Asymmetric Total Synthesis of Phosphatidylinositol 3-Phosphate and 4-Phosphate Derivatives

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New asymmetric syntheses of phosphatidylinositol 3-phosphate (PtdIns(3)P) and phosphatidylinositol 4-phosphate (PtdIns(4)P) derivatives are described. Key intermediates were used to prepare diacylglyceryl moieties with dibutyryl, dioctanoyl, and dihexadecanoyl chains. In addition, a modified route provided PtdIns(3)P and PtdIns(4)P triesters with P-1-linked aminopropyl groups for preparation of affinity probes. The synthesis of the inosityl precursor employed a dibutyltin oxide-mediated *p*-methoxybenzyl (PMB) etherification to give either the 2-PMB- or the 3-PMB-protected glucopyranosides. The Ferrier rearrangement was used to convert suitably protected glucose derivatives to enantiomerically pure, differentially protected D-*myo*-inositol key intermediates. A versatile phosphoramidite reagent was employed to allow synthesis of $PtdInsP_n$ derivatives with diacylglyceryl moieties of different chain lengths.

Introduction

Phosphatidylinositol polyphosphates ($PtdInsP_n$s) are key signaling molecules in cellular communication via protein kinases in endo- and exocytosis and in vesicular trafficking of proteins.[1,2] The central molecule, L-α-phosphatidyl-D-*myo*-inositol 4,5-bis(phosphate) (PtdIns-$(4,5)P_2$) serves four different cellular roles, each utilizing different portions of the total molecule. First, PtdIns-$(4,5)P_2$ is a substrate for phospholipase C (PLC), releasing the calcium-mobilizing second messenger $Ins(1,4,5)P_3$.[3] Second, $PtdIns(4,5)P_2$ itself functions in the recruitment of proteins to membranes via pleckstrin homology (PH) domains.[4] Third, $PtdIns(4,5)P_2$ may bind to and regulate cytoskeletal signaling proteins such as gelsolin and profilin[5] or it may regulate the GTPase function of ARF or the phospholipase activity of PLD.[6,7] Fourth, PtdIns-$(4,5)P_2$ can be converted by agonist-stimulated, receptor-mediated activation of phosphoinositide 3-kinase (PI 3-K)[8] to $PtdIns(3,4,5)P_3$, an effector molecule in a new intracellular signaling system.[9] The PI 3-K pathway and the corresponding D-3 $PtdInsP_n$ products[10] have been linked to mechanisms of oncogene transformation, cytoskeletal rearrangements, membrane association of signaling proteins, and trafficking of proteins by coated vesicles. Characteristics of the three families of PI 3-Ks were recently reviewed.[11]

The phosphoinositide monophosphates PtdIns(3)P and PtdIns(4)P and their protein targets have been less extensively examined for their roles in cell signaling. Studies have revealed that PtdIns(3)P, the product of the PI 3-K *VPS34*, is required for proper targeting of newly synthesized and endocytosed macromolecules in yeast.[1] PtdIns(3)P and other D-3 phosphoinositides bind to proteins that regulate vesicle coating, such as assembly proteins AP-2[12] and AP-3 (also known as AP-180),[13] and proteins that mediate communication between the actin cytoskeleton and membrane signaling proteins.[14,15] PtdIns(3)P is also a substrate for a 5-kinase that produces $PtdIns(3,5)P_2$ in mammalian and yeast cells.[16−18]

PtdIns(4)P is a substrate for PI 5-kinases, which may operate on substrate bound to phosphoinositide transport proteins, for the biosynthesis of $PtdIns(4,5)P_2$.[19] Two specific PtdIns(4)P 5-kinases are known that will also phosphorylate D-3 phosphoinositides to give bis- and tris-(phosphate) products.[20,21] In addition, PtdIns(4)P shows affinity for dynamin[18] and modest inhibition of a PtdIns-$(3,4,5)P_3$ 5-phosphatase.[16]

One constraint for the exploration of the biological roles of PtdIns(3)P and PtdIns(4)P has been limited access to synthetic materials with defined acyl chains; commer-

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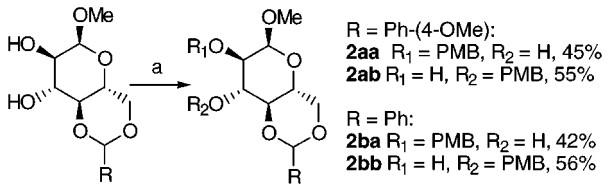
cially available materials from biological sources of PtdIns have unavoidable heterogeneity in the glyceryl acyl chains. Indeed, biologists have frequently resorted to comparisons of binding or activation by symmetrical dioctanoyl or dipalmitoyl PtdInsP_n derivatives with naturally occurring PtdInsP_ns, such as the *sn*-1-*O*-stearoyl-2-*O*-arachidonyl PtdIns(4,5)P_2, which is most abundant in animal systems. To continue our efforts to prepare a complete "matched set" of diacylglyceryl derivatives of the PtdInsP_ns, which all derive their D-*myo*-inositol chirality retrosynthetically from α-D-glucose,[22] we describe herein the preparation of PtdIns(3)P and PtdIns(4)P with short (dibutyryl), medium (dioctanoyl), and long (dipalmitoyl) chains. We also describe the preparation of the corresponding P-1-linked aminopropyl triesters[23,24] and their use for the preparation of photoactivatable reagents that probe the water−bilayer interface for ligand−protein interactions.[22]

Results and Discussion

The strategy for the synthesis of enantiomerically pure PtdIns(3)P and PtdIns(4)P derivatives followed the route developed to synthesize soluble inositol polyphosphates (InsP_n) and PtdInsP_n congeners[22−28] via the Ferrier rearrangement.[22,29] For these syntheses, methyl D-α-glucopyranoside was chosen as the optically pure starting material for the inositol moiety, and protecting groups are installed to establish the desired regiochemistry for the phosphate and hydroxyl groups. The key step involves the unique protection of the glucosyl C-2 OH or C-3 OH (corresponding to the C-3 OH or C-4 OH of D-*myo*-inositol) relative to the other hydroxyl groups; *p*-methoxybenzyl (PMB) was chosen for this purpose because it could be easily removed by DDQ without affecting other protecting groups.[22] This protection strategy was accomplished using dibutyltin oxide-mediated[30−34] selective PMB protection of the 2-OH of methyl 4,6-*O*-(*p*-methoxybenzylidene)-D-α-glucopyranoside (**1a**), giving the 2-PMB ether **2aa** in ca. 45% isolated yield (Scheme 1). Alternatively, the 3-PMB protected glycopyranoside **2ab** was obtained in 55% yield. The two isomers were readily separable by chromatography on silica gel. Use of either tetra-*n*-butylammonium bromide or iodide was necessary for optimal etherification and for

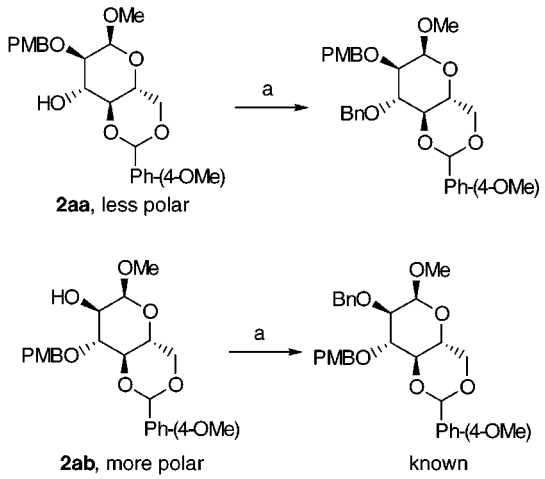
Scheme 1[a]



1a R = Ph-(4-OMe)
1b R = Ph

[a] Reaction conditions: (a) Bu_2SnO, *n*-Bu_4NBr, or *n*-Bu_4NI, toluene, reflux for 2 h; then PMBCl, reflux 2 h to overnight.

Scheme 2[a]



[a] Reaction conditions: (a) NaH, BnBr, DMF, rt, 2h.

shorter reaction time. Although better regioselectivity has been reported using CH_3CN instead of toluene as solvent and by omission of the tetra-*n*-butylammonium salt,[28−31] lower yields and unacceptably long reaction times were experienced for a modest increase in regioselectivity. The 3-PMB ether **2ab** was useful as the precursor for synthesis of Ins(1,4,5)P_3[27] and PtdIns(4,5)P_2.[23,25] Using the conditions described above, no 2,3-di-PMB ether was detected. Similar yields and regiospecificity were achieved from the commercially available methyl 4,6-*O*-benzylidene-D-α-glucopyranoside (**1b**).

To confirm the structures of the two isomers, a short chemical transformation was performed. Isomers **2aa** and **2ab** were converted to benzyl ethers (Scheme 2). Comparison of the ^1H NMR and melting points with the known compounds[27] allowed identification of the less polar starting material as the 2-PMB ether **2aa** and the more polar isomer as the 3-PMB ether **2ab**.

As shown in Scheme 3, hydrolytic deprotection of the benzylidene acetal in **2aa** and **2bb** under mild acidic conditions unmasked the 4- and 6-hydroxyls (**3a**,**b**) in high yield without affecting the PMB group. The primary hydroxyl was selectively tritylated,[28,35−37] the remaining secondary hydroxyls were benzylated, and mild acidic hydrolysis of the trityl group afforded alcohols **6a**,**b**. Swern oxidation[38] gave aldehydes **7a**,**b**, which were

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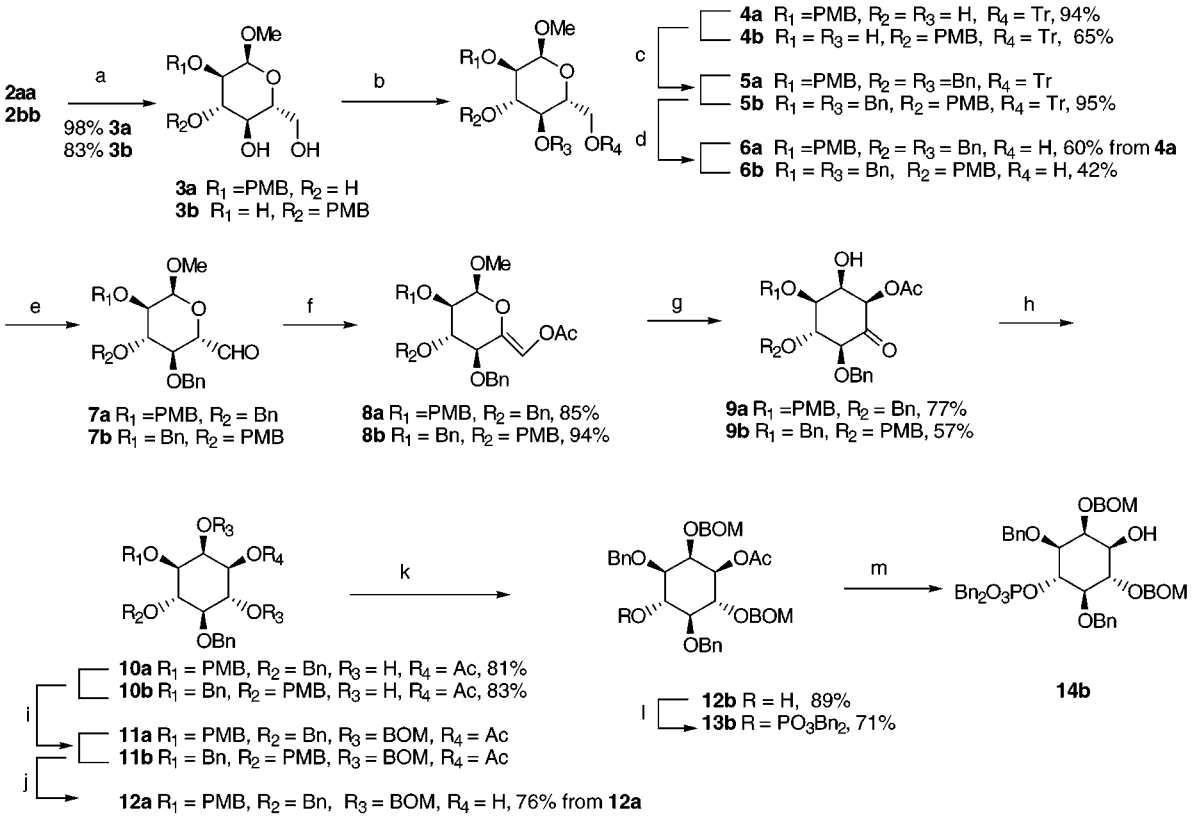
Scheme 3[a]



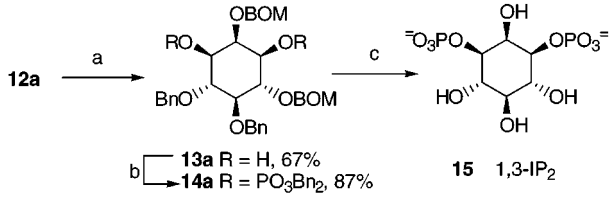
[a] Reaction conditions: (a) 5% *p*-TsOH monohydrate (pH ~ 2), MeOH, rt, 1 h; (b) TrCl, DMAP (cat.), Et_3N, DMF, rt, overnight; (c) NaH, BnBr, DMF, rt, 2 h; (d) 5% *p*-TsOH monohydrate or sulfuric acid (pH ~ 2), MeOH, rt, 2 h; (e) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 1 h; (f) K_2CO_3, Ac_2O, CH_3CN, reflux, overnight; (g) $Hg(OAc)_2$, acetone−water (3:2), 45 min, then saturated NaCl solution, rt, overnight; (h) $NaBH(OAc)_3$, CH_3CN, HOAc, 45 min; (i) BOMCl, proton sponge, *n*-Bu_4NBr, rt, 8 h, then, 35 °C, overnight, then 55 °C, 10 h to overnight; (j) 0.35 M NaOH, MeOH, reflux, 2 h; (k) DDQ, $CH_2Cl_2-H_2O$ (100:1, v/v), rt, 3 h; (l) $(BnO)_2PNPr_2$-*i*, 1*H*-tetrazole, rt, 30 min, then *m*-CPBA, −40 °C to room temperature, 60 min; (m) K_2CO_3, MeOH, 30 min.

directly acetylated to form the precursors **8a**,**b**, respectively. Ferrier rearrangement[22,29] with $Hg(OAc)_2$ generated the inositol skeletons **9a**,**b**. Highly stereoselective reduction of the carbonyl group with triacetoxyborohydride[39] furnished the desired hydroxyl derivatives **10a**,**b**. Careful reaction[22] of the diols **10a** and **10b** with BOMCl in the presence of proton sponge gave the bis-BOM compounds **11a**,**b** with no detectable acyl migration. DDQ removed the 4-PMB in **11b** to give a free OH, which was phosphorylated to triester **13b**; hydrolysis of the acetyl group then gave alcohol **14b**, which was ready for introduction of the phosphoglyceryl moiety.

We required the soluble Ins(1,3)P_2 for competitive displacement studies in the study of protein−PtdInsP_n interactions. This ligand was obtained (Scheme 4) by basic hydrolysis of the acetyl group of **11a**, removal of the PMB with DDQ, phosphorylation, and finally hydrogenolysis at 50 psi with Pd/C to give the *meso*-*myo*-inositol 1,3-bis(phosphate) **15**, in sodium salt form.[40]

The differentially protected D-*myo*-inositol precursors to PtdIns(3)P and PtdIns(4)P, **12a** and **14b**, respectively, were employed for two sets of syntheses. In the first set (Scheme 5), the dipalmitoyl glyceryl affinity probes bearing the P-1-linked aminopropyl phosphotriester[22−24] were prepared. Thus, coupling **12a** or **14b** with (cyanoethyl)phosphoramidite **16** gave **17a**,**b**, respectively. Removal of PMB (from **17b**) with DDQ gave phosphate **18** in 60% yield in two steps. If ceric ammonium nitrate[41,42] was used for oxidative deprotection of the PMB group, a slightly higher yield was obtained. Further phosphorylation furnished the fully protected phosphate **19** in 80% yield. The cyanoethyl group could be reduced to an aminopropyl group during hydrogenolysis of the benzyl protecting groups.[23] Thus, hydrogenation at 50 psi removed all the protecting groups of **17b** and **19** giving PtdIns(3)P and PtdIns(4)P triesters **20a**,**b**, respectively, as their sodium salts. Alternatively, initial removal of

Scheme 4[a]



[a] Reaction conditions: (a) DDQ, $CH_2Cl_2-H_2O$ (100:1, v/v), rt, 2 h; (b) $(BnO)_2PNPr_2$-*i*, 1*H*-tetrazole, rt, 30 min, then *m*-CPBA, −40 °C to room temperature, 60 min; (c) 10% Pd/C, $NaHCO_3$, *t*-BuOH−H_2O (6:1, v/v), H_2, 50 psi, rt, 5 h; then Chelex (Na^+ form) ion exchange.

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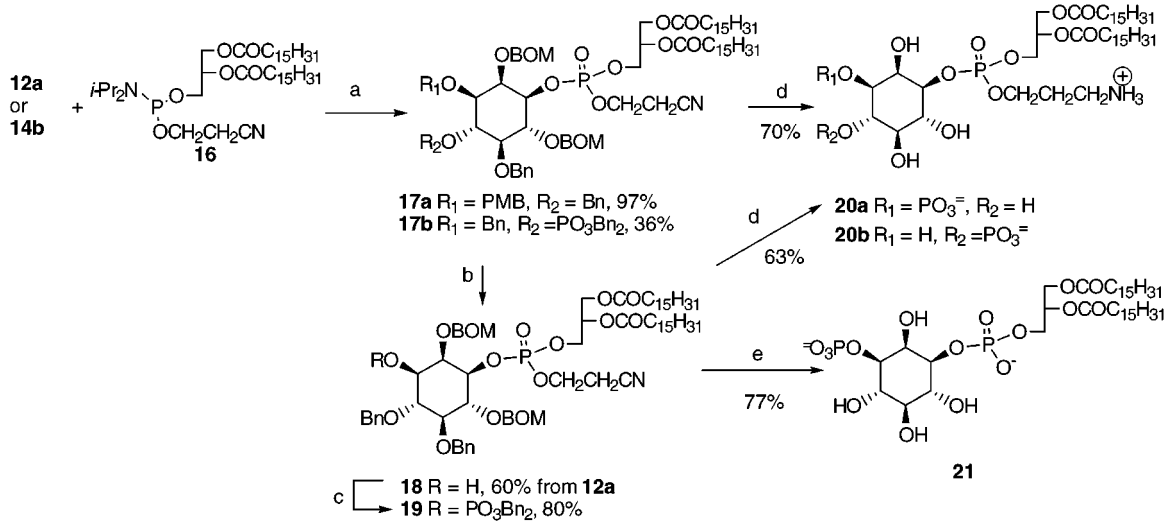
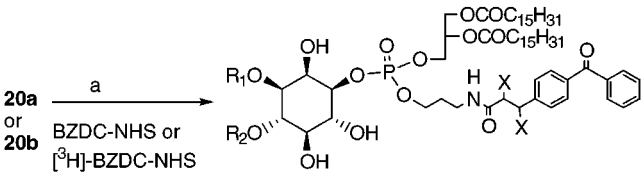
Scheme 5[a]



[a] Reaction conditions: (a) 1*H*-tetrazole, rt, 30 min, then *m*CPBA, −40 °C to room temperature, 60 min; (b) DDQ, CH_2Cl_2−H_2O (100:1, v/v), rt, 2 h; (c) $(BnO)_2PNPr_2$-*i*, 1*H*-tetrazole, rt, 30 min, then *m*-CPBA, −40 °C to room temperature, 60 min; (d) 10% Pd/C, $NaHCO_3$, *t*-BuOH−H_2O (6;1, v/v), H_2, 50 psi, rt, 5 h; (e) *i*-Pr_2NEt, MeOH, rt, overnight, then 10% Pd/C, $NaHCO_3$, *t*-BuOH−H_2O (6:1, v/v), H_2, 50 psi, rt, 5 h.

Scheme 6[a]



[a] Reaction conditions: (a) BZDC−NHS or [^{3}H]-BZDC−NHS, Et_3N, DMF, rt, overnight; then DEAE chromatography.

the cyanoethyl group of **19** with *i*-Pr_2NEt[23] followed by hydrogenation gave the desired PtdIns(3)P diester **21** in 77% yield.[43]

The aminopropyl triesters were used in the preparation of photoactivatable probes for the proteins recognizing the inositol headgroup in the context of a lipid bilayer.[22] Thus, reaction of the triester **20a** with unlabeled *p*-benzoyldihydrocinnamoyl *N*-hydroxysuccinimide ester (BZDC−NHS) in DMF using Et_3N as base gave BZDC-*triester*-PtdIns(3)P (**22a**) in ca. 50% yield.[44] When high specific activity [^{3}H]BZDC−NHS was employed in a mixed 0.25 M TEAB buffer−DMF solvent system, the tritium-labeled **22a′** was obtained in 8% radiochemical yield (Scheme 6).

The long-chain diacyl derivatives of the phosphatidylinositol mono- and bis(polyphosphate)s are insoluble in water and form micelles and vesicles. However, the dioctanoyl analogues of $PtdInsP_2$ and $PtdInsP_3$ regioisomers are water soluble. It was unknown if the octanoyl derivative of PtdInsP regioisomers would be water soluble. To explore a variety of potential symmetrical diacylglyceryl derivatives from a common PtdInsP precursor, we prepared a versatile phosphoramidite (Scheme 7). Thus, glycerylphosphoramidite **23**[45] was prepared from reaction of benzyl *N*,*N*,*N*,*N*-tetraisopropylphosphoramidite with (*S*)-(+)-1,2-*O*-isopropylidene-*sn*-glycerol and showed chemical properties similar to those reported for similar phosphoramidites.[46] Reaction of inositol-protected 3-PMB intermediate **12** with the protected glycerylphosphoramidite **23** gave phosphate **24** in good yield. Removal of PMB (DDQ) and further phosphorylation gave bis-(phosphotriester) **26** in 60% yield. Hydrolysis of the acetal gave diol **27**,[47] which could be readily acylated to give a fully protected PtdIns(3)P precursor. As an example, we coupled **27** with octanoic acid and butyric acid in the presence of DCC and DMAP[48,49] to give the protected products **28a**,**b**, respectively, in high yields. Hydrogenation gave PtdIns(3)P derivatives **29a**,**b** in 63% and 92% yields, respectively.

The ^{1}H NMR of **21**, the dipalmitoyl derivative of PtdIns(3)P, illustrates the curious solubility of the PtdInsP materials and the intrinsic difficulty in obtaining high-quality NMR spectroscopic data. In $CDCl_3$, the ^{1}H NMR resonances of the acylglyceryl moiety are reasonably well resolved, while only broad, poorly resolved resonances can be detected for the inositol phosphate headgroup. In contrast, in D_2O, the inositol phosphate headgroup becomes better-resolved, while the resonances for the fatty acyl chains and the glyceryl moiety become severely broadened. Furthermore, ^{31}P NMR in D_2O showed one very broad resonance of poor diagnostic utility. Use of other solvents, e.g., DMSO-d_6, makes recovery of precious materials for biological studies not feasible. Mixed solvents containing D_2O, CD_3OD, and $CDCl_3$ did not improve the situation. Changing cations to ammonium or to the acidic form also simply made spectra worse. In contrast, the dibutyryl and dioctanoyl

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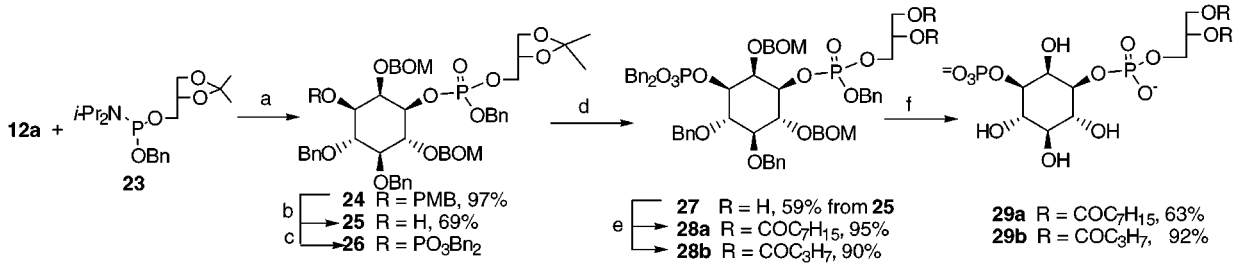
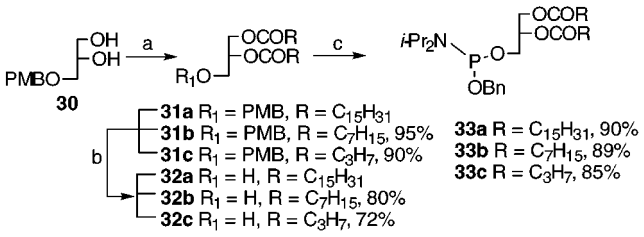
Scheme 7[a]



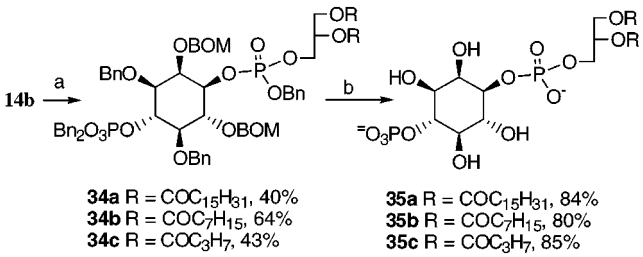
[a] Reaction conditions: (a) 1*H*-tetrazole, rt, 30 min, then *m*CPBA, −40 °C to room temperature, 60 min; (b) DDQ, $CH_2Cl_2-H_2O$ (100:1, v/v), rt, 2 h; (c) $(BnO)_2PNPr_2$-*i*, 1*H*-tetrazole, rt, 30 min, then *m*-CPBA, −40 °C to room temperature, 60 min; (d) 5% *p*-TsOH monohydrate (pH ∼ 2), MeOH, rt, 2 h; (e) fatty acid, DMAP (cat.), DCC, CH_2Cl_2, rt, overnight; (f) 10% Pd/C, $NaHCO_3$, *t*-BuOH−H_2O (6:1, v/v), H_2, 50 psi, rt, 5 h; then Chelex (Na^+ form) ion exchange.

Scheme 8[a]



[a] Reaction conditions: (a) Fatty acid, DMAP (cat.), DCC, CH_2Cl_2, rt, overnight; (b) DDQ, $CH_2Cl_2-H_2O$ (100:1, v/v), rt, 2 h; (c) (BnO)P(Cl)(NPr_2-*i*), *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 2 h.

Scheme 9[a]



[a] Reaction conditions: (a) 1*H*-tetrazole, rt, 30 min, then *m*-CPBA, −40 °C to room temperature, 60 min; (b) 10% Pd/C, $NaHCO_3$, *t*-BuOH−H_2O (6:1, v/v), H_2, 50 psi, rt, 5 h; then Chelex (Na^+ form) ion exchange.

derivatives were water soluble and gave high-resolution ^1H and ^{31}P NMR spectra samples with a concentration of 10 mg/mL. The narrow ^{31}P lines (0.028−0.075 ppm at half-height) for both dibutyryl and dioctanoyl PtdIns(3)P and PtdIns(4)P suggest monomeric and not micellar forms at this concentration.

In the preparation of the series of PtdIns(4)P diesters, an alternative strategy of using different phosphoramidites with preattached long, medium, and short diacyl chains was followed (Scheme 8). Following reported procedures,[23−25] the 3-*O*-PMB-*sn*-glycerol **30** was esterified with various fatty acids using DCC/DMAP to give compounds **31a**−**c** in high yields. Oxidative removal of the PMB groups with DDQ gave the corresponding alcohols **32a**−**c** in good yields with no evidence of acyl migration. Finally, coupling these alcohols with benzyl *N*,*N*-isopropylchlorophosphoamidite gave reagents **33a**−**c** in high yields. Subsequent coupling of 4-phosphorylated inosityl precursor **14b** with **33a**, **33b**, or **33c** followed by mild oxidation gave the three protected PtdIns(4)P precursors **34a**−**c** in moderate to good yields (Scheme 9). Hydrogenolysis provided PtdIns(4)P derivatives with dipalmitoyl (**35a**), dioctanoyl (**35b**), and dibutyryl (**35c**) acyl chains. Both diester and triester with dipalmitoyl glyceryl groups showed poor solubility in water and good solubility in methanol−chloroform−water mixtures, while the dibutyryl and dioctanoyl derivatives were water soluble.

Recently, a variety of synthetic approaches to PtdInsP_ns have been summarized.[22,50] Several recent approaches to PtdIns(3)P include preparation from D-1-*O*-*tert*-butyldiphenylsilyl-*myo*-inositol[43] or from enzymatically resolved 1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositol.[51] The soluble Ins(1,3)P_2 headgroup was synthesized from racemic *myo*-inositol derivatives.[40,52] The synthesis reported herein now allows preparation of diester reagents or triester affinity probes[22] for further examination of the roles of these phosphoinositide monophosphates in cell signaling. Applications of the [^{3}H]BZDC−PtdIns(3)P and −PtdIns(4)P photoaffinity labels for the identification of new target proteins will be presented in due course. Finally, with these syntheses and the synthesis of both PtdIns(5)P and PtdIns(3,5)P_2,[53] biological researchers may now select from a complete "matched set" of dibutryl, dioctanoyl, or dipalmitoyl PtdInsP_n derivatives with either complete water solubility or complete bilayer localization to determine the preferred number and regiochemistry of phosphates required for optimal biological activity.

Experimental Section

NMR spectra (^1H, ^{13}C, and ^{31}P) were recorded in $CDCl_3$ or D_2O on QE-300, AC-250, or AC-200 NMR spectrometers, and shifts are reported relative to δ(TMS) = 0 ppm. When necessary, solvents and reagents were dried using standard procedures. Elemental analysis was performed by M-H-W Laboratories (Phoenix, AZ), and the mass spectra (low solution and high resolution) were measured at The University of California at Riverside (Riverside, CA) or at The University of Utah (Salt Lake City, UT) using chemical ionization (CI, with NH_3 giving MNH_4^+ peaks), EI, or FAB (BNA as matrix giving MNa^+ peaks). Chemicals from Aldrich Chemical Co. (Milwaukee, WI) and Sigma Chemical Co. (St. Louis, MO) were used without further purification. TLC (SiO_2) plates for inositol precursors were developed in ethyl acetate (EtOAc)

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(53) Peng, J.; Prestwich, G. D. *Tetrahedron Lett.* **1998**, *39*, 3965−3968.

and hexane mixtures and visualized by dipping in 5% phosphomolybdic acid in absolute ethanol followed by heating; for acylglycerol derivatives, compounds were visualized by dipping in anisaldehyde stains (ratio *p*-anisaldehyde:acetic acid:sulfuric acid:ethanol 2.5:1:3.5:93, v/v/v/v) followed by heating.

Methyl 2-*O*-(*p*-Methoxybenzyl)-4,6-*O*-(*p*-methoxybenzylidene)-α-D-glucopyranoside (2aa). A mixture of methyl 4,6-*O*-(*p*-methoxybenzylidene)-α-D-glucopyranoside (**1a**, 5.21 g, 16.7 mmol), Bu_2SnO (4.2 g, 16.9 mmol), and Bu_4NI (0.6 g, 1.63 mmol) in 100 mL of toluene was refluxed for 2 h, then *p*-methoxybenzyl chloride (PMBCl, 2.88 g, 18.3 mmol) was added, and the mixture was stirred under reflux for 2 h, at which point TLC showed no starting material. The mixture was cooled, diluted with EtOAc, washed (H_2O, brine), dried ($MgSO_4$), and concentrated in vacuo to a brown oil. Chromatography on SiO_2 (50% EtOAc−hexane) gave two products at $R_f \sim 0.7$. The first eluting product was the 2-PMB ether (**2aa**, 3.30 g, yield 45%), and the second product was 3-PMB ether (**2ab**, 3.8 g, 55% yield); the latter was less soluble in EtOAc−hexane. No bis-PMB product was detected.

Data for compound **2aa**: mp 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36, 7.34, 7.26, 7.23 (4s, 4H, aromatic), 6.84−6.81 (m, 4H, aromatic), 5.41 (s, 1H, CH), 4.61 (q, J = 11.7 Hz, 2H), 4.50 (d, J = 3.6 Hz, 1H), 4.15 (dd, J = 4.5, 4.2 Hz, 1H), 4.05 (dt, J = 9.2, 1.8 Hz, 1H), 3.74, 3.37 (2s, 6H, OMe), 3.43−3.35 (m, 2H), 3.31 (s, 3H, OMe) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.9, 129.8, 129.6, 127.6, 113.9, 113.6, 101.8, 98.7, 81.2, 79.1, 77.2, 73.0, 70.2, 68.9, 62.0, 55.4, 55.3 ppm. Anal. Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 63.64; H, 6.77.

Methyl 3-*O*-(*p*-methoxybenzyl)-4,6-*O*-(*p*-methoxybenzylidene)-α-D-glucopyranoside (2ab) was isolated from the chromatography above: mp 163−165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (4s, 4H, aromatic), 6.84−6.81 (m, 4H, aromatic), 5.51 (s, 1H, CH), 4.81 (q, J = 11.7 Hz, 2H), 4.78 (d, J = 3.6 Hz, 1H), 4.30 (q, J = 3.5 Hz, 1H), 3.74, 3.37 (2s, 6H, OMe), 3.43−3.35 (m, 2H), 3.31 (s, 3H, OMe) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.7, 129.0, 128.3, 126.0, 113.8, 101.3, 98.7, 82.0, 78.4, 77.2, 73.0, 70.2, 69.0, 62.6, 55.4, 55.3 ppm. Anal. Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 63.53; H, 6.45.

Methyl 2-*O*-(*p*-Methoxybenzyl)-4,6-*O*-benzylidene-α-D-glucopyranoside (2ba). A mixture of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1b**, 25 g, 88.6 mmol), and Bu_2SnO (22 g, 88.6 mmol), Bu_4NBr (2.86 g, 8.86 mmol) in 300 mL of toluene was refluxed for 3 h, then PMBCl (16.7 g, 106.3 mmol) was added, and the mixture was stirred under reflux overnight. After workup as above and SiO_2 chromatography with 50% EtOAc−hexane, two products were isolated. The first eluting product ($R_f \sim 0.7$) was identified as methyl 2-*O*-(*p*-methoxybenzyl)-4,6-*O*-benzylidene-α-D-glucopyranoside (2-PMB ether **2ba**) (15 g, yield 42%). The second eluting compound was methyl 3-*O*-(*p*-methoxybenzyl)-4,6-*O*-benzylidene-α-D-glucopyranoside (3-PMB ether **2bb**) (20 g, 56% yield), which was less soluble in EtOAc−hexane mixtures and easier to recrystallize.

Data for compound **2ba**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.20 (m, 7H, aromatic), 6.90, 6.86 (2s, 2H, PMB), 5.50 (s, 1H, CH), 4.63 (q, J = 11.8 Hz, 2H), 4.55 (d, J = 3.6 Hz, 1H), 4.25 (dd, J = 4.5, 4.2 Hz, 1H), 4.10 (t, J = 9.2 Hz, 1H), 3.76 (s, 3H, OMe), 3.84−3.75 (m, 1H), 3.70 (q, J = 10.1 Hz, 1H), 3.43−3.35 (m, 2H), 3.31 (s, 3H, OMe) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.0, 129.8, 129.2, 128.3, 126.4, 114.0, 101.9, 98.7, 81.3, 79.2, 73.0, 70.2, 69.0, 62.1, 55.4, 55.3 ppm. Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.40; H, 6.55.

Data for methyl 3-*O*-(*p*-methoxybenzyl)-4,6-*O*-benzylidene-α-D-glucopyranoside (2bb): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.30 (m, 7H, aromatic), 6.86, 6.82 (2s, 2H, PMB), 5.56 (s, 1H, CH), 4.81 (q, J = 11.7 Hz, 2H), 4.78 (d, J = 3.6 Hz, 1H), 4.30 (q, J = 3.5 Hz, 1H), 3.78 (s, 3H, OMe), 3.90−3.60 (m, 2H), 3.31 (s, 3H, OMe), 1.60 (br s, 1H, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.7, 129.0, 128.3, 126.0, 113.8, 101.3, 98.7, 82.0, 78.4, 77.2, 73.0, 70.2, 69.0, 62.6, 55.4, 55.3 ppm. Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.46; H, 6.52.

Methyl 2-*O*-(*p*-Methoxybenzyl)-α-D-glucopyranoside (3a). A mixture of methyl 2-*O*-(*p*-methoxybenzyl)-4,6-*O*-(*p*-methoxybenzylidene)-α-D-glucopyranoside (**2aa**, 4 g, 9.25 mmol) and *p*-TsOH monohydrate (400 mg) in 100 mL of MeOH was stirred for 1 h. TLC ($R_f \sim 0.5$), ether) showed no starting material. Then, 10 mL of 10% $NaHCO_3$ solution was added and the mixture was evaporated to dryness. The product was extracted five times from the solid material with EtOAc and then recrystallized from EtOAc−hexane to give 2.85 g of pure methyl 2-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside **3a** (98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22, 7.19, 6.82, 6.79 (4s, 4H, aromatic), 4.56 (AB type, J_{AB} = 11.4 Hz, 2H, CH_2O), 4.48 (s, 1H), 3.85−3.70 (m, 2H), 3.72 (s, 3H, OMe), 3.61 (s, 1H), 3.49 (s, 2H), 3.37 (s, 2H), 3.25 (s, 3H, OMe), 2.52 (s, 1H), 2.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.9, 129.7, 113.9, 97.9, 79.0, 77.2, 72.8, 72.7, 55.2 ppm. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.06. Found: C, 57.47; H, 6.79.

Methyl 3-*O*-(*p*-Methoxybenzyl)-α-D-glucopyranoside (3b). A mixture of methyl 3-*O*-(*p*-methoxybenzyl)-4,6-*O*-benzylidene-α-D-glucopyranoside (**2bb**, 11.0 g, 27.3 mmol) and *p*-TsOH monohydrate (930 mg) in 250 mL of MeOH was stirred for 2 h. Then, 2 g of $NaHCO_3$ was added, the $NaHCO_3$ solid was removed by filtration, and the filtrate was evaporated to dryness. The crude product was extracted from the residue with five portions of EtOAc, concentrated, and then purified on SiO_2 (75% EtOAc−hexane) to give 7.5 g of pure methyl 3-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside **3b** (83%) with $R_f \sim$ 0.21 (20% EtOAc−hexane): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31, 7.28, 6.89, 6.85 (4s, 4H, PMB), 4.78 (J_{AB} = 11.2 Hz, 2H, CH_2O), 4.72 (s, 1H), 3.78 (m, 5H), 3.57−3.54 (m, 4H), 3.40 (s, 3H, OMe), 3.02 (s, 1H), 2.45 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1, 129.5, 113.8, 106.5, 104.5, 99.4, 82.0, 74.4, 72.4, 70.9, 69.7, 61.7, 55.1 ppm. MS(EI$^+$): *m/e* 314 (M^+), 150, 137, 121. HRMS (EI$^+$): calcd for $C_{15}H_{22}O_7$ (M^+), *m/e* 314.1366; found, *m/e* 314.1349.

Methyl 2-*O*-(*p*-Methoxybenzyl)-6-*O*-trityl-α-D-glucopyranoside (4a). A mixture of methyl 2-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (**3a**, 2.85 g, 9.10 mmol), trityl chloride (2.79 g, 1.0 mmol), DMAP (40 mg), and triethylamine (3 mL) in 100 mL of dry DMF was stirred overnight. TLC ($R_f \sim 0.3$, 50% EtOAc−CH_2Cl_2) showed essentially complete conversion. The mixture was then poured into water, extracted with EtOAc, concentrated, and purified (SiO_2) to give 4.79 g (94%) of methyl 2-*O*-(*p*-methoxybenzyl)-6-*O*-trityl-α-D-glucopyranoside (**4a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.10 (m, 17H, aromatic), 6.79 (d, J = 9.6 Hz, 2H, PMB), 4.61−4.51 (m, 3H), 3.80 (t, J = 0.6 Hz, 1H), 3.73 (s, 3H, OMe), 3.64−3.59 (m, 2H), 3.43−3.20 (m, 3H), 3.31 (s, 3H, OMe), 3.00 (s, br, 1H, OH), 1.93 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.8, 130.1, 129.6, 128.6, 128.0, 127.8, 127.0, 113.9, 97.6, 86.8, 78.8, 77.3, 73.1, 72.6, 71.7, 69.7, 64.0, 55.2, 55.1 ppm. MS (EI$^+$): *m/e* 556 (M^+), 313, 243, 165, 121, 91. HRMS (EI$^+$): calcd for $C_{34}H_{36}O_7$ (M^+), *m/e* 556.2461; found, *m/e* 556.2467.

Methyl 3-*O*-(*p*-Methoxybenzyl)-6-*O*-trityl-α-D-glucopyranoside (4b). A mixture of methyl 3-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (**3b**, 7.1 g, 22.4 mmol), trityl chloride (6.3 g, 22.5 mmol), DMAP (317 mg), and triethylamine (4.77 mL) in 150 mL of dry DMF was stirred overnight. TLC showed essentially complete conversion. The mixture was then poured into water, extracted with EtOAc, washed (brine, water), dried ($MgSO_4$), and purified (SiO_2) to give 8.2 g (65%) of methyl 3-*O*-(*p*-methoxybenzyl)-6-*O*-trityl-α-D-glucopyranoside (**4b**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52−7.21 (m, 17H, Ph + PMB), 6.88 (d, 2H, J = 8.0 Hz, PMB), 4.91−4.72 (m, 3H), 3.79 (s, 3H, OMe), 3.76−3.57 (m, 4H), 3.47 (s, 3H, OMe), 3.41−3.37 (m, 2H), 2.46 (s, 1H, OH), 2.33 (d, 1H, J = 6.0 Hz, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.5, 143.6, 130.5, 129.5, 128.5, 127.7, 126.9, 113.8, 105.5, 99.1, 86.7, 82.2, 74.5, 72.3, 71.3, 70.0 63.7, 55.1, 54.9 ppm. MS (EI$^+$): *m/e* 555 ($M - H^+$), 313, 243, 165, 137, 121. HRMS (EI$^+$): calcd for $C_{34}H_{36}O_7$ (M^+), *m/e* 556.2461; found, *m/e* 556.2426.

Methyl 3-*O*-(*p*-Methoxybenzyl)-2,4-*O*-dibenzyl-6-*O*-trityl-α-D-glucopyranoside (5b). A mixture of methyl 3-*O*-(*p*-methoxybenzyl)-6-*O*-trityl-α-D-glucopyranoside (**4b**, 8.0 g, 14.3 mmol) and NaH (1.5 g, ~60% oil, 37.5 mmol), and benzyl

bromide (5.76 g, 33.6 mmol) in 150 mL of dry DMF was stirred for 2 h at room temperature. The reaction was quenched with methanol, poured into 150 mL of water, extracted (3 volumes of CH_2Cl_2), and purified on SiO_2 (33% EtOAc−hexane) to give 10 g of pure **5b** (95%), $R_f \sim 0.49$ (20% EtOAc−hexane): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51−7.21 (m, 27H, Ph + PMB), 6.87 (d, J = 8.8 Hz, 2H, PMB), 4.93−4.71 (m, 6H), 4.31 (d, J = 10.6 Hz, 1H), 3.98 (t, J = 9.2 Hz, 1H), 3.86−3.81 (m, 4H), 3.69−3.59 (m, 2H), 3.55−3.49 (m, 1H), 3.47 (s, 3H, OMe), 3.19 (dd, J = 4.6, 10.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 159.0, 143.7, 138.2, 137.5, 130.7, 129.6, 128.6−127.3 (m), 126.7, 113.6, 108.5, 97.7, 86.1, 81.6, 80.0, 77.9, 75.5, 74.8, 73.2, 70.0, 62.4, 55.1, 54.8 ppm. MS (EI$^+$): *m/e* 735 (M − H$^+$), 645, 615, 493, 461, 243, 121, 91. HRMS (EI$^+$): calcd for $C_{48}H_{48}O_7$, *m/e* 736.3400; found, *m/e* 736.3364.

Methyl 2-*O*-(*p*-Methoxybenzyl)-3,4-*O*-dibenzyl-α-D-glucopyranoside (6a). A mixture of methyl 2-*O*-(*p*-methoxybenzyl)-6-*O*-trityl-α-D-glucopyranoside (**4a**, 4.79 g, 8.6 mmol) and NaH (1.03 g, ∼60% oil, 25.8 mmol) and benzyl bromide (4.4 g, 25.8 mmol) in 100 mL of dry DMF was stirred for 2 h. TLC ($R_f \sim 0.9$, 50% EtOAc−hexane) showed nearly complete conversion. Then the mixture was poured into water and extracted with EtOAc. The crude product **5a** was dissolved in 100 mL of MeOH containing *p*-TsOH monohydrate (40 mg, to give pH ∼ 2), and the mixture was stirred for 1 h. TLC ($R_f \sim 0.45$, 50% EtOAc−hexane) showed no starting material. Then, 10 mL of 10% $NaHCO_3$ solution was added and the mixture was evaporated to dryness. The product was extracted from the solid material with five portions of EtOAc, concentrated, and then purified on SiO_2 using 50% EtOAc−hexane as eluent to give 2.53 g of pure methyl 2-*O*-(*p*-methoxybenzyl)-4,5-*O*-dibenzyl-α-D-glucopyranoside (**6a**) (60% in two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.10 (m, 12H, aromatic), 6.80 (d, J = 8.4 Hz, 2H, PMB), 4.93 (d, J = 11.1 Hz, 1H), 4.80 (AB type, J = 10.8 Hz, 1H), 4.68 (d, J = 12 Hz, 1H), 4.56 (t, J = 13.2, Hz, 2H), 4.46 (d, J = 3 Hz, 1H), 3.94 (t, J = 9.3 Hz, 1H), 3.75 (3H, OMe), 3.70−3.55 (m, 4H), 3.49−3.40 (m, 2H), 3.20 (s, 3H, OMe), 1.65 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.1, 130.2, 129.7, 128.4−127.3 (m), 113.8, 98.2, 81.9, 79.6, 77.4, 77.2, 75.7, 75.0, 73.0, 70.6, 61.8, 55.2, 55.1 ppm. MS (CI$^+$, NH_3): *m/e* 512 (MNH_4^+), 493, 461, 403, 373, 121, 108, 91. HRMS (CI$^+$, NH_3): calcd for $C_{29}H_{38}NO_7$ (MNH_4^+), *m/e* 512.2648; found, *m/e* 512.2632.

Methyl 3-*O*-(*p*-Methoxybenzyl)-2,4-*O*-dibenzyl-α-D-glucopyranoside (6b). Compound **5b** in 100 mL of MeOH/acetone containing 5% sulfuric acid (pH ∼ 2) was stirred for 1 h. Then the reaction was quenched by 10% $NaHCO_3$ solution, the mixture was evaporated to dryness, and the residue was extracted with three volumes of EtOAc and the combined organic phases were washed with 10% $NaHCO_3$. Purification on SiO_2 (25% EtOAc−hexane) gave 2.8 g of glucopyranoside **6b** (yield 42%), $R_f \sim 0.16$ (33% EtOAc−hexane): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.27 (m, 12H, Bn + PMB), 6.86 (d, J = 8.6 Hz, 2H, PMB), 4.95−4.57 (m, 7H), 4.01 (t, J = 9.1 Hz, 1H), 3.80 (s, 3H, OMe), 3.76−3.63 (m, 3H), 3.56−3.47 (m, 2H), 3.37 (s, 3H, OMe), 1.80 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.0, 137.9, 131.0, 129.5, 128.3−127.7 (m), 113.6, 98.0, 81.5, 79.9, 76.2, 75.3, 74.9, 73.2, 70.1, 61.6, 55.1, 55.0 ppm. MS (EI$^+$): *m/e* 493 (M − H$^+$), 403, 373, 253, 175, 121, 91. HRMS (EI$^+$): calcd for $C_{29}H_{34}O_7$ (M$^+$), *m/e* 494.2305; found, *m/e* 494.2299.

Methyl (*Z*)-3,4-*O*-Dibenzyl-2-*O*-(*p*-methoxybenzyl)-6-*O*-acetyl-α-D-glucos-5-enopyranoside (8a). A solution of $(COCl)_2$ (1.05 mL, 1.94 mmol) in 100 mL of CH_2Cl_2 was cooled to −78 °C, dry DMSO (1.71 mL, 3.87 mmol) was added dropwise, and the mixture was stirred 10 min at −78 °C. Next, a solution of **6a** (2.40 g, 4.86 mmol) in 5 mL of CH_2Cl_2 was added over 10 min. The cloudy solution was stirred for 30 min, 5.4 mL of Et_3N was added to produce a clear solution, and the mixture was warmed to room temperature. The usual workup gave oil **7a** that was used directly in the next step. Thus, oil **7a** was dissolved in 75 mL of dry CH_3CN, anhydrous K_2CO_3 (4.13 g) was added, the mixture was stirred for 10 min, acetic anhydride (2.7 mL) was added, and the mixture was refluxed overnight under nitrogen. The volume was reduced to one-third, and the residue was diluted with water and extracted with ether. The usual workup gave 2.2 g of enol acetate **8a** (85% in two steps), $R_f \sim 0.6$, 50% EtOAc−hexane: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4−7.2 (m, 12H), 6.80, 6.76 (2s, 2H, PMB), 4.90−4.60 (m, 8H), 4.00−3.90 (m, 2H), 3.80 (s, 3H, OMe), 3.60−3.50 (m, 1H), 3.35 (s, 3H), 2.20 (s, 3H) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.3, 159.2, 153.3, 138.0, 135.1, 130.8, 129.8, 128.5, 128.1, 123.0, 113.9, 113.8, 99.8, 81.1, 79.1, 75.4, 74.2, 73.7, 60.4, 56.2, 55.3 ppm. MS (CI$^+$, NH_3): *m/e* 552 (MNH_4^+), 432, 383, 325, 211, 137, 121, 108. HRMS (CI$^+$): calcd for $C_{31}H_{38}NO_8$ (MNH_4^+), *m/e* 552.2597; found, *m/e* 552.2597.

Methyl (*Z*)-2,4-*O*-Dibenzyl-3-*O*-(*p*-methoxybenzyl)-6-*O*-acetyl-α-D-glucos-5-enopyranoside (8b). A solution of $(COCl)_2$ (1.29 mL, 14.78 mmol) in 50 mL of CH_2Cl_2 was cooled to −78 °C, dry DMSO (2.1 mL, 29.6 mmol) was added dropwise, the mixture was stirred at −78 °C for 10 min, and a solution of alcohol **6b** (2.8 g, 5.6 mmol) in 5 mL of CH_2Cl_2 was added over 10 min. The milky solution was stirred for 30 min, 6.6 mL of Et_3N was added to give a clear solution, and the mixture was warmed to room temperature and washed (2 × 0.5 M $KHSO_4$, water) to give crude aldehyde **7b.** The crude product was dissolved in 50 mL of dry CH_3CN, and anhydrous K_2CO_3 (5.25 g) was added. After the mixture was stirred for 10 min, acetic anhydride (3.0 mL) was added and the mixture was refluxed overnight under nitrogen. The volume was reduced by rotary evaporation, and the residue was diluted with water, extracted with ether, and purified on SiO_2 (33% EtOAc−hexane) to give 2.6 g of enol acetate **8b** (94% in two steps): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.17 (m, 12H, Bn + PMB), 6.86 (d, 2H, J = 8.7 Hz, PMB), 4.95−4.64 (m, 7H), 3.98−3.95 (m, 1H), 3.89−3.79 (m, 4H), 3.60−3.55 (m, 2H), 3.47 (s, 3H, OMe), 2.16 (s, 3H, Ac) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.9, 159.0, 137.4, 134.8, 129.5−127.7 (m), 122.8, 113.7, 113.6, 108.5, 107.5, 105.5, 99.6, 80.6, 78.8, 75.2, 74.3, 73.5, 73.3, 72.6, 56.0, 55.0, 20.4 ppm. MS (EI$^+$): *m/e* 534 (M$^+$), 459, 443, 415, 383, 311, 301, 211, 91. HRMS (EI$^+$): calcd for $C_{31}H_{34}O_8$ (M$^+$), *m/e* 534.2254; found, *m/e* 534.2243.

1-*O*-Acetyl-3-*O*-(*p*-methoxybenzyl)-4,5-*O*-dibenzyl-2-deoxyl-2-oxo-*myo*-inositol (9a). To a solution of enol acetate **8a** (2.20 g, 4.12 mmol) in 100 mL of acetone−water (3:2) was added mercuric acetate (13.20 g, 41.2 mmol); the solution was stirred for 45 min, 57 mL of saturated NaCl solution was added, and the mixture was stirred for 24 h. The acetone was evaporated, and the residue was extracted (EtOAc), concentrated, and purified on SiO_2 (30−50% EtOAc−hexane) to give 1.85 g of inositol **9a** (86% yield, 90% pure): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.10 (m, 12H, Bn + PMB), 6.86, 6.83 (2s, 2H, PMB), 5.12 (bs, 1H), 4.86 (d, J = 11.1 Hz, 2H), 4.75 (d, J = 10.8 Hz, 2H), 4.64 (q, J = 11.4 Hz, 2H), 4.47 (d, J = 11.1 Hz, 1H), 4.25 (s, 1H), 4.09 (m, 1H), 3.80−3.70 (m, 1H), 3.74 (s, 3H, OMe), 2.17 (s, 3H, Ac) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 159.9, 137.3, 129.8−128.1 (m), 114.1, 113.9, 83.5, 81.8, 78.5, 76.1, 74.9, 73.5, 73.1, 69.4, 55.3, 45.7 ppm. MS (CI$^+$, NH_3): *m/e* 538 (MNH_4^+), 494, 461, 429, 418, 211, 181, 154, 137, 121, 108, 91. HRMS (CI$^+$, NH_3): calcd for $C_{30}H_{36}NO_8$ (MNH_4^+), *m/e* 538.2441; found, *m/e* 538.2457.

1-*O*-Acetyl-4-*O*-(*p*-methoxybenzyl)-3,5-*O*-dibenzyl-2-deoxyl-2-oxo-*myo*-inositol (9b). To a solution of enol acetate **8b** (3.0 g, 5.6 mmol) in 200 mL of acetone−water (3:2) was added mercuric acetate (18.6 g, 58.3 mmol). The solution was stirred for 45 min, and 100 mL of saturated NaCl solution was added. The mixture was stirred for 24 h and concentrated in vacuo, and the residue was extracted (3 volumes of $CHCl_3$) and purified by flash chromatography (33% EtOAc−hexane) to give 1.7 g of protected inositol **9b** (57% yield), $R_f \sim 0.36$ (50% EtOAc−hexane): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41−7.23 (m, 12H, Bn + PMB), 6.89, 6.84 (d, J = 8.6 Hz, 2H, PMB), 5.17 (d, J = 2.4 Hz, 1H), 4.98−4.52 (m, 6H), 4.34 (m, 1H), 4.20−4.04 (m, 2H), 3.87 (m, 1H), 3.82 (s, 3H, OMe), 2.73 (s, 1H, OH), 2.23 (s, 3H, Ac) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.7, 169.7, 159.1, 137.2, 130.2−127.7 (m), 113.6, 106.5, 105.5, 83.4, 81.3, 78.7, 75.7, 74.7, 73.4, 73.2, 69.1, 55.1, 20.3 ppm. MS (FAB):

m/e 519 ($M - H^+$) 429, 399, 386, 273, 211, 121. HRMS (FAB): calcd for $C_{30}H_{34}O_8$ ($M - H^+$), *m/e* 519.2019; found, *m/e* 519.2020.

1-*O*-Acetyl-3-*O*-(*p*-methoxybenzyl)-4,5-*O*-dibenzyl-*myo*-inositol (10a). To a solution of inosose **9a** (1.85 g, 3.56 mmol) in 60 mL of dry acetonitrile was added $NaBH(OAc)_3$ (7.55 g, 35.6 mmol) and 19 mL of glacial HOAc. The mixture was stirred for 45 min at room temperature, and the excess $NaBH(OAc)_3$ was destroyed by dropwise addition of 0.5 M $NaHSO_4$. The mixture was extracted with EtOAc, washed (0.5 M $NaHSO_4$, saturated Na_2HPO_4), dried (Na_2SO_4), and concentrated. The residue was recrystallized from EtOAc/H to yield 1.5 g of **10a** (81%), $R_f \sim 0.21$ (67% EtOAc−hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.10 (m, 12H, aromatic), 6.78 (m, 2H, PMB), 5.20−4.37 (m, 7H), 4.20 (m, 1H), 4.10−3.41 (m, 6H), 3.74 (s, 3H, OMe), 2.10 (s, 3H, Ac) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.3, 158.7, 130.0, 129.6, 128.1, 128.0, 113.8, 113.6, 82.6, 80.6, 80.1, 75.5, 72.9, 67.1, 55.8 ppm. MS (CI^+, NH_3): *m/e* 540 (MNH_4^+), 431, 401, 330, 311, 295, 277, 205, 181, 137, 121, 108, 91. HRMS: calcd for $C_{30}H_{38}NO_8$ (MNH_4^+), *m/e* 540.2597; found, *m/e* 540.2596.

1-*O*-Acetyl-4-*O*-(*p*-methoxybenzyl)-3,5-*O*-dibenzyl-*myo*-inositol (10b). To a solution of inosose **9b** (970 mg, 1.8 mmol) in 50 mL of dry acetonitrile was added $NaBH(OAc)_3$ (4.0 g, 18.8 mmol) and 8.8 mL of glacial HOAc. The mixture was stirred for 45 min at room temperature, and the excess $NaBH(OAc)_3$ was destroyed by dropwise addition of 0.5 M $NaHSO_4$. The mixture was extracted (EtOAc), washed (0.5 M $NaHSO_4$), dried (Na_2SO_4), and purified on deactivated SiO_2 to give 800 mg of compound **10b** (83% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−7.22 (m, 12H, Bn + PMB), 6.85 (d, J = 8.6 Hz, 2H, PMB), 4.99−4.70 (m, 7H), 4.28 (t, J = 2.6 Hz, 1H), 4.10 (t, J = 9.4 Hz, 1H), 3.80 (s, 3H, OMe), 3.55 (dd, J = 2.6, 9.4 Hz, 1H), 3.36 (t, J = 9.4 Hz, 1H), 2.42 (s, 1H, OH), 2.22 (s, 1H, OH), 2.16 (s, 3H, Ac) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8, 129.4−127.7 (m), 113.5, 108.5, 106.5, 83.0, 80.5, 80.0, 76.3, 75.5, 73.1, 73.0, 70.1, 68.0, 55.1, 21.1 ppm. HRMS (FAB): calcd for $C_{30}H_{34}O_8$ (M^+), *m/e* 522.2254; found, *m/e* 522.2267.

3-*O*-(*p*-Methoxybenzyl)-4,5-*O*-dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inositol (12a). A mixture of protected inositol **10a** (1.50 g, 2.87 mmol), proton sponge (1.5 g), *n*-Bu_4NBr (100 mg), and benzoxyl chloromethyl ether (BOMCl, 2 mL) in 40 mL of dry acetonitrile was stirred overnight at room temperature, then at 35 °C for 10 h, and then at 55 °C overnight. TLC (product $R_f \sim 0.57$, 33% EtOAc−hexane) showed no starting material. The mixture was concentrated 3-fold, diluted with water, and extracted with EtOAc, and the extracts were washed (water), dried ($MgSO_4$), and concentrated to give oil **11a**. The crude material **11a** was dissolved in 50 mL of MeOH, 0.35 M NaOH (20 mL) was added, and the mixture was refluxed 2 h. The usual workup gave 1.52 g of protected inositol **12a** (76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.10 (m, 22H), 6.90−6.70 (m, 2H, PMB), 5.00−4.50 (m, 15H), 4.20−4.10 (m, 1H), 3.96 (t, J = 9 Hz, 1H), 3.88−3.80 (m, 2H), 3.76 (s, 3H, OMe), 3.43 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 130.1−127.0 (m), 113.8, 113.7, 96.6, 95.9, 83.0, 82.8, 81.7, 79.6, 75.8, 72.3, 71.1, 70.1, 69.8, 65.3, 55.3 ppm. MS (FAB): *m/e* 743 (MNa^+), 599, 491, 371, 227, 211, 181, 176, 121. HRMS: calcd for $C_{44}H_{48}NaO_9$ (MNa^+), *m/e* 743.3196; found, *m/e* 743.3192.

1-*O*-Acetyl-3,5-*O*-dibenzyl-4-*O*-(*p*-methoxybenzyl)-2,6-*O*-bis(benzoxymethyl)-*myo*-inositol (11b). A mixture of inositol **10b** (800 mg, 1.5 mmol), proton sponge (830 mg), *n*-Bu_4NBr (25 mg), and BOMCl (0.86 mL) in 40 mL of dry acetonitrile was stirred overnight at room temperature, at 35 °C for 10 h, and then 55 °C overnight. The mixture was concentrated 3-fold, diluted with water, and extracted with EtOAc, and the extracts were washed (water), dried ($MgSO_4$), concentrated, and purified on SiO_2 to give intermediate **11b** as a colorless oil in 57% yield: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36−7.18 (m, 22H, Bn + PMB), 6.81 (d, J = 8.7 Hz, 2H, PMB), 5.04−4.70 (m, 14H), 4.56 (t, J = 9.6 Hz, 1H), 4.41−4.39 (m, 1H), 4.27 (t, J = 10.0 Hz, 1H), 4.06 (t, J = 9.5 Hz, 1H), 3.80 (s, 3H, OMe), 3.59−3.48 (m, 2H), 1.85 (s, 3H, Ac) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.3, 159.0, 138.3, 137.7, 137.5, 129.5−127.2 (m), 113.5, 95.7, 95.0, 83.1, 81.0, 80.0, 76.3, 75.6, 75.4, 72.8, 72.6, 69.4, 69.1, 55.0, 20.7 ppm. HRMS (FAB): calcd for $C_{46}H_{50}O_{10}$ ($M - H^+$), *m/e* 761.3326; found, *m/e* 761.3355.

1-*O*-Acetyl-3,5-*O*-dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inositol (12b). To the intermediate **11b** (660 mg, 0.866 mmol) in 30 mL of wet CH_2Cl_2 was added DDQ (231 mg, 1.01 mmol). The mixture was stirred at room temperature for 3 h, diluted to 60 mL CH_2Cl_2, washed (2 × 10% aqueous $NaHCO_3$, brine, water), dried ($MgSO_4$), concentrated, and purified on SiO_2 (25% EtOAc−hexane) to give 4-hydroxy compound **12b** (500 mg, 89%) as a colorless oil, $R_f \sim 0.3$ (25% EtOAc−hexane): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37−7.26 (m, 20H, Bn), 5.03−4.52 (m, 13H), 4.41 (t, J = 2.4 Hz, 1H), 4.23 (t, J = 8.8 Hz, 1H), 4.14 (t, J = 9.6 Hz, 1H), 3.49−3.35 (m, 2H), 2.52 (s, 1H, OH), 1.85 (s, 3H, Ac); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.3, 138.3, 137.6, 137.2, 128.4−127.3 (m), 107.5, 105.5, 95.7, 94.7, 82.8, 79.1, 75.1, 72.7, 72.1, 71.7, 69.5, 69.1, 20.7 ppm. HRMS (FAB): calcd for $C_{38}H_{42}O_9$ (MH^+): *m/e* 643.2907; found, *m/e* 643.2926.

4,5-*O*-Dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inositol (13a). A mixture of protected inositol **12a** (40 mg, 0.056 mmol) and DDQ (50 mg) in 10 mL of $CH_2Cl_2-H_2O$ (100/1 v/v) was stirred at room temperature for 2 h. The usual workup gave 22 mg (67% yield) of diol **13a** ($R_f \sim 0.36$, 1.5:1 EtOAc−hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.00 (m, 22H, aromatic), 5.00−4.50 (m, 12H), 4.25−4.00 (m, 1H), 3.85−3.30 (6H), 3.00 (br, s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6−137.4 (m), 129.0−128.0 (m), 82.4, 77.2, 75.5, 75.4, 71.8, 71.0, 70.3, 70.1, 64.8 ppm. MS (FAB): *m/e* 623 (MNa^+).

1-*O*-Acetyl-3,5-*O*-dibenzyl-4-*O*-(dibenzylphosphoryl)-2,6-*O*-bis(benzoxymethyl)-*myo*-inositol (13b). To 4-alcohol **12b** (100 mg, 0.159 mmol) and 1*H*-tetrazole (134 mg, 1.91 mmol) in 10 mL of dry CH_2Cl_2 was added a solution of dibenzyl *N*,*N*-diisopropylphosphoramidite (132 mg, 0.38 mmol). The solution was stirred at room temperature under nitrogen for 1 h and cooled to −40 °C, and a solution of *m*-CPBA (83 mg, 0.65 mmol) was added. The mixture was stirred for 1 h at room temperature, diluted with 50 mL of CH_2Cl_2, washed (10% aqueous $NaHCO_3$, brine), dried ($MgSO_4$), concentrated, and purified on SiO_2 (50% EtOAc−hexane) to give 100 mg (71%) of product **13b** as a colorless oil, $R_f \sim 0.72$ (50% EtOAc−hexane): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−7.04 (m, 30H, Bn), 4.98−4.59 (m, 17H), 4.49 (J = 12.0 Hz, 1H), 4.37 (m, 1H), 4.27 (t, J = 12.0 Hz, 1H), 3.60−3.50 (m, 2H), 1.81 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 138.1, 137.7, 137.1, 128.4−127.4 (m), 106.7, 105.7, 104.7, 96.0, 95.0, 81.8, 81.7, 79.6, 79.5, 78.0, 75.0, 72.4, 72.3, 72.0, 69.7, 69.3, 69.2, 69.1, 69.0, 20.7 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.56 ppm. HRMS (FAB): calcd for $C_{52}H_{55}O_{12}P$ (M^+), *m/e* 902.3431; found, *m/e* 902.3480.

Tetrabenzyl 1,3-(4,5-*O*-dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inosityl) Bis(phosphate) (14a). A solution of diol **13a** (20 mg, 0.038 mmol) in 2 mL of CH_2Cl_2 and 1*H*-tetrazole (10 mg, 0.14 mmol) was stirred at room temperature, while a solution of dibenzyl *N*,*N*-diisopropylphosphoramidite (40 mg, 0.12 mmol) in 1 mL of CH_2Cl_2 was added. The mixture was stirred at room temperature for 1 h and cooled to −40 °C, *m*-CPBA (20 mg) was added, and the reaction was stirred for 30 min at 0 °C and then 30 min at room temperature. The mixture was diluted with CH_2Cl_2, washed (10% aqueous $NaHCO_3$), dried (Na_2SO_4), concentrated, and chromatographed on SiO_2 using 50% EtOAc−hexane to give 40 mg (87%) of protected bis(phosphate) **14a** as a viscous colorless oil, $R_f \sim 0.3$: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 40H, phenyl), 5.0−4.4 (m, 22H), 4.4−4.1 (m, 2H), 4.0 (m, 1H), 3.4 (m, 1H) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 138.1, 137.8, 135.7, 130−127 (m), 96.1, 75−74 (m), 76−69 (m) ppm; ^{31}P NMR (101 MHz, $CDCl_3$) δ 0.33, 0.09 (1:1) ppm.

1,3-*myo*-Inosityl Bis(phosphate) Tetrasodium Salt (15). A solution of bis(phosphate) **14a** (140 mg, 0.125 mmol), $NaHCO_3$ (42 mg, 0.5 mmol), and Pd/C (10%, 50 mg) in *t*-BuOH−H_2O (6:1 v/v, 35 mL) was shaken at 50 psi initial pressure for 5 h. The catalyst was filtered off and washed with 2 × 5 mL of EtOH, 2 × 5 mL of EtOH−H_2O (1:1 v/v), and 2 × 5 mL of water. Removal of solvent gave 50 mg of solid bis(phosphate) **15**: ^{1}H NMR (200 MHz, D_2O) δ 4.27 (t, J = 2.8

Hz, 1H), 4.0−3.80 (m, 2H), 3.72 (t, J = 9.2 Hz, 2H), 3.35 (t, J = 9.2 Hz, 1H) ppm; ^{31}P NMR (81 MHz, D_2O) δ 6.70, 5.0 (1:1) ppm.

Cyanoethyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-[3-(*p*-Methoxybenzyl-4,5-*O*-dibenzyl)-2,6-*O*-bis(benzoxymethyl)-*myo*-inosityl] Phosphate (17a). To a mixture of protected inositol **12a** (400 mg, 0.556 mmol) and 1*H*-tetrazole (155 mg, 2.21 mmol) in 5 mL of dry CH_2Cl_2 was added phosphoramidite **16** (840 mg, 1.09 mmol) in 2 mL of CH_2Cl_2, and the mixture was stirred at room temperature for 30 min. The mixture was cooled to −40 °C, and *m*-CPBA (250 mg, 60−85%) was added and stirred as it warmed to room temperature. The mixture was diluted to 20 mL with CH_2Cl_2, washed (10% $NaHCO_3$, water), dried (Na_2SO_4), concentrated, and chromatographed on SiO_2 using 50% EtOAc−hexane to give 760 mg (97%) of protected phosphoinositide **17a** ($R_f \sim 0.3$) as a viscous, colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35−7.20 (m, 22H, aromatic), 6.80−6.60 (m, 2H, PMB), 5.30−5.10 (m, 1H), 5.05−4.40 (m, 14H), 4.35−4.15 (m, 10H), 3.78 (s, 3H, OMe), 3.80−3.30 (m, 2H), 2.52 (J = 6.1 Hz, CH_2CN), 2.28 (t, J = 7.2 Hz, 4H, $COCH_2$), 1.70−1.50 (m, 4H), 1.30−1.10 (m, 48H), 0.90 (t, J = 4.8 Hz, 6H, 2 × CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.1, 133.4, 129.4−127.6 (m), 113.8, 95.5, 87.5, 82.8, 81.4, 75.7, 72.6, 70.3, 69.8, 69.7, 61.5, 55.2, 34.1, 34.0, 29.7−29.1 (m), 24.8, 22.7, 22.5, 14.3 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.44, −0.63 (1:1) ppm.

3,5-*O*-Dibenzyl-4-*O*-dibenzylphosphoryl-2,6-*O*-bis(benzoxymethyl)-*myo*-inositol (14b). To a solution of acetate **13b** (200 mg, 0.221 mmol) in 20 mL of methanol was added K_2CO_3 (61.3 mg, 0.443 mmol), and the mixture was stirred at room temperature for 45 min until TLC showed that the reaction was complete. The solvent was evaporated, and the residue was dissolved in water and extracted with 3 × with EtOAc. The combined organics were washed (water, brine), and dried ($MgSO_4$), and the crude product was purified on SiO_2 with 4% EtOAc−CH_2Cl_2 to give 130 mg of **14b** (68%) ($R_f \sim 0.48$, 50% EtOAc−hexane): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.08 (m, 30H, aromatic), 5.02−4.52 (m, 17H), 4.26 (s, 1H), 3.94−3.84 (m, 2H), 3.56−3.45 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.2−136.8 (m), 128.3−127.1 (m), 96.4, 95.5, 82.8, 81.1, 79.7, 79.5, 74.8, 74.7, 71.7, 70.8, 70.0, 69.5, 69.0, 68.9, 66.8 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.56 ppm. HRMS (FAB): calcd for $C_{50}H_{54}O_{11}P$ (MH^+), *m/e* 861.3404; found, *m/e* 861.3438.

Cyanoethyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 3,5-*O*-dibenzyl-4-*O*-dibenzylphosphoryl-2,6-*O*-dibenzoxymethyl-*myo*-inositol Phosphate (17b). To a mixture of inositol **14b** (43 mg, 0.050 mmol) and 14 mg (0.20 mmol) of 1*H*-tetrazole in dry CH_2Cl_2 (10 mL) was slowly added cyanoethyl 1,2-*O*-dipalmitoyl-*sn*-glyceryl *N,N*-diisopropylphosphoramidite (**16**) (150 mg, 0.20 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred for 1 h at room temperature. The reaction was cooled to −40 °C, and *m*-CPBA (43 mg, 0.25 mmol) was added and stirred as it warmed to room temperature for another 1 h. Workup as above gave phosphate **17b** (28 mg, 36% yield) as a colorless oil that slowly solidified: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.00 (m, 30H, Bn), 5.31−5.13 (m, 1H), 5.00−4.48 (m, 17H), 4.26−4.09 (m, 9H), 3.67−3.48 (m, 2H), 2.51−2.45 (t, J = 6.2 Hz, 2H), 2.28 (t, J = 7.0 Hz, 2H, CH_2CO), 2.27 (t, J = 7.2 Hz, 2H, CH_2CO), 1.80−1.50 (m, 4H), 1.25 (m, 48H), 0.95−0.91 (t, J = 6.2 Hz, 6H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.2, 172.8, 138.0, 137.7, 137.6, 137.3, 136.1, 136.0, 135.8, 128.3−127.3 (m), 116.5, 96.5, 95.3, 81.3, 79.5, 79.3, 75.0, 73.1, 72.4, 70.3, 69.6, 69.1−68.0 (m), 67.9, 66.0, 65.9, 62.3, 62.3, 61.5, 34.1, 33.9, 31.9, 29.7−29.1 (m), 25.5, 24.8, 22.7, 19.5, 19.4, 14.1 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.47 (1 P), −1.09 (1 P) ppm. MS (FAB): *m/e* 1567 (MNa^+), 551, 313, 181. HRMS (FAB): calcd for $C_{88}H_{123}NNaO_{18}P_2$ (MNa^+), *m/e* 1566.8113; found, *m/e* 1566.8078.

The low yields (36−40%) in the coupling reactions to give **17b** and **34a** below do not reflect a fundamental limitation in the reaction. Instead, low recoveries simply reflect difficulties in workup, primarily due to (a) loss of material at foamy aqueous/organic interfaces and (b) irreversible adsorption to silica gel during purification.

Cyanoethyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-(4,5-*O*-dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inosityl) Phosphate (18). A mixture of PMB ether **17a** (800 mg, ∼90% pure, 0.556 mmol) and DDQ (150 mg, 0.661 mmol) was stirred in 50 mL of CH_2Cl_2−H_2O (100:1, v:v) at room temperature for 2 h. The mixture was washed (10% aqueous $NaHCO_3$), dried ($MgSO_4$), and purified on SiO_2 using 67% EtOAc−hexane to give 430 mg of phosphate **18** (60% yield from **12a**) as an oil, $R_f \sim 0.34$: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35−7.20 (m, 20H, aromatic), 5.30−5.10 (m, 1H), 5.05−4.40 (m, 12H), 4.35−4.15 (m, 10H), 3.80−3.30 (m, 2H), 3.00 (br, 1H, OH), 2.52 (J = 6.1 Hz, CH_2CN), 2.28 (t, J = 7.2 Hz, 4H, $COCH_2$), 1.70−1.50 (m, 4H), 1.30−1.10 (m, 48H), 0.90 (t, J = 4.8 Hz, 6H, 2 × CH_3) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.63, −0.81 (1:1) ppm.

Cyanoethyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-(3-*O*-Dibenzylphosphoryl-4,5-*O*-dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inosityl) Phosphate (19). A solution of hydroxy compound **18** (430 mg, 0.335 mmol) in 5 mL of CH_2Cl_2 and 1*H*-tetrazole (95 mg, 1.36 mmol) was stirred at room temperature, while a solution of dibenzyl *N,N*-diisopropylphosphoramidite (230 mg, 0.67 mmol) in 1 mL of CH_2Cl_2 was added. The mixture was stirred at room temperature for 1 h and cooled to −40 °C, *m*-CPBA (115 mg) was added, and the reaction was stirred for 30 min at 0 °C and then 30 min at room temperature. The mixture was diluted with CH_2Cl_2 and washed (10% $NaHCO_3$, water), dried (Na_2SO_4), concentrated, and chromatographed on SiO_2 using 50% EtOAc−hexane to give 414 mg (80%) of compound **19** ($R_f \sim 0.38$) as a viscous colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 40H, phenyl), 5.0−4.4 (m, 22H), 4.4−4.1 (m, 2H), 4.0 (m, 1H), 3.4 (m, 1H) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ 0.33, 0.09 (1:1) ppm. MS (FAB): *m/e* 1567 (MNa^+), 808, 553, 552, 550, 313, 281, 267, 221, 207, 147, 136, 133. HRMS (FAB): calcd for $C_{88}H_{123}NNaO_{18}P_2$ (MNa^+), *m/e* 1566.8113; found, *m/e* 1566.8160.

3-Aminopropyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-(3-*O*-Phosphoryl-*myo*-inosityl) Phosphate (20a). A solution of fully protected precursor **19** (170 mg, 0.11 mmol), $NaHCO_3$ (9 mg, 0.10 mmol), and Pd/C (10%, 100 mg) in *t*-BuOH−H_2O (6:1, v:v, 35 mL) was added, and the mixture was shaken at 50 psi initial pressure for 5 h. The catalyst was filtered off and washed with 3 × 5 mL of EtOH, 5 mL of EtOH−H_2O (v/v 1:1), and 1 × 5 mL of water. Removal of solvent gave 52 mg (63% yield) of solid PtdIns(3)P triester **20a**: ^{1}H NMR (200 MHz, D_2O) δ 4.30−3.20 (m, 13H), 2.70 (m, 2H), 2.30−2.20 (m, 4H, $COCH_2$), 1.7−1.4 (m, 6H), 1.30−1.00 (m, 48H), 0.90−0.70 (m, 6H) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ 8.8 (s and sharp), 1.9 (br) (∼ 1:1) ppm.

3-Aminopropyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 4-*O*-Phosphoryl-D-*myo*-inositol Phosphate Sodium Salt (20b). A mixture of cyanoethyl ester **17b** (43 mg, 0.028 mmol), sodium bicarbonate (2.4 mg, 0.028 mmol), and Pd/C (10%) (100 mg) in 14 mL of *t*-BuOH/water (6:1) was shaken under hydrogen (50 psi) for 10 h and filtered, the catalyst was washed with a $CHCl_3$−CH_3OH−H_2O mixture, and the filtrate was concentrated under N_2 to give PtdIns(4)P triester **20b**: ^{1}H NMR (200 MHz, D_2O) δ 5.24 (s, 1H), 5.00−2.60 (br), 2.40−2.14 (m, 4H), 1.77−1.50 (m, 4H), 1.47−1.04 (m, 48H), 0.95−0.84 (m, 6H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 0.09 (s), 2.6 (s) ppm.

1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-[3-*O*-Phosphoryl-*myo*-inosityl] Phosphate (21). A solution of precursor **19** (130 mg, 0.086 mmol) and *i*-Pr_2NEt (200 μL) in 2 mL of MeOH was stirred overnight (TLC showed no remaining starting material) and evaporated to dryness. The residue was dissolved in *t*-BuOH−H_2O (6:1 v/v, 35 mL) and $NaHCO_3$ (10 mg, 0.11 mmol), Pd/C (10%, 100 mg) was added, and the mixture was shaken at 50 psi initial pressure for 5 h. The catalyst was filtered off and washed with 5 × 5 mL of EtOH, 3 × 5 mL of EtOH−H_2O (v/v 1:1), and 2 × 5 mL of water. Removal of solvent gave 62 mg (77% yield) of solid PtdIns(3)P di-C_{16}-diester **21**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30−3.50 (very broad and poorly resolved peaks, 11H), 2.30−2.10 (m, 4H), 1.70−1.30 (m, 52H), 0.90−0.80 (m, 6H) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ 3.8, 0.1 (∼1:1) ppm.

In the processing of this and other hydrogenolytic deprotection reactions of these detergent-like molecules, an esti-

mated equimolar (according to the number of negative phosphate charges in the molecule) amount of $NaHCO_3$ was generally added during hydrogenation to suppress acyl migration. When traces of Na^+ salts remain, the ^{31}P NMR peaks become complex as the different counterions result in different chemical shifts. Thus, the hydrogenolysis reaction mixture was first passed through a Dowex 50WX8-200 ion-exchange resin and concentrated to dryness to remove excess HCO_3^-. It was then passed through a Chelex column to exchange the cation back to Na^+. When $NaHCO_3$ was not used, this extra step was unnecessary.

3-((*p*-Benzoyldihydrocinnamyl)amino)propyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-(3-*O*-Phosphoryl-*myo*-inosityl) Phosphate (22a). PtdIns(3)P aminopropyl triester **20a** (5 mg, 0.0056 mmol) was suspended in 2.5 mL of anhydrous DMF, and *N*-hydroxysuccinimido *p*-benzoyldihydrocinnamate ester (BZDC−NHS ester, 3.6 mg, 0.010 mmol) was added, followed by 0.2 mL of dry Et_3N. The suspension was stirred overnight and concentrated in vacuo, and the residue was evaporated with 2 mL of water. The residue was centrifuged with acetone several times until the acetone showed no remaining UV-absorbing material. Then the solid was dissolved in 1 mL of water and applied to a 50 × 6 mm column of DEAE cellulose (OH^- form). The column was washed with 2 × 1 mL of water and then eluted with 2 × 1 mL of 0.1 M TEAB, 2 × 1 mL of 0.2 M TEAB, 2 × 1 mL of 0.3 M TEAB, and 1 mL of 0.4 M TEAB buffer. The product eluted in 0.2 M buffer. Evaporation of these fractions in vacuo followed by evaporating with several small volumes of methanol gave the triethylamine salt of BZDC−PtdIns(3)P triester **22a**. After ion-exchange using a column packed with Bio-Rad Chelex 100 resin (Na form), the sodium salt of **22a** (2.5 mg, 40% yield) was obtained as a glass: ^1H NMR (250 MHz, D_2O) δ 7.86−7.75 (m, 5H), 7.50 (t, 2H), 7.36 (t, 2H), 4.30−3.20 (m, 13H), 3.10 (m, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.45 (t, J = 7.5 Hz, 2H), 2.30−2.20 (m, 4H, $COCH_2$), 1.7−1.4 (m, 6H), 1.30−1.00 (m, 48H), 0.90−0.70 (m, 6H) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ 8.8 (s), 1.9 (s) (∼1:1) ppm.

3-((*p*-Benzoylditritiocinnamyl)amino)propyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-[3-*O*-Phosphoryl-*myo*-inosityl] Phosphate (22a′). [$^3H_2$]-*N*-Hydroxysuccinimido *p*-benzoyldihydrocinnamate ester ([^{3}H]BZDC−NHS ester, 2 mCi, 40 Ci/mmol) in EtOAc was gently concentrated with dry N_2, and then 3-aminopropyl triester **20a** (800 μg/mL of DMF stock solution, 15 μL) was added followed by 10 mL of dry triethylamine. The suspension was stirred overnight. The solvents were evaporated in vacuo, the residue was evaporated with 1 mL of water, and the residue was dissolved in 1 mL of water and then applied to 50 × 6 mm column of DEAE cellulose (OH^- form). The column was washed with 2 × 1 mL of water and then eluted with 2 × 1 mL of 0.1 M TEAB, 2 × 1 mL of 0.2 M TEAB, 2 × 1 mL of 0.3 M TEAB, and 1 mL of 0.4 M TEAB buffer. The product **22a′** eluted in 0.1 M buffer. Radioactive fractions were pooled to give ca. 150 μCi of purified **22a′**, specific activity 42.5 Ci/mmol (radiochemical yield, 7.5%).

3-((*p*-Benzoyldihydrocinnamyl)amino)propyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-(4-*O*-phosphoryl-*myo*-inosityl) Phosphate (22b). To aminopropyl triester **20b** (5 mg, 0.0056 mmol) in 2 mL of DMF (distilled after incubation with P_2O_5 for 5 days) was added BZDC−NHS ester (3.6 mg, 0.010 mmol), and the mixture was stirred for 30 min. Dry Et_3N (0.2 mL) was then added, and the suspension was stirred overnight. DMF was removed under a stream of N_2, and the residue was washed with acetone (5 × 1 mL) to give **22b** as a white powder (2.3 mg, 37% yield), which was homogeneous by TLC: ^1H NMR (250 MHz, D_2O) δ 7.83−7.71 (m, 5H), 7.64−7.54 (m, 2 H), 7.45−7.38 (m, 2H), 4.29−3.40 (m, 13H), 3.23−3.09 (m, 2H), 2.75−2.70 (m, 4H), 2.03−1.96 (m, 4H), 1.67−1.49 (m, 4H), 1.31−1.20 (m, 48H), 0.96−0.79 (m, 6H) ppm; ^{31}P NMR (81 Hz, D_2O) 4.89 (br) ppm.

Benzyl 1,2-*O*-Diisopropylidene-*sn*-glyceryl *N*,*N*-Diisopropylphosphoramidite (23). A mixture of $BnOP(NPr_2\text{-}i)_2$ (800 mg, 2.36 mmol), 1,2-*O*-diisopropylidene-*sn*-glycerol (312 mg, 2.36 mmol), and diisopropylammonium tetrazole (200 mg) in 10 mL of dry CH_2Cl_2 was stirred at room temperature for 1 h and then washed (10% $NaHCO_3$), dried ($MgSO_4$), and purified on SiO_2 using EtOAc−hexane−Et_3N (100:300:10, v/v/v), to give 732 mg of phosphoramidite **23** (84%), $R_f \sim 0.95$: ^1H NMR (200 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H, aromatic), 4.89 (d, J = 8.4 Hz, CH_2O), 4.80−4.50 (m, 1H), 4.30−4.10 (m, 2H), 4.01, 3.99 (2t, J = 8.2 Hz, 2H), 3.80−3.50 (m, 2H), 1.41, 1.35 (2s, 6H, isopropylidene) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ 148.8, 148.7 (∼1:1) ppm.

Benzyl 1,2-*O*-Diisopropylidene-*sn*-glyceryl 1-[3-(*p*-Methoxybenzyl)-4,5-*O*-dibenzyl-2,6-*O*-dibenzoxymethyl-*myo*-inosityl] Phosphate (24). To a mixture of precursor **12a** (200 mg, 0.28 mmol) and 1*H*-tetrazole (80 mg, 1.1 mmol) in 5 mL of dry CH_2Cl_2 was added phosphoramidite **23** (200 mg, 1.09 mmol) in 2 mL of CH_2Cl_2, and the mixture was stirred at room temperature for 30 min. The mixture was cooled to −40 °C, and *m*-CPBA (250 mg, 60−85%) was added and stirred as the reaction warmed to room temperature. The mixture was diluted to 20 mL with CH_2Cl_2, washed (10% $NaHCO_3$, water), dried (Na_2SO_4), concentrated, and chromatographed on SiO_2 using 50% EtOAc−hexane to give 240 mg (97%) of compound **24** as a viscous colorless oil ($R_f \sim 0.4$): ^1H NMR (200 MHz, $CDCl_3$) δ 7.40−7.20 (m, 27H, aromatic), 6.80 (m, 2H, PMB), 5.20−4.50 (m, 14H), 4.30−3.90 (m, 8H), 3.78 (s, 3H, OMe), 3.70−3.40 (m, 6H), 1.37, 1.31 (2s, 6H, isopropylidene) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ:−0.19, −0.34 (∼1:1) ppm. MS (FAB): *m/e* 1027 (MNa^+), 669, 386, 370, 328, 211, 181, 121. HRMS (FAB): calcd for $C_{57}H_{65}NaO_{14}P$ (MNa^+), *m/e* 1027.4010; found, *m/e* 1027.4031.

Benzyl 1,2-*O*-Diisopropylidene-*sn*-glyceryl 1-[4,5-*O*-Dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inosityl] Phosphate (25). A mixture of phosphate **24** (230 mg, 0.23 mmol) and DDQ (80 mg, 0.35 mmol) in 20 mL of $CH_2Cl_2-H_2O$ (100/1 v/v) was stirred at room temperature for 2 h. The mixture was washed (10% $NaHCO_3$), dried ($MgSO_4$), and purified on SiO_2 using 50% EtOAc−hexane to give 140 mg (69% yield) of phosphate **25** as an oil ($R_f \sim 0.20$): ^1H NMR (200 MHz, $CDCl_3$) δ 7.40−7.15 (m, 25H, aromatic), 5.20−4.50 (m, 12H), 4.30−3.90 (m, 7H), 3.80−3.40 (m, 6H), 3.30 (br., 1H, OH), 1.39, 1.32 (2s, 6H, isopropylidene) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.45, −0.56 (∼1:1) ppm. MS (FAB): *m/e* 907 (MNa^+), 855 (MH^+), 777, 669, 657, 579, 393, 271, 182, 181, 165, 154, 136, 115. HRMS: calcd for $C_{49}H_{57}NaO_{13}P$ (MNa^+), *m/e* 907.3435; found, *m/e* 907.3476.

Benzyl *sn*-glyceryl 1-(3-*O*-Dibenzylphosphoryl-4,5-*O*-dibenzyl-2,6-*O*-dibenzoxymethyl-*myo*-inosityl) Phosphate (27). A solution of protected phosphoinositide **25** (136 mg, 0.154 mmol) in 2 mL of CH_2Cl_2 and 1*H*-tetrazole (43 mg, 0.61 mmol) was stirred at room temperature, while a solution of dibenzyl *N*,*N*-diisopropylphosphoramidite (110 mg, 0.32 mmol) in 1 mL of CH_2Cl_2 was added. The mixture was stirred at room temperature for 1 h and cooled to −40 °C, and *m*-CPBA (20 mg) was added. The reaction was stirred for 30 min at 0 °C and then 30 min at room temperature, and the mixture was diluted with CH_2Cl_2, washed (10% $NaHCO_3$, water), dried (Na_2SO_4), and concentrated to give a crude residue **26** (33% EtOAc−hexane, $R_f \sim 0.5$). This residue was dissolved in MeOH, 10 mg of *p*-TsOH monohydrate was added, and the mixture was stirred at room temperature for 1 h. The acid was neutralized (0.5 mL of 10% aqueous $NaHCO_3$), and the solvent was evaporated. Purification on SiO_2 eluting with 67% EtOAc−hexane gave 100 mg ($R_f \sim 0.12$) of compound **27** (59% for two steps) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 7.40−7.10 (m, 35H, aromatic), 5.20−4.50 (m, 18H), 4.45−3.50 (m, 11H), 2.0 (br, 2H, OH) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ 0.98, −0.64, 0.75, −1.09 (∼1:1:1:1) ppm.

Benzyl 1,2-*O*-Diacyl-*sn*-glyceryl 1-(3-*O*-Dibenzylphosphoryl-4,5-*O*-dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inosityl) Phosphate (28). A solution of diol **27** (1 equiv) and fatty acid (octanoic acid or butyric acid, 3 equiv), DCC (3 equiv), and DMAP (0.05−0.1 equiv) in 5 mL of dry CH_2Cl_2 was stirred overnight. The solid was removed by filtration, washed with ether, and concentrated, the residue was dissolved in 50% EtOAc−hexane, and the precipitate was removed by filtration and washed with the same solvent. Concentration of the

filtrates gave an oil that was purified on SiO_2 using 50% EtOAc−hexane to give the phosphoinositides **28a** or **28b** with $R_f \sim 0.2$.

Data for benzyl 1,2-*O*-dioctanoyl-*sn*-glyceryl 1-(3-*O*-dibenzylphosphoryl-4,5-*O*-dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inosityl) phosphate (28a): 40 mg yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35−7.10 (m, 35H, aromatic), 5.15−4.00 (m, 27H), 3.60−3.40 (m, 2H), 2.2 (m, 4H, $COCH_2$), 1.70−1.20 (m, 20H), 0.9−0.7 (m, 6H, 2 × CH_3) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.48, −0.53, −0.58, −0.64 (∼1:1:1:1) ppm. MS (FAB): *m/e* 1380 (MNa^+), 327, 255, 181, 127. HRMS (FAB): calcd for $C_{76}H_{94}NaO_{18}P_2$ (MNa^+), *m/e* 1379.5813; found, *m/e* 1379.5759.

Data for benzyl 1,2-*O*-dibutyroyl-*sn*-glyceryl 1-(3-*O*-dibenzylphosphoryl-4,5-*O*-dibenzyl-2,6-*O*-bis(benzoxymethyl)-*myo*-inosityl) phosphate (28b): 50 mg yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.10 (m, 35H, aromatic), 5.20−4.50 (m, 20H), 4.40−3.90 (m, 7H), 3.60−3.40 (m, 2H), 2.30−2.20 (m, 4H, $COCH_2$), 1.70−1.50 (m, 4H), 1.00−0.80 (m, 6H, 2 × CH_3) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.22, −0.45, −0.53 (∼1:1:2) ppm. MS (FAB): *m/e* 1267 (MNa^+), 215, 181. HRMS: calcd for $C_{68}H_{78}NaO_{18}P_2$ (MNa^+), *m/e* 1267.4561; found, *m/e* 1267.4610.

1,2-*O*-Dioctanoyl-*sn*-glyceryl 1-(3-*O*-Phosphoryl-*myo*-inosityl) Phosphate (29a). To a solution of fully protected phosphate **28a** (50 mg, 0.037 mmol), *t*-BuOH−H_2O (6:1 v/v, 35 mL) and $NaHCO_3$ (9 mg, 0.10 mmol) was added Pd/C (10%, 50 mg), and the mixture was shaken at 50 psi initial pressure for 5 h. The catalyst was filtered off and washed with 5 mL of EtOH, 5 mL of EtOH−H_2O (v/v 1:1), and 3 × 5 mL of water. Removal of solvent gave 17 mg (63% yield) of solid PtdIns(3)P di-C_8-ester **29a**: ^{1}H NMR (200 MHz, D_2O) δ 5.35−5.15 (m, 1H), 4.45−4.20 (m, 2H), 4.10−3.60 (m, 7H), 3.35 (t, J = 9.2 Hz, 1H), 2.38, 2.34 (2t, J = 7.2 Hz, 4H, $COCH_2$), 1.7−1.2 (m, 20H), 0.82 (t, J = 6.2 Hz, 6H) ppm; ^{31}P NMR (81 MHz, D_2O) δ 7.04, 2.65 ppm.

1,2-*O*-Dibutyryl-*sn*-glyceryl-1-(3-*O*-phosphoryl-*myo*-inosityl) Phosphate (29b). A solution of protected phosphoinositide **28b** (50 mg, 0.040 mmol), $NaHCO_3$ (10 mg, 0.11 mmol), and Pd/C (10%, 50 mg) in *t*-BuOH−H_2O (6:1 v/v, 35 mL) was shaken at 50 psi initial pressure for 5 h. The catalyst was filtered off and washed with 5 mL of EtOH, 5 mL of EtOH−H_2O (1:1 v/v), and 3 × 5 mL of water. Removal of solvent gave 22 mg (92%) of solid PtdIns(3)P di-C_4-ester **29b**: ^{1}H NMR (200 MHz, D_2O) δ 5.35−5.25 (m, 1H), 4.50−4.20 (m, 2H), 4.10−3.37 (m, 7H), 3.35 (t, J = 9.2 Hz, 1H), 2.37, 2.34 (2t, J = 7.2 Hz, 4H), 1.70−1.50 (m, 4H), 0.88, 0.86 (2t, J = 6.2 Hz, 6H, 2 × CH_3) ppm; ^{31}P NMR (81 MHz, D_2O) δ 7.43, 2.65 (∼1:1) ppm.

General Procedure for the DCC/DMAP-Promoted Esterification. A mixture of a PMB-protected glycerol **30** (1 equiv), DMAP (0.05−0.1 equiv), fatty acid (2.5 equiv), and DCC (2.5 equiv) in dry CH_2Cl_2 (10 mL) was stirred at room temperature overnight. The mixture was filtered and concentrated. The residue was then dissolved in EtOAc, and the precipitate was filtered again and washed with EtOAc. The filtrate was concentrated and purified on SiO_2 column eluting with EtOAc−hexane mixtures to give the corresponding 1,2-*O*-diacyl-3-*O*-(*p*-methoxybenzyl)-*sn*-glycerol **31**.

Data for 1,2-*O*-dioctanoyl-3-*O*-(*p*-methoxybenzyl)-*sn*-glycerol (31b): obtained in 95% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24, 7.20, 6.88, 6.83 (4s, 4H, PMB), 5.28−5.17 (m, 1H), 4.46−4.45 (m, 2H), 4.31 (dd, J = 4.0, 12.0 Hz, 1H), 4.15 (dd, J = 6.4 Hz, 11.8 Hz, 1H), 3.79 (s, 3H, OMe), 3.54 (d, J = 5.2 Hz, 2H), 2.30, 2.26 (2t, J = 7.8 Hz, 4H), 1.60−1.57 (m, 4H), 1.48−1.05 (m, 16H), 0.86 (t, J = 6.6 Hz, 6H, CH_3) ppm. MS (EI^+): *m/e* 464 (M^+) 352, 327, 226, 201, 135, 121. HRMS (EI^+): calcd for $C_{27}H_{44}O_6$ (M^+), *m/e* 464.3139; found, *m/e* 464.3120.

Data for 1,2-*O*-dibutyryl-3-*O*-(*p*-methoxybenzyl)-*sn*-glycerol (31c): obtained in 90% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23, 7.19, 6.86, 6.84 (4s, 4H, PMB), 5.25−5.17 (m, 1H), 4.44 (AB, J = 11.7 Hz, 2H, OCH_2), 4.20 (d, AB, J = 3.8 Hz, 2H), 3.77 (s, 3H, OMe), 3.53 (d, J = 5.2 Hz, 2H), 2.26, 2.24 (2t, J = 7.4 Hz, 4H, $COCH_2$), 1.70−1.53 (m, 4H), 0.92, 0.91 (2t, J = 7.3 Hz, 6H, CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ: 173.2, 172.9, 159.3, 129.8, 129.3, 113.8, 87.7, 72.9, 70.0, 67.9, 62.7, 55.2, 36.2, 35.9, 18.4, 18.3, 13.6 ppm. MS (CI^+): *m/e* 352 (M^+) 281, 215, 145, 136, 121, 71. HRMS (CI^+): calcd for $C_{19}H_{28}O_6$, *m/e* 352.1886; found, *m/e* 352.1881. Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.77; H, 7.95. Found: C, 65.00, H, 7.88.

General Procedure for Deprotection of PMB Ethers. A mixture of a PMB ether **31** (1 equiv) in 20 mL of wet CH_2Cl_2 (CH_2Cl_2−H_2O, 100:1 v/v) and DDQ (1.2 equiv) was stirred at room temperature for 3 h. It was then washed with 10% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Purification on SiO_2 gel using 95% ether−CH_2Cl_2 mixtures gave the corresponding 1,2-*O*-diacyl-*sn*-glycerol **32**.

Data for 1,2-*O*-dioctanoyl-*sn*-glycerol (32b): obtained in 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.07 (quint, J = 5.6 Hz, 1H), 4.30−4.08 (m, 2H), 3.70 (d, J = 5.0 Hz, 2H), 3.37−2.27 (m, 4H), 1.66−1.54 (m, 4H), 1.28−1.20 (m, 16H), 0.89−0.83 (m, 6H) ppm. MS (CI+): *m/e* 362 (MNH_4^+), 345, 327, 269, 226, 127, 98. HRMS (CI^+): calcd for $C_{19}H_{40}NO_5$ (MNH_4^+), *m/e* 362.2906; found, *m/e* 362.2909.

Data for 1,2-*O*-dibutyroyl-*sn*-glycerol (32c) ($R_f \sim 0.35$, 33% EtOAc−hexane): obtained in72% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.09 (quint., J = 5.0 Hz, 1H), 4.29, 4.26 (2q, J = 11.9 Hz, 2H), 3.72 (d, J = 4.9 Hz, 2H), 2.33, 2.30 (2t, J = 7.4 Hz, 4H, $COCH_2$), 1.70−1.53 (m, 4H), 0.95, 0.94 (2t, J = 7.2 Hz, 6H, CH_3) ppm. MS (CI^+): 250 (MNH_4^+), 233 (MH^+), 215, 145, 88, 71. HRMS (CI^+): calcd for $C_{11}H_{24}NO_5$ (MNH_4^+), *m/e* 250.1654; found, *m/e* 250.1661.

General Procedure for Preparation of Phosphoramidites 33. A mixture of 1,2-*O*-diacyl-*sn*-glycerol and benzyl *N*,*N*-diisopropylchlorophosphoramidite and *N*,*N*-diisopropylethylamine was stirred at 0 °C for 2 h. It was washed with 10% aqueous $NaHCO_3$ solution and dried over $MgSO_4$. Purification on SiO_2 eluting with EtOAc−hexane-Et_3N (from 10:50:3 to 10:30:3, v/v/v) gave the phosphoramidites **33**. Spectroscopic data are shown; however, analytical data on these unstable materials were not obtained. These materials were employed directly for the coupling reactions to give adducts **34**.

Data for benzyl 1,2-*O*-dioctanoyl-*sn*-glycerol *N*,*N*-diisopropylphosphoramidite (33b): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H, Bn), 5.25−5.12 (m, 1H), 4.70 (t, J = 10.0 Hz, 2H), 4.40−4.31 (m, 1H), 4.23−4.10 (m, 1H), 3.81−3.53 (m, 4H), 2.30 (t, J = 7.4 Hz, 4H), 1.67−1.56 (m, 4H), 1.27−1.17 (m, 28H), 0.92−0.85 (m, 6H) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ 149.6 (s), 149.4 (s) (1:1) ppm.

Data for benzyl 1,2-*O*-dibutyryl-*sn*-glycerol *N*,*N*-diisopropylphosphoramidite (33c): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H, Bn), 5.20−5.10 (m, 1H), 4.72 (d, J = 7.4 Hz, 2H), 4.40−4.20 (m, 2H), 3.80−3.50 (m, 4H), 2.30 (t, J = 7.2 Hz, 4H, $COCH_2$), 1.80−1.60 (m, 4H), 1.30 (m, 12H), 0.94 (2t, J = 7.4 Hz, 6H) ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ 149.5 (s), 149.4 (s) (1:1) ppm.

Benzyl 1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-[3,5-*O*-Dibenzyl-2,6-*O*-dibenzoxymethyl-4-*O*-(dibenzylphosphoryl)-D-*myo*-inositol] Phosphate (34a). To a mixture of alcohol **14b** (40 mg, 0.047 mmol) and 1*H*-tetrazole (24 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) was added a solution of benzyl 1,2-*O*-dipalmitoyl-*sn*-glyceryl *N*,*N*-diisopropylphosphoramidite (**33a**, 190 mg) in 3 mL of dry CH_2Cl_2. Workup as in the preparation of **13b** gave phosphate **34a** (25 mg, 40% yield) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−6.99 (m, 35H, aromatic), 5.19−4.45 (m, 20H), 4.26−3.99 (m, 7H), 3.53−3.43 (m, 2H), 2.27−2.16 (m, 4H, CH_2CO), 1.64−1.44 (m, 4H), 1.25 (m, 48H), 0.88 (t, 6H, J = 6.6 Hz, 6H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.9−135.8 (m), 128.4−127.0 (m), 107.5, 106.4, 105.5, 71.8, 69.9−66.7 (m), 61.3, 33.9−33.7 (m), 31.7, 29.5−28.9 (m), 24.6, 22.5, 13.9 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.22, −0.50 (∼1:1) ppm. MS (FAB): *m/e* 1604 (MNa^+), 551, 313, 181. HRMS (FAB): calcd for $C_{92}H_{126}NaO_{18}P_2$ (MNa^+), *m/e* 1603.8317; found, *m/e* 1603.8382.

Benzyl 1,2-*O*-dioctanoyl-*sn*-glyceryl 1-[3,5-*O*-dibenzyl-2,6-*O*-bis(benzoxymethyl)-4-*O*-(dibenzylphosphoryl)-D-*myo*-inositol] phosphate (34b) was synthesized as described above: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.01 (m, 35H, Bn),

5.15−4.45 (m, 20 H), 4.25−3.96 (m, 7H), 3.49−3.44 (m, 2H), 2.35−2.17 (m, 4H, CH_2CO), 1.70−1.45 (m, 4H), 1.26−1.24 (m, 16H), 0.88−0.84 (m, 6H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 172.5, 137.6−137.0 (m), 128.5−127.0 (m), 110.5, 109.5, 107.5, 106.5, 104.5, 102.5, 69.9−69.0 (m), 61.3, 33.8, 33.7, 31.4, 28.8−28.7 (m), 24.6, 22.4, 13.8 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.20, −0.24 (combined as 1P), −0.53 (1P) ppm. MS (FAB): *m/e* 1380 (MNa^+), 551, 327, 255, 181. HRMS (FAB): calcd for $C_{76}H_{94}NaO_{18}P_2$ (MNa^+), *m/e* 1379.5813; found, *m/e* 1379.5795.

Benzyl 1,2-*O*-dibutanoyl-*sn*-glyceryl 1-[3,5-*O*-dibenzyl-2,6-*O*-bis(benzyloxymethyl)-4-*O*-(dibenzylphosphoryl)-D-*myo*-inositol] phosphate (34c) was synthesized as described above: ^1H NMR (200 MHz, $CDCl_3$) δ 7.38−7.00 (m, 35H, Bn), 5.20−4.51 (m, 20H), 4.27−4.00 (m, 7H), 3.53−3.43 (m, 2H), 2.27−2.16 (m, 4H, CH_2CO), 1.66−1.53 (m, 4H), 0.95−0.85 (m, 6 H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7, 172.4, 137.9, 137.6, 137.5, 137.0, 128.5−127.1 (m), 112.5, 109.5, 108.5, 107.5, 106.5, 105.5, 104.5, 99.5, 69.9−66.9 (m), 61.3, 35.7, 35.6, 18.1, 13.4, 13.3 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ −0.19, −0.25 (combined as 1P), −0.53 (1P) ppm. HRMS (FAB): calcd for $C_{68}H_{78}O_{18}P_2$ (MH^+), *m/e* 1245.4742; found, *m/e* 1245.4836.

1,2-*O*-Dipalmitoyl-*sn*-glyceryl 1-(4-*O*-Phosphoryl-D-*myo*-inositol) Phosphate Sodium Salt (35a). A mixture of protected phosphoinositide **34a** (36 mg, 0.023 mmol), $NaHCO_3$ (6 mg, 0.072 mmol), and Pd/C (10%) (100 mg) in 12 mL of *t*-BuOH/water (6:1) was shaken under hydrogen (50 psi) for 14 h. The mixture was filtered, washed with a mixed solution of chloroform, methanol, and water, the solvents were evaporated, and the remaining product **35a** (17 mg, 84% yield) was lyophilized: ^1H NMR (200 MHz, $CDCl_3$) δ 5.20−3.70 (br), 3.20−2.50 (br), 2.20−1.90 (m, 4H), 1.55−1.35 (m, 4H), 1.35−1.00 (m, 48H), 0.90−0.84 (m, 6H); ^{31}P NMR (81 MHz, D_2O) δ 7.67 (sharp), 2.92 (br) ppm.

1,2-*O*-Dioctanoyl-*sn*-glyceryl 1-(4-*O*-Phosphoryl-D-*myo*-inositol) Phosphate Sodium Salt (35b). Preparation as above from protected phosphoinositide **34b** gave final product **35b** (80% yield) as the sodium salt: ^1H NMR (200 MHz, D_2O) δ 5.31−5.22 (m, 1H), 4.41 (dd, J = 4.0, 13.4 Hz, 1H), 4.28−3.87 (m, 5 H), 3.77 (t, J = 9.2 Hz, 1H), 3.58 (dd, J = 2.6, 9.6 Hz, 1H), 3.41 (t, J = 9.0 Hz, 1H), 3.21 (J = 7.4 Hz, 1H), 2.43−2.31 (m, 4H), 1.66−1.47 (m, 4H), 1.29−1.16 (m, 16H), 0.84−0.78 (m, 6H, CH_3) ppm; ^{31}P NMR (81 MHz, D_2O) δ 7.66 (s, 1P), 2.76 (s, 1P) ppm.

1,2-*O*-Dibutyryl-*sn*-glyceryl 1-(4-*O*-Phosphoryl-D-*myo*-inositol) Phosphate Sodium Salt (35c). Preparation as above from protected phosphoinositide **34c** gave final product **35b** (85% yield) as the sodium salt: ^1H NMR (200 MHz, D_2O) δ 5.40−5.26 (m, 1H), 4.37 (dd, J = 3.2, 12.0 Hz, 1H), 4.30−4.17 (m, 2H), 4.12−4.03 (m, 3H), 3.98−3.88 (m, 1H), 3.79 (t, J = 9.6 Hz, 1H), 3.60 (dd, J = 2.6, 9.8 Hz, 1H), 3.43 (t, J = 9.3 Hz, 1H), 2.41−2.31 (m, 4H), 1.69−1.47 (m, 4H), 0.89, 0.87 (2t, J = 7.4 Hz, 6H, CH_3) ppm; ^{31}P NMR (81 MHz, D_2O) δ 7.81 (s, 1P), 2.73 (s, 1P) ppm.

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