3-(Hydroxymethyl)-Bearing Phosphatidylinositol Ether Lipid Analogues and Carbonate Surrogates Block PI3-K, Akt, and Cancer Cell Growth

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Phosphatidylinositol 3-kinase (PI3-K) phosphorylates the 3-position of phosphatidylinositol to give rise to three signaling phospholipids. Binding of the pleckstrin homolgy (PH) domain of Akt to membrane PI(3)P's causes the translocation of Akt to the plasma membrane bringing it into contact with membrane-bound Akt kinase (PDK1 and 2), which phosphorylates and activates Akt. Akt inhibits apoptosis by phosphorylating Bad, thus promoting its binding to and blockade of the activity of the cell survival factor Bcl-x. Herein we present the synthesis and biological activity of several novel phosphatidylinositol analogues and demonstrate the ability of the carbonate group to function as a surrogate for the phosphate moiety. Due to a combination of their PI3-K and Akt inhibitory activities, the PI analogues **2**, **3**, and **5** proved to be good inhibitors of the growth of various cancer cell lines with IC_{50} values in the 1−10 μM range. The enhanced Akt inhibitory activity of the axial hydroxymethyl-bearing analogue **5** compared to its equatorial counterpart **6** is rationalized based upon postulated differences in the H-bonding patterns of these compounds in complex with a homology modeling generated structure of the PH domain of Akt. This work represents the first attempt to examine the effects of 3-modified PI analogues on these two crucial cell signaling proteins, PI3-K and Akt, in an effort to better understand their cell growth inhibitory properties.

Introduction

Phosphatidylinositol 3-kinase (PI3-K) phosphorylates the 3-position of phosphatidylinositol (PI), PI(4)P, and $PI(4,5)P_2$ to give rise to three signaling phospholipids: PI(3)P, $PI(3,4)P_2$, and $PI(3,4,5)P_3$, respectively.[1] These 3-phosphorylated PI's have the unique ability to bind to specific protein domains, the so-called pleckstrin homology (PH) domains, of a number of signaling proteins. One of the most extensively studied of the PH domain-regulated signaling proteins acting downstream of PI3-K is the proto-oncogenic serine/threonine kinase Akt [also known as RAC-PK or protein kinase B (PKB)]. In particular, while the PH domain of Akt binds both $PI(3,4)P_2$ and $PI(3,4,5)P_3$ in vitro, only $PI(3,4)P_2$ activates Akt. Binding of the PH domain of Akt to membrane PI(3)P's causes the translocation of Akt to the plasma membrane bringing it into contact with membrane-bound Akt kinases [phosphatidylinositol-dependent kinase-1 and -2 (PDK1 and 2)], which phosphorylate and activate Akt. Akt is a proto-oncogene that inhibits apoptosis by phosphorylating a number of downstream targets. This includes phosphorylation of Bad, which promotes its binding to and blockade of the activity of the cell survival factor Bcl-x.[2] Thus, the inhibition of Akt activation induces cancer cell apoptosis. Three mammalian isoforms of Akt have been identified: Akt1, Akt2, and Akt3. Akt1 has been found to be overexpressed in gastric adenocarcinomas, while Akt2 is overexpressed in breast, ovarian, and pancreatic cancer.[3] An important counterpart to PI3-K is the tumor suppressor PTEN, a protein that is able to bring about the dephosphorylation of $PI(3,4,5)P_3$, with specificity being shown for the phosphate at the D-3 position of the inositol ring. Mutations in the PTEN tumor suppressor gene appear to be a common occurrence in a number of human cancers.[4] Thus, PI3-K and Akt provide novel targets for drugs to inhibit the repression of apoptosis in cancer cells and thereby the opportunity to overcome the effects of the loss of the tumor supressor PTEN.

Our earlier work has shown that certain D-3-deoxy-substituted *myo*-inositols are taken up by the *myo*-inositol transporter of cells and incorporated into cellular PI's by PI synthetase leading to selective cell growth inhibition of some transformed cells.[5] However, the activity of these compounds is inhibited by physiological concentrations of the natural substrate, *myo*-inositol. To overcome the transport and synthesis problem, we were led to investigate the activity of certain 3-modified PI analogues. The 3-deoxy PI ether lipid **1** (DPIEL), for example, was found to inhibit PI3-K with an IC_{50} of 14.8 ± 5.6 μM and to block the growth of HT-29 colon cancer cells with an IC_{50} of 2.1 μM. This compound was also found to inhibit the growth of MCF-7 human breast cancer xenografts in scid mice (T/C < 16%) when administered ip as a micellar suspension daily for 17 days at 400 mg/kg.[6] DPIEL is presently under development by the RAID program of the National Cancer Institute (NCI). Because of the interesting biology shown by DPIEL, we deemed it valuable to investigate the activity of other 3-modified PI ether lipid analogues with the aim to further improve

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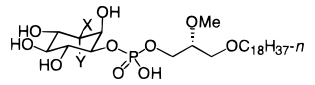
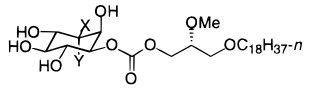
Chart 1



1 X = H, Y = H
2 X = H, Y = CH_2OH
3 X = CH_2OH, Y = H



4 X = H, Y = H
5 X = H, Y = CH_2OH
6 X = CH_2OH, Y = H

upon Akt inhibition and antiproliferative action. In the present article we report on the synthesis and biology of analogues that bear a hydroxymethyl group at position 3 and which also contain in two cases a second modification in which a carbonate group has been introduced as a surrogate for the phosphate linkage between the inositol ring and ether lipid.

Chemistry

The starting material **7** was obtained from L-quebrachitol as reported previously.[7] Swern oxidation of the free axial hydroxyl group gave an unstable ketone that was transformed into alkene **8** through a Wittig reaction.[8] Hydroboration with 9-BBN followed by oxidation with alkaline hydrogen peroxide solution converted **8** into alcohols **9a,b** (approximately 1:1) in 90% yield after chromatography. Compounds **9a**,**b** were readily distinguished through the ^{1}H NMR signals of the protons at C-3. Furthermore, we confirmed the stereochemistry of **9a** by X-ray crystal structure analysis of its (1*S*)-(−)-camphanate ester **10** (Figure 1). The availability of both intermediates **9a**,**b** allowed us to investigate the effect of C-3 stereochemistry on activity (Scheme 1).

Following similar procedures as published before,[5] compounds **9a,b** were protected with a benzyl group, and the *trans*-acetonide moieties were then removed by controlled acidic hydrolysis to give compounds **11a,b**. Both of the resulting hydroxyl groups were again benzylated, and the remaining *cis*-acetonide was removed by acidic hydrolysis. The compounds **12a**,**b** were selectively allylated at position 1 via a 1,2-*O*-stannylene intermediate. After benzylation at position 2, isomerization of the double bond in the allyl group with RhCl(PPh$_3$)$_3$ and DABCO in ethanol and subsequent acidic hydrolysis furnished the desired intermediates **14a**,**b**. Installation of the phospholipid side chain and deprotection were performed in a similar manner as in the synthesis of **1** (Scheme 2).

To prepare the carbonate analogues **5** and **6**, compounds **14a**,**b** were refluxed in toluene with 1,1-carbonyldiimidazole to form the carbamates **16a**,**b**. The second imidazolyl group was then replaced by the ether lipid by refluxing the reactants in toluene in the presence of DBU to give compounds **17a**,**b**. Final hydrogenolysis then delivered the desired carbonate analogues **5** and **6** in good purity (Scheme 3). Carbonate **4** was prepared in a similar fashion using the appropriately protected 3-deoxyinositol.

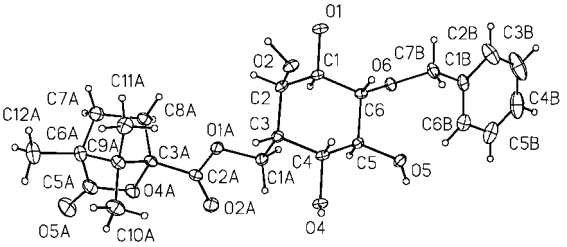
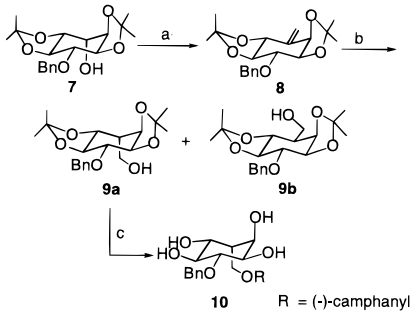


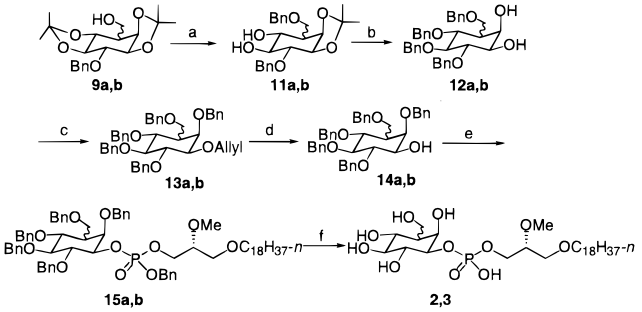
Figure 1. Single-crystal X-ray structure of the camphanate ester **10**.

Scheme 1[a]



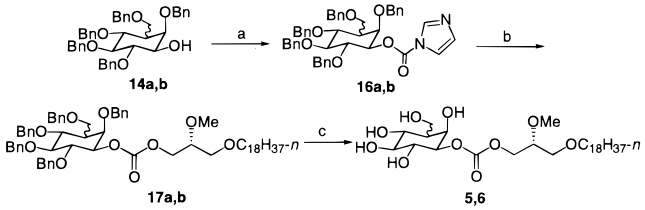
[a] Reagents and conditions: (a) (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, (ii) $MePPh_3Br$, *n*-BuLi, THF, −78 °C to rt; (b) 9-BBN, NaOH, H_2O_2, THF, 0−50 °C; (c) (i) (*S*)-(−)-camphanic chloride, Et_3N, CH_2Cl_2, rt, (ii) 1 N HCl, MeOH, rt.

Scheme 2[a]



[a] Reagents and conditions: (a) (i) NaH, BnBr, DMF, 0 °C to rt, (ii) AcCl (cat.), CH_2Cl_2−MeOH, rt; (b) (i) NaH, BnBr, DMF, 0 °C to rt, (ii) concd HCl, MeOH, rt; (c) (i) Bu_2SnO, toluene, reflux, (ii) allyl-Br, CsF, −50 °C to rt, (iii) NaH, BnBr, DMF, 0 °C to rt; (d) (i) $RhCl(PPh_3)_3$ (cat.), DABCO, EtOH, reflux, (ii) 1 N HCl, acetone, reflux; (e) (i) $BnOP(Ni\text{-}Pr_2)_2$, diisopropylammonium tetrazolide, CH_2Cl_2, rt, (ii) 2-*O*-methyl-1-*O*-octadecyl-*sn*-glycerol, tetrazole, CH_2Cl_2, rt, (iii) *t*-BuOOH, CH_2Cl_2, rt; (f) H_2, 20% $Pd(OH)_2$/C, *t*-BuOH, rt.

Scheme 3[a]



[a] Reagents and conditions: (a) 1,1′-carbonyldiimidazole, toluene, reflux; (b) DBU, 2-*O*-methyl-1-*O*-octadecyl- *sn*-glycerol, toluene, reflux; (c) H_2, 20% $Pd(OH)_2$/C, *t*-BuOH, rt.

Biological Activity

The five new PI analogues were tested for their ability to inhibit p100/p85 PI3-K using the methods described previously.[5c] To measure the effects of these compounds on Akt activity, cells were grown in 6-well plates in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum

(FBS), 4.5 g/L glucose, 100 U/mL penicillin, and 100 μg/mL streptomycin in a 5% CO_2 atmosphere. Before the experiment, the medium was replaced by DMEM without FBS for 16 h. The cells were incubated with the different drugs for 3 h at 37 °C. The concentrations tested ranged from 0 to 20 μM. Monolayers were then stimulated with PDGF (50 ng/mL) for another hour at 37 °C. Control cells were incubated with DMEM without PDGF. After the stimulation, the culture medium was aspirated, and cells were lyzed in Laemmli buffer.[9] Lysates were boiled for 5 min, and an equivalent amount of protein was loaded on a 7.5% SDS−PAGE. Proteins were electrophoretically transferred to PVDF membranes, preincubated in blocking buffer (phosphate-buffered saline containing 5% bovine serum albumin), and incubated with anti-phospho-Akt polyclonal antibodies (New England Biolabs). Immunoreactive bands were detected using an anti-rabbit antibody coupled to horseradish peroxidase and the Renaissance chemluminescence kit (NEN). Phosphorylation of Akt was quantified using Eagle Eye software (Biorad) and Kodak film.

For the cell growth inhibition studies MCF-7 (breast), HT-29 (colon), Hela (cervical), and PC-3 (prostate) cells were seeded into 12-well plates in DMEM supplemented with 10% FBS; 30 000 cells/well were plated, and after 16 h the drugs were added to the wells. After 3 days in DMEM/10% FBS in the absence or presence of different concentration of the drugs, cells were counted using a hemocytometer.

Modeling

The 3-modified inositol analogues in complex with the PH domain of Akt have been modeled using homology modeling and docking methods.[10,11] In cells, the PI analogues are likely to have undergone some level of phosphorylation at positions 4 and 5, and therefore we chose to use the phosphorylated analogues in the docking studies.[12] The complex models generated for the 4,5-bisphosphorylated derivatives of **5** and **6** are shown in Figure 2 and are further discussed in the following section.

Results and Discussion

Data for the five new PI analogues from the PI3-K and Akt activity studies are presented in Table 1 along with comparison data obtained previously for DPIEL (**1**). It is interesting to note that the PI analogues bearing a hydroxymethyl group at position 3 all exhibit some activity for the inhibition of Akt and PI3-K. The phosphate-containing analogues **2** and **3** show comparable Akt inhibitory activity, while **3** is slightly more potent than **2** in the inhibition of PI3-K. Among these newly synthesized compounds, the axial hydroxymethyl-bearing PI analogue **5** is the best inhibitor of Akt with an IC_{50} of 5.0 ± 1.9 μM, although it is about 3-fold less potent than **1**. Nevertheless, it is also important to notice that **5** is more specific than DPIEL for Akt inhibition. DPIEL exhibits an IC_{50} of 14.8 ± 5.6 μM as compared to 83.0 ± 21.0 μM for compound **5** in the inhibition of PI3-K. In fact, among all of these analogues, carbonate **5** is the least potent for inhibition of PI3-K. Positioning of the hydroxymethyl group in the equatorial orientation as in the carbonate **6** leads to a 6-fold reduction in Akt inhibitory activity compared to **5**. In terms of PI3-K inhibition, the equatorial carbonate **6** is more active than its axial counterpart **5**; this same trend is observed in comparing the phosphate analogues **3** versus **2**. In general, both carbonates are relatively poor inhibitors of PI3-K, which suggests the importance of the phosphate moiety to recognition by this enzyme.

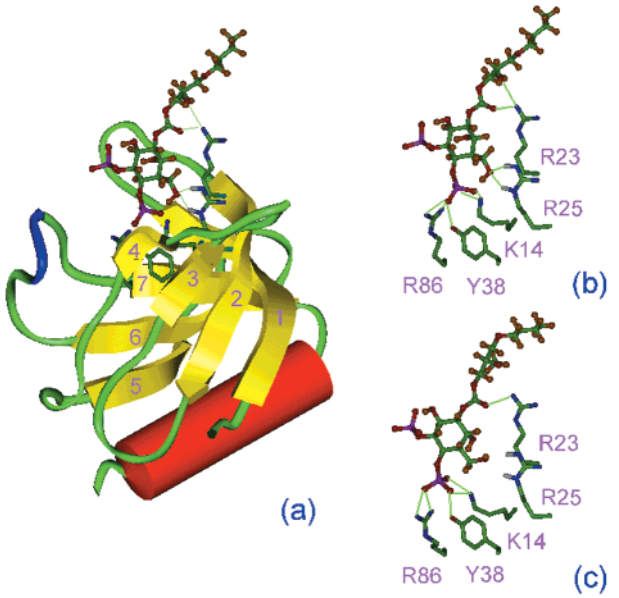


Figure 2. (a) Ribbon diagram of the PH domain of Akt in complex with the phosphorylation product of **5**. The β-strands, α-helix, turn, and coils are colored yellow, red, blue, and green, respectively. Homology modeling was done using the homology package of InsightII (Molecular Simulation, Inc., San Diego, CA) with the crystal structure of the Btk PH domain (PDB code: 1BWN) as the template. (b) Model of **5** in complex with the PH domain of Akt. (c) Model of **6** in complex with the PH domain of Akt. Hydrogen bonds are depicted in the figures. Docking was performed using the program FlexX.[11]

Table 1. IC_{50} Values for Inhibition of Akt and PI3-K Activity by Compounds **1**−**6**

	IC_{50} (μM)			IC_{50} (μM)	
compd	Akt	PI3-K	compd	Akt	PI3-K
1	1.5 ± 0.3	14.8 ± 5.6	**4**	12.5 ± 2.0	15.5 ± 1.8
2	7.8 ± 0.8	31.0 ± 7.0	**5**	5.0 ± 1.7	83.0 ± 21.0
3	9.1 ± 1.7	18.5 ± 1.7	**6**	32.0 ± 3.5	21.3 ± 7.6

The modeling results show that these 4,5-phosphorylated PI's interact in a complementary fashion with the positively charged pocket formed by the β1−β2 and β3−β4 loops of the PH domain of Akt (Figure 2a). The axial hydroxymethyl group in **5** is anchored through hydrogen bonds with Arg25 (Figure 2b), whereas the equatorial hydroxymethyl group in **6** is improperly situated to interact with Arg25, thus resulting in the loss of this H-bond interaction, as well as one additional H-bond between the headgroup and Arg23 (Figure 2c). The differences in the binding interactions may be used in a qualitative fashion to rationalize the differences in the activities of **5** and **6** for Akt inhibition. Further efforts to evaluate the accuracy of this model by utilizing it in the design of analogues of possibly improved Akt inhibitory activity are being made.

In terms of inhibition of cell growth of the various cell lines tested, the PI analogues **2**, **3**, and **5** generally proved to be slightly more potent than the others, with

Table 2. Effects of Compounds **1**−**6** on the Growth Inhibition of Cancer Cell Lines in Vitro

	IC_{50} (μM)			
compd	HT-29	MCF-7	Hela	PC-3
1	2.1	7.2	7.0	ND
2	4.5	5.0	1.0	4.0
3	7.5	2.0	7.5	2.0
4	2.5	12.0	30.0	7.0
5	10.0	1.2	2.5	2.0
6	12.0	12.5	>20.0	10.0

IC_{50} values in the 1−10 μM range (Table 2). It is likely that the cell growth inhibitory effects of these compounds are due to a combination of their PI3-K and Akt inhibitory activities, in addition to nonspecific effects on membrane structure. However, upon the basis of the present data set, growth inhibition appears to correlate best with the inhibition of the downstream target Akt. To the best of our knowledge, this work represents the first attempt to examine the effects of 3-modified PI analogues on these two crucial cell signaling proteins, in an effort to better understand their cell growth inhibitory properties.

In summary, we present the synthesis and biological activity of several novel phosphatidylinositol analogues and demonstrate the ability of the carbonate group to function as a surrogate for the phosphate moiety. The stereochemistry of the hydroxymethyl substituent at the 3-position is also shown to play some role in Akt and PI3-K inhibition. Of general interest is the finding that while deletion of the 3-hydroxy group from the inositol ring as in DPIEL leads to an antiproliferative agent, this activity is retained by an inositol homologue modified by insertion of a single carbon atom between the cyclohexane ring and the 3-OH. The present findings in concert with results gleaned from the modeling studies are being used to further improve compound potency and to simplify analogue design.

Experimental Section

General Methods. NMR spectra were acquired at a proton frequency of 300 MHz, using $CDCl_3$ as solvent unless noted otherwise. ^{1}H chemical shifts are reported with Me_4Si (δ = 0.00 ppm) or $CHCl_3$ (δ = 7.26 ppm) as internal standards. ^{31}P chemical shifts are relative to external aqueous 85% H_3PO_4 (δ = 0.00 ppm), and ^{13}C chemical shifts as reported with $CDCl_3$ (δ = 77.00 ppm) or TMS (δ = 0.00 ppm) as internal standards. Optical rotations were measured at room temperature. 1-*O*-Octadecyl-2-*O*-Me-*sn*-glycerol was prepared from (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol by a reported procedure.[6b]

1D-6-*O*-Benzyl-3-deoxy-1,2:4,5-di-*O*-isopropylidene-3-methylene-*myo*-inositol (8). To a solution of $(COCl)_2$ (0.50 mL, 5.50 mmol) in dry CH_2Cl_2 (5 mL) was added DMSO (0.8 mL, 9.30 mmol) in CH_2Cl_2 (3 mL) at −78 °C. After 15 min, a solution of **7** (1.60 g, 4.57 mmol) in CH_2Cl_2 (10 mL) was added dropwise at −78 °C, and stirring was continued for an additional 2 h. Et*N*i-Pr_2 (8 mL) was added, and the mixture was warmed slowly to room temperature. The organic phase was washed with H_2O (4 × 50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated, and the crude product was used for the next step without purification.

To a well-stirred suspesion of $CH_3(PPh_3)_3Br$ (4.20 g, 11.6 mmol) in THF (20 mL) was added dropwise *n*-BuLi (5 mL, 11.6 mmol) at 0 °C. After 1 h, a solution of the crude ketone in THF (20 mL) was added at −78 °C, and the mixture was allowed to warm to room temperature overnight. Et_2O (100 mL) was added, and the organic phase was washed with H_2O (50 mL) and brine (50 mL) and dried over $MgSO_4$. After concentration, the residue was purified by column chromatography on silica gel (EtOAc/hexanes 1:10) to give the product (850 mg, 54%): mp 110.5 °C; $[\alpha]_D$ −63.8° (*c* 0.77, $CHCl_3$); ^{1}H NMR δ 7.43−7.24 (m, 5H), 5.40 (d, 1H, *J* = 0.9 Hz), 5.31 (s, 1H), 4.84 (s, 2H), 4.64 (d, 1H, *J* = 5.7 Hz), 4.25 (d, 1H, *J* = 9.6 Hz), 4.19 (t, 1H, *J* = 6.0 Hz), 3.75 (dd, 1H, *J* = 10.5, 6.3 Hz), 3.39 (t, 1H, *J* = 10.2 Hz), 1.51 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H); ^{13}C NMR δ 138.28, 138.22, 128.16, 127.95, 127.43, 113.40, 112.19, 110.02, 81.97, 81.68, 80.89, 79.34, 76.12, 72.96, 27.75, 27.22, 26.91, 25.92.

1L-3-*O*-Benzyl-6-deoxy-6-(hydroxymethyl)-1,2:4,5-di-*O*-isopropylidene-*chiro*-inositol (9a) and 1D-6-*O*-Benzyl-3-deoxy-3-(hydroxymethyl)-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (9b). To a solution of compound **8** (1.80 g, 5.2 mmol) in anhydrous THF (20 mL) was added 9-BBN (2.0 g, 8.2 mmol) at room temperature under N_2. The mixture was stirred at room temperature for 12 h and at 50 °C for 2 h, then cooled in an ice bath. Ethanol (8 mL), 3 M NaOH (4 mL) and 35% H_2O_2 (4 mL) were added dropwise. The mixture was warmed to 50 °C for 1 h and evaporated, and H_2O (10 mL) was added. The product was extracted into CH_2Cl_2 (3 × 100 mL) and the organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexanes 1:2) to give **9a** (910 mg, 48%) and **9b** (790 mg, 42%). Compound **9a**: mp 113−114 °C; $[\alpha]_D$ −103.5° (*c* 0.68, $CHCl_3$); ^{1}H NMR δ 7.42−7.23 (m, 5H), 4.83 (s, 2H), 4.22 (d, 1H, *J* = 5.4 Hz), 4.12 (t, 1H, *J* = 6.0 Hz), 3.97 (dd, 1H, *J* = 10.2, 5.7 Hz), 3.91 (m, 1H), 3.85 (t, 1H, *J* = 9.9 Hz), 3.73 (m, 1H), 3.62 (dd, 1H, *J* = 9.9, 6.6 Hz), 2.85 (dd, 1H, *J* = 12.9, 5.4 Hz), 2.46 (d, 1H, *J* = 8.1 Hz), 1.46 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C NMR δ 138.19, 128.17, 127.97, 127.45, 111.24, 108.52, 80.99, 80.61, 77.01, 76.66, 76.17, 72.09. 60.73, 39.36, 27.77, 26.99, 26.77, 25.81. Anal. ($C_{20}H_{28}O_6$) C, H. Compound **9b:** mp 117 °C; $[\alpha]_D$ −63.5° (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 7.42−7.23 (m, 5H), 4.83 (s, 2H), 4.42 (t, 1H, *J* = 4.5 Hz), 4.16 (t, 1H, *J* = 6.3 Hz), 3.97 (dd, 1H, *J* = 11.4, 5.4 Hz), 3.89 (m, 1H), 3.76 (dd, 1H, *J* = 10.8, 9.0 Hz), 3.63 (dd, 1H, *J* = 10.5, 6.6 Hz), 3.46 (t, 1H, *J* = 9.6 Hz), 2.28 (m, 1H), 2.14 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.33 (s, 6H); ^{13}C NMR δ 138.22, 128.16, 127.96, 127.43, 111.99, 109.63, 106.57, 81.67, 81.37, 80.35, 77.06, 74.97, 71.97, 62.22, 41.67, 27.84, 27.08, 27.03, 25.92. Anal. ($C_{20}H_{28}O_6$) C, H.

1L-3-*O*-Benzyl-6-deoxy-6-[(1′-(*S*)-(camphanoyloxy)-methyl]-*chiro*-inositol (10). To a solution of **9a** (50 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) were added, under N_2, Et_3N (130 μL, 0.72 mmol), DMAP (10 mg), and (1*S*)-(−)-camphanic chloride (61 mg, 0.28 mmol). The mixture was then stirred for 18 h at room temperature. CH_2Cl_2 (50 mL) was added and the solution was washed with 5% HCl (10 mL), aqueous $NaHCO_3$ (10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexane 1:2) to give the ester: ^{1}H NMR δ 7.35 (m, 5H), 4.83 (s, 2H), 4.53 (dd, 1H, *J* = 4.2, 11.7 Hz), 4.34 (d, 1H, *J* = 5.4 Hz), 4.29−4.20 (m, 2H), 3.94 (dd, 1H, *J* = 5.7, 9.9 Hz), 3.69−3.60 (br m, 2H), 2.93 (m, 1H), 2.43 (m, 1H), 2.09−1.87 (br m, 2H), 1.74−1.62 (br m, 2H), 1.46 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H).

To a solution of the ester in MeOH (2 mL) was added concentrated HCl (2 drops) at room temperature, and the solution was stirred for 2 h. The solvent was evaporated, and the residue was crystallized from EtOAc/EtOH (5 mL, 4:1). The resulting crystalline solid was analyzed by X-ray diffraction.

1L-3-*O*-Benzyl-6-deoxy-6-(benzyloxymethyl)-1,2-*O*-isopropylidene-*chiro*-inositol (11a) and 1D-6-*O*-Benzyl-3-deoxy-3-(benzyloxymethyl)-1,2-*O*-isopropylidene-*myo*-inositol (11b). To a suspension of NaH (56 mg, 1.41 mmol) in DMF (5 mL) was added a solution of compound **9a** (343 mg, 0.94 mmol) in DMF (5 mL) at 0 °C. After 30 min, BnBr (0.16 mL, 1.41 mmol) was added dropwise. The mixture was stirred overnight, then poured into ice water and extracted with EtOAc (3 × 50 mL). The organic phase was washed with H_2O

(50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was used direactly in the next step.

To a solution of the above crude product in CH_2Cl_2/MeOH (12 mL, 5:1) was added acetyl chloride (3 drops). The mixture was stirred under close TLC control for 20 min, then the reaction was quenched with Et_3N (100 μL). After evaporation, the residue was purified by column chromatography on silica gel (EtOAc/hexane 1:2) to give product (278 mg, 72%): ^{1}H NMR δ 7.32 (m, 10H), 4.92, 4.62 (ABq, 2H, J = 11.7 Hz), 4.49, 4.43 (ABq, 2H, J = 12.0 Hz), 4.27 (m, 2H), 3.94 (dd, 1H, J = 7.8, 5.4 Hz), 3.75 (m, 2H), 3.60 (dd, 1H, J = 9.3, 4.8 Hz), 3.44 (t, 1H, J = 7.2 Hz), 3.32 (s, 1H), 3.07 (s, 1H), 2.46 (m, 1H), 1.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR δ 138.32, 137.75, 128.31, 128.24, 127.94, 127.57, 127.54, 127.38, 108.33, 83.24, 79.50, 75.59, 73.22, 72.89, 70.37, 67.21, 40.39, 27.97, 25.84. Anal. ($C_{24}H_{30}O_6$) C, H. Compound **11b** was prepared in the same manner in 64% yield: mp 66−67 °C; $[\alpha]_D$ +2.8° (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 7.34 (br m, 10H), 4.98, 4.69 (ABq, 2H, J = 11.7 Hz), 4.57, 4.52 (ABq, 2H, J = 12.0 Hz), 4.34 (t, 1H, J = 4.5 Hz), 4.10 (t, 1H, J = 6.9 Hz), 3.93 (dd, 1H, J = 9.0, 6.9 Hz), 3.75 (t, 1H, J = 8.1 Hz), 3.68 (t, 1H, J = 10.2 Hz), 3.43 (m, 3H), 2.92 (s, 1H), 2.14 (m, 1H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 138.17, 137.82, 128.32, 128.30, 127.97, 127.65, 127.62, 127.47, 108.89, 82.06, 79.92, 75.33, 74.06, 73.33, 73.30, 70.63, 69.94, 41.12, 28.12, 26.03. Anal. ($C_{24}H_{30}O_6$) C, H.

1L-1,2,3-*O*-Benzyl-6-deoxy-6-(benzyloxymethyl)-*chiro*-inositol (12a) and 1D-4,5,6-*O*-Benzyl-3-deoxy-3-(benzyloxymethyl)-*myo*-inositol (12b). To a suspension of NaH (81 mg, 2.01 mmol) in DMF (2 mL) was added a solution of compound **11a** (278 mg, 0.67 mmol) in DMF (3 mL) at 0 °C. After 30 min, BnBr (0.24 mL, 2.01 mmol) was added dropwise and the solution was stirred for 5 h. The mixture was poured into ice water and extracted with EtOAc (3 × 50 mL). The organic phase was washed with H_2O (50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was used directly in the next step.

To a solution of the above crude product in MeOH (20 mL) was added concentrated HCl (0.10 mL) at room temperature and the solution was stirred for 24 h. After evaporation, the residue was purified by column chromatography on silica gel (EtOAc/hexane 1:1) to give the product (333 mg, 90%): ^{1}H NMR δ 7.30 (m, 20H), 4.88, 4.63 (ABq, 2H, J = 11.4 Hz), 4.83, 4.69 (ABq, 2H, J = 11.1 Hz), 4.59 (s, 2H), 4.51, 4.48 (ABq, 2H, J = 12.3 Hz), 4.18 (s, 1H), 4.02 (dd, 1H, J = 7.8, 6.0 Hz), 3.88 (m, 1H), 3.79−3.58 (br m, 4H), 2.57 (m, 3H); ^{13}C NMR δ 138.50, 138.42, 138.11, 128.55, 128.37, 128.34, 128.27, 127.94, 127.84, 127.81, 127.68, 127.61, 127.57, 127.51, 81.22, 82.80, 78.36, 74.78, 74.69, 73.19, 72.60, 71.50, 69.75, 67.11, 41.21. Compound **12b** was prepared in the same manner in 98% yield: mp 103−104 °C; $[\alpha]_D$ +10.8° (*c* 3.2, $CHCl_3$); ^{1}H NMR δ 7.30 (m, 20H), 4.94, 4.91 (ABq, 2H, J = 11.1 Hz), 4.92, 4.50 (ABq, 2H, J = 11.1 Hz), 4.89, 4.79 (ABq, 2H, J = 11.1 Hz), 4.49, 4.48 (ABq, 2H, J = 12.6 Hz), 4.25 (m, 1H), 4.34−3.81 (m, 3 H), 3.73 (dd, 1H, J = 9.0, 3.0 Hz), 3.58−3.49 (m, 2H), 3.33 (s, 1H), 2.41 (d, 1H, J = 5.1 Hz), 1.75 (m, 1H); ^{13}C NMR δ 138.58, 138.29, 137.50, 137.49, 128.49, 128.37, 127.96, 127.88, 127.71, 127.63, 127.51, 86.50, 82.26, 77.30, 75.61, 75.48, 75.40, 74.50, 73.47, 70.79, 68.71, 43.35. Anal. ($C_{35}H_{38}O_6$) C, H.

1L-2-Allyl-3,4,5-*O*-Benzyl-6-deoxy-6-(benzyloxymethyl)-*chiro*-inositol and 1D-1-Allyl-4,5,6-*O*-Benzyl-3-deoxy-3-(benzyloxymethyl)-*myo*-inositol. A solution of compound **12a** (333 mg, 0.60 mmol) in toluene (10 mL) was refluxed with Bu_2SnO (179 mg, 0.72 mmol) until a clear solution was obtained (approximately 2 h). The solution was evaporated, and the residue was dried in vacuo and taken up in 5 mL of dry DMF. To this solution were added CsF (300 mg, 1.9 mmol) and allyl bromide (90 μL, 1.04 mmol) at −50 °C. The mixture was warmed to room temperature overnight, then poured into ice water and extracted with EtOAc (3 × 50 mL). The organic phase was washed with H_2O (3 × 50 mL) and brine (50 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 1:3) to give the product (310 mg, 87%): $[\alpha]_D$ −21.7° (*c* 1.14, $CHCl_3$); ^{1}H NMR δ 7.31 (m, 20H), 5.91 (m, 1H), 5.26 (dd, 1H, J = 17.1, 1.5 Hz), 5.17 (d, 1H, J = 10.2 Hz), 4.85, 4.77 (ABq, 2H, J = 10.8 Hz), 4.80 (s, 2H), 4.63 (s, 2H), 4.53, 4.46 (ABq, 2H, J = 12.3 Hz), 4.26 (s, 1H), 4.14 (d, 2H, J = 5.4 Hz), 4.04 (dd, 1H, J = 9.3, 6.3 Hz), 3.81−3.66 (m, 4H), 3.53 (t, 1H, J = 8.4 Hz), 2.67 (m, 1H), 2.56 (s, 1H); ^{13}C NMR δ 138.95, 138.86, 138.63, 138.18, 134.74, 128.40, 128.31, 128.29, 128.27, 128.03, 127.92, 127.64, 127.61, 127.50, 127.42, 117.25, 82.79, 81.75, 80.20, 78.38, 75.83, 75.52, 73.13, 72.78, 71.71, 68.44, 66.39. 41.44. Anal. ($C_{38}H_{42}O_6$) C, H. **1D-1-Allyl-4,5,6-*O*-Benzyl-3-deoxy-3-(benzyloxymethyl)-*myo*-inositol** was prepared in the same manner in 77% yield: ^{1}H NMR δ 7.33 (m, 20H), 6.01 (m, 1H), 5.36 (dd, 1H, J = 17.4, 1.2 Hz), 5.24 (d, 1H, J = 10.5 Hz), 4.99−4.86 (m, 5H), 4.56 (d, 2H), 4.52 (s, 1H), 4.38 (s, 1H), 4.26 (m, 2H), 4.02 (t, 1H, J = 9.3 Hz), 3.99−3.79 (m, 3H), 3.60 (t, 1H, J = 9.3 Hz), 3.40 (dd, 1H, J = 9.6, 2.7 Hz), 3.09 (s, 1H), 1.81 (m, 1H).

1L-2-Allyl-1,3,4,5-*O*-Benzyl-6-deoxy-6-(benzyloxymethyl)-*chiro*-inositol (13a) and 1D-1-Allyl-2,4,5,6-*O*-Benzyl-3-deoxy-3-(benzyloxymethyl)-*myo*-inositol (13b). To a suspension of NaH (32 mg, 0.78 mmol) in DMF (5 mL) was added dropwise the above product (310 mg, 0.52 mmol) in DMF (5 mL) at 0 °C. After 30 min, BnBr (93 μL, 0.78 mmol) and *n*-Bu_4NI (20 mg) were added, and the solution was stirred overnight. The mixture was poured into ice water (20 mL) and extracted with Et_2O (3 × 30 mL). The organic phase was washed with H_2O (30 mL) and brine (30 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 1:4) to give the product **13a** (356 mg, 99%): ^{1}H NMR δ 7.30 (m, 25H), 5.94 (m, 1H), 5.26 (dd, 1H, J = 17.4, 1.5 Hz), 5.14 (dd, 1H, J = 10.2, 1.2 Hz), 4.89, 4.79 (ABq, 2H, J = 10.5 Hz), 4.86, 4.82 (ABq, 2H, J = 10.8 Hz), 4.74, 4.54 (ABq, 2H, J = 12.0 Hz), 4.59, 4.54 (ABq, 2H, J = 11.4 Hz), 4.50, 4.40 (ABq, 2H, J = 12.0 Hz), 4.08 (m, 3H), 4.00−3.89 (br m, 2H), 3.71 (dd, 1H, J = 8.4, 4.5 Hz), 3.62−3.56 (m, 2H), 3.38 (t, 1H, J = 9.9 Hz), 2.65 (m, 1H); ^{13}C NMR δ 138.96, 138.87, 138.53, 138.17, 135.13, 128.37, 128.29, 128.26, 128.19, 128.16, 127.90, 127.82, 127.58, 127.55, 127.48, 127.41, 127.35, 83.09, 81.97, 79.64, 78.42, 75.94, 75.70, 74.89, 73.06, 72.78, 72.51, 71.64, 66.62, 40.35. Compound **13b** was prepared in the same manner in 99% yield: ^{1}H NMR δ 7.35−7.17 (m, 25H), 5.96 (m, 1H), 5.34 (dd, 1H, J = 17.4, 1.5 Hz), 5.17 (dd, 1H, J = 10.8, 0.9 Hz), 4.98, 4.82 (ABq, 2H, J = 11.1 Hz), 4.94, 4.82 (ABq, 2H, J = 10.5 Hz), 4.84. 4.72 (ABq, 2H, J = 10.5 Hz), 4.51, 4.43 (ABq, 2H, J = 13.8 Hz), 4.40 (s, 2H), 4.20 (t, 2H, J = 5.4 Hz), 4.16 (m, 1H), 4.00 (t, 1H, J = 9.0 Hz), 3.69−3.44 (br m, 4H). 3.36 (dd, 1H, J = 9.9, 2.1 Hz), 1.87 (m, 1H).

1L-1,3,4,5-*O*-Benzyl-6-deoxy-6-(benzyloxymethyl)-*chiro*-inositol (14a) and 1D-2,4,5,6-*O*-Benzyl-3-deoxy-3-(benzyloxymethyl)-*myo*-inositol (14b). A solution of compound **13a** (356 mg, 0.52 mmol) in EtOH (10 mL) was refluxed with RhCl(PPh_3)$_3$ (25 mg, 0.026 mmol) and DABCO (147 mg, 1.3 mmol) for 5 h. After evaporation, Et_2O (100 mL) was added, and the organic phase was washed with 3 N HCl (20 mL), H_2O (20 mL) and brine (20 mL) and dried over $MgSO_4$. After concentration, the residue was dissolved in acetone/1 N HCl (20 mL, 9:1) and the solution was refluxed for 4 h. After evaporation, Et_2O (100 mL) was added and the solution was washed with aqueous $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel (EtOAc/hexane 1:4) to give the product **14a** (294 mg, 88%): $[\alpha]_D$ −14.6° (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 7.31 (m, 25H), 4.84, 4.80 (ABq, 2H, J = 11.1 Hz), 4.83, 4.74 (ABq, 2H, J = 10.5 Hz), 4.60, 4.54 (ABq, 2H, J = 11.7 Hz), 4.51, 4.49 (ABq, 2H, J = 8.4 Hz), 4.50, 4.48 (ABq, 2H, J = 8.4 Hz), 4.02 (t, 1H, J = 3.0 Hz), 4.01−3.87 (m, 2H). 3.75−3.60 (br m, 3H), 3.46 (t, 1H, J = 9.3 Hz), 2.65 (m, 1H), 2.40 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 138.75, 138.68, 138.41, 138.21, 138.10, 128.38, 128.36, 128.32, 127.99, 127.95, 127.89, 127.68, 127.61, 127.53, 127.44, 82.87, 82.21, 78.10, 75.41, 73.19, 72.80, 72.18, 71.74, 66.48, 39.50. Anal. ($C_{42}H_{44}O_6$) C, H. Compound **14b** was prepared in the same manner in 100% yield: $[\alpha]_D$ +20.2° (*c* 4.6, $CHCl_3$); ^{1}H NMR δ 7.27 (m, 25H), 4.93, 4.82 (ABq, 2H, J = 10.8 Hz), 4.89 (s, 2H), 4.82, 4.74 (ABq,

2H, J = 11.1 Hz), 4.53, 4.45 (ABq, 2H, J = 11.4 Hz), 4.42, 4.40 (ABq, 2H, J = 12.0 Hz), 4.13 (m, 1H), 3.83 (t, 1H, J = 9.3 Hz), 3.70 (dd, 1H, J = 8.7, 4.2 Hz), 3.64 (m, 1H), 3.60−3.52 (m, 2H), 3.48 (t, 1H, J = 9.0 Hz), 2.18 (d, 1H, J = 4.2 Hz), 1.96 (m, 1H); ^{13}C NMR δ 139.06, 138.46, 138.13, 138.08, 128.53, 128.38, 128.34, 128.33, 128.19, 128.01, 127.94, 127.82, 127.76, 127.68, 127.59, 127.55, 127.37, 86.69, 82.10, 78.72, 75.80, 75.53, 75.49, 75.16, 75.15, 73.07, 67.08, 44.13. Anal. ($C_{42}H_{44}O_6$) C, H.

1L-1,3,4,5-*O*-Benzyl-6-deoxy-6-(benzyloxymethyl)-*chiro*-inositol 2-[Benzyl (*R*)-2-*O*-methyl-3-*O*-octadecyl phosphate] (15a) and 1D-2,4,5,6-*O*-Benzyl-3-deoxy-3-(benzyloxymethyl)-*myo*-inositol 2-[Benzyl (*R*)-2-*O*-methyl-3-*O*-octadecyl phosphate] (15b). To a suspension of diisopropylammonium tetrazolide (80 mg, 0.46 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise under N_2 at room temperature *O*-benzyl-*N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite (0.23 mL, 0.64 mmol), followed by a solution of compound **14a** (274 mg, 0.42 mmol) in dry CH_2Cl_2 (3 mL). The mixture was stirred overnight at room temperature, then aqueous $NaHCO_3$ solution (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel previously deactivated with Et_3N (1 mL) (EtOAc/hexane 1:4) to give the phosphoramidite intermediate which was used directly in the next step.

To a solution of 2-*O*-methyl-1-*O*-octadecyl-*sn*-glycerol (150 mg, 0.42 mmol) and 1*H*-tetrazole (50 mg, 0.7 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of the preceding phosphoramidite in dry CH_2Cl_2 (3 mL) under N_2 at room temperature. The mixture was stirred overnight at room temperature, then aqueous $NaHCO_3$ solution (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and evaporated. The residue was used directly in the next step.

To a solution of the preceding phosphite in dry CH_2Cl_2 (10 mL) was added *t*-BuOOH (0.15 mL, 0.64 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 4 h. The solvent was evaporated, and the product was isolated by column chromatography on silica gel (EtOAc/hexane 1:3) to yield **15a** (270 mg, 55%): $[\alpha]_D$ −4.4° (*c* 0.82, $CHCl_3$); ^{1}H NMR δ 7.25 (m, 30H), 5.05−4.42 (m, 12H), 4.25 (m, 1H), 4.08−3.98 (m, 4H), 3.79 (t, 1H, J = 9.0 Hz), 3.59 (m, 2H), 3.40−3.27 (br m, 8H), 2.52 (m, 1H), 1.48 (m, 2H), 1.26 (m, 30H), 0.88 (t, 3H, J = 6.0 Hz); ^{13}C NMR δ 138.72, 138.61, 138.51, 138.45, 138.38, 138.08, 136.05, 136.03, 128.37, 128.32, 128.27, 128.22, 128.19, 128.14, 127.95, 127.80, 127.65, 127.57, 127.41, 82.45, 80.29, 78.43 (J = 7.6 Hz), 77.98, 77.42, 75.49, 73.20, 72.89, 72.77, 71.69, 69.47, 68.95 (J = 5.4 Hz), 67.89, 66.52, 66.48, 57.87, 40.39, 31.87, 29.65, 29.61, 29.56, 29.51, 29.45, 29.31, 25.98, 22.64, 14.08; ^{31}P NMR δ −0.95, −1.04. Anal. ($C_{71}H_{95}O_{11}P$) C, H. Compound **15b** was prepared in the same manner in 38% yield: $[\alpha]_D$ +21.0° (*c* 0.80, $CHCl_3$); ^{1}H NMR δ 7.28 (m, 30H), 5.06−4.78 (br m, 8H), 4.50 (d, 1H, J = 10.8 Hz), 4.45−4.33 (m, 5H), 4.13−3.97 (br m, 3H), 3.66−3.52 (br m, 3H), 3.43−3.28 (br m, 9H), 1.92 (m, 1H), 1.48 (m, 2H), 1.26 (m, 30H), 0.88 (t, 3H, J = 6.3 Hz); ^{13}C NMR δ 138.90, 138.53, 138.49, 138.37, 138.10, 138.08, 128.48, 128.43, 128.35, 128.19, 128.15, 128.12, 128.03, 127.81, 127.74, 127.71, 127.65, 127.63, 127.56, 127.36, 86.27, 81.70, 80.42, 78.67 (J = 7.6 Hz), 77.96, 75.83, 75.50, 75.39, 75.32, 75.20, 73.05, 71.79, 69.36 (J = 6.0 Hz), 69.07, 66.79, 66.57, 57.93, 43.54, 30.89, 29.68, 29.63, 29.59, 29.54, 29.47, 29.33, 26.01, 25.74, 22.66, 14.11; ^{31}P NMR δ −0.74, −0.92. Anal. ($C_{71}H_{95}O_{11}P$) C, H.

1L-6-Hydroxymethyl-*chiro*-inositol 2-[(*R*)-2-*O*-Methyl-3-*O*-octadecyl hydrogen phosphate] (2) and 1D-3-Hydroxymethyl-*myo*-inositol 1-[(*R*)-2-*O*-Methyl-3-*O*-octadecyl hydrogen phosphate] (3). A solution of compound **15a** (280 mg, 0.242 mmol) in *t*-BuOH (10 mL) was hydrogenated for 5 h in a Parr shaker under 60 psi of H_2 at room temperature, using 20% $Pd(OH)_2$/C (103 mg) as catalyst. The catalyst was filtered off through a Celite pad, and the filtrate was evaporated. The residue was dried in vacuo to give a white powder (131 mg, 88%): mp 64 °C dec; $[\alpha]_D$ −18.8° (*c* 1.92, $CHCl_3$/MeOH 1:1); ^{1}H NMR ($CDCl_3$/CD_3OD 1:1, TMS) δ 4.34−4.07 (m, 4H), 4.01 (dd, 1H, J = 9.3, 6.0 Hz), 3.87 (dd, 1H, J = 11.7, 5.1 Hz), 3.80 (t, 1H, J = 8.7 Hz), 3.64−3.45 (m, 10H), 2.37 (m, 1H), 1.58 (m, 2H), 1.27 (m, 30H), 0.89 (t, 3H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD 1:1) δ 79.95 (J = 6.0 Hz), 79.53 (J = 7.6 Hz), 74.87, 72.64 (J = 5.5 Hz), 72.43, 70.52, 69.91, 69.57, 66.73 (J = 5.5 Hz), 59.21, 58.19, 47.31, 32.48, 30.94, 30.23, 30.19, 30.09, 30.05, 29.90, 26.58, 23.20, 14.35; ^{31}P NMR δ −0.09. Anal. ($C_{29}H_{59}O_{11}P\cdot 0.3H_2O$) C, H. Compound **3** was prepared in the same manner in 88% yield: mp 60−61 °C; $[\alpha]_D$ −4.9° (*c* 0.42, $CHCl_3$/MeOH 1:1); ^{1}H NMR ($CDCl_3$/CD_3OD 2:1, TMS) δ 4.29 (m, 1H), 4.17−3.82 (m, 5H), 3.73 (t, 1H, J = 9.6 Hz), 3.60−3.44 (m, 8H), 3.35 (m, 1H), 3.39 (t, 1H, J = 8.7 Hz),1.58 (m, 3H), 1.27 (m, 30H), 0.89 (t, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD 2:1) δ 81.33, 79.41, 78.05, 72.32, 71.89, 69.97, 69.75, 69.44, 66.49, 61.75, 58.09, 44.73, 32.30, 30.88, 30.06, 30.01, 29.91, 29.87, 29.73, 26.40, 23.04, 14.24; ^{31}P NMR (DMSO-d_6) δ 0.02. Anal. ($C_{29}H_{59}O_{11}P\cdot 2H_2O$) C, H.

1L-1,3,4,5-*O*-Benzyl-6-deoxy-6-(benzyloxymethyl)-*chiro*-inositol 2-[Benzyl (*R*)-2-*O*-methyl-3-*O*-octadecylcarbonate] (17a) and 1D-2,4,5,6-*O*-Benzyl-3-deoxy-3-(benzyloxymethyl)-*myo*-inositol 2-[Benzyl (*R*)-2-*O*-methyl-3-*O*-octadecylcarbonate] (17b). To a solution of compound **14a** (60 mg, 94 μmol) in toluene (2 mL) was added 1,1′-carbonyldiimidazole (24 mg, 0.14 mmol), and the mixture was refluxed for 40 min. The mixture was cooled to room temperature and diluted with EtOAc (30 mL). The solution was washed with H_2O (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated. The crude product was used directly in the next step.

To a solution of the above crude product in toluene (2 mL) was added DBU (17 μL, 0.010 mmol) and 2-*O*-methyl-1-*O*-octadecyl-*sn*-glycerol (35 mg, 0.10 mmol). The mixture was refluxed for 4 h, then evaporated and the product was isolated by column chromatography on silica gel (EtOAc/hexane 1:10) to yield the product (52 mg, 54%): $[\alpha]_D$ −15.8° (*c* 2.32, $CHCl_3$); ^{1}H NMR δ 7.10 (m, 25 H), 5.11 (dd, 1H, J = 10.2, 2.7 Hz), 4.84, 4.76 (ABq, 2H, J = 10.5 Hz), 4.82, 4.76 (ABq, 2H, J = 10.8 Hz), 4.60, 4.50 (ABq, 2H, J = 11.7 Hz), 4.51 (s, 2H), 4.54, 4.48 (ABq, 2H, J = 11.7 Hz), 4.27 (dd, 1H, J = 11.1, 3.9 Hz), 4.18 (d, 1H, J = 5.7 Hz), 4.13 (m, 1H), 4.04−3.96 (br m, 2H), 3.78 (t, 1H, J = 9.0 Hz), 3.67 (dd, 1H, J = 9.9, 4.2 Hz), 3.56−3.38 (br m, 9 H), 2.59 (m, 1H), 1.57 (m, 2H), 1.25 (m, 30H), 0.88 (t, 3H, J = 6.3 Hz); ^{13}C NMR δ 154.81, 138.72, 138.56, 138.40, 138.33, 138.09, 128.36, 128.31, 128.29, 128.25, 127.98, 127.84, 127.73, 127.59, 127.54, 127.51, 127.42, 82.85, 80.01, 78.16, 78.01, 77.93, 76.07, 75.65, 75.55, 73.31, 72.84, 72.67, 71.85, 69.71, 67.29, 66.42, 58.10, 40.68, 31.90, 29.68, 29.59. 29.48, 29.34, 29.20, 26.05, 22.68, 14.12. Compound **17b** was prepared in the same manner in 89% yield: $[\alpha]_D$ +12.3° (*c* 1.45, $CHCl_3$); ^{1}H NMR δ 7.28 (m, 25 H), 4.92−4.75 (br m, 7H), 4.46−4.35 (br m, 4H), 4.28 (dd, 1H, J = 11.4, 3.9 Hz), 4.22 (m, 1H), 4.19 (dd, 1H, J = 11.4, 5.7 Hz), 4.06 (t, 1H, J = 9.0 Hz), 3.69−3.37 (m, 12H), 2.01 (m, 1H), 1.54 (m, 2H), 1.25 (bm, 30H), 0.88 (t, 3H, J = 6.3 Hz); ^{13}C NMR δ 154.80, 138.59, 138.44, 138.10, 138.06, 128.36, 128.27, 128.17, 128.01, 127.81, 127.76, 127.71, 127.63, 127.49, 127.45, 86.34, 80.90, 80.08, 78.06, 77.98, 76.58, 75.81, 75.65, 75.22, 74.44, 73.08, 71.85, 69.59, 67.41, 66.82, 58.06, 43.72, 31.90, 29.68, 29.58, 29.47, 29.33, 26.03, 22.67, 24.11. Anal. ($C_{65}H_{88}O_{10}$) C, H.

1L-6-Hydroxymethyl-*chiro*-inositol 2-[(*R*)-2-*O*-Methyl-3-*O*-octadecylcarbonate] (5) and 1D-3-Hydroxymethyl-*myo*-inositol 1-[(*R*)-2-*O*-Methyl-3-*O*-octadecylcarbonate] (6). A solution of compound **17a** (60 mg, 0.058 mmol) in *t*-BuOH (5 mL) was hydrogenated for 6 h in a Parr shaker under 60 psi of H_2 at room temperature, using 20% $Pd(OH)_2$/C (30 mg) as catalyst. The catalyst was filtered off through a Celite pad, and the filtrate was evaporated. The residue was dried in vacuo to give white powder (28 mg, 83%): mp 62 °C dec; $[\alpha]_D$ −25.8° (*c* 0.96, $CHCl_3$/MeOH 1:1); ^{1}H NMR ($CDCl_3$/CD_3OD 1:1, TMS) δ 4.37 (m, 1H), 4.32 (dd, 1H, J = 11.7, 3.9 Hz), 4.25 (t, 1H, J = 3.0 Hz), 4.19(dd, 1H, J = 11.4, 5.7 Hz), 4.01 (dd, 1H, J = 9.3, 5.7 Hz), 3.91 (dt, 1H, J = 11.1, 5.4 Hz), 3.82 (d, 1H, J = 9.6 Hz), 3.64−3.34 (m, 10H), 2.38 (m, 1H),

1.58 (m, 2H), 1.27 (m, 30H), 0.89 (t, 3H, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3/CD_3OD$ 1:1) δ 155.65, 79.44, 78.67, 75.00, 72.40, 71.73, 70.68, 69.95, 68.33, 67.66, 59.47, 58.13, 47.59, 32.47, 30.90, 30.21, 30.07, 30.00, 29.89, 26.58, 23.19, 14.28. Anal. ($C_{30}H_{58}O_{10}\cdot 0.5H_2O$) C, H. Compound **6** was prepared in the same manner in 72% yield: $[\alpha]_D$ −15.8° (*c* 0.74, $CHCl_3$/MeOH 1:1); ^{1}H NMR ($CDCl_3/CD_3OD$ 2:1, TMS) δ 4.35−4.29 (m, 2H), 4.20 (dd, 1H, $J = 11.4$, 5.7 Hz), 3.97−3.85 (m, 3H), 3.74 (t, 1H, $J = 9.6$ Hz), 3.63 (m, 1H), 3.55−3.29 (m, 9H), 1.58 (m, 3H), 1.27 (m, 30H), 0.89 (t, 3H, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3/CD_3OD$ 2:1) δ 155.36, 80.96, 78.41, 78.12, 72.31, 70.82, 69.86, 69.29, 68.58, 67.54, 61.62, 58.11, 44.78, 32.39, 30.68, 30.03, 29.88, 29.82, 29.71, 26.39, 23.01, 14.24. Anal. ($C_{30}H_{58}O_{10}\cdot 0.5H_2O$) C, H.

Compound **4** was prepared from 1D-2,4,5,6-tetra-*O*-benzyl-3-deoxy-*myo*-inositol [5e] in the same manner: $[\alpha]_D$ −28.3° (*c* 1.30, $CHCl_3$/MeOH 1:1); ^{1}H NMR ($CDCl_3/CD_3OD$ 1:1, TMS) δ 4.49 (dd, 1H, $J = 9.9$, 3.0 Hz), 4.32 (dd, 1H, $J = 11.4$, 3.6 Hz), 4.21 (m, 2H), 3.83 (t, 2H, $J = 9.3$ Hz), 3.63 (m, 1H), 3.55 (m, 2H), 3.49 (m, 5H), 3.26 (t, 1H, $J = 9.0$ Hz), 2.13 (dt, 1H, $J = 4.5$, 14.1 Hz), 1.56 (m, 3H), 1.40−1.25 (m, 30H), 0.89 (t, 3H, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3/CD_3OD$ 1:1) δ 155.49, 81.32, 78.55, 72.36, 71.04, 69.84, 68.46, 67.60, 66.39, 58.11, 35.84, 32.37, 30.12, 30.05, 29.98, 29.91, 29.80, 26.49, 23.10, 14.25. Anal. ($C_{29}H_{56}O_9$) C, H.

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Supporting Information Available: X-ray structural data for **10** is available free of charge via the Internet at http://pubs.acs.org.

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(12) Full details of our Akt PH domain model will be published separately.

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