Intracellular Mediators: Synthesis of L-α-Phosphatidyl-D-*myo*-inositol 3,4,5-Trisphosphate and Glyceryl Ether Analogs

K. Kishta Reddy, Mourad Saady, and J. R. Falck*

Departments of Molecular Genetics and Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75235

Gregg Whited

Genencor International, Inc., South San Francisco, California 94089

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L-α-Phosphatidyl-D-*myo*-inositol 3,4,5-trisphosphate (3,4,5-PIP_3), the most prominent member of a new class of intracellular second messengers, and two ether analogs were conveniently prepared from the differentially functionalized D-*myo*-inositol intermediate **7** which was ultimately derived from the unique cyclitol precursor dehydroshikimic acid (**1**). Critical transformations included the stereoselective hydride reduction of the shikimate ketone, exclusive osmylation from the α-face to give **3**, controlled enolization of **4**, and dioxirane epoxidation with in situ rearrangement affording ketone **5**. Dioctanoyl 3,4,5-PIP_3 (**9a**) and its dioctyl ether analog **9b** selectively activated the δ, ϵ, and η-isotypes of protein kinase C (PKC).

Introduction

Recent studies[1] have revealed that activation and/or translocation of phosphatidylinositol (PI) 3-kinase is a central event in cellular stimulation by growth factors, insulin, and other mitogens. The products of phosphatidylinositol 3-kinase include phosphatidylinositol 3-phosphate (3-PIP), L-α-phosphatidyl-D-*myo*-inositol 3,4-bisphosphate (3,4-PIP_2), and L-α-phosphatidyl-D-*myo*-inositol 3,4,5-trisphosphate (3,4,5-PIP_3). The former is present in some quiescent cells, whereas the latter two are virtually undetectable until stimulation.[2] Importantly, these lipidic autacoids, in contrast with the PIs of the canonical turnover pathway, are not enzymatically hydrolyzed to lower molecular weight second messengers but instead are thought to directly regulate other cell components, e.g., actin, protein kinase C (PKC), and c-fos. The overall cascade constitutes a novel, metabolically distinct conduit for intracellular signal transduction[3] and, accordingly, offers some unique opportunities for pharmacologic intervention in cell physiology. As part of a comprehensive program[4] to elucidate the structure and mechanism of the action of biogenic cyclitols, we describe herein an enantioselective total synthesis of L-α-phosphatidyl-D-*myo*-inositol 3,4,5-trisphosphate[5] (**10a**) to help alleviate the critical shortfall of material isolable from natural sources. To expedite current in vitro studies, we also report on the preparation of two glyceryl ether analogs, **10b,d**.

Results and Discussion

Our strategy as outlined in Scheme 1 was based on a stereocontrolled elaboration of the commercial, but underutilized, chiral cyclitol precursor dehydroshikimic acid (**1**). Taking care to avoid excess reagent or prolonged reaction times, **1** was esterified with diazomethane, silylated under standard conditions, and then stereoselectively reduced[6] using lithium tri-*tert*-butoxyaluminohydride at 0 °C to give **2** whose structure was confirmed by desilylation and comparison with authentic methyl shikimate, its C(3)-epimer. Protection of the newly created β-alcohol by (benzyloxy)methyl (BOM) chloride and OsO_4 glycolization of the olefin from the less hindered α-face furnished **3** as the sole product in excellent overall yield. The C(1)-acetate of **3** displayed a ^1H NMR coupling ($J_{1,6} \cong 9.5$ Hz) consistent with an axial–axial orientation between the C(1)- and C(6)-alcohol methines (*myo*-inositol numbering). Exclusive etherification of the secondary alcohol in **3** via trityl cation-promoted[7] addition of 4-methoxybenzyl (MPM) trichloroacetimidate set the stage for the one-pot degradation of the α-hydroxy ester by sequential $NaBH_4$ reduction and periodate cleavage. The resultant ketone **4** was smoothly transformed to the corresponding silyl enol ether according to the method of Corey et al.[8] None of the regioisomeric enol could be detected spectroscopically.[9] Epoxidation using buffered 3-chloroperbenzoic acid or dimethyldioxirane[10] afforded the surprisingly

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(1) Review: Kapeller, R.; Cantley, L. C. *BioEssays* **1994**, *16*, 565–576.

(2) Traynor-Kaplan, A. E.; Harris, A. L.; Thompson, B. L.; Taylor, P.; Sklar, L. A. *Nature* **1988**, *334*, 353–356.

(3) Review: Cantley, L. C.; Auger, K. R.; Carpenter, C.; Duckworth, B.; Graziani, A.; Kapeller, R.; Soltoff, S. *Cell* **1991**, *64*, 281–302.

(4) Falck, J. R.; Abdali, A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 717–720. Reddy, K. K.; Falck, J. R.; Capdevila, J. *Tetrahedron Lett.* **1993**, *34*, 7869–7872.

(5) Previous asymmetric syntheses: Falck, J. R.; Abdali, A. In *Inositol Phosphates and Derivatives. Synthesis, Biochemistry, and Therapeutic Potential*; Reitz, A. B., Ed.; American Chemical Society: Washington, DC, 1991; pp 145–154. Gou, D.-M.; Chen, C.-S. *J. Chem. Soc., Chem. Commun.* **1994**, 2125–2126. For a concise, but racemic, synthesis, see: Watanabe, Y.; Hirofuji, H.; Ozaki, S. *Tetrahedron Lett.* **1994**, *35*, 123–124.

(6) Other reagents, e.g., $NaBH_4$, gave mixtures of isomers. Reduction of the 4,5-*O*-isopropylidene of **1** (2-methoxypropene, DMF, TsOH, 23 °C, 12 h; 70%) with $LiB[CH(CH_3)C_2H_5]_3H$ provided the α-alcohol exclusively.

(7) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139–4142.

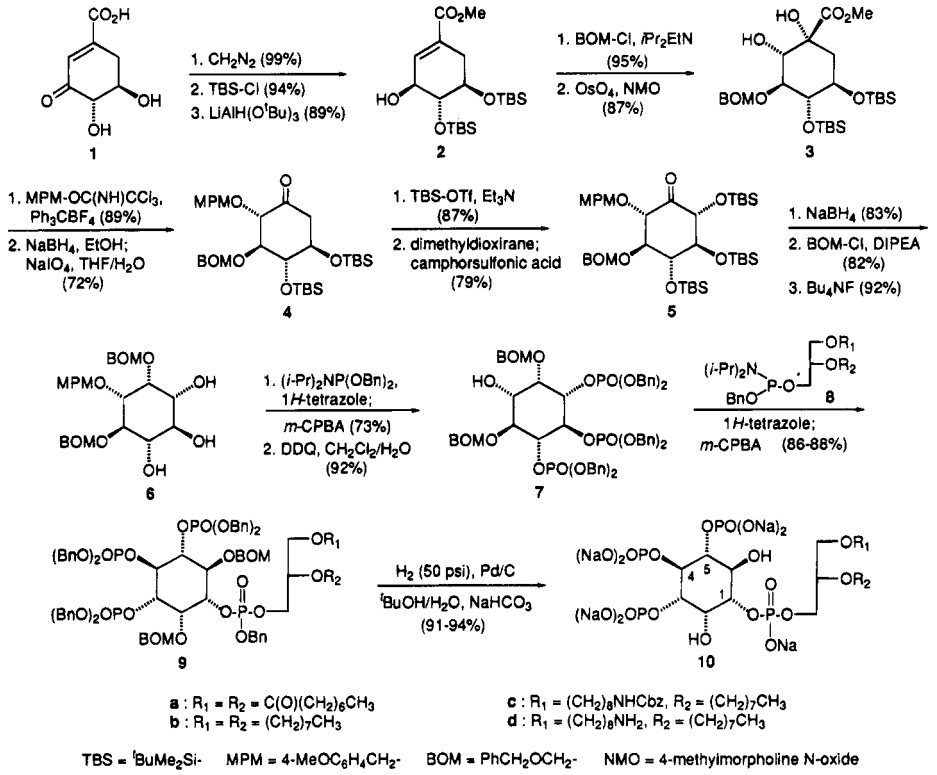
(8) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455–3458.

(9) The $\Delta^{1,6}$-regioisomer was the major product using the 4,5-*O*-isopropylidene derivative of **4**.

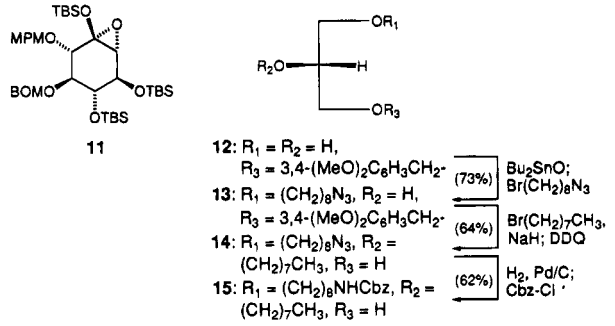
(10) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666.

0022-3263/95/1960-3385$09.00/0

Scheme 1



robust α-(silyloxy)oxirane **11** that could be isolated and characterized.[11] As anticipated from inspection of models, the epoxy hydrogen appears as a singlet (3.07 ppm) in the ^{1}H NMR spectrum. In practice, however, **11** was rearranged in situ with concomitant silyl migration to give **5** by stirring for 1 h at ambient temperature with a catalytic amount of camphorsulfonic acid (CSA).



Preferential equatorial hydride delivery to **5**, a consequence of the congested environment around the carbonyl, created the C(2)-alcohol and completed the basic *myo*-inositol skeleton. The stereochemistry of the reduction was clearly established by inspection of the ^{1}H NMR for the derived acetate which showed a triplet at 5.42 ppm ($J \cong 4.1$ Hz). Alkylation of the hydroxyl with BOM Cl and desilylation with fluoride anion led to triol **6** from whence the pivotal trisphosphate **7** was obtained by the two-step phosphoramidite procedure of Tegge and Ballou,[12] followed by DDQ cleavage[13] of the 4-methoxybenzyl ether. Condensation of **7** with freshly prepared 1,2-di-*O*-octanoyl-*sn*-glycerobenzyl (*N*,*N*-diisopropylamino)phosphoramidite[14] (**8a**) and peracid oxidation gave rise to the fully protected phosphatidylinositide **9a**. Catalytic hydrogenolysis of **9a** in the presence of stoichiometric $NaHCO_3$ afforded 3,4,5-PIP_3 **10a**, isolated as the heptasodium salt. In the absence of base, the reaction medium becomes acidic and a rapid transesterification between the *sn*-2-glycerylacyl and the inositol hydroxyls occurs as confirmed by integration of the ^{1}H NMR spectrum and loss of the glyceryl *sn*-2 methine absorption (5.12–5.24 ppm).

Repetition of the above sequence from **7** using **8b**[17] and **8c** furnished the dioctyl glyceryl ether analog **10b** and the ω-amino version **10d**, respectively. Access to **8c** was achieved from the known[18] *sn*-3-protected glyceryl ether **12** by regioselective alkylation of the in situ-generated stannylene[19] with 8-azidooctyl bromide, generating **13**. Etherification of the remaining secondary alcohol and DDQ deprotection provided **14** from which **15** was secured by reduction with hydrogen over Pd/C and Cbz Cl protection of the thus-produced amine. Condensation[14] with *O*-benzyl-*N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite led uneventfully to **8c**. In contrast to their higher homologs,[5] **10a,b** are water soluble and easily handled yet are still capable of activating specific components of the signal transduction cascade.[20] **10b,d**

(11) Epoxy enol ethers are quite labile and are often only detected as transient intermediates: Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 295–400.

(12) Tegge, W.; Ballou, C. E. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 94–98.

(13) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885–888.

(14) Prepared from the known[15] 1,2-di-*O*-octanoyl-*sn*-glycerol by coupling with benzyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite[16] (CH_2Cl_2, 1*H*-tetrazole, 23 °C, 2 h; 85%).

(15) Ganong, B. R.; Loomis, C. R.; Hannun, Y. A.; Bell, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1184–1188.

(16) Bannwarth, W.; Trzeciak, A. *Helv. Chim. Acta* **1987**, *70*, 175–186.

(17) Prepared from the known[15] 1,2-di-*O*-octyl-*sn*-glycerol as described in ref 14.

(18) Lebeau, L.; Dudet, P.; Mioskowski, C. *Helv. Chim. Acta* **1991**, *74*, 1697–1706.

(19) Ogawa, T.; Horisaka, T. *Carbohydr. Res.* **1983**, *123*, C1–C4.

are anticipated to be chemically more stable than **10a** and to be resistant to phospholipase A and B degradation. Furthermore, **10d** will be of value in preparing labeled compounds and for coupling to antigens/affinity matrixes.

Experimental Section

General. Unless otherwise stated, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-250 spectrometer using tetramethylsilane as internal standard. Purification, chromatography, analyses, and routine laboratory manipulations were as previously reported.[21]

Methyl 3(*S*)-Hydroxy-4(*S*),5(*R*)-bis[(*tert*-butyldimethylsilyl)oxy]-1-cyclohexene-1-carboxylate (2). To a −15 °C solution of dehydroshikimic acid (15.0 g, 87.2 mmol) in methanol (100 mL) was added dropwise an ethereal solution of diazomethane until TLC analysis showed no remaining starting material. All volatiles were carefully removed in vacuo to give methyl dehydroshikimate (16.06 g, 99%) as a white solid, mp 124−125 °C (lit.[22] mp 124−126 °C).

Imidazole (10.98 g, 161.29 mmol) and *tert*-butyldimethylsilyl chloride (19.44 g, 129 mmol) were added to a solution of methyl dehydroshikimate (10 g, 53.76 mmol) in dry DMF (60 mL) being stirred at 0 °C. After 12 h at ambient temperature, the reaction mixture was recooled to 0 °C, the reaction quenched with H_2O (100 mL), and the mixture extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried and evaporated in vacuo, and the residue was purified by chromatography (SiO_2) to give the bis-silyl ether of methyl dehydroshikimate (20.96 g, 94%) as a colorless oil: TLC (SiO_2) 5% EtOAc/hexane, R_f ~0.5; ^1H NMR δ 6.60 (dd, J = 1.6, 1.7 Hz, 1H), 4.00−4.10 (m, 1H), 3.80 (d, J = 6.9 Hz, 1H), 3.70 (s, 3H), 2.86 (ddd, J = 1.8, 3.9, 18.6 Hz, 1H), 2.48 (ddd, J = 1.6, 5.4, 18.6 Hz, 1H), 0.78 (s, 9H), 0.76 (s, 9H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR δ 197.96, 166.68, 143.70, 131.26, 71.46, 52.66, 31.92, 25.73, 18.27, 17.95, −4.60, −4.83, −4.85; MS (CI, CH_4) m/z (relative intensity) 414 (M^+, 6), 399 ($M^+ - CH_3$, 20), 357 (100), 325 (4); HRMS (CI, CH_4) calcd for $C_{20}H_{39}O_5Si_2$ (M^+ + H) m/z 415.2336, found 415.2340.

To a stirred solution of the above bis-silyl ether (10 g, 24.12 mmol) in anhydrous THF (100 mL) was added lithium tri-*tert*-butoxyaluminohydride (12.26 g, 48.25 mmol) in portions at 0 °C. After 1 h, the reaction was quenched with 0.5% aqueous HCl (100 mL), the mixture was extracted with EtOAc, and the combined organic extracts were washed with brine and dried. The solvent was evaporated in vacuo, and the residue was purified by column chromatography to give **2** (8.93 g, 89%) as a colorless oil: TLC (SiO_2) 4% EtOAc/hexane, R_f ~0.5; $[\alpha]^{24}_D$ 10.31 (*c* 2.23, $CHCl_3$); ^1H NMR δ 6.95 (br s, 1H), 4.01 (br s, 1H), 3.89−3.91 (m, 1H), 3.82−3.84 (m, 1H), 3.75 (s, 3H), 3.04 (d, J = 11.3 Hz, 1H, D_2O exchangeable), 2.40−2.46 (m, 2H), 0.83 (s, 18H), 0.06 (s, 12H); ^{13}C NMR δ 167.70, 136.09, 126.91, 70.54, 69.42, 68.79, 51.84, 28.26, 25.73, 25.65, 17.97, 17.91, −4.89; MS (CI, CH_4) m/z (relative intensity) 416 (M^+, 100), 415 (35), 413 (20); HRMS (CI, CH_4) calcd for $C_{20}H_{41}O_5Si_2$ (M^+ + 1) m/z 417.2492, found 417.2478.

Methyl 1(*R*),2(*S*)-Dihydroxy-3(*R*)-[(benzyloxy)methoxy]-4(*S*),5(*R*)-bis[(*tert*-butyldimethylsilyl)oxy]-1-cyclohexanecarboxylate (3). To a solution of **2** (5 g, 12.02 mmol) in CH_2Cl_2 (25 mL) was added *N,N*-diisopropylethylamine (8.37 mL, 48.07 mmol), followed by (benzyloxy)methyl chloride (5.55 mL, 36.05 mmol). The reaction mixture was stirred at room temperature for 16 h and then evaporated in vacuo. The residue was chromatographed (SiO_2) to yield the (benzyloxy)-methyl ether of **2** (6.12 g, 95%) as a colorless oil: TLC (SiO_2) 25% Et_2O/hexane, R_f ~0.45; ^1H NMR δ 7.24−7.35 (m, 5H), 6.88−6.91 (m, 1H), 4.85 (s, 2H), 4.73 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.02−4.09 (m, 1H), 3.71−3.88 (m, 4H), 2.60 (ddd, J = 1.5, 2.8, 17.5 Hz, 1H), 2.29 (ddd, J = 2.0, 4.3, 17.5 Hz, 1H), 0.86 (s, 18H), 0.06 (s, 12H); ^{13}C NMR δ 167.08, 137.65, 136.78, 128.42, 128.29, 128.00, 127.74, 95.60, 79.14, 74.42, 69.49, 51.84, 31.70, 26.03, 25.97, 18.21, 18.04, −3.95, −4.48, −4.72; MS (CI, CH_4) m/z (relative intensity) 536 (M^+, 50), 521 (35), 505 (40), 491 (50), 479 (100); HRMS (CI, CH_4) calcd for $C_{28}H_{49}O_6Si_2$ (M^+ + 1) m/z 537.3067, found 537.3061.

A solution of the above (benzyloxy)methyl ether (6 g, 11.19 mmol), OsO_4 (28 mg, 0.11 mmol), and 4-methylmorpholine *N*-oxide (3.93 g, 33.58 mmol) in acetone/water (20 mL, 9:1) was stirred for 3 h at room temperature and then the reaction quenched at 0 °C with sodium metabisulfite (6.38 g, 33.58 mmol). The reaction mixture was extracted with EtOAc (3 × 100 mL), the combined organic extracts were washed with brine and dried, and the solvent was evaporated. The residue was chromatographed (SiO_2) to give **3** (5.55 g, 87%) as a colorless oil: TLC (SiO_2) 30% Et_2O/hexane, R_f ~0.5; ^1H NMR δ 7.24−7.36 (m, 5H), 4.89 (d, J = 6.6 Hz, 1H), 4.75 (d, J = 11.9 Hz, 1H), 4.66 (d, J = 6.7 Hz, 1H), 4.58 (d, J = 1.5 Hz, 1H, D_2O exchangeable), 4.53 (d, J = 11.9 Hz, 1H), 3.87 (ddd, J = 4.5, 8.3, 15.9 Hz, 1H), 3.78 (s, 3H), 3.72 (dd, J = 1.6, 8.9 Hz, 1H), 3.30−3.50 (m, 3H), 1.98 (dd, J = 4.6, 13.6 Hz, 1H), 1.75 (ddd, J = 2.5, 11.7, 16.0 Hz, 1H), 0.83 (s, 18H), 0.07 (s, 12H); ^{13}C NMR δ 174.31, 136.47, 128.57, 128.14, 127.97, 97.44, 87.50, 75.66, 73.77, 70.40, 52.99, 38.51, 26.21, 26.14, 18.13, 18.01, −3.09, −3.21, −4.53; MS (CI, CH_4) m/z (relative intensity) 570 (M^+, 100), 553 (70), 541 (40), 525 (30); HRMS (CI, CH_4) calcd for $C_{28}H_{51}O_8Si_2$ (M^+ + 1) m/z 571.3122, found 571.3132.

2(*S*)-[(4-Methoxybenzyl)oxy]-3(*S*)-[(benzyloxy)methoxy]-4(*R*),5(*R*)-bis[(*tert*-butyldimethylsilyl)oxy]cyclohexan-1-one (4). To a solution of **3** (5.0 g, 8.77 mmol) in anhydrous Et_2O (50 mL) was added freshly prepared 4-methoxybenzyl trichloroacetimidate (6.19 g, 21.92 mmol), followed by triphenylcarbenium tetrafluoroborate (87 mg, 0.263 mmol). After 3 h, 20 mL of 10% aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine, dried, and evaporated, and the residue was purified by chromatography (SiO_2) to yield the C(3) 4-methoxybenzyl ether of **3** (5.38 g, 89%) as a colorless oil: TLC (SiO_2) 15% EtOAc/hexane, R_f ~0.5; ^1H NMR δ 7.26−7.29 (m, 5H), 7.13 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 4.97 (s, 2H), 4.83 (d, J = 10.5 Hz, 2H), 4.64 (d, J = 3.8 Hz, 2H), 4.38 (d, J = 10.6 Hz, 2H), 3.73−3.90 (m, 5H), 3.50−3.67 (m, 4H), 3.47 (t, J = 9.8 Hz, 1H), 3.30 (s, 1H, D_2O exchangeable), 1.98 (dd, J = 4.7, 14.0 Hz, 1H), 1.78 (t, J = 14.0 Hz, 1H), 0.80−0.90 (m, 18H), 0.11−0.20 (m, 12H); ^{13}C NMR δ 174.45, 159.19, 138.18, 130.09, 129.61, 128.22, 127.46, 127.36, 113.66, 97.80, 82.43, 80.53, 78.39, 76.03, 74.75, 70.71, 70.36, 55.23, 52.76, 39.21, 26.40, 26.26, 18.17, 17.99, −3.01, −3.72, −4.58; MS (CI, CH_4) m/z (relative intensity) 690 (M^+, 100), 633 (20); HRMS (CI, CH_4) calcd for $C_{36}H_{59}O_9Si_2$ (M^+ + 1) m/z 691.3697, found 691.3701.

Sodium borohydride (437 mg, 11.59 mmol) was added to a 0 °C solution of the above 4-methoxybenzyl ether (4.0 g, 5.79 mmol) in absolute ethanol (30 mL) during 5 min. After 3 h at room temperature, the solvent was evaporated, the residue was dissolved in THF/H_2O (10 mL, 9:1), and $NaIO_4$ (7.44 g, 34.78 mmol) was added in one portion. At the end of 3 h, the mixture was filtered and the filter cake was washed with EtOAc. The combined filtrate was washed with water (50 mL) and dried, and the solvent was evaporated under reduced pressure. The residue was purified by SiO_2 chromatography to give **4** (2.63 g, 72%) as a colorless oil: TLC (SiO_2) 15% Et_2O/hexane, R_f ~0.5; ^1H NMR δ 7.27−7.30 (m, 7H), 6.79 (d, J = 8.6 Hz, 2H), 4.84 (s, 2H), 4.82 (d, J = 10.9 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 3.4 Hz, 1H), 4.48 (d, J = 10.9 Hz, 1H), 3.97−4.02 (m, 2H), 3.79−3.81 (m, 1H), 3.77 (s, 3H), 2.71 (dd, J = 3.8, 17.7 Hz, 1H), 2.29 (dd, J = 2.4, 17.8 Hz, 1H), 0.88 (s, 9H), 0.81 (s, 9H), 0.15 (s, 3H), 0.09 (s, 6H), 0.03 (s, 3H); ^{13}C NMR δ 207.19, 159.21, 137.78, 129.89, 128.27, 127.80, 127.52, 113.66, 94.65, 84.06, 83.30, 74.70, 72.82, 70.61, 69.44, 55.20, 43.40, 25.63, 17.83, −4.73; MS (CI, CH_4) m/z (relative intensity) 630 (M^+, 20), 493 (15),

(20) For example, **10a,b** cause a 5−15-fold stimulation in vitro of the calcium insensitive PKC δ, ϵ, and η-isotypes: Louis Cantley (Harvard University), personal communication. Also see: Toker, A.; Meyer, M.; Reddy, K. K.; Falck, J. R.; Aneja, R.; Burns, D. J.; Ballas, L. M.; Cantley, L. C. *J. Biol. Chem.* **1994**, *269*, 32358−32367.

(21) Bhatt, R. K.; Chauhan, K.; Wheelan, P.; Murphy, R. C.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 5050−5056.

(22) Grewe, R.; Peterjeschke, J. *Chem. Ber.* **1956**, *89*, 2080−2081.

448 (15), 435 (25), 407 (100); HRMS (CI, CH_4) calcd for $C_{34}H_{55}O_7Si_2$ ($M^+ + 1$) m/z 631.3486, found 631.3492.

2(*S*)-[(4-Methoxybenzyl)oxy]-3(*S*)-[(benzyloxy)methoxy]-4(*R*),5(*S*),6(*R*)-tris[(*tert*-butyldimethylsilyl)oxy]cyclohexan-1-one (5). To a 0 °C solution of **4** (1.9 g, 3.01 mmol) in anhydrous CH_2Cl_2 (10 mL) was added triethylamine (2.1 mL, 15.08 mmol), followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.73 mL, 7.54 mmol). After 6 h at room temperature, the reaction mixture was poured into ice-cold, saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with water and brine, dried, and evaporated. The residue was chromatographed (SiO_2) to yield a single silyl enol ether (1.95 g, 87%) as a colorless oil that was used immediately in the next step: TLC (SiO_2) 5% Et_2O/hexane, R_f ~0.5; ^1H NMR δ 7.15–7.28 (m, 7H), 6.74 (d, J = 8.7 Hz, 2H), 4.99 (d, J = 6.4 Hz, 1H), 4.87 (d, J = 6.4 Hz, 1H), 4.80 (d, J = 10.4 Hz, 1H), 4.76 (dd, J = 0.7, 1.9 Hz, 1H), 4.63 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 10.4 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 4.20 (dt, J = 2.2, 6.9 Hz, 1H), 4.04 (ddd, J = 0.7, 2.3, 7.1 Hz, 1H), 3.75 (s, 3H), 3.74 (dd, J = 9.4, 7.2 Hz, 1H), 3.56 (dd, J ~ 6.9, 9.4 Hz, 1H), 0.84–0.94 (m, 27H), 0.20 (s, 3H), 0.18 (s, 3H), 0.11 (s, 6H), 0.09 (s, 6H); ^{13}C NMR δ 158.79, 148.88, 138.22, 130.92, 129.14, 128.14, 127.58, 127.23, 113.43, 109.25, 96.18, 80.25, 78.73, 71.85, 69.90, 55.18, 26.29, 25.79, 18.16, 18.00, −3.53, −3.81, −4.31, −4.46; MS (CI, CH_4) m/z (relative intensity) 687 ($M^+ - C_4H_9$, 3), 607 (10), 591 (3), 549 (10), 475 (10), 450 (100).

Dimethyldioxirane was prepared by slowly adding Oxone (25 g) to a mixture of 7 M aqueous $NaHCO_3$ solution (30 mL) and acetone (13 mL) being stirred at room temperature. The evolved dioxirane was bubbled directly into a 0 °C solution of the above silyl enol ether (100 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) by using a slow entrainment stream of argon and by simultaneously applying a slight vacuum (~180 Torr) to the receiving flask. After 30 min, TLC (SiO_2) showed complete conversion of the starting material. The volatiles were evaporated in vacuo, and the residue was redissolved in dry CH_2Cl_2 (2 mL) containing a catalytic amount of camphorsulfonic acid (2 mg) at 0 °C. After 30 min, the reaction was quenched with 5% aqueous $NaHCO_3$ solution (0.5 mL), the mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phases were washed with brine. After drying, the solvent was removed under reduced pressure and the residue was chromatographed (SiO_2) to give **5** (79 mg, 79%) as a colorless oil: TLC (SiO_2) 10% Et_2O/hexane, R_f ~0.41; ^1H NMR δ 7.22–7.39 (m, 7H), 6.81 (d, J = 8.2 Hz, 2H), 4.81 (d, J = 6.7 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.75 (d, J = 10.3 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.2 Hz, 1H), 4.37 (d, J = 6.0 Hz, 1H), 3.89–4.03 (m, 4H), 3.77 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.81 (s, 9H), 0.18 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ 205.07, 159.24, 137.75, 129.87, 128.29, 127.87, 127.55, 113.65, 93.91, 84.89, 81.11, 80.88, 80.65, 72.48, 71.99, 69.26, 55.19, 25.94, 25.65, 25.59, 18.45, 17.88, 17.77, −4.03, −4.62, −4.87, −4.95, −5.81; MS (CI, CH_4) m/z (relative intensity) 761 [($M + 1$)$^+$, 4], 703 (25), 607 (18), 565 (65), 475 (100); HRMS (CI, CH_4) calcd for $C_{40}H_{68}O_8Si_3$ m/z 760.4222, found 760.4230.

Epoxide 11. To a suspension of the silyl enol ether from **4** (500 mg, 0.67 mmol) and anhydrous Na_2HPO_4 (1.62 g, 11.42 mmol) in CH_2Cl_2 (8 mL) being stirred at −20 °C was added 3-chloroperoxybenzoic acid (85%, 408 mg, 2.01 mmol) under an argon atmosphere. The reaction mixture was slowly warmed to 0 °C, stirred for 3 h at that temperature, and then recooled to −20 °C, and the reaction was quenched with a saturated aqueous solution of $NaHSO_3$/$NaHCO_3$ (10 mL, 1:1). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with 10% $NaHCO_3$ solution (15 mL) and brine and dried, and the solvent was removed under reduced pressure. The residue was chromatographed to give epoxide **11** (403 mg, 79%) as a colorless syrup: TLC (SiO_2) 10% Et_2O/hexane, R_f ~0.46; ^1H NMR δ 7.05–7.38 (m, 7H), 6.74 (d, J = 8.1 Hz, 2H), 4.97 (d, J = 10.8 Hz, 1H), 4.90 (d, J = 5.1 Hz, 1H), 4.83 (d, J = 5.1 Hz, 1H), 4.77 (d, J = 10.8 Hz, 1H), 4.54 (d, J = 12.8 Hz, 1H), 4.43 (d, J = 12.8 Hz, 1H), 3.93 (d, J = 7.6 Hz, 1H), 3.76 (s, 3H), 3.55 (t, J = 7.7 Hz, 1H), 3.45 (d, J = 8.9 Hz, 1H), 3.34 (apparent t, J = 8.9 Hz, 1H), 3.07 (s, 1H), 0.92 (s, 9H), 0.86 (s, 18H), 0.19 (s, 3H), 0.14 (s, 3H), 0.12 (s, 6H), 0.10 (s, 6H); ^{13}C NMR δ 158.21, 137.89, 131.23, 128.81, 128.05, 127.44, 127.12, 113.43, 96.81, 83.92, 81.73, 76.32, 75.83, 74.36, 73.14, 70.13, 64.04, 55.15, 26.29, 26.08, 25.64, 17.79, 17.46, 17.09, −3.44, −3.27, −3.11, −4.65.

1-*O*-(4-Methoxybenzyl)-2,6-bis-*O*-[(benzyloxy)methyl]-D-*myo*-inositol (6). To a solution of **5** (560 mg, 0.73 mmol) in anhydrous MeOH (3 mL) being stirred at 0 °C was added $NaBH_4$ (56 mg, 1.47 mmol). After 1 h, the reaction mixture was diluted with EtOAc (50 ml), washed with water (5 mL) and brine (10 mL), and dried. All volatiles were removed in vacuo, and the residue was chromatographed (SiO_2) to give 1-*O*-(4-methoxybenzyl)-3,4,5-tris-*O*-(*tert*-butyldimethylsilyl)-6-*O*-[(benzyloxy)methyl]-D-*myo*-inositol (466 mg, 83%) as a colorless syrup: TLC (SiO_2) 15% Et_2O/hexane, R_f ~0.15; $[\alpha]^{24}_D$ −4.09 (*c* 0.83, $CHCl_3$); ^1H NMR δ 7.25–7.40 (m, 7H), 6.81 (d, J = 8.6 Hz, 2H), 4.85 (d, J = 6.7 Hz, 1H), 4.82 (d, J = 6.7 Hz, 1H), 4.65 (d, J = 17.4 Hz, 1H), 4.63 (d, J = 11.3 Hz, 1H), 4.60 (d, J = 17.4 Hz, 1H), 4.57 (d, J = 11.4 Hz, 1H), 4.03 (dd, J = 2.2, 7.4 Hz, 1H), 3.92 (ddd, J = 3.2, 5.3, 9.6 Hz, 1H), 3.82–3.87 (m, 1H), 3.77 (s, 3H), 3.73–3.76 (m, 2H), 3.71 (dd, J = 3.2, 7.4 Hz, 1H), 3.22 (d, J = 9.6 Hz, 1H, D_2O exchangeable), 0.89 (s, 9H), 0.87 (s, 18H), 0.10 (s, 3H), 0.90 (s, 3H), 0.08 (s, 12H); ^{13}C NMR δ 159.04, 138.04, 130.70, 129.59, 128.25, 127.76, 127.43, 113.58, 94.69, 80.55, 79.15, 76.80, 76.18, 75.83, 71.83, 69.40, 67.78, 55.21, 25.90, 25.82, 25.71, 18.25, 17.92, 17.79, −4.51, −4.59, −4.63, −4.78; MS (CI, CH_4) m/z (relative intensity) 641 ($M - C_8H_9O$)$^+$, 616, 590, 502, 412. HRMS (CI, CH_4) calcd for $C_{32}H_{61}O_7Si_3$ ($M^+ - C_8H_9O$) m/z 641.3725, found 641.3719.

A solution of the above alcohol (360 mg, 0.47 mmol) and (benzyloxy)methyl chloride (BOM Cl) (222 mg, 1.41 mmol) in diisopropylethylamine (DIPEA) (2 mL) was stirred at 55 °C for 6 h. All volatiles were evaporated under reduced pressure, and the residue was purified by chromatography (SiO_2) to give 1-*O*-(4-methoxybenzyl)-2,6-bis-*O*-[(benzyloxy)methyl]-3,4,5-tris-*O*-(*tert*-butyldimethylsilyl)-D-*myo*-inositol (339 mg, 81.5%) as a colorless oil: TLC (SiO_2) 15% Et_2O/hexane, R_f ~0.37; $[\alpha]^{24}_D$ 22.9 (*c* 1.22, $CHCl_3$); ^1H NMR δ 7.24–7.40 (m, 10H), 7.20 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 4.95 (d, J = 6.0 Hz, 1H), 4.92 (d, J = 6.7 Hz, 1H), 4.85 (d, J = 6.2 Hz, 1H), 4.82 (d, J = 6.7 Hz, 1H), 4.71 (d, J = 12.2 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.61 (d, J = 12.2 Hz, 1H), 4.59 (d, J = 11.2 Hz, 1H), 4.58 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.12 (dd, J = 2.5, 3.2 Hz, 1H), 3.96 (t, J = 7.4 Hz, 1H), 3.90 (t, J = 6.2 Hz, 1H), 3.75 (s, 3H), 3.58 (dd, J = 2.2, 6.4 Hz, 1H), 3.50 (t, J = 6.6 Hz, 1H), 3.49 (dd, J = 3.4, 7.6 Hz, 1H), 0.94 (s, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.16 (s, 3H), 0.14 (s, 6H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR δ 159.12, 138.33, 138.15, 130.69, 129.34, 128.43, 128.25, 128.20, 127.94, 127.62, 127.61, 127.37, 127.32, 113.46, 95.80, 93.93, 78.98, 78.13, 75.74, 74.71, 74.28, 73.77, 71.98, 70.02, 69.52, 69.13, 55.18, 26.55, 26.31, 18.56, 18.27, 18.07, −3.15, −3.21, −3.24, −3.34, −3.89, −3.98; HRMS (FAB in 3-NBA) calcd for $C_{48}H_{78}O_9Si_3$ m/z 882.4953, found 882.4964.

To a stirred solution of the above fully protected *myo*-inositol (55 mg, 0.06 mmol) in THF (1 mL) was added Bu_4NF (1.0 M solution in THF, 310 μL). After 5 h, the reaction mixture was diluted with water (5 mL) and extracted with Et_2O (2 × 10 mL). The combined ethereal extracts were washed with 5% $NaHCO_3$ (5 mL), water, and brine and dried. The solvents were concentrated in vacuo, and the residue was chromatographed (SiO_2) to yield **6** (31 mg, 92%) as an off-white solid, mp 103–104 °C: TLC (SiO_2) EtOAc (100%), R_f ~0.32; $[\alpha]^{24}_D$ 63.9 (*c* 0.84, $CHCl_3$); ^1H NMR δ 7.24–7.42 (m, 10H), 7.20 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 5.00 (d, J = 6.5 Hz, 1H), 4.97 (d, J = 6.0 Hz, 1H), 4.91 (d, J = 6.6 Hz, 1H), 4.79 (d, J = 11.9 Hz, 1H), 4.75 (d, J = 12.5 Hz, 1H), 4.73 (d, J = 6.2 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 12.3 Hz, 1H), 4.56 (s, 2H), 4.03 (br s, 1H), 3.84 (br s, 1H), 4.79 (t, J = 5.0 Hz, 1H), 3.78 (s, 3H), 3.64–3.76 (m, 1H), 3.28–3.43 (m, 4H), 2.89 (br s, 1H); ^{13}C NMR δ 159.31, 137.06, 129.91, 129.31, 128.51, 127.99, 127.93, 113.83, 96.66, 96.39, 82.67, 78.35, 78.23, 74.04, 73.60, 72.57, 71.23, 70.31, 55.23; MS (CI, CH_4) m/z (relative intensity) 419 [($M^+ - C_8H_9O$), 20], 389 (5), 311

(8), 134 (25), 121 (100); HRMS calcd for $C_{22}H_{27}O_8$ ($M^+ - C_8H_9O$) m/z 419.1705, found 419.1710.

2,6-Bis-*O*-[(Benzyloxy)methyl]-3,4,5-tris-*O*-(dibenzylphosphoryl)-D-*myo*-inositol (7). To a suspension of **6** (30 mg, 0.05 mmol) and 1*H*-tetrazole (62 mg, 0.88 mmol) in anhydrous CH_2Cl_2 (1 mL) was added a solution of dibenzyl *N,N*-diisopropylphosphoramidite (115 mg, 0.33 mmol) in CH_2Cl_2 (0.5 mL). After 2 h, the reaction mixture was cooled to −40 °C and a solution of 3-chloroperoxybenzoic acid (85%, 130 mg, 0.64 mmol) in CH_2Cl_2 (0.5 mL) was added slowly. Following an additional 1 h, the mixture was diluted with CH_2Cl_2 (20 mL), washed with 5% $Na_2S_2O_5$ (2 × 5 mL), 10% $NaHCO_3$ (2 × 5 mL), and brine, and dried. The solvent was removed in vacuo, and the residue was purified by chromatography (SiO_2) to give 1-*O*-(4-methoxybenzyl)-2,6-bis-*O*-[(benzyloxy)methyl]-3,4,5-tris-*O*-(dibenzylphosphoryl)-D-*myo*-inositol (53 mg, 73%) as a colorless syrup: TLC (SiO_2) 20% CH_2Cl_2/EtOAc, R_f ~0.42; ^{1}H NMR δ 7.14−7.39 (m, 40H), 7.10 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 4.85−5.15 (m, 17H), 4.65 (s, 2H), 4.56 (d, J = 6.8 Hz, 2H), 4.51 (d, J = 11.6 Hz, 1H), 4.44 (t, J = 10.7 Hz, 1H), 4.36 (t, J = 9.7 Hz, 1H), 4.33 (d, J = 11.1 Hz, 1H), 4.20 (t, J = 9.4 Hz, 1H), 4.15 (dd, J = 2.0, 7.7 Hz, 1H), 3.73 (s, 3H), 3.30 (dd, J = 1.9, 9.8 Hz, 1H); ^{13}C NMR δ 159.19, 138.21, 137.84, 136.13, 136.08, 136.02, 135.96, 135.84, 135.74, 135.61, 129.56, 129.18, 128.53, 128.51, 128.37, 128.32, 128.26, 128.22, 128.13, 128.02, 127.97, 127.87, 127.79, 127.52, 127.38, 127.23, 113.71, 96.34, 95.46, 78.50 (m), 77.75, 75.90 (m), 75.65 (d, J = 2.1 Hz), 75.13, 72.43, 71.84, 70.23, 69.70, 69.64, 69.59, 69.55, 69.44, 69.41, 69.32, 55.15; HRMS (FAB in 3-NBA) calcd for $C_{72}H_{75}O_{18}P_3$ m/z 1320.4166, found 1320.4150.

A mixture of the above trisphosphate ester (38 mg, 0.03 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (13 mg, 0.06 mmol) in CH_2Cl_2/H_2O (3 mL, 20:1) was stirred for 4 h at room temperature. The reaction mixture was diluted with 10% $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine and dried, and the solvent was removed in vacuo. The residue was chromatographed (SiO_2) to give **7** (31 mg, 92%) as a colorless syrup: TLC (SiO_2) 40% EtOAc/CH_2Cl_2, R_f ~0.46; ^{1}H NMR δ 7.11−7.48 (m, 40H), 4.92−5.17 (m, 10H), 4.90 (d, J = 9.7 Hz, 1H), 4.89 (d, J = 6.7 Hz, 1H), 4.83 (d, J = 6.7 Hz, 1H), 4.58−4.70 (m, 6H), 4.47 (t, J = 9.1 Hz, 1H), 4.43 (s, 2H), 4.40 (d, J = 8.5 Hz, 1H), 4.26 (dd, J = 2.3, 10.0 Hz, 1H), 4.21 (d, J = 3.6 Hz, 1H, D_2O exchangeable), 3.83 (t, J = 9.4 Hz, 1H), 3.45 (ddd, J = 2.9, 3.6, 8.9 Hz, 1H); ^{13}C NMR δ 137.54, 136.81, 136.09, 135.98, 135.87, 135.75, 135.66, 135.60, 135.55, 135.49, 128.49, 128.39, 128.28, 128.14, 128.09, 128.03, 127.99, 127.94, 127.85, 127.82, 127.57, 97.05, 96.21, 82.38, 78.67 (m), 76.73, 76.21 (d, J = 8.6 Hz), 75.32 (m), 70.38, 70.02, 69.69, 69.60, 69.53, 69.44, 69.38, 69.29, 69.21; ^{31}P NMR ($CDCl_3$/TMS, 202 MHz; 85% H_3PO_4 external standard) δ −0.54, −0.99, −1.03; HRMS (FAB in 3-NBA) calcd for $C_{64}H_{67}O_{17}P_3$ m/z 1200.3591, found 1200.3601.

1,2-Di-*O*-octanoyl-*sn*-glycerol Benzyl (*N,N*-Diisopropylamino)phosphoramidite (8a). To a solution of 1,2-di-*O*-octanoyl-*sn*-glycerol[15] (96 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (2 mL) was added a solution of benzyl *N,N,N′,N′*-tetraisopropylphosphorodiamidite[16] (162 mg, 0.42 mmol) in CH_2Cl_2 (1 mL), followed by 1*H*-tetrazole (30 mg, 0.42 mmol) under an argon atmosphere. After 2 h, the volatiles were removed in vacuo and the residue was purified by flash chromatography (SiO_2), eluting with hexane/EtOAc/Et_3N (20:4:1) to give **8a** (140 mg, 86%) as a colorless oil: TLC (SiO_2) 30% EtOAc/hexane, R_f ~0.77; ^{1}H NMR δ 7.16−7.40 (m, 5H), 5.13−5.25 (m, 1H), 4.58−4.80 (m, 2H), 4.35 (ddd, J = 3.8, 5.2, 11.9 Hz, 1H), 4.16 (ddd, J = 3.0, 6.3, 11.9 Hz, 1H), 3.49−3.83 (m, 4H), 2.30 (t, J = 7.4 Hz, 4H), 1.52−1.68 (m, 4H), 1.22−1.40 (m, 16H), 1.20 (d, J = 2.1 Hz, 6H), 1.17 (d, J = 2.2 Hz, 6H), 0.88 (t, J = 7.0 Hz, 6H). A satisfactory elemental analysis or HRMS could not be obtained.

2,6-Di-*O*-[(benzyloxy)methyl]-3,4,5-tris-*O*-(dibenzylphosphoryl)-D-*myo*-inositol 1-*O*-(1,2-Di-*O*-octanoyl-*sn*-glycerol benzyl phosphate) (9a). To a mixture of **7** (70 mg, 0.06 mmol) and 1*H*-tetrazole (31 mg, 0.0437 mmol) being stirred in anhydrous CH_2Cl_2 (2 mL) was added a solution of **8a** (85 mg, 0.14 mmol) in CH_2Cl_2 (1 mL). After 2 h, the reaction mixture was cooled to −40 °C and a solution of 3-chloroperoxybenzoic acid (65 mg, 0.32 mmol) in CH_2Cl_2 (2 mL) was added. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with saturated aqueous $Na_2S_2O_5$ solution (10 mL), 10% aqueous $NaHCO_3$ solution (10 mL), and brine, and dried. Following concentration in vacuo, the residue was chromatographed (SiO_2) to give **9a** (122 mg, 86%) as a colorless syrup: TLC (SiO_2) 30% EtOAc/CH_2Cl_2, R_f ~0.41; ^{1}H NMR δ 7.09−7.43 (m, 45H), 4.64−5.18 (m, 22H), 4.61 (d, J = 11.9 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.13−4.42 (m, 7H), 3.84−4.13 (m, 2H), 2.20 (t, J = 7.0 Hz, 2H), 2.17 (t, J = 7.1 Hz, 2H), 1.40−1.75 (m, 4H), 1.04−1.40 (m, 16H), 0.86 (t, J = 6.3 Hz, 3H), 0.85 (t, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$/TMS, 202 MHz; 85% H_3PO_4 as external reference) δ −0.22, −0.23, −0.35, −0.42, −0.50, −0.90, −0.91; HRMS (FAB in 3-NBA) calcd for $C_{82}H_{99}O_{23}P_4$ ($M^+ - C_8H_9O$) m/z 1575.5527, found 1575.5539.

3,4,5-Tris-*O*-phosphoryl-D-*myo*-inositol 1-*O*-(1,2-Di-*O*-octanoyl-*sn*-glycerol phosphate) Heptasodium Salt (10a). A mixture of **9a** (80 mg, 0.047 mmol), $NaHCO_3$ (27 mg, 0.33 mmol), and Pd black (120 mg) in 35 mL of *t*-BuOH/H_2O (6:1) was shaken under H_2 (52 psi) in a Parr apparatus for 4 h. The catalyst was removed by filtration over a pad of Celite 577, and the filter cake was washed with water (10 mL), EtOH (10 mL), and EtOAc (5 mL). The combined filtrates were evaporated in vacuo at room temperature, and the residue was triturated with acetone to give **10a** as a white amorphous solid: ^{1}H NMR (D_2O) δ 5.19 (br s, 1H), 4.08−4.40 (m, 4H), 3.69−4.05 (m, 6H), 2.28 (t, J = 6.9 Hz, 2H), 2.25 (t, J = 6.8 Hz, 2H), 1.32−1.56 (m, 4H), 0.90−1.30 (m, 16H), 0.74 (apparent t, J = 6.8 Hz, 6H); ^{31}P NMR (D_2O, 161.97 MHz; 85% H_3PO_4 as external reference) δ 5.157, 3.988, 2.185, 0.458; HRMS (FAB in 3-NBA/NaI) calcd for $C_{25}H_{43}O_{22}P_4Na_8$ $(M + Na)^+$ m/z 1003.0378, found 1003.0370.

Preparation of 8b. Following the procedure used for ester analogue **8a**, 1,2-di-*O*-octyl-*sn*-glycerol[15] (200 mg, 0.63 mmol) furnished **8b** (304 mg, 87%) as a colorless oil: TLC (SiO_2) 30% EtOAc/hexane, R_f ~0.8; ^{1}H NMR δ 7.21−7.42 (m, 5H), 4.63−4.82 (m, 2H), 3.36−4.00 (m, 9H), 1.50−1.67 (m, 4H), 1.22−1.40 (m, 20H), 1.21 (d, J = 2.1 Hz, 6H), 1.18 (d, J = 2.2 Hz, 6H), 0.88 (t, J = 6.1 Hz, 6H).

Preparation of 9b. Following the procedure used for ester analogue **9a**, **7** (20 mg, 0.016 mmol), 1*H*-tetrazole (9 mg, 0.124 mmol), and **8b** (23 mg, 0.042 mmol) in 12 h furnished **9b** (24 mg, 88%) as a colorless syrup: TLC (SiO_2) 30% EtOAc/CH_2Cl_2, R_f ~0.5; ^{1}H NMR δ 7.08−7.41 (m, 45H), 4.51−5.17 (m, 26H), 4.01−4.47 (m, 4H), 3.25−3.54 (m, 7H), 1.38−1.56 (m, 4H), 1.10−1.38 (m, 20 H), 0.89 (t, J = 6.0 Hz, 3H), 0.88 (t, J = 6.1 Hz, 3H); HRMS (FAB in 3-NBA) calcd for $C_{82}H_{103}O_{21}P_4$ $(M - C_8H_9O)^+$ m/z 1547.5942, found 1547.5954.

Preparation of 10b. In the same manner as described for the ester analogue **10a**, **9b** (25 mg, 0.015 mmol), $NaHCO_3$ (9 mg, 0.105 mmol), and Pd black (35 mg) gave **10b** (13 mg, 94%) as a white deliquescent solid: ^{1}H NMR (D_2O, 250 MHz) δ 4.10−4.37 (m, 2H), 3.15−3.99 (m, 13H), 1.36−1.57 (m, 4H), 0.87−1.36 (m, 20H), 0.61−0.82 (m, 6H); ^{31}P NMR (D_2O, 161.97 MHz; external standard 85% H_3PO_4) δ 5.173, 3.991, 2.114, 0.087; HRMS (FAB in 3-NBA/NaI) calcd for $C_{25}H_{47}O_{20}P_4Na_8$ $(M + Na)^+$ m/z 975.0793, found 975.0780.

Preparation of 8c. Following the same procedure used for the ester analogue **8a**, **15** (100 mg, 0.21 mmol), benzyl *N,N,N′N′*-tetraisopropylphosphorodiamidite[16] (109 mg, 0.322 mmol), and 1*H*-tetrazole (23 mg, 0.322 mmol) furnished **8c** (133 mg, 81%) as a colorless oil: TLC (SiO_2) 30% EtOAc/hexane, R_f ~0.57; ^{1}H NMR δ 7.15−7.48 (m, 10H), 4.59−5.17 (m, 4H), 3.30−3.82 (m, 11H), 3.17 (q, J = 6.5 Hz, 2H), 1.40−1.62 (m, 6H), 1.22−1.40 (m, 18H), 1.21 (d, J = 7.1 Hz, 6H), 1.19 (d, J = 7.1 Hz, 6H), 0.87 (t, J = 6.2 Hz, 3H).

Preparation of 9c. In the same manner as described for the ester analogue **9a**, **7** (35 mg, 0.03 mmol), 1*H*-tetrazole (15 mg, 0.218 mmol), and **8c** (51 mg, 0.073 mmol) in 12 h gave **9c** (45 mg, 86%) as a colorless syrup: TLC (SiO_2) 40% EtOAc/hexane, R_f ~0.29; ^{1}H NMR δ 7.08−7.42 (m, 50H), 4.50−5.15 (m, 20H), 3.91−4.50 (m, 4H), 3.20−3.71 (m, 15H), 3.14 (q, J = 6.2 Hz, 2H), 1.32−1.69 (m, 6H), 1.12−1.32 (m, 18H), 0.87 (t, J

= 6.3 Hz, 3H); HRMS (FAB in 3-NBA) calcd for $C_{90}H_{110}NO_{23}P_4$ $(M - C_8H_9O)^+$ m/z 1696.6419, found 1696.6427.

Preparation of 10d. Following the procedure used for ester analogue **10a**, **9c** (35 mg, 0.019 mmol), $NaHCO_3$ (10 mg, 0.115 mmol), and Pd black (40 mg) gave **10d** (15 mg, 87%) as an off-white deliquescent solid: ^1H NMR (D_2O) δ 4.08–4.35 (m, 2H), 3.02–3.95 (m, 15H), 1.31–1.60 (m, 6H), 0.90–1.31 (m, 18H), 0.68 (t, J = 6.0 Hz, 3H); HRMS (FAB in 3-NBA/NaI) calcd for $C_{25}H_{49}NO_{20}P_4Na_7$ $(M + Na)^+$ m/z 968.1082, found 968.1088.

1-*O*-(8-Azidooctyl)-3-*O*-(3,4-dimethoxybenzyl)-*sn*-glycerol (13). A mixture of **12** (100 mg, 0.412 mmol) and Bu_2SnO (113 mg, 0.453 mmol) in toluene/MeOH (2 mL, 9:1) was refluxed using a Dean–Stark separator for 8 h. The volatiles were evaporated under reduced pressure, and the residue was dissolved in dry DMF (2 mL) containing 1-azido-8-bromooctane (97 mg, 0.412 mmol). After 14 h at room temperature, water (5 mL) was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with water (3 mL) and brine and dried. The solvent was evaporated in vacuo, and the residue was chromatographed (SiO_2) to give **13** (119 mg, 73%) as a colorless oil: TLC (SiO_2) 1:1 EtOAc/hexane, R_f ~0.28; ^1H NMR δ 6.82–6.92 (m, 3H), 4.51 (s, 2H), 3.92–4.05 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.35–3.57 (m, 6H), 3.25 (t, J = 6.8 Hz, 2H), 2.50 (br s, 1H, D_2O exchangeable), 1.50–1.70 (m, 4H), 1.22–1.43 (m, 8H); ^{13}C NMR δ 149.01, 148.67, 130.52, 120.33, 111.07, 110.88, 73.34, 71.81, 71.55, 71.13, 69.51, 55.88, 55.81, 51.40, 29.51, 29.23, 29.02, 28.76, 26.60, 25.93; HRMS calcd for $C_{20}H_{33}N_3O_5$ m/z 395.2420, found 395.2429.

1-*O*-(8-Azidooctyl)-2-*O*-octyl-*sn*-glycerol (14). A solution of **13** (900 mg) in anhydrous DMF (3 mL) was added to a suspension of NaH (60% in mineral oil, 182 mg, 4.55 mmol) in DMF (3 mL) at 0°C under an inert atmosphere. The mixture was stirred for 30 min before the addition of 1-bromooctane (787 μL, 4.55 mmol). After an additional 4 h at room temperature, the reaction was quenched with ice–water (10 mL), the mixture was extracted with Et_2O (3 × 40 mL), and the combined ethereal extracts were washed with water (10 mL) and brine and dried. The solvent was removed in vacuo, and the residue was purified by chromatography (SiO_2) to yield 1-*O*-(8-azidooctyl)-2-*O*-octyl-3-*O*-(3,4-dimethoxybenzyl)-*sn*-glycerol (890 mg, 77%) as a colorless oil: TLC (SiO_2) 30% EtOAc/hexane, R_f ~0.5; ^1H NMR δ 6.79–6.92 (m, 3H), 4.49 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.35–3.64 (m, 9H), 3.24 (t, J = 6.8 Hz, 2H), 1.47–1.65 (m, 6H), 1.20–1.40 (m, 18H), 0.88 (t, J = 6.0 Hz, 3H); ^{13}C NMR δ 148.82, 148.36, 130.84, 120.01, 110.79, 110.65, 77.78, 73.11, 71.42, 70.66, 70.44, 69.86, 55.74, 55.63, 51.29, 31.70, 29.97, 29.47, 29.32, 29.16, 28.96, 28.67, 26.52, 25.96, 25.88, 22.53, 13.97; HRMS calcd for $C_{28}H_{49}N_3O_5$ m/z 507.3672, found 507.3681.

To a 0 °C solution of the above glycerol (680 mg, 1.34 mmol) in CH_2Cl_2/H_2O (10 mL, 9:1) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (609 mg, 2.68 mmol). After 4 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine, dried, and evaporated in vacuo. The residue was purified by chromatography (SiO_2) to give **14** (397 mg, 83%) as a colorless oil: TLC (SiO_2) 20% EtOAc/hexane, R_f ~0.21; ^1H NMR δ 3.47–3.78 (m, 7H), 3.44 (t, J = 6.5 Hz, 2H), 3.25 (t, J = 6.9 Hz, 2H), 2.40 (t, J = 6.4 Hz, 1H, D_2O exchangeable), 1.47–1.70 (m, 6H), 1.18–1.47 (m, 18H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR δ 78.23, 71.60, 70.70, 70.26, 62.84, 51.31, 31.70, 29.94, 29.44, 29.30, 29.15, 28.96, 28.69, 26.52, 25.96, 25.86, 22.53, 13.97; HRMS calcd for $C_{19}H_{39}N_3O_3$ m/z 357.2991, found 357.2985.

1-*O*-[[*N*-(Benzyloxycarbonyl)amino]octyl]-2-*O*-octyl-*sn*-glycerol (15). A solution of **14** (357 mg, 1.0 mmol) in EtOH (10 mL) was stirred with 10% Pd/C (35 mg) under hydrogen (1 atm) for 4 h. The catalyst was removed by filtration over a pad of Celite 577, and the filter cake was washed with EtOAc (10 mL). The combined filtrate was evaporated in vacuo, and the crude amine was immediately protected.

The above amine was dissolved in THF (5 mL), and to this solution was added anhydrous Na_2CO_3 (140 mg, 1.31 mmol) at 0 °C, followed by benzyl chloroformate (Cbz Cl) (150 μL, 1.05 mmol). The reaction mixture was stirred for 4 h at 0 °C before dilution with 10% aqueous $NaHCO_3$ solution (5 mL) and extraction with EtOAc (2 × 20 mL). The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue on chromatography (SiO_2) gave **15** (288 mg, 62% overall yield) as a colorless oil: TLC (SiO_2) 20% EtOAc/hexane, R_f ~0.34; ^1H NMR δ 7.30–7.44 (m, 5H), 5.10 (s, 2H), 4.75 (br s, 1H, D_2O exchangeable), 3.40–3.80 (m, 9H), 3.18 (q, J = 6.6 Hz, 2H), 2.15–2.28 (m, 1H, D_2O exchangeable), 1.40–1.71 (m, 6H), 1.15–1.40 (m, 18H), 0.88 (t, J = 6.2 Hz, 3H); ^{13}C NMR δ 156.31, 136.57, 128.39, 127.97, 127.95, 78.20, 71.63, 70.73, 70.28, 66.44, 62.90, 40.98, 31.72, 29.96, 29.44, 29.32, 29.17, 29.06, 26.54, 25.99, 25.87, 22.56, 14.01; HRMS calcd for $C_{27}H_{47}NO_5$ m/z 465.3454, found 465.3459.

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Supplementary Material Available: ^1H, ^{13}C, and ^{31}P NMR spectra for all new compounds (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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