (4 × inositol ring C), 76.01, 74.23 (2 × OCH_2), 74.16, 73.60 (2 × inositol ring C), 71.69 (OCH_2), 52.90, 48.28 (2 × quaternary C of camphor), 46.17 (CH_2 of camphor), 44.98 (CH of camphor), 28.98, 26.71 (2 × CH_2 of camphor), 20.30, 20.16, 9.71 (3 × CH_3).

1D-5-*O*-Allyl-2,6-di-*O*-benzyl-3-*O*-*endo*,4-*O*-*exo*-(L-1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylidene)-*myo*-inositol (−)-28 and 1D-5-*O*-allyl-2,4-di-*O*-benzyl-1-*O*-*endo*,6-*O*-*exo*-(D-1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylidene)-*myo*-inositol (+)-28 from enantiomerically enriched triol 16

To a solution of the mixture of less polar acetals, R_f 0.46, described above (1.82 g, 3.40 mmol) in methanol (100 cm^3) under air was added Amberlite IR-120(plus) acidic ion exchange resin (1.16 g) and the solution was stirred for 2 days. The ion exchange resin was removed by filtration and the solvent was removed *in vacuo* to give enantiomerically enriched triol **16** as an off white solid which was further resolved with the camphor acetal (−)-**17**. The solid triol **16** was dissolved in dry dichloromethane (35 cm^3), the camphor acetal (−)-**17** (2.60 cm^3, 13.6 mmol) and *p*TsOH·H_2O (cat.) were added, and the solution was heated to reflux under argon for 16 h. The reaction mixture was cooled to room temperature and quenched by the addition of triethylamine (2 cm^3). The solvent was removed *in vacuo*, and the residue was submitted to flash chromatography eluting with 2–5% ethyl acetate in dichloromethane to give a mixture of the less polar acetals, the yields of which were not determined. Further elution gave the more polar L-camphor acetal (−)-**28** (241 mg, 9% yield from (±)-**16**); this was identical by ^{1}H NMR and optical rotation to material prepared as described above. The acetal (+)-**28** (628 mg, 1.17 mmol, 24%) was then prepared from the mixture of less polar acetals (R_f 0.46) *via* hydrolysis to enantiomerically enriched triol **16** with AcCl in MeOH followed by treatment with the *opposite*

camphor acetal (+)-**17**. Spectroscopic data was identical to that of (−)-**28**; $[\alpha]_D^{22}$ +12.5 (*c* 0.70 in $CHCl_3$).

1D-5-*O*-Allyl-2,6-di-*O*-benzyl-1-*O*-(4′-methoxybenzyl)-3-*O*-*endo*,4-*O*-*exo*-(L-1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylidene)-*myo*-inositol (−)-29

Sodium hydride (64.0 mg, 60% dispersion in mineral oil, 1.60 mmol) was washed with dry hexane (2 cm^3) under an argon atmosphere. Following removal of the hexane *via* cannulation the remaining solid was suspended in dry DMF (2 cm^3). To this stirred suspension at 0 °C was cannulated a solution of the alcohol (−)-**28** (431 mg, 0.806 mmol) in dry DMF (5 cm^3, then washed in with 2 cm^3) and the suspension warmed to room temperature and stirred for 20 min. To the resulting yellow–brown suspension was added 4-methoxybenzyl chloride (0.170 cm^3, 1.25 mmol) dropwise. The reaction mixture was stirred for 4 h then quenched by the addition of methanol (1 cm^3) and the solvent removed *in vacuo*. The residue was partitioned between ethyl acetate (50 cm^3) and water (50 cm^3) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (2 × 50 cm^3) and the combined organic layers dried ($MgSO_4$). After filtration the solvent was removed *in vacuo*. Flash chromatography eluting with 10–30% ethyl acetate in hexane afforded (−)-**29** (524 mg, 0.800 mmol, 99%) as a gum; $[\alpha]_D^{22}$ −20.1 (*c* 2.6 in $CHCl_3$) (Found: C, 75.0; H, 7.8. $C_{41}H_{50}O_7$ requires C, 75.2; H, 7.7%); δ_H(400 MHz; $CDCl_3$) 7.43–7.17 (12 H, m, Ph and $CH_2C_6H_4OMe$), 6.81–6.78 (2 H, m, $CH_2C_6H_4$-OMe), 6.00–5.90 (1 H, m, C*H*=CH_2), 5.30 (1 H, dq, *J* 17.2, 1.6, CH=C*H*H), 5.14 (1 H, dd, *J* 10.4, 1.5, CH=CH*H*), 4.89–4.77 (4 H, m, OCH_2Ph), 4.50 (2 H, s, OCH_2Ph), 4.36 (1 H, ddt, *J* 13.0, 5.2, 1.5, OC*H*HCH), 4.18 (1 H, ddt, *J* 13.0, 5.7, 1.4, OCH*H*CH), 4.10 (1 H, dd, *J* 2.7, 1.8, 2-H), 4.00 (1 H, t, *J* 9.7, inositol ring H), 3.84 (1 H, t, *J* 9.0, inositol ring H), 3.47 (1 H, dd, *J* 9.5, 8.6, inositol ring H), 3.43 (1 H, dd, *J* 9.5, 3.1, 3-H or 1-H), 3.15 (1 H, dd, *J* 9.5, 1.5, 1-H or 3-H), 2.10 (1 H, dt, *J* 13.5, 3.7, CH of camphor), 1.91 (1 H, ddd, *J* 12.4, 9.9, 3.4, CH of camphor), 1.75–1.67 (2 H, m, CH of camphor), 1.42–1.35 (2 H, m, CH of camphor), 1.22–1.15 (1 H, m, CH of camphor), 1.00 (3 H, s, CH_3), 0.85 (3 H, s, CH_3), 0.84 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 159.20 (CH_3OC), 139.11, 138.51 (OCH_2C of Ph), 135.42 (*C*H=CH_2), 129.43, 128.23, 128.13, 128.00, 127.44 (CH of Ph and $CH_2C_6H_4OMe$), 120.42 (CO_2 of camphor), 116.39 (CH=*C*H_2), 113.76 ($CH_2C_6H_4OMe$), 82.83, 81.13, 80.84, 77.17 (4 × inositol ring C), 76.36, 73.38, 73.24, 71.68 (4 × OCH_2), 71.03 (inositol ring C), 55.26 (OCH_3), 71.69 (2 × OCH_2), 52.91, 48.23 (2 × quaternary C of camphor), 46.18 (CH_2 of camphor), 44.97 (CH of camphor), 28.96, 26.73 (2 × CH_2 of camphor), 20.31, 20.15, 9.67 (3 × CH_3).

1D-1-(1′,2′-Di-*O*-hexadecanoyl-*sn*)-glycero(3′)phospho-*myo*-inositol 3,4,5-tris(phosphate) (+)-6[12,14,16,17]

Palladium hydroxide on carbon (52.5 mg) was suspended in *tert*-butanol (7.5 cm^3) and the catalyst hydrogenated at 60 psi for 3 h then degassed and a solution of the protected lipid (−)-**33** (117 mg, 0.0630 mmol) in *tert*-butanol (7.5 cm^3) was added. The suspension was hydrogenated at 60 psi and 30 °C for 2 days. The catalyst was removed by centrifugation and then washed with *tert*-butanol (15 cm^3) and re-centrifuged. The combined supernatant was passed through a plug of Celite which was then washed with a further portion of *tert*-butanol (7.5 cm^3). Evaporation of the solvent followed by freeze-drying (from water) gave dipalmitoyl PtdIns(3,4,5)P_3 (+)-**6** (55.4 mg, 85%) as a white solid; $[\alpha]_D^{22}$ +6.7 [*c* 0.30 in H_2O (Na salt)] [lit.,[17] $[\alpha]_D^{23}$ +3.7 (*c* 0.5 in $CHCl_3$)]; δ_H(400 MHz; d_6-DMSO) 5.19–5.11 (1 H, m, 2'-H), 4.47 (1 H, q, inositol ring H), 4.31–3.99 (8 H, m), 3.75 (1 H, t, *J* 9.4, inositol ring H), 2.33–2.22 (4 H, m, $OCOCH_2$), 1.54–1.45 (4 H, m, $OCOCH_2CH_2$), 1.29–1.19 (48 H, m, methylene envelope), 0.85 (6 H, t, *J* 6.6, CH_3); δ_P(101 MHz; d_6-DMSO) 1.22, 0.98, 0.59, −0.20; *m*/*z* (FAB, Glycerol) 1052.7 [(M + 2H)$^+$, 0.2%], 1002.0 (0.2), 912.2 (0.3), 835.7 (1), 822.0 (1.5), 489.5 (9), 421.1 (8), 393.3 (13), 331.3 (22), 313.3 (100) [Found: (M + H)$^+$ 1051.4350. $C_{41}H_{83}O_{22}P_4$ requires *M*, 1051.4326].

(1*R*,5*S*,6*R*,7*S*,8*S*,9*S*)-6,7,8,9-Tetrakis(benzyloxy)-2,4-dioxabicyclo[3.3.1]nonane 38

Sodium hydride (1.71 g, 60% dispersion in mineral oil, 42.8 mmol) was washed with dry hexane (2 × 10 cm^3) under an argon atmosphere. Following removal of the solvent *via* cannula the remaining solid was suspended in dry DMF (40 cm^3) and cooled to 0 °C. To this stirred suspension was added **36** (13.0 g, 28.1 mmol) in dry DMF (60 cm^3). The suspension was stirred for 1 h at room temperature and then cooled to 0 °C and benzyl bromide (5.00 cm^3, 7.19 g, 42.0 mmol) was added dropwise. The suspension was allowed to reach room temperature and stirred for 20 h. The reaction was quenched by the addition of water (2 cm^3) and the solvent removed *in vacuo*. The residue was partitioned between ethyl acetate (200 cm^3) and water (200 cm^3).The organic layer was separated and the aqueous layer extracted with ethyl acetate (4 × 200 cm^3) and the combined organic layers dried ($MgSO_4$). Evaporation of the solvent and flash chromatography eluting with 25–50% diethyl ether in hexane afforded the acetal **36** (13.8 g, 26.1 mmol, 93%) as an oil which slowly solidified to an amorphous solid which could not be crystallised (Found: C, 76.1; H, 6.6. $C_{35}H_{36}O_6$ requires C, 76.1; H, 6.6%); δ_H(250 MHz; $CDCl_3$) 7.28–7.04 (20 H, m, Ph), 5.08 (1 H, d, *J* 5.5, C*H*HO_2), 4.72 (1 H, d, *J* 5.5, CH*H*O_2), 4.53 (4 H, s, 7-OCH_2Ph and 9-OCH_2Ph), 4.48 (2 H, d, J_{AB} 11.6, OCH_AH_BPh), 4.40 (2 H, d, J_{AB} 11.6, OCH_AH_BPh), 4.15 (2 H, br s, 2 × inositol ring H), 3.84 (2 H, d, *J* 5.5, 2 × inositol ring H), 3.73 (1 H, t, *J* 1.8, inositol ring H), 3.50 (1 H, t, *J* 5.5, inositol ring H); δ_C(100 MHz; $CDCl_3$) 138.27, 137.66, 128.46, 128.42, 128.33, 127.87, 127.81, 127.65 (CH of Ph), 89.49 (CO_2), 82.02, 80.03 (2 × inositol ring C), 73.46 (OCH_2), 71.96 (inositol ring C), 71.70, 70.98 (2 × OCH_2), 70.20 (inositol ring C).

(1*R*,3*R*,5*S*,6*R*,7*R*,8*R*,9*R*)- and (1*R*,3*R*,5*S*,6*S*,7*R*,8*S*,9*R*)-6,8,9-Tris(benzyloxy)-7-[(4′-methoxyphenyl)methoxy]-3-methyl-2,4-dioxabicyclo[3.3.1]nonane 39

Sodium hydride (960 mg, 60% dispersion in mineral oil, 24.0 mmol) was washed with dry hexane (10 cm^3) under an argon atmosphere. After removal of the solvent *via* cannula the solid was suspended in dry DMF (40 cm^3) and cooled to 0 °C. To this suspension was added a solution of the alcohol **37** (7.11 g, 14.9 mmol) and tetrabutylammonium iodide (54 mg, 0.15 mmol) in dry DMF (100 cm^3). The suspension was stirred for 2 h at room temperature and then cooled to 0 °C when 4-methoxybenzyl chloride (3.00 cm^3, 22.1 mmol) was added dropwise and the solution stirred for 20 h at room temperature. The reaction was quenched by the addition of water (2 cm^3) and the solvent removed *in vacuo*. The residue was partitioned between ethyl acetate (100 cm^3) and water (100 cm^3) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (100 cm^3 then 2 × 50 cm^3) and the combined organic layers dried ($MgSO_4$). Evaporation of the solvent and flash chromatography (twice) eluting with 20% ethyl acetate in hexane afforded the bicyclo **39** (7.92 g, 89%) as a gum (Found: C, 74.35; H, 6.95. $C_{37}H_{40}O_7$ requires C, 74.5; H, 6.8%); δ_H(400 MHz; $CDCl_3$) 7.39–7.06 (17 H, m, Ph and C_6H_4OMe), 6.81–6.77 (2 H, m, C_6H_4OMe), 5.35 (1 H, q, *J* 4.8, 3-H), 4.76 (1 H, d, J_{AB} 12.0, OCH_ACH_B), 4.75 (1 H, d, J_{AB} 12.4, OCH_ACH_B), 4.71 (1 H, d, J_{AB} 12.4, OCH_ACH_B), 4.67 (1 H, d, J_{AB} 11.6, OCH_ACH_B), 4.58 (1 H, d, J_{AB} 11.2, OCH_ACH_B), 4.46 (1 H, d, J_{AB} 11.6, CH_ACH_BPh), 4.45 (1 H, d, J_{AB} 11.6, CH_ACH_BPh), 4.43–4.40 (1 H, m, 1-H), 4.38 (1 H, d, J_{AB} 11.6, CH_ACH_BPh), 4.38 (1 H, dd, *J* 3.6, 2.4, 5-H), 4.26 (1 H, t, *J* 8.0, 7-H or 8-H), 4.07 (1 H, t, *J* 7.4, 8-H or 7-H), 4.02 (1 H, br d, *J* 8.0, 6-H), 3.95 (1 H, td, *J* 4.0, 0.4, 9-H), 3.79 (3 H, s, OCH_3), 1.23 (3 H, s, 3-Me); δ_C(100 MHz; C_6D_6) 159.10 (CH_3OC), 138.58, 137.89, 137.62

(OCH_2C), 129.70, 129.29, 128.46, 128.41, 128.33, 12.24, 128.01, 127.96, 127.86, 127.79, 127.63, 113.60 (CH of Ph and PMB), 90.90 (CO_2), 80.96, 75.78, 73.39, 73.23 (4 × inositol ring C), 72.42, 72.19, 71.81, 71.81, 71.27 (5 × OCH_2), 69.76, 68.52 (2 × inositol ring C), 55.23 (OCH_3), 20.76 (3-Me); *m*/*z* (CI) 614 [$(M^+ NH_4)^+$, 24%], 596 (16), 565 (2), 475 (43), 385 (5), 277 (8), 211 (7), 121 (100) (Found: M^+ 596.277. $C_{37}H_{40}O_7$ requires *M*, 596.277).

1D-2,4,5,6-Tetra-*O*-benzyl-3-*O*-[(1′*S*)-camphanoyl]-1-*O*-(4′-methoxybenzyl)-*myo*-inositol 43 and 1D-2,4,5,6-tetra-*O*-benzyl-1-*O*-[(1′*S*)-camphanoyl]-3-*O*-(4′-methoxybenzyl)-*myo*-inositol 44

To a stirred solution of the alcohol **42** (1.07 g, 1.62 mmol) in dry dichloromethane (20 cm^3) at room temperature under argon was added triethylamine (1.60 cm^3, 8.61 mmol), DMAP (cat.) and (1*S*)-(−)-camphanic chloride (780 mg, 3.60 mmol). The solution was stirred for 18 h when TLC analysis indicated complete consumption of starting material and the presence of two products of R_f 0.19 and 0.11 (2% ethyl acetate in dichloromethane). The solution was diluted with dichloromethane (100 cm^3) and washed with aqueous hydrochloric acid (50 cm^3, 2 mol dm^{-3}), sodium hydroxide (50 cm^3, 2 mol dm^{-3}) and brine (50 cm^3) then dried (Na_2SO_4) and evaporated. Flash chromatography eluting with 2% ether in dichloromethane (twice) gave the *less polar camphanate* **43** (585 mg, 43%) as a white solid, mp 164.5–165.5 °C (from dichloromethane) (Found: C, 74.28; H, 6.72. $C_{52}H_{56}O_{10}$ requires C, 74.26; H, 6.72%); $\nu_{max}(CCl_4)/cm^{-1}$ 3089, 3065, 3044, 3032, 3030, 3026 (CH), 1787 (CO, lactone), 1733 (CO, ester), 1612, 1586, 1513, 1497, 1466, 1454, 1358, 1341, 1316, 1273, 1170, 1124, 1100, 1069, 1018, 992; δ_H(400 MHz; $CDCl_3$) 7.42–7.23 (22 H, m, Ph and $OCH_2CH_2C_6H_4OMe$), 6.90–6.86 (2 H, m, C_6H_4OMe), 5.00 (1 H, dd, *J* 10.3, 2.4, 3-H), 4.96–4.65 (10 H, m, OCH_2), 4.19 (1 H, t, *J* 9.8, inositol ring H), 4.12 (1 H, t, *J* 2.5, 2-H), 4.10 (1 H, t, *J* 9.6, inositol ring H), 3.82 (3 H, s, OCH_3), 3.59 (1 H, t, *J* 9.2, inositol ring H), 3.58 (1 H, dd, *J* 9.2, 1.9, 1-H), 1.91-1.61 (4 H, m, CH of camphanate), 1.10 (3 H, s, CH_3), 1.02 (3 H, s, CH_3), 0.92 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 178.04, 167.37 (CO), 159.33 (CH_3OC), 138.73, 138.48, 138.40, 135.21 (OCH_2C), 130.22, 129.29, 128.69, 128.61, 128.38, 128.28, 128.05, 127.86, 127.62, 127.54, 127.44, 127.30 (CH of Ph and $OCH_2C_6H_4OMe$), 113.90 ($OCH_2C_6H_4OMe$), 90.90 (OC of camphanate), 83.50, 81.52, 80.67, 79.15, 76.06 (5 × inositol ring C), 75.96, 75.93, 75.27 (3 × OCH_2), 75.04 (inositol ring C), 72.79 (OCH_2), 55.31 (OCH_3), 54.82, 54.24 (2 × quaternary C of camphanate), 30.77, 28.94 (2 × CH_2 of camphanate), 16.79, 16.65, 9.71 (3 × CH_3 of camphanate); *m*/*z* (FAB, 2-nitrobenzyl alcohol) 839 [$(M - H)^+$, 1%], 749 (0.7), 719 (1.2), 391 (0.4), 271 (1.1), 241 (1.6), 227 (1.3), 181 (9), 121 (100) (Found: M^+ 840.3866. $C_{52}H_{56}O_{10}$ requires *M*, 840.3873). Further elution gave the *more polar camphanate* **44** (545 mg, 40%) as a white solid, mp 111–113 °C (from diisopropyl ether–pentane); $[a]_D^{21}$ −11.9 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CCl_4)/cm^{-1}$ 3088, 3064, 3044, 3033, 3024, 3016, 3014 (CH), 1787 (CO, lactone), 1733 (CO, ester), 1613, 1586, 1514, 1497, 1466, 1454, 1358, 1315, 1273, 1171, 1124, 1100, 1069, 1017, 992; δ_H(400 MHz; $CDCl_3$) 7.38–7.17 (22 H, m, Ph and $CH_2C_6H_4OMe$), 6.87–6.82 (2 H, m, C_6H_4OMe), 4.98–4.60 (11 H, m, OCH_2 and 1-H), 4.18–4.14 (2 H, m, 2 × inositol ring H), 4.08 (1 H, t, *J* 9.6, inositol ring H), 3.81 (3 H, s, OCH_3), 3.59–3.54 (2 H, m, 2 × inositol ring H), 2.31–2.23 (1 H, m, CH of camphanate), 1.94–1.81 (3 H, m, CH of camphanate), 1.07 (3 H, s, CH_3), 0.95 (3 H, s, CH_3), 0.83 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 177.95, 167.47 (CO), 159.30 (CH_3OC), 138.68, 138.42, 138.37 (OCH_2C), 130.14, 129.23, 128.36, 128.30, 128.02, 127.85, 127.59, 127.43, 127.23 (CH of Ph and $OCH_2C_6H_4OMe$), 113.90 ($OCH_2C_6H_4OMe$), 90.88 (CO_2 of camphanate), 83.56, 81.43, 80.72, 78.92 (4 × inositol ring C), 76.00, 75.89 (2 × OCH_2), 75.28 (inositol ring C), 74.68, 72.79 (2 × OCH_2), 55.30 (OCH_3), 54.80, 54.10 (2 × quaternary C of camphate), 30.92, 28.97 (2 × CH_2 of camphanate), 16.65, 16.58, 9.65 (3 × CH_3 of camphanate).

1D-2,4,5,6-Tetra-*O*-benzyl-1-*O*-(4′-methoxybenzyl)-*myo*-inositol (+)-42 [17]

To a stirred solution of the less polar camphanate **43** (614 mg, 0.720 mmol) in THF (27 cm^3) and water (3 cm^3) was added lithium hydroxide (136 mg, 7.50 mmol) and the solution was stirred at room temperature under air for 21 h. The solvent was evaporated and the residue partitioned between water (25 cm^3) and ethyl acetate (50 cm^3). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 10 cm^3) and the combined organic layers dried ($MgSO_4$). Evaporation and flash chromatography eluting with 5% ethyl acetate in dichloromethane gave the alcohol (+)-**42** (467 mg, 98%) as a slowly crystallising oil, mp 89.5–90 °C (from light petroleum, bp 60–80 °C); $[a]_D^{26}$ +9.8 (*c* 0.70 in $CHCl_3$) [lit.,[17] $[a]_D^{23}$ +7.5 (*c* 0.2 in $CHCl_3$)].

1D-2,4,5,6-Tetra-*O*-benzyl-3-*O*-(4′-methoxybenzyl)-*myo*-inositol (−)-42 [27]

Saponification of the more polar camphanate **44** (628 mg, 0.74 mmol) as above gave (−)-**42** (453 mg, 93%) as a white solid, mp 90 °C $[a]_D^{21}$ −10.1 (*c* 0.35 in $CHCl_3$) [lit.,[27] $[a]_D$ −7.9 (*c* 1.9 in $CHCl_3$)].

1D-1,2,4,5,6-Penta-*O*-benzyl-*myo*-inositol (+)-51 [34,35]

To a solution of the alcohol (−)-**42** (59 mg, 0.089 mmol) in dry DMF (3 cm^3) at room temperature under argon was added sodium hydride (30 mg, 60% dispersion in mineral oil, 0.75 mmol) and the suspension stirred for 30 min then benzyl bromide (25 μL, 0.21 mmol) was added and the yellow solution was stirred for 3 h. TLC analysis indicated the complete conversion to a product of R_f 0.29 (20% ethyl acetate in hexane). The reaction was quenched by the addition of water (0.5 cm^3) and partitioned between water (10 cm^3) and ethyl acetate (25 cm^3). The organic layer was separated, washed with brine (10 cm^3) and evaporated. The residue was dissolved in acetonitrile (10 cm^3) and water (2.5 cm^3) and cooled to 0 °C with stirring under air. To this solution was added cerium(IV) ammonium nitrate (300 mg, 0.56 mmol) in one portion. The solution was stirred for 1 h at 0 °C then diluted with ethyl acetate (25 cm^3) and water (10 cm^3). The aqueous layer was separated and the organic layer washed with saturated sodium hydrogen carbonate solution (10 cm^3) then dried ($MgSO_4$). Evaporation and flash chromatography eluting with 10–30% ethyl acetate in hexane gave 1D-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol (+)-**51** (33 mg, 59% over 2 steps) as a gum; $[a]_D^{22}$ +9.4 (*c* 1.1 in $CHCl_3$) {lit.,[35] $[a]_D^{22}$ +9.7 (*c* 1.5 in $CHCl_3$); lit.,[35] $[a]_D^{20}$ +13.9 (*c* 0.3 in $CHCl_3$)} (Found: C, 78.3; H, 6.8. $C_{41}H_{42}O_6$ requires C, 78.1; H, 6.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 3570 (OH), 3066, 3032, 2874 (CH), 1553, 1514, 1497, 1454, 1360, 1208, 1130, 1071, 1028; δ_H(400 MHz; $CDCl_3$) 7.42–7.25 (25 H, m, Ph), 5.02–4.68 (10 H, m, CH_2Ph), 4.08 (1 H, t, *J* 9.5, inositol ring H), 4.05 (1 H, t, *J* 2.4, 2-H), 3.83 (1 H, t, *J* 9.5, inositol ring H), 3.52–3.46 (3 H, m, 3 × inositol ring H), 2.22 (1 H, d, *J* 6.3, OH); δ_C(100 MHz; $CDCl_3$) 138.77, 138.68, 138.65 (OCH_2C), 128.53, 128.46, 128.42, 128.37, 128.10, 128.07, 127.88, 127.82, 127.72, 127.66, 127.60 (CH of Ph), 83.64, 82.21, 81.94, 81.16, 77.15 (5 × ring C), 75.91, 75.79, 75.56, 74.78, 73.02 (5 × OCH_2), 72.45 (ring C).

1D-1-(1′,2′-Di-*O*-hexadecanoyl-*sn*-glycero(3′)phospho)-*myo*-inositol 3-phosphate (+)-7 [14,17,18]

Palladium hydroxide on carbon (57 mg) was suspended in *tert*-butanol (7.5 cm^3) and the catalyst hydrogenated at 60 psi for 3 h then degassed and a solution of (−)-**47** (129 mg, 76.4 μmol) in *tert*-butanol (7.5 cm^3) was added. The suspension was

hydrogenated at 60 psi and 30 °C for 2 days. The catalyst was removed by centrifugation and the catalyst washed with *tert*-butanol (15 cm^3) and re-centrifuged. The combined solvent was passed through a plug of Celite and washed with a further portion of *tert*-butanol (10 cm^3). Evaporation followed by freeze-drying (from water) afforded dipalmitoyl PtdIns(3)P (+)-**7** (59.0 mg, 89%) as a white solid, mp 108–110 °C $[a]_D^{22}$ +0.7 [*c* 1.1 in $CHCl_3$–methanol (1:1)]; δ_H(400 MHz; d_6-DMSO) 5.19–5.11 (1 H, m, 2′-H), 4.34–4.27 (1 H, m, inositol ring H), 4.20 (1 H, br s, 2-H), 4.13–4.04 (3 H, m), 3.83 (2 H, br t, *J* 9.1), 3.59–3.52 (2 H, m), 3.01 (1 H, t, *J* 9.0, inositol ring H), 2.33–2.23 (4 H, m, $OCOCH_2$), 1.54–1.44 (4 H, m, $OCOCH_2CH_2$), 1.31–1.20 (48 H, m, methylene envelope), 0.85 (6 H, t, CH_3); δ_P(101 MHz; d_6-DMSO) 1.28, −0.09; *m*/*z* (FAB, glycerol) 891.7 [$(M + H)^+$, 0.7%], 653.3 (0.7), 613.3 (1), 565.7 (1), 551.8 (11), 460.3 (7), 385.1 (4), 331.3 (5), 307.1 (92), 289.1 (61), 232.0 (100) [Found: $(M + H)^+$ 891.5024. $C_{41}H_{81}O_{16}P_2$ requires *M*, 891.5000].

2,4,6-Tri-*O*-benzyl-1-*O*-(4′-methoxybenzyl)-*myo*-inositol 48

To a stirred solution of the acetal **39** (7.47 g, 12.5 mmol) in chloroform (25 cm^3) and methanol (50 cm^3) was added concentrated hydrochloric acid (5 drops) and stirring continued at 25 °C for 10 h. The reaction mixture was neutralised by the addition of solid sodium hydrogen carbonate and the solvent removed *in vacuo*. Flash chromatography eluting with 20–50% ethyl acetate in hexane afforded **48** (6.55 g, 11.5 mmol, 92%) as a thick oil which solidified slowly to give an amorphous white solid which could not be crystallised (Found: C, 73.8; H, 6.8. $C_{35}H_{38}O_7$ requires C, 73.65; H, 6.7%); ν_{max} (CCl_4)/cm^{-1} 3576 (OH), 3066, 3032, 2909, 2836 (CH), 1612, 1514, 1497, 1454, 1361, 1302, 1249, 1209, 1172, 1111, 1070, 1040, 1027; δ_H(400 MHz; $CDCl_3$) 7.38–7.22 (17 H, m, Ph and $OCH_2C_6H_4OMe$), 6.87–6.82 (2 H, m, $OCH_2C_6H_4OMe$), 4.98 (1 H, d, J_{AB} 11.7, CH_AH_BPh), 4.97 (1 H, d, J_{AB} 11.0, CH_AH_BPh), 4.88 (1 H, d, J_{AB} 11.4, CH_AH_BPh), 4.78 (1 H, d, *J* 11.4, CH_AH_BPh), 4.74 (1 H, d, *J* 11.4, CH_AH_BPh), 4.72 (1 H, d, *J* 11.4, CH_AH_BPh), 4.59 (2 H, s, OCH_2Ph), 4.00 (1 H, t, *J* 2.6, 2-H), 3.87 (1 H, t, *J* 9.3, inositol ring H), 3.79 (3 H, s, OCH_3), 3.68 (1 H, t, *J* 9.3, inositol ring H), 3.51 (1 H, td, *J* 9.2, 2.0, 5-H), 3.46 (1 H, ddd, *J* 9.4, 6.3, 2.8, 3-H), 3.41 (1 H, dd, *J* 9.7, 2.4, 1-H), 2.53 (1 H, d, *J* 2.2, 5-OH), 2.34 (1 H, d, *J* 6.2, 3-OH); δ_C(100 MHz; $CDCl_3$) 159.26 (CH_3OC), 138.73, 138.67 ($OCHC$), 130.17, 129.24, 128.55, 128.44, 128.32, 127.96, 127.92, 127.73, 127.71, 127.68, 127.57, 113.83 ($OCH_2C_6H_4OMe$), 81.67, 81.24, 80.57, 77.31 (4 × inositol ring C), 75.35 (OCH_2), 74.99, 74.99 (2 × inositol ring C), 74.84, 74.82, 72.38 (3 × OCH_2), 72.90 (inositol ring C), 55.21 (CH_3); *m*/*z* (CI, NH_3) 588 [$(M + NH_4)^+$, 11%], 570 (5, M^+), 479 (8), 449 (17), 360 (6), 269 (2), 198 (3), 121 (100) [Found: $(M + NH_4)^+$ 588.296. $C_{35}H_{42}O_7N$ requires *M*, 588.296].

1D-2,4,6-Tri-*O*-benzyl-3-*O*-[(1′*S*)-camphanoyl]-1-*O*-(4′-methoxybenzyl)-2,4,6-benzyl-*myo*-inositol 49 and 1D-2,4,6-tri-*O*-benzyl-1-*O*-[(1′*S*)-camphanoyl]-3-*O*-(4′-methoxybenzyl)-*myo*-inositol 50

To a stirred solution of the diol **48** (3.99 g, 6.99 mmol) in dry dichloromethane (150 cm^3) under an argon atmosphere was added pyridine (1.70 cm^3, 21.0 mmol), DMAP (cat.) and the solution cooled to 0 °C. To this stirred solution was added (1*S*)-(−)-camphanic chloride (1.67 g, 7.71 mmol) in one portion. Stirring was continued at this temperature for 24 h when the solution was washed with ice cold aqueous hydrochloric acid (2 mol dm^{-3}, 2 × 50 cm^3), brine (50 cm^3) then dried ($MgSO_4$) and evaporated. Repeated flash chromatography eluting with 0–5% ethyl acetate in dichloromethane gave a less polar product presumed to be the bis-camphanates (372 mg, 0.495 mmol, 6%) as a solid which was not examined further. Further elution gave the less polar camphanate **49** (1.25 g, 1.66 mmol, 24%) as a white solid, mp 203–204 °C (from ethyl acetate–ether–hexane); $[a]_D^{22}$ +17.1 (*c* 0.48 in $CHCl_3$) (Found: C, 71.95; H, 6.8. $C_{45}H_{50}O_{10}$ requires C, 72.0; H, 6.7%); ν_{max}(CCl_4)/cm^{-1} 3583 (OH), 3066, 3032, 2935, 2875, 2836 (CH), 1798 (CO, lactone), 1736 (CO, ester), 1613, 1553, 1542, 1514, 1464, 1454, 1395, 1360, 1341, 1314, 1265, 1250, 1210, 1168, 1118, 1097, 1056, 1028, 1018, 994, 932; δ_H(400 MHz; $CDCl_3$) 7.38–7.21 (17 H, m, Ph and C_6H_4OMe), 6.86–6.84 (2 H, m, C_6H_4OMe), 4.96–4.60 (9 H, m, CH_2Ph and 3-H), 4.11 (1 H, t, *J* 2.2, 2-H), 4.02 (1 H, t, *J* 9.6, inositol ring H), 3.90 (1 H, t, *J* 9.4, inositol ring H), 3.80 (3 H, s, OCH_3), 3.60 (1 H, t, *J* 9.2, inositol ring H), 3.53 (1 H, dd, *J* 9.7, 2.1, 1-H), 2.32–2.25 (1 H, m, CH of camphanate), 1.88–1.80 (2 H, m, CH_2 of camphanate), 1.66–1.61 (2 H, m, CH of camphanate and OH), 1.07 (3 H, s, CH_3), 0.99 (3 H, s, CH_3), 0.87 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 177.98 (CO), 167.25 (CO), 159.34 (CH_3OC), 138.64, 138.50, 138.37 (OCH_2C), 130.04, 129.27, 128.52, 128.35, 128.33, 128.01, 127.80, 127.63, 127.54, 127.47 (CH of Ph and C_6H_4OMe), 113.90 (C_6H_4OMe), 90.87 (OC of camphanate), 80.85, 80.39, 78.67, 76.08 (4 × inositol ring C), 75.51 (OCH_2), 75.09 (inositol ring C), 75.06 (OCH_2), 74.75 (inositol ring C), 74.68, 72.56 (2 × OCH_2), 55.29 (OCH_3), 54.80, 54.22 (2 × quaternary C of camphanate), 30.74, 28.93 (2 × CH_2 of camphanate), 16.70, 16.63, 9.67 (3 × CH_3); *m*/*z* (CI, NH_3) 769 ([$M + NH_4$]$^+$, 17%), 658 (8), 630 (16), 523 (3), 449 (2), 216 (28), 172 (11), 137 (29), 121 (100) (Found: M^+ 750.339. $C_{45}H_{50}O_{10}$ requires *M*, 750.340). Further elution gave the more polar camphanate **50** (1.34 g, 1.78 mmol, 25%) as a white solid mp 203–204 °C (from ethyl acetate–ether–hexane); $[a]_D^{22}$ −20.8 (*c* 1.2 in $CHCl_3$) (Found: C, 72.2; H, 6.7. $C_{45}H_{50}O_{10}$ requires C, 72.0; H, 6.7%); ν_{max}(CCl_4)/cm^{-1} 3583 (OH), 3089, 3066, 3032, 2935, 2909, 2875, 2836 (CH), 1799 (CO, lactone), 1733 (CO, ester), 1613, 1586, 1567, 1554, 1546, 1514, 1497, 1464, 1454, 1396, 1360, 1341, 1315, 1271, 1264, 1250, 1210, 1165, 1099, 1057, 1028, 1018, 994, 932; δ_H(400 MHz; $CDCl_3$) 7.39–7.21 (17 H, m, Ph and C_6H_4OMe), 6.87–6.84 (2 H, m, C_6H_4OMe), 4.95 (1 H, d, J_{AB} 11.2, CH_ACH_BPh), 4.94 (1 H, d, J_{AB} 11.6, CH_BCH_BPh), 4.87 (1 H, dd, *J* 10.1, 2.5, 1-H), 4.86 (1 H, d, J_{AB} 11.4, CH_AH_BPh), 4.73 (1 H, d, J_{AB} 11.2, CH_ACH_B-Ph), 4.72 (1 H, d, J_{AB} 11.4, CH_ACH_BPh), 4.66 (1 H, d, J_{AB} 11.6, CH_ACH_BPh), 4.62 (1 H, d, J_{AB} 11.2, CH_ACH_BPh), 4.58 (1 H, d, J_{AB} 11.2, CH_ACH_BPh), 4.18 (1 H, t, *J* 2.2, 2-H), 4.03 (1 H, t, *J* 9.6, inositol ring H), 3.91 (1 H, t, *J* 9.4, inositol ring H), 3.80 (3 H, s, OCH_3), 3.60 (1 H, t, *J* 9.1, inositol ring H), 3.53 (1 H, dd, *J* 9.7, 2.1, 3-H), 2.33–2.25 (1 H, m, CH of camphanate), 1.94–1.82 (2 H, m, CH of camphanate), 1.69–1.58 (2 H, m, CH of camphanate and OH), 1.07 (3 H, s, CH_3), 0.94 (3 H, s, CH_3), 0.86 (3 H, s, CH_3).

1D-2,4,6-Tri-*O*-benzyl-1-*O*-(4′-methoxybenzyl)-*myo*-inositol (+)-48

To a stirred solution of the camphanate **49** (1.17 g, 1.56 mmol) in THF (54 cm^3) and water (6 cm^3) under air was added lithium hydroxide monohydrate (697 mg, 16.6 mmol). The reaction mixture was stirred for 19 h then the solvent removed *in vacuo* and the residue partitioned between water (50 cm^3) and ethyl acetate (100 cm^3). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 25 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated. Flash chromatography eluting with 20–50% ethyl acetate in hexane afforded (+)-**48** (804 mg, 1.41 mmol, 90%) as a gum; $[a]_D^{18}$ +8.9 (*c* 1.7 in $CHCl_3$) (Found: C, 73.8; H, 6.8. $C_{35}H_{38}O_7$ requires C, 73.65; H, 6.7%); ν_{max}(CCl_4)/cm^{-1} 3576 (OH), 3066, 3032, 2909, 2836 (CH), 1612, 1514, 1497, 1454, 1361, 1302, 1249, 1209, 1172, 1111, 1070, 1040, 1027; δ_H(400 MHz; $CDCl_3$) 7.38–7.22 (17 H, m, Ph and $OCH_2C_6H_4OMe$), 6.87–6.82 (2 H, m, $OCH_2C_6H_4OMe$), 4.98 (1 H, d, J_{AB} 11.7, CH_AH_BPh), 4.97 (1 H, d, J_{AB} 11.0, CH_AH_BPh), 4.88 (1 H, d, J_{AB} 11.4, CH_AH_B-Ph), 4.78 (1 H, d, *J* 11.4, CH_AH_BPh), 4.74 (1 H, d, *J* 11.4, CH_AH_BPh), 4.72 (1 H, d, *J* 11.4, CH_AH_BPh), 4.59 (2 H, s,

OCH_2Ph), 4.00 (1 H, t, *J* 2.6, 2-H), 3.87 (1 H, t, *J* 9.3, inositol ring H), 3.79 (3 H, s, OCH_3), 3.68 (1 H, t, *J* 9.3, inositol ring H), 3.51 (1 H, td, *J* 9.2, 2.0, 5-H), 3.46 (1 H, ddd, *J* 9.4, 6.3, 2.8, 3-H), 3.41 (1 H, dd, *J* 9.7, 2.4, 1-H), 2.53 (1 H, d, *J* 2.2, 5-OH), 2.34 (1 H, d, *J* 6.2, 3-OH); δ_C(100 MHz; $CDCl_3$) 159.26 (CH_3OC), 138.73, 138.67 (OCH*C*), 130.17, 129.24, 128.55, 128.44, 128.32, 127.96, 127.92, 127.73, 127.71, 127.68, 127.57, 113.83 ($OCH_2C_6H_4OMe$), 81.67, 81.24, 80.57, 77.31 (4 × inositol ring C), 75.35 (OCH_2), 74.99, 74.99 (2 × inositol ring C), 74.84, 74.82, 72.38 (3 × OCH_2), 72.90 (inositol ring C), 55.21 (CH_3); *m*/*z* (CI, NH_3) 588 [$(M + NH_4)^+$, 11%], 570 (5, M^+), 479 (8), 449 (17), 360 (6), 269 (2), 198 (3), 121 (100) [Found: $(M + NH_4)^+$ 588.296. $C_{35}H_{42}O_7N$ requires *M*, 588.296].

Elucidation of the absolute configuration of the diol (+)-48

1D-2,3,4,5,6-Penta-*O*-benzyl-*myo*-inositol (−)-51.[36] To a solution of the diol (+)-**48** (94 mg, 0.16 mmol) in dry DMF (2 cm^3) at room temperature under argon was added sodium hydride (52 mg, 60% dispersion in mineral oil, 1.3 mmol) and the suspension stirred for 15 min then benzyl bromide (0.08 cm^3, 0.67 mmol) was added and the yellow solution stirred for 3.5 h. The reaction was quenched by the addition of methanol (1 cm^3) and partitioned between water (10 cm^3) and ethyl acetate (25 cm^3). The organic layer was separated and evaporated. The residue was dissolved in acetonitrile (10 cm^3) and water (2.5 cm^3) and cooled to 0 °C with stirring under air. To this solution was added cerium(IV) ammonium nitrate (540 mg, 1.0 mmol) in one portion. The solution was stirred for 1 h at this temperature then diluted with ethyl acetate (25 cm^3) and water (10 cm^3), the aqueous layer was separated and the organic layer washed with saturated sodium hydrogen carbonate solution (10 cm^3) and brine (10 cm^3) then dried ($MgSO_4$). Evaporation and flash chromatography eluting with 10–30% ethyl acetate in hexane gave (−)-**51** (48 mg, 46% over 2 steps) as a gum; $[\alpha]_D^{18}$ −10.0 (*c* 2.3 in $CHCl_3$) [lit.,[36] $[\alpha]_D^{18}$ −9.0 (*c* 1 in $CHCl_3$)].

1D-2,4,6-Tri-*O*-benzyl-1-*O*-(4′-methoxybenzyl)-*myo*-inositol 3,5-bis(dibenzyl phosphate) (−)-52

To a stirred solution of (+)-**48** (2.76 g, 4.68 mmol) and 1*H*-tetrazole (1.46 g, 20.8 mmol) in dry dichloromethane (50 cm^3) at room temperature under argon was added bis(benzyloxy)(diisopropylamino)phosphine (4.95 g, 14.3 mmol) in dry dichloromethane (50 cm^3, washed in with 10 cm^3). The reaction mixture was stirred for 80 min when TLC analysis showed the presence of a single product of R_f 0.26 (50% ethyl acetate in hexane). The solution was cooled to −78 °C and MCPBA (6.20 g, *ca.* 35.9 mmol) was added in one portion and the suspension was stirred for 1 h at this temperature then at RT for a further 1 h. The reaction mixture was diluted with dichloromethane (100 cm^3) and poured onto a stirred 10% sodium sulfite solution (200 cm^3). The mixture was then concentrated *in vacuo*, to remove most of the organic solvent, then extracted with ether (3 × 200 cm^3). The combined ethereal extract was washed with a saturated solution of sodium hydrogen carbonate (250 cm^3) and brine (25 cm^3) then dried ($MgSO_4$). Evaporation and flash chromatography eluting with 40–70% ethyl acetate in hexane afforded (−)-**52** (4.38 g, 86%) as a gum; $[\alpha]_D^{21}$ −6.5 (*c* 2.3 in $CHCl_3$) (Found: C, 69.2; H, 6.0; P, 5.8. $C_{63}H_{64}O_{13}P_2$ requires C, 69.35; H, 5.9; P, 5.7%); δ_H(400 MHz; $CDCl_3$) 7.35–6.98 (37 H, m, Ph and 2 × C_6H_4OMe), 6.81–6.76 (2 H, m, 2 × C_6H_4OMe), 4.93–4.67 (15 H, m, OCH_2), 4.48–4.39 (2 H, m, 5-H and OCH_2), 4.32 (1 H, br s, 2-H), 4.23 (1 H, ddd, *J* 9.8, 7.5, 2.3, 3-H), 4.10 (1 H, t, *J* 10.2, inositol ring H), 4.02 (1 H, t, *J* 9.6, inositol ring H), 3.77 (3 H, s, OCH_3), 3.39 (1 H, dd, *J* 9.8, 1.9, 1-H); δ_C(400 MHz; $CDCl_3$) 159.26 (CH_3OC), 138.65, 138.25, 136.11, 135.60, 129.82, 129.32, 128.56, 128.52, 128.47, 128.29, 128.25, 128.10, 128.06, 127.82, 127.62, 127.57, 127.51, 127.43, 127.22, 127.18, 113.80 (Ph and C_6H_4OMe), 80.45 (d, *J* 7.0, inositol ring C), 79.65 (inositol ring C), 78.92 (inositol ring C), 78.34 (m, C-4), 78.10 (d, *J* 5.7, inositol ring C), 75.93 (inositol ring C), 75.07 (OCH_2), 74.62 (d, *J* 5.8, OCH_2), 72.36 (OCH_2), 69.46 (d, *J* 5.5, OCH_2), 69.29 (d, *J* 5.3, OCH_2), 69.07 (d, *J* 5.0, OCH_2), 55.26 (OCH_3); δ_P(101 MHz; $CDCl_3$) −1.10, −1.61; *m*/*z* (ESI) 1113 [$(M + Na)^+$, 100%], 915 (8), 835 (10), 803 (12), 745 (10), 637 (5) [Found: $(M + Na)^+$ 1113.3660. $C_{63}H_{64}O_{13}P_2Na$ requires *M*, 1113.3720].

1D-2,4,6-Tri-*O*-benzyl-*myo*-inositol 3,5-bis(dibenzyl phosphate) (−)-53

To a solution of the 4-methoxybenzyl ether (−)-**52** (4.38 g, 4.02 mmol) in acetonitrile (100 cm^3) and water (25 cm^3) at 0 °C under air was added cerium(IV) ammonium nitrate (13.0 g, 23.8 mmol) and the solution was stirred for 45 min. The reaction mixture was then concentrated *in vacuo* to 1/5 the original volume, diluted with H_2O (50 cm^3) and extracted with ether (3 × 200 cm^3). The combined ethereal extract was washed with brine (200 cm^3) and dried ($MgSO_4$). Evaporation and flash chromatography eluting with 20–50% ethyl acetate in hexane afforded (−)-**53** (3.63 g, 3.74 mmol, 93%) as a gum; $[\alpha]_D^{22}$ −4.9 (*c* 0.94 in $CHCl_3$) (Found: C, 67.7; H, 5.9; P, 6.4. $C_{55}H_{56}O_{12}P_2$ requires C, 68.0; H, 5.8; P, 6.4%); δ_H(400 MHz; $CDCl_3$) 7.40–7.00 (35 H, m, Ph), 4.95–4.64 (14 H, m, OCH_2), 4.42 (1 H, q, *J* 9.2, 5-H), 4.27 (1 H, td, *J* 8.8, 2.2, 1-H), 4.19 (1 H, br s, 2-H), 4.04 (1 H, t, *J* 9.6, inositol ring H), 3.82 (1 H, t, *J* 9.6, inositol ring H), 3.50 (1 H, ddd, *J* 9.7, 5.7, 2.2, 3-H), 2.13 (1 H, d, *J* 5.9, OH); δ_P(101 MHz; $CDCl_3$) −0.97, −1.26; *m*/*z* (FAB, NOBA) 972 [$(M + H)^+$, 20%], 181 (100), 154 (50) [Found: $(M + H)^+$ 971.3412. $C_{55}H_{57}O_{12}P_2$ requires *M*, 971.3325].

1D-2,4,6-Tri-*O*-benzyl-1-[1′,2′-di-*O*-hexadecanoyl-*sn*-glycero-(3′)benzylphosphonato]-*myo*-inositol 3,5-bis(dibenzyl phosphate) (−)-54[6]

Dry dichloromethane (30 cm^3) was cannulated onto a mixture of the alcohol (−)-**53** (551 mg, 0.567 mmol), 1*H*-tetrazole (155 mg, 2.21 mmol) and the phosphoramidite (+)-**26** (1.25 g, 1.55 mmol) under argon. The reaction mixture was stirred for 3 h when TLC analysis indicated no starting material remained (50% ethyl acetate in hexane). The reaction mixture was cooled to −78 °C and MCPBA (1.01 g, 5.85 mmol) was added in one portion and the suspension was allowed to warm to RT over 3 h with stirring. The reaction mixture was diluted with dichloromethane (60 cm^3) and poured onto a stirred solution of 10% sodium hydrogen sulfite (100 cm^3). After stirring for 10 min the organic solvent was removed *in vacuo* and the remaining aqueous phase was extracted with ether (3 × 100 cm^3) and the combined organic layer washed with a saturated solution of sodium hydrogen carbonate (2 × 50 cm^3) then dried ($MgSO_4$). Evaporation and flash chromatography eluting with 20–60% ethyl acetate in hexane afforded (−)-**54** (795 mg, 0.470 mmol, 83%) as a thick oil; $[\alpha]_D^{22}$ −0.8 (*c* 4 in $CHCl_3$) (Found: C, 68.8; H, 7.7; P, 5.6. $C_{97}H_{129}O_{19}P_3$ requires C, 68.9; H, 7.7; P, 5.5%); δ_H(400 MHz; $CDCl_3$) 7.39–7.11 (36 H, m, Ph), 7.00–6.95 (4 H, m, Ph), 5.06–4.64 (17 H, m), 4.53–4.18 (4 H, m), 4.11–3.72 (6 H, m), 2.23–2.13 (4 H, m, $OCOCH_2$), 1.59–1.44 (4 H, m, $OCOCH_2CH_2$), 1.31–1.17 (48 H, m, methylene envelope), 0.87 (6 H, t, *J* 6.8, CH_3); δ_P(101 MHz; $CDCl_3$) −1.06, −1.30, −1.34, −1.38, −1.41; *m*/*z* (ESI) 1713 [$(M + Na)^+$, 10%], 998 (100), 984 (90), 970 (20), 941 (50) [Found: $(M + Na)^+$ 1713.8284. $C_{97}H_{129}O_{19}P_3Na$ requires *M*, 1723.8238].

1D-1-(1′,2′-Di-*O*-hexadecanoyl-*sn*-glycero(3′)phospho)-*myo*-inositol 3,5-bis(phosphate) (−)-4[5,6]

Palladium hydroxide on carbon (103 mg) was suspended in *tert*-butanol (15 cm^3) and the catalyst hydrogenated at 60 psi for 3 h then degassed and a solution of (−)-**54** (234 mg, 0.139 mmol) in *tert*-butanol (15 cm^3) was added. The suspension was hydrogenated at 60 psi and 30 °C for 2 days. The catalyst was removed

by centrifugation, washed with *tert*-butanol (30 cm^3) and re-centrifuged. The combined solvent was passed through a plug of Celite which was then washed with a further portion of *tert*-butanol (15 cm^3). Evaporation followed by freeze-drying afforded dipalmitoyl PtdIns(3,5)P_2 (−)-**4** (136 mg, quantitative) as a white solid, mp 100–103 °C; $[\alpha]_D^{22}$ −3.4 [*c* 0.29 in H_2O (Na salt)]; δ_H(400 MHz; d_6-DMSO) 5.19–5.11 (1 H, m, 2′-H), 4.31–4.22 (2 H, m), 4.13–3.74 (8 H, m), 2.33–2.24 (4 H, m, $OCOCH_2$), 1.55–1.44 (4 H, m, $OCOCH_2CH_2$), 1.30–1.18 (48 H, m, methylene envelope), 0.85 (6 H, t, *J* 6.6, CH_3); δ_P(101 MHz; d_6-DMSO) 3.09, 1.00, −0.12; *m/z* (FAB, Glycerol) 972.4 [$(M + H + H)^+$, 1%], 825.9 (0.8), 73.8 (5), 551.8 (10, dipalmitoyl-glycerol-OH), 441.1 (7), 403.1 (6), 369.2 (16), 313.3 (26), 277.2 (81), 239.2 (61), 223.1 (42), 195.1 (100) [Found: $(M + 2H)^+$ 972.4724. $C_{41}H_{83}O_{19}P_3$ requires *M*, 972.4741].

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