General Method for the Synthesis of Phospholipid Derivatives of 1,2-*O*-Diacyl-*sn*-glycerols

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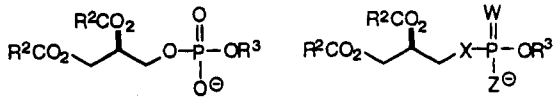
An efficient phosphite coupling protocol is described for the syntheses of the major classes of phospholipids that are derived from 1,2-*O*-diacyl-*sn*-glycerols and analogues thereof. The symmetrical diacyl glycerols **10c,d** were prepared by straightforward acylation of 3-*O*-benzyl-*sn*-glycerol (**7**) with the appropriate carboxylic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP). A simple method for preparing saturated and unstaturated mixed 1,2-*O*-diacyl-*sn*-glycerols was then devised that involved stepwise acylation of **7** with different alkyl carboxylic acids and debenzylation; this procedure is exemplified by the preparation of **10a,b**. The 1,2-*O*-diacyl-*sn*-glycerols **10a–d** were then coupled with suitably protected lipid head groups employing reactive alkyl or aryl dichlorophosphites to give intermediate phosphite triesters in high overall yields. Oxidation or sulfurization of these phosphites proceeded smoothly to give the corresponding phosphate or phosphorothioate triesters, deprotection of which then provided the phosphatidylcholines **16** and **17**, the phosphatidylethanolamine **20**, the phosphatidylserine **28**, and the phosphatidylinositols **37** and **38**. Preparation of **37** and **38** required the invention of an improved method for resolving the isopropylidene-protected D-*myo*-inositol derivative **33**. This phosphite coupling procedure was modified to assemble phospholipids bearing polyunsaturated acyl side chains at the *sn*-2-position as exemplified by the preparation of the phosphatidylethanolamine **26**. The one-pot phosphite coupling procedure is also applicable to the syntheses of a variety of other biologically interesting phospholipid analogues. For example, the phosphatidylinositol analogues **49–51**, in which the hydroxyl group at C(2) of the inositol ring has been modified, were prepared in excellent overall yields by conjoining the 1,2-*O*-diacyl-*sn*-glycerol **10c** with the protected inositol derivatives **44**, **45**, and **48**. Phospholipid analogues that contain other replacements of the phosphate group including phosphoramidates and thiophosphates may be prepared as evidenced by the syntheses of **56** and **61** in which the *sn*-3 oxygen atom of the 1,2-*O*-diacyl-*sn*-glycerol moiety is replaced with an *N*-benzyl group or a sulfur atom, respectively.

Introduction

Members of one major subclass of the phospholipid family of natural products are represented generally by the structure **1**. The fatty acid side chains R^1 and R^2 may vary in length and level of unsaturation, and the nature of the head group R^3 determines whether the phospholipid is a phosphatidylcholine ($R^3 = CH_2CH_2NMe_3^+$), a phosphatidylethanolamine ($R^3 = CH_2CH_2NH_3^+$), a phosphatidylserine [$R^3 = CH_2CH(NH_3^+)CO_2^-$], or a phosphatidylinositol [R^3 = cyclo-$C_6H_6(OH)_5$]. Phospholipids are the primary structural subunits of the bilayers that constitute cell membranes, and they play critical roles in many biological events through their interactions with other membrane components, including other lipids, proteins, and DNA.[1-5] Enzymatic processing of phospholipids is a key step in signal transduction.[6] Some phospholipid derivatives exhibit promising chemotherapeutic applications as antitumor,[7] antihypertensive,[8] and antiinflammatory[9] agents, whereas other analogues are valuable as tools for elucidating mechanistic aspects of enzymatic reactions involving phospholipid processing in cells.[10,11]



1 2

R^1 = saturated alkyl
R^2 = saturated or unsaturated alkyl
$R^3 = CH_2CH_2\overset{\oplus}{N}Me_3$, $CH_2CH_2\overset{\oplus}{N}H_3$, $CH_2CH(S)(NH_2)CO_2H$, *cyclo*-$C_6H_6(OH)_5$
X = O, NR, S, CH_2, CF_2
W, Z, = O, S, combinations

The importance of phospholipids in physiological processes coupled with the use of their analogues as enzyme

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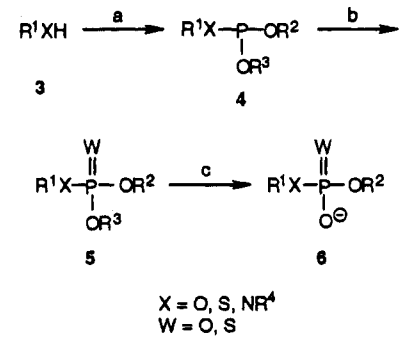
(1) Yeagle, P. L. *Acc. Chem. Res.* **1978**, *11*, 321.
(2) Eibl, H. *Angew. Chem., Int. Ed. Eng.* **1984**, *23*, 257.
(3) Hanahan, D. J. *Ann. Rev. Biochem.* **1986**, *55*, 483.
(4) (a) Low, M. G.; Saltiel, A. R. *Science* **1988**, *239*, 268. (b) Tartakoff, A. M.; Singh, N. *Trends Biochem. Sci.* **1992**, *17*, 470.
(5) Datema, K. P.; Spruijt, R. B.; Verduin, J. M.; Hemminga, M. A. *Biochemistry* **1987**, *26*, 6217.
(6) (a) Berridge, M. J. *Scientific American* **1985**, *253*, 142. (b) Majerus, P. W.; Wilson, D. B.; Connolly, T. M.; Bross, T. E.; Neufeld, E. J. *Trends Biochem. Sci.* **1985**, *10*, 168. (b) Nishizuka, Y. *Science* **1986**, *233*, 305. (c) Nishizuka, Y. *Nature* **1988**, *334*, 661. (d) Rhee, S. G.; Suh, P.-G.; Ryu, S.-H.; Lee, S. Y. *Science* **1989**, *244*, 546. (e) Billah, M. M.; Anthes, J. C. *Biochem. J.* **1990**, *269*, 281. (f) Exton, J. H. *J. Biol. Chem.* **1990**, *265*, 1. (g) Liscovitch, M. *Trends Biochem. Sci.* **1992**, *17*, 393. (h) Nishizuka, Y. *Science* **1992**, *258*, 607. (i) Rhee, S. G.; Choi, K. D. *J. Biol. Chem.* **1992**, *267*, 12393. (j) Cockroft, S. *Biochim. Biophys. Acta* **1992**, *1113*, 135.
(7) (a) Herrmann, D. B. J.; Neumann, H. A. *J. Biol. Chem.* **1986**, *261*, 7742. (b) Marx, M. H.; Piantadosi, C.; Noseda, A.; Daniel, L. W.; Modest, E. J. *J. Med. Chem.* **1988**, *31*, 858. (c) Ukawa, K.; Imamiya, E.; Yamamoto, H.; Mizuno, K.; Tasaka, A.; Terashita, Z.-I.; Okutani, T.; Nomura, H.; Kasukabe, T.; Hozumi, M.; Kudo, I.; Inoue, K. *Chem. Pharm. Bull.* **1989**, *37*, 1249.
(8) (a) Wissner, A.; Schaub, R. E.; Sum, P.-E.; Kohler, C. A.; Goldstein, B. M. *J. Med. Chem.* **1986**, *29*, 328. (b) Ohno, M.; Fujita, K.; Shiraiwa, M.; Izumi, A.; Kobayashi, S.; Yoshiwara, H.; Kudo, I.; Inoue, K.; Nojima, S. *J. Med. Chem.* **1986**, *29*, 1812.
(9) Shen, T. Y. *J. Med. Chem.* **1981**, *24*, 1.

0022-3263/94/1959-4805$04.50/0

inhibitors and drug candidates has stimulated the development of methods for the efficient chemical synthesis of structurally defined, enantiomerically pure congeners of phospholipids.[12] The key steps in the synthesis of phospholipids are the formation of the two requisite phosphodiester bonds, one to the diacylglycerol subunit and the other to the appropriate head group. Phosphorylation methods using phosphate chemistry have been commonly employed to effect these constructions, but these techniques may be inefficient or ineffective, especially when bulky alcohols are the reactants. The alternative tactic of coupling two alcohols using phosphite reagents followed by oxidation of the intermediate phosphite triester has been well established and extensively used to synthesize oligonucleotides;[13] however, the application of this tactic for the construction of phospholipids and their derivatives has only recently been reported.[14-17]

Scheme 1[a]



[a] (a) R^3OPCl_2 (1 equiv); R^2OH (1 equiv); (b) [O] or S_8; (c) deprotect.

In the course of a program directed toward elucidating the mechanism of hydrolysis of the phosphodiester bond of phospholipids by enzymes of the phospholipase C (PLC) class, we required a number of phospholipid analogues of the general type **2**. Mindful of the limitations of phosphate-based technologies, we developed an efficient procedure in which alkyl dichlorophosphites were exploited as the coupling agents (Scheme 1).[14] The intermediate phosphite triesters **4** were converted by oxidation or sulfurization into the phosphate **5** (W = O) or phosphorothioate triesters **5** (W = S), respectively. Selective cleavage of the alkyl residue that served as the oxygen protecting group then afforded the corresponding phosphate **6** (W = O) and phosphorothioate diesters **6** (W = S). This sequence represents an extremely effective and simple protocol that allows coupling of *equimolar* amounts of the two alcohol subunits of the phospholipid analogue to give the phosphotriester in a *single synthetic operation* and in high overall yield. On the basis of the encouraging results revealed in our initial development of this method,[14] we elected to explore its scope to ascertain whether this technique could be used to prepare all classes of 1,2-*O*-diacyl phospholipids and their analogues. We now report additional findings that convincingly establish the generality of the alkyl dichlorophosphite method for the syntheses of phospholipids containing a wide range of head groups and a variety of diacyglycerol, mixed diacyl glycerol, and unsaturated diacylglycerol subunits.

Results and Discussion

Synthesis of Diacylglycerols. Naturally occurring phospholipids typically have two different acyl chains, and the syntheses of such phospholipids has historically been problematic. Some mixed diacyl phosphatidylcholine derivatives may be prepared from *lyso*-phospholipids that are formed by selective hydrolysis of the *sn*-2 acyl side chain of a phosphatidylcholine with PLA_2.[18] However, the applicability of this tactic is limited as it cannot be readily applied to the syntheses of mixed diacyl phospholipids of other classes because protection and deprotection of the ethanolamine, serine, or inositol head groups require additional steps. A more general strategy for the preparation of mixed diacyl phospholipids would entail the direct coupling of a mixed 1,2-*O*-diacyl-*sn*-

(10) For phospholipase A_2, see: (a) Yuan, W.; Berman, R. J.; Gelb, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 8071. (b) Yuan, W.; Quinn, D. M.; Sigler, P. B.; Gelb, M. H. *Biochemistry* **1990**, *29*, 6082. (c) Scott, D. L.; White, S. P.; Otwinowski, Z.; Yuan, W.; Gelb, M. H.; Sigler, P. B. *Science* **1990**, *250*, 1541. (d) White, S. P.; Scott, D. L.; Otwinowski, Z.; Gelb, M. H.; Sigler, P. B. *Science* **1990** *250*, 1560. (e) Scott, D. L.; Otwinowski, Z.; Gelb, M. H.; Sigler, P. B. *Science* **1990** *250*, 1563. (f) Yu, L.; Deems, R. A.; Hajdu, J.; Dennis, E. A. *J. Biol. Chem.* **1990**, *265*, 2657. (g) Washburn, W. N.; Dennis, E. A. *J. Biol. Chem.* **1991**, *266*, 5042. (h) Jain, M. K.; Tao, W.; Rogers, J.; Arenson, C.; Eibl, H.; Yu, B.-Z. *Biochemistry* **1991**, *30*, 10256. (i) Noel, J. P.; Bingman, C. A.; Deng, T.; Dupureur, C. M.; Hamilton, K. J.; Jiang, R.-T.; Kwak, J.-G.; Sekharudu, C.; Sundaralingam, M.; Tsai, M.-D. *Biochemistry* **1991**, *30*, 11801. (j) Rogers, J.; Yu, B.-Z.; Jain, M. K. *Biochemistry* **1992**, *31*, 6056. (k) Peters, A. R.; Dekker, N.; van den Berg, L.; Boelens, R.; Kaptein, R.; Slotboom, A. J.; de Haas, G. H. *Biochemistry* **1992**, *31*, 10024. (l) Bennion, C.; Connolly, S.; Gensmantel, N. P.; Hallam, C.; Jackson, C. G.; Primrose, W. U.; Roberts, C. K.; Robinson, D. H.; Slaich, P. K. *J. Med. Chem.* **1992**, *35*, 2939. (m) Tomoo, K.; Ohishi, H.; Doi, M.; Ishida, T.; Inoue, M.; Ikeda, K.; Mizuno, H. *Biochem. Biophys. Res. Commun.* **1992**, *187*, 821.

(11) For phospholipase C and D, see: (a) Orr, G. A.; Brewer, C. F.; Heney, G. *Biochemistry* **1982**, *21*, 3202. (b) Bruzik, K.; Gupte, S. M.; Tsai, M.-D. *J. Am. Chem. Soc.* **1982**, *104*, 4682. (c) Bruzik, K.; Jiang, R.-T.; Tsai, M.-D. *Biochemistry* **1983**, *22*, 2478. (d) Bruzik, K.; Tsai, M. -D. *Biochemistry* **1984**, *23*, 1656. (e) Jiang, R.-T.; Shyy, Y.-J.; Tsai, M.-D. *Biochemistry* **1984**, *23*, 1661. (f) Lin, G.; Bennett, C. F.; Tsai, M.-D. *Biochemistry* **1990**, *29*, 2747. (g) Bruzik, K. S.; Morocho, A. M.; Jhon, D.-Y.; Rhee, S. G.; Tsai, M.-D. *Biochemistry* **1992**, *31*, 5183. (h) Lewis, K. A.; Garigapati, V. R.; Zhou, C.; Roberts, M. F. *Biochemistry* **1993**, *32*, 8836. (i) Bruzik, K. S.; Tsai, M.-D. *BioMed. Chem.* **1994**, *2*, 49.

(12) For reviews, see: (a) Eibl, H. *Chem. Phys. Lipids* **1980**, *26*, 405. (b) Ramirez, F.; Marecek, J. F. *Synthesis* **1985**, 449.

(13) For reviews of the phosphoramidite approach to oligonucleotides and other phosphorylated biomolecules, see: (a) Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223; **1993**, *49*, 10441.

(14) Martin, S. F.; Josey, J. A. *Tetrahedron Lett.* **1988**, *29*, 3631.

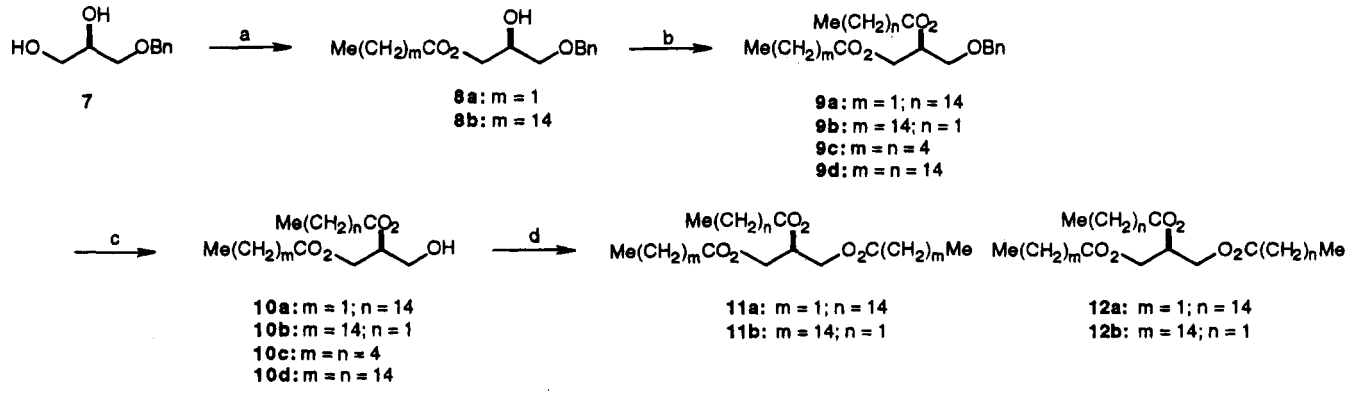
(15) For the use of cyclic phosphites, see: (a) Nifantev, E. E.; Predvoditelev, D. A.; Alarkon, K. H. *J. Org. Chem. USSR (Engl. Transl.)* **1978**, *14*, 56. (b) McGuigan, C. *J. Chem. Soc., Chem. Commun.* **1986**, 533. (c) Mlotkowska, B.; Markowska, A. *Liebigs Ann. Chem.* **1988**, 191. (d) Anson, M. S.; McGuigan, C. *J. Chem. Soc., Perkin Trans. I* **1989**, 715. (e) McGuigan, C.; Swords, B. *J. Chem. Soc., Perkin Trans. I* **1990**, 783. (f) McGuigan, C.; Anson, M. S.; Swords, B. *J. Chem. Soc., Perkin Trans. I* **1992**, 2075.

(16) For recent applications of phosphoramidites and other trivalent phosphorus coupling reagents, see: (a) Bruzik, K. S.; Salamonczyk, G.; Stec, W. J. *J. Org. Chem.* **1986**, *51*, 2368. (b) Lamant, V.; Chap, H.; Klaébé, A.; Périé, J. J.; Willson, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1608. (c) Rosario-Jansen, T.; Jiang, R.-T.; Tsai, M.-D.; Hanahan, D. J. *Biochemistry* **1988**, *27*, 4619. (d) Bruzik, K. S. *J. Chem. Soc., Perkin Trans. I* **1988**, 423. (e) Elie, C. J. J.; Dreef, C. E.; Verduyn, R.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1989**, *45*, 3477. (f) Loffredo, W. M.; Tsai, M.-D. *Bioorganic Chem.* **1990**, *18*, 78. (g) Salamonczyk, G. M.; Bruzik, K. S. *Tetrahedron Lett.* **1990**, *31*, 2015. (h) Garcia, M. L.; Pascual, J.; Andreu, J. A.; Fos, E.; Mauleón, D.; Carganico, G.; Arcamone, F. *Tetrahedron* **1991**, *47*, 10023. (i) Kazi, A. B.; Hajdu, J. *Tetrahedron Lett.* **1992**, *33*, 2291. (j) Seitz, S. P.; Kaltenbach, R. F., III; Vreekamp, R. H.; Calabrese, J. C.; Perrella, F. W. *BioMed. Chem. Lett.* **1992**, *2*, 171. (k) Sawabe, A.; Filla, S. A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 7685. (l) Hébert, N.; Beck, A.; Lennox, B. R.; Just, G. *J. Org. Chem.* **1992**, *57*, 1777. (m) Garigapati, V. R.; Roberts, M. F. *Tetrahedron Lett.* **1993**, *34*, 769.

(17) For the use of H-phosphonates, see: Lindh, I.; Stawinski, J. *J. Org. Chem.* **1989**, *54*, 1338.

(18) (a) Delfino, J. M.; Schreiber, S. L.; Richards, F. M. *Tetrahedron Lett.* **1987**, *28*, 2327. (b) Ali, S.; Bittman, R. *Chem. Phys. Lipids* **1989**, *50*, 11.

Scheme 2[a]



[a] (a) $Me(CH_2)_mCO_2H$, DCC, DMAP, 0 °C. (b) $Me(CH_2)_nCO_2H$, DCC, DMAP, 20 °C; (c) Pd/C, EtOH, AcOH, 20–40 °C; (d) $Me(CH_2)_mCO_2H$ or $Me(CH_2)_nCO_2H$, DCC, DMAP, 20 °C.

glycerol with a suitably protected head group followed by global deprotection to give the phospholipid. Although a number of procedures for preparing differentially substituted 1,2-*O*-diacyl-*sn*-glycerols by sequential acylations of protected glycerol derivatives have been developed, these are typically somewhat cumbersome as several steps and protective maneuvers are required.[19]

A more direct approach to mixed 1,2-*O*-diacyl-*sn*-glycerols was clearly indicated, and it occurred to us that the simple plan outlined in Scheme 2 could provide a concise and efficient route to mixed 1,2-*O*-diacyl-*sn*-glycerols. The critical question to be addressed was whether sequential acylation of the primary and secondary hydroxyl groups of a 3-protected *sn*-glycerol derivative could be cleanly achieved. We discovered that the *sn*-1-hydroxyl group of 3-*O*-benzyl-*sn*-glycerol (**7**) could be selectively acylated with several representative carboxylic acids using dicyclohexylcarbodiimide (DCC)[20] in the presence of 4-(dimethylamino)pyridine (DMAP) (Scheme 2). Careful control of the reaction temperature was necessary to avoid diacylation. Subsequent acylation of the monoesters **8a,b** thus obtained with a second carboxylic acid in the presence of DCC and DMAP proceeded *without* deleterious 1,2-acyl migration (*vide infra*) to furnish the mixed 1,2-*O*-diacyl-*sn*-glycerols **10a,b**. The DCC/DMAP-mediated acylation of **7** with alkyl carboxylic acids to provide the monoacylated glycerols **8a,b** was superior to using the corresponding acid chlorides or anhydrides. The symmetrical 1,2-*O*-diacyl-*sn*-glycerol derivatives **9c,d** were simply obtained by *O*-diacylation of **7** with 2 equiv of the appropriate carboxylic acid in the presence of DCC and DMAP. The benzyl protecting group was removed from **9a–d** by *careful* hydrogenolysis to give the 1,2-*O*-diacyl-*sn*-glycerols **10a–d**. It was necessary to monitor the progress of the deprotection closely by TLC and to work the reaction up as soon as the starting material was consumed (typically 2–4 h) in order to avoid 2→3-acyl migration. Thus, following this protocol, the mixed 1,2-*O*-diacyl-*sn*-glycerols **10a,b** were consistently obtained in ≥55% overall yield and in only three steps from commercially available **7**. This represents a significant improvement over other known methods for the preparation of mixed 1,2-*O*-diacyl-*sn*-glycerols.

On the basis of quantitative ^{13}C NMR analysis, the mixed 1,2-*O*-diacyl-*sn*-glycerols **10a,b** were judged to be ≥98% homogeneous, but the possibility that *complete* 1→2-acyl migration occurred to give an intermediate 2-acyl-*sn*-glycerol derivative prior to the second acylation step could not be rigorously excluded. To verify that no such 1→2-acyl migration had occurred, the triacyl glycerides **11a,b** and **12a,b** were prepared from the 1,2-*O*-diacyl-*sn*-glycerols **10a,b**. Analysis of the possible pairs of product triglycerides **11a/12b** and **11b/12a** using ^{13}C NMR and capillary GLC, respectively, revealed that each of the triglycerides **11a,b** and **12a,b** was ≥98% pure on the basis of the limits of detection of the method. Thus, we conclude that ≤2% of 1,2-acyl migration accompanied any of the acylation steps or the deprotection of **9a,b** by hydrogenolysis.

Synthesis of Phospholipid Analogues. After surveying several phosphite coupling and oxidation procedures that had been employed for the synthesis of DNA oligonucleotides,[13,21] we discovered that alkyl and aryl dichlorophosphites could be used to prepare 1,2-*O*-diacyl-*sn*-glycerol derived phospholipids provided some simple modifications of the original techniques were implemented.[14,22] For example, *N,N*-diisopropylethylamine was superior to triethylamine as a base. Methyl dichlorophosphite and phenyl dichlorophosphite, which are commercially available, and 2-(trimethylsilyl)ethyl dichlorophosphite[23] may each be employed as the coupling agent. Although 2-(trimethylsilyl)ethyl dichlorophosphite must be synthesized, the (trimethylsilyl)ethyl group may be easily removed under selective and mild conditions that are compatible with functionality and protecting groups that might be present on the head groups. In the first step, the alkyl dichlorophosphite was usually coupled with the bulkier of the two alcohol partners at −78 °C to minimize the deleterious reaction of the intermediate

(19) (a) Lok, C. M. *Chem. Phys. Lipids* **1978**, *22*, 323. (b) Eibl, H.; Wooley, P. *Chem. Phys. Lipids* **1986**, *41*, 53. (c) Burgos, C. E.; Ayer, D. E.; Johnson, R. A. *J. Org. Chem.* **1987**, *52*, 4973. (d) Hasegawa, E.; Eshima, K.; Matsushita, Y.; Nishide, H.; Tsuchida, E. *Synthesis* **1987**, 60. (e) Eibl, H.; Wooley, P. *Chem. Phys. Lipids* **1988**, *47*, 47. (f) Hermetter, A.; Stütz, H.; Franzmair, R.; Paltauf, F. *Chem Phys. Lipids* **1989**, *50*, 57. (g) Duralski, A. A.; Spooner, P. J. R.; Watts, A. *Tetrahedron Lett.* **1989**, *30*, 3585.

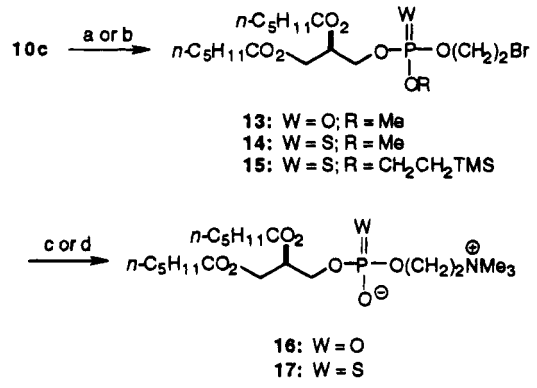
(20) (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (b) Hasser, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475. (c) Ziegler, F. E.; Berger, G. D. *Synth. Commun.* **1979**, *9*, 539.

(21) (a) Letsinger, R. L.; Finnan, J. L.; Heavner, G. A.; Lunsford, W. B. *J. Am. Chem. Soc.* **1975**, *97*, 3278. (b) Letsinger, R. L.; Lunsford, W. B. *J. Am. Chem. Soc.* **1976**, *98*, 3655.

(22) For a discussion of some of the problems associated with oxidation of phosphites to phosphates, see: Bannworth, W.; Treciak, A. *Helv. Chim. Acta* **1987**, *70*, 175.

(23) Mautz, D. S.; Davisson, V. J.; Poulter, C. D. *Tetrahedron Lett.* **1989**, *30*, 7333. See also: Sawabe, A.; Filla, S. A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 7685.

Scheme 3[a]



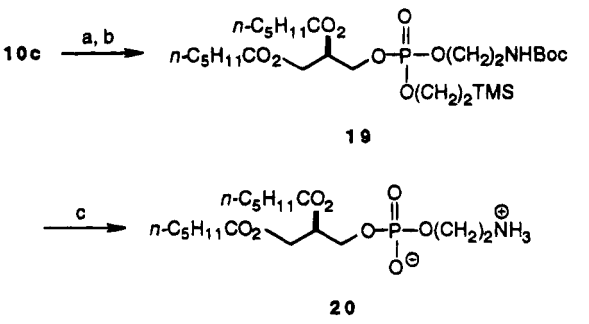
[a] (a) $MeOPCl_2$, $(i\text{-Pr})_2NEt$, THF, −78 °C; $HO(CH_2)_2Br$, −78 → 20 °C; 30% aqueous H_2O_2, THF, 0 °C → rt; (b) $TMSCH_2CH_2OPCl_2$, $(i\text{-Pr})_2NEt$, −78 °C; $HO(CH_2)_2Br$, −78 → 20 °C; S_8, Py, PhMe, rt or 3*H*-1,2-benzodithiol-3-one 1,1-dioxide (**18**); (c) Me_3N; (d) Me_3N; aqueous HF.

dialkyl chlorophosphite with a second equivalent of this alcohol. Only small amounts of symmetrical, disubstituted products derived from this side reaction were generally detected, and they could be readily removed either by chromatography at this stage to give the desired phosphite triesters **4** or after the oxidation or sulfurization step to give **5**. One advantage of this one-pot procedure is that *only equimolar quantities* of the 1,2-*O*-diacyl-*sn*-glycerol, the phosphite coupling reagent, and the protected head group are required. To achieve optimal yields of the phosphate **5** (W = O) and phosphorothioate **5** (W = S) triesters, it was necessary to remove the excess *N,N*-diisopropylethylamine and its hydrochloride salt prior to oxidation or sulfurization of **4**. Removal of the protecting groups from **5** (W = O or S) then gave the phospholipids **6** in good overall yields. To establish the scope of this procedure, a number of phospholipid analogues were then prepared as summarized in Schemes 3–6.

1. Synthesis of Phosphatidylcholines, Phosphatidylethanolamines, and Phosphatidylserines. The coupling procedures outlined herein may be applied equally well to the syntheses of phospholipid analogues having either the same or different acyl side chains at the *sn*-1 and *sn*-2 positions. The following discussion will focus upon the preparation of those phospholipid derivatives that have dihexanoyl side chains, since these compounds were subsequently used in biological studies.[24] Several important aspects of the generality of this method may be illustrated by the syntheses of the phosphatidylcholine derivatives **16** and **17** (Scheme 3), the phosphatidylethanolamine **20** (Scheme 4), and the phosphatidylserine **28** (Scheme 6).

Methyl dichlorophosphite was used to couple the diacylglycerol **10c** with bromoethanol to give an intermediate phosphite triester that was oxidized with aqueous hydrogen peroxide to furnish the phosphate triester **13** (Scheme 3). Deprotection of **13** by the action of trimethylamine proceeded smoothly with concomitant nucleophilic displacement of bromide ion to give the phosphatidylcholine analogue **16**. Although the phosphorothioate analogue **14** could be readily prepared by sulfurization of the intermediate phosphite triester with sulfur in pyridine or 3*H*-1,2-benzodithiol-3-one 1,1-dioxide (**18**),[25] the efficient removal of the *O*-methyl group from **14** could not be induced to deliver **17**. An alternate protecting group for the phosphate triester was thus indicated. In the event, we discovered that coupling **10c** with 2-bromoethanol using 2-(trimethylsilyl)ethyl dichlorophosphite followed by sulfurization provided **15**. Reaction of **15** with trimethylamine and subsequent deprotection of the intermediate phosphothioate triester under mild conditions using dilute aqueous hydrofluoric acid at room temperature gave **17**. When the intermediate triphosphites were sulfurized with **18** instead of elemental sulfur, the product thiophosphate triesters were sometimes easier to purify. However, commercial **18** is somewhat expensive, and even though it may be readily prepared, we routinely used S_8 for these sulfurizations.

Scheme 4[a]



[a] (a) $TMSCH_2CH_2OPCl_2$, $(i\text{-Pr})_2NEt$, THF, −78 °C; $HO(CH_2)_2NHBoc$, −78 → 20 °C; (b) *t*-BuOOH, CH_2Cl_2, 0 °C; (c) CF_3CO_2H, CH_2Cl_2, 0 °C.

Although methyl and phenyl dichlorophosphites may be employed as coupling reagents to prepare phosphatidylethanolamines, use of 2-(trimethylsilyl)ethyl dichlorophosphite has the advantage that the conversion of **19** into **20**, which requires the removal of two protecting groups, may be conveniently performed in a single step as shown in Scheme 4.

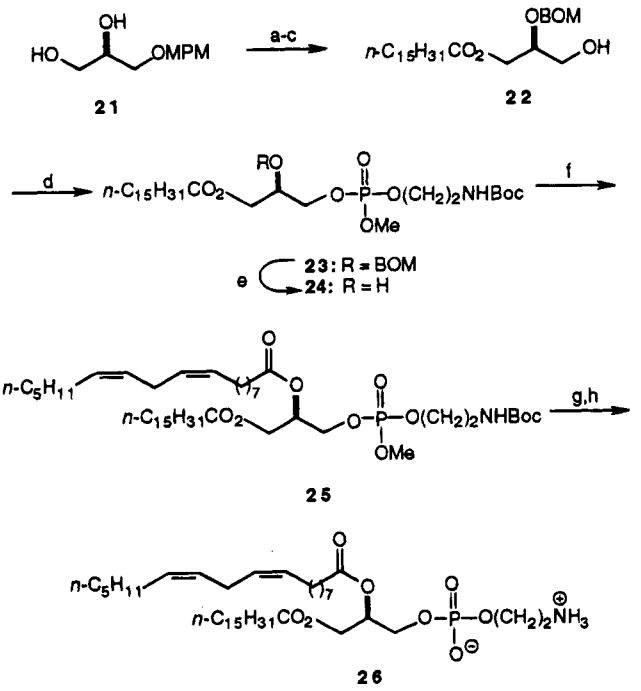
Many naturally occurring phospholipids contain unsaturated *sn*-2-acyl chains possessing from one to four double bonds. However, methods for the synthesis of such phospholipids have been somewhat restricted owing to the reactivity of the unsaturated acid side chains and their propensity to undergo facile oxidation. Furthermore, groups that are employed to protect the polar head groups and the phosphate triester must be removable under conditions that do not adversely affect the acyl side chains. Although the coupling protocol outlined in Schemes 2–4 could be applied to the syntheses of phospholipids bearing oleic acid at the *sn*-2 position, side chains having two or more double bonds were too susceptible to oxidation under the conditions employed to convert the intermediate phosphites to the corresponding phosphates. Consequently, we developed an efficient and general entry to complex mixed-acid and polyunsaturated phospholipids that is exemplified by the preparation of the unsaturated phosphatidylethanolamine derivative **26** (Scheme 5). This modified strategy features use of the phosphite coupling procedure to provide a simplified route to protected *lyso*-phospholipids such as **24** that may then be acylated with unsaturated fatty acids at the *sn*-2 position.

Selecting a protecting group stategy that would minimize unnecessary operations was a critical feature in the

(24) See: Martin, S. F.; Wong, Y. L.; Wagman, A. S. *J. Org. Chem.*, following paper in this issue.

(25) (a) Iyer, R. P.; Eagen, W.; Regan, J. B.; Beaucage, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 1253. (b) Regan, J. B.; Phillips, L. R.; Beaucage, S. L. *Org. Prep. Proc. Intl.* **1992**, *24*, 488.

Scheme 5[a]



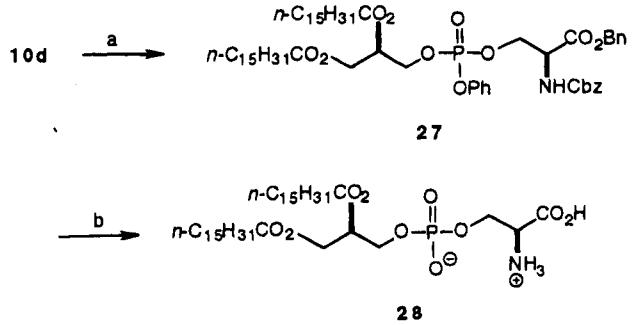
[a] (a) Palmitic acid, DCC, DMAP, CH_2Cl_2, 0 °C; (b) BOM-Cl, (*i*-Pr)$_2$NEt, CH_2Cl_2; (c) DDQ, CH_2Cl_2, H_2O, 0 °C; (d) $MeOPCl_2$, (*i*-Pr)$_2$NEt, THF, −78 °C; $HO(CH_2)_2NHBoc$, −78 → 20 °C; 30% aqueous H_2O_2, CH_2Cl_2; (e) Raney Ni, H_2, EtOH; (f) linoleic acid, DCC, DMAP, CH_2Cl_2; (g) NaI, 2-butanone, 80 °C; (h) CF_3CO_2H, CH_2Cl_2, 0 °C.

design of the approach. After exploring various possibilities, the protected glycerol **21**, which was prepared in two steps (92% overall yield) from 1,2-*O*-isopropylidene-*sn*-glycerol,[26] emerged as the starting material of choice (Scheme 5). The conversion of **21** into **22** was straightforward, and execution of the phosphite coupling and oxidation procedure proceeded without event to give the phosphate triester **23** in 81% overall yield. Removal of the benzyloxymethyl (BOM) protecting group from the *sn*-2 position of **23** by catalytic hydrogenolysis using Raney nickel ensued under mild conditions *without* detectable (based upon ^{13}C NMR) 1,2-acyl or phosphoryl migration to deliver the *lyso*-phospholipid **24**. Subsequent acylation of **24** with linoleic acid followed by deprotection of the intermediate **25** furnished the *sn*-2 unsaturated phosphatidylethanolamine **26**.[18a]

When phenyl dichlorophosphite was used as the coupling agent to prepare phosphatidylserine derivatives, the protecting groups on the serine subunit *and* the phenyl phosphate ester group of **27** could be cleaved simultaneously by catalytic hydrogenolysis[27] to give **28** in 71% yield (Scheme 6). (Trimethylsilyl)ethyl dichlorophosphite could be employed as the coupling agent to allow differential protection of the phosphate triester and the serine moiety with groups that could be readily and selectively removed under mild conditions.

2. Synthesis of Phosphatidylinositols. Since *myo*-inositol 1,4,5-trisphosphate is a secondary messenger in cellular signal transduction,[28] there has been temendous interest in the design of asymmetric syntheses of derivatives of *myo*-inositol[29] and the phosphatidylinositols.[30] It

Scheme 6[a]



[a] (a) $PhOPCl_2$, Cbz-NH(OH)Ser-OBn, (*i*-Pr)$_2$NEt, THF, −78 °C; **10d**, −78 → 20 °C; 30% H_2O_2, CH_2Cl_2, 0 °C; (b) PtO_2, Pd black, H_2, HOAc.

occurred to us that the phosphite coupling/oxidation procedure might be exploited to synthesize unnatural analogues of phosphatidylinositols as inhibitors and mechanistic probes to study the details of the hydrolysis of the phosphatidylinositols by the phospholipase C class of enzymes.[31]

The first task in this venture entailed developing practical routes to analogues of *myo*-inositol that were suitably protected for coupling with diacylglycerols. Although several routes to optically active inositols were known at the outset of our investigations several years ago, most of them suffered from being somewhat lengthy and inefficient, and we set to the task of devising an alternate method to resolve protected *myo*-inositol derivatives. Toward this end, the racemic bis-acetonide **29**, which was prepared from commercially available *myo*-inositol,[32] was selectively acylated[33] at the C(1) hydroxyl group with (1*S*)-(−)-camphanoyl chloride to give a diastereomeric mixture of **30a** and **31a** (Scheme 7). Isola-

(26) (a) Eibl, H. *Chem. Phys. Lipids* **1981**, *28*, 1. (b) Jackson, D. Y. *Synth. Commun.* **1988**, *18*, 337.

(27) Baer, E.; Maurukas, J. *J. Biol. Chem.* **1955**, *212*, 25.

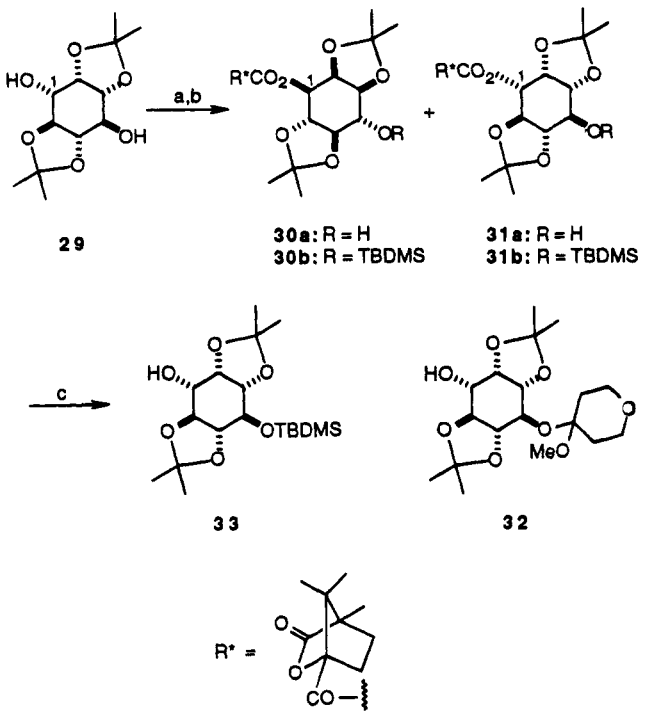
(28) For some recent, leading reviews, see: (a) Berridge, M. J. *Biochem. J.* **1984**, *220*, 345. (b) Berridge, M. J. *Scientific American* **1985**, *253*, 142. (c) Hokin, L. E. *Ann. Rev. Biochem.* **1985**, *54*, 205. (d) Nishizuka, Y. *Nature* **1988**, *334*, 661. (e) Berridge, M. J.; Irvine, R. F. *Nature* **1989**, *341*, 197. (f) Rana, R. S.; Hokin, L. E. *Physiol. Rev.* **1990**, *70*, 115. (g) Liscovitch, M. *Trends Biochem. Sci.* **1992**, *17*, 393. (h) Nishizuka, Y. *Science* **1992**, *258*, 607. (i) Potter, B. V. L.; Gigg, R. *Carbohydr. Res.* **1992**, *234*, xi. (j) Berridge, M. J. *Nature* **1993**, *361*, 315.

(29) (a) Jiang, C.; Moyer, J. D.; Baker, D. C. *J. Carbohydr. Chem.* **1987**, *6*, 319. (b) Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83. (c) Potter, V. L. *Nat. Prod. Rep.* **1990**, 1. (d) Reitz, A. B., Ed. *Inositol Phosphates and Derivatives: Synthesis, Biochemistry, and Therapeutic Potential*; ACS Symposium Series 463; American Chemical Society: Washington, DC, 1991. See also: (e) Bruzik, K. S.; Tsai, M.-D. *J. Am. Chem. Soc.* **1992**, *114*, 6361. (f) Pietrusiewicz, K. M.; Salamonczyk, G. M.; Bruzik, K. S.; Wieczorek, W. *Tetrahedron* **1992**, *48*, 5523. (g) Sawyer, D. A.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 923. (h) Lampe, D.; Potter, B. V. L. *Tetrahedron Lett.* **1993**, *34*, 2365. (i) Guidot, J. P.; Le Gall, T. *Tetrahedron Lett.* **1993**, *34*, 4647.

(30) (a) Gigg, R. *Chem. Phys. Lipids* **1980**, *26*, 287. (b) Ward. J. G.; Young, R. C. *Tetrahedron Lett.* **1988**, *29*, 6013. (c) Dreef, C. E.; Elie, C. J. J.; Hoogerhout, P.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1988**, *29*, 6513. (d) Elie, C. J. J.; Dreef, C. E.; Verduyn, R.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1989**, *45*, 3477. (e) Jones, M.; Rana, K. K.; Ward, J. G.; Young, R. C. *Tetrahedron Lett.* **1989**, *30*, 5353. (f) Salamonczyk, G. M.; Brusik, K. S. *Tetrahedron Lett.* **1990**, *31*, 2015. (g) Dreef, C. E.; Elie, C. J. J.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1991**, *32*, 955. (h) Seitz, S. P.; Kaltenbach, R. F., III; Vreekamp, R. H.; Calabrese, J. C.; Perrella, F. W. *BioMed. Chem. Lett.* **1992**, *2*, 171. (i) Pratt, C.; Liu, Y.-J.; Chu, T.-Y.; Melkonian, K.; Tropp, B. E.; Engel, R. *Can. J. Chem.* **1992**, *70*, 2135.

(31) For some leading references to the phospholipase C enzymes, see: (a) Shukla, S.D. *Life Sciences* **1982**, *30*, 1323. (b) Hokin L. E. *Ann. Rev. Biochem.* **1985**, *54*, 205. (c) Rhee, S. G.; Suh, P.-G.; Ryu, S.-H.; Lee, S. Y. *Science* **1989**, *244*, 546. (d) Berridge, M. J.; Irvine, R. F. *Nature* **1989**, *341*, 197. (e) Rhee, S.-G.; Choi, K. D. *J. Biol. Chem.* **1992**, *267*, 12393. (f) Cockcroft, S.; Thomas, G. M. H. *Biochem. J.* **1992**, *288*, 1. (g) Titball, R. W. *Microbio. Rev.* **1993**, 347. (h) See also in ref 24.

Scheme 7[a]

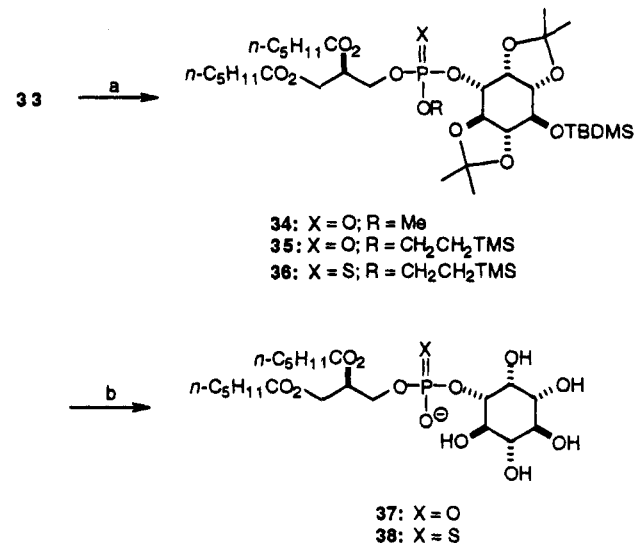


[a] (a) (1*S*)-(−)-Camphanoyl chloride (R*COCl), imidazole, DMF, 0 → 20 °C; (b) TBDMS-Cl, imidazole, DMF, 0 → 20 °C; (c) KOH, EtOH, rt.

tion of the pure alcohols **30a** and **30b** required the use of HPLC, but we discovered that the corresponding (*tert*-butyldimethyl)silyl ethers **30b** and **31b** could be readily separated by flash chromatography. The protons at C-2 of **30b** and **31b** were clearly distinguishable by ^{1}H NMR, and each of these isomers was judged to be ≥95% diastereomerically pure. The absolute stereochemistry of the more polar camphanate ester **31b** was confirmed by sequential desilylation (*n*-Bu_4NF, THF, 25 °C), ketal formation (4,5-dihydro-4-methoxypyran, Dowex 50-X, CH_2Cl_2, 25 °C), and ester hydrolysis (KOH, EtOH, Δ) to furnish the known alcohol (+)-**32** $[\alpha]^{25}_D = +31.4°$, *c* 1.7, CH_3CN; lit.[30b] $[\alpha]^{20}_D = +34.9°$, *c* 0.53, CH_3CN. Saponification of the camphanate ester **31b** then gave enantiomerically pure **33** in 35−40% overall yield from **29**.[34] Since this procedure was originally developed,[35] other efficient entries to protected inositols have been devised that are better suited to the preparation of many inositol analogues.[29e,f]

Coupling the *myo*-inositol derivative **33** with 1,2-*O*-dihexanoyl-*sn*-glycerol (**10c**) using methyl dichlorophosphite followed by oxidation of the intermediate phosphite afforded the protected phosphatidylinositol **34** in 68% yield, but we were unable to cleanly deprotect **34** to give the phospholipid **37** (Scheme 8). To solve this problem, **33** and **10c** were coupled with (trimethylsilyl)ethyl dichlorophosphite to give an intermediate phosphite triester that was converted by oxidation or sulfurization

Scheme 8[a]



[a] (a) $MeOPCl_2$ or $TMSCH_2CH_2OPCl_2$, (*i*-Pr)$_2$NEt, THF, −78 °C; **10c**, −78 → 20 °C; *t*-BuOOH, CH_2Cl_2, 0 °C or S_8, Py, CS_2, rt; (b) aqueous HF, MeCN/THF (2:1), rt.

into the corresponding phosphate triester **35** or the phosphorothioate triester **36** in 75−80% overall yield. Global deprotection of **35** and **36** by treatment with aqueous hydrofluoric acid under mild conditions then gave the phosphatidylinositols **37** and **38** in good yield.

The hydroxyl group at C(2) of the inositol moiety of phosphatidylinositols participates as a neighboring group during the hydrolysis of the phosphodiester bond by some phosphatidylinositol-specific phospholipase C (PI-PLC) enzymes.[11f,g] We therefore reasoned that phosphatidylinositol analogues in which the stereochemistry or the functionality at the C(2) position of the inositol moiety was altered might be effective inhibitors of these PI-PLC's. Since the protecting group array in **33** does not lend itself to the ready preparation of such phospholipid derivatives, the enantiomerically pure tetra-*O*-benzyl-*myo*-inositol **39**[36] was used as the starting material to access the optically pure inositols **44**, **45**, and **48**. The procedures that were adopted for the syntheses of enantiomerically pure **44** and **45** closely followed prior art for the preparation of the corresponding racemic inositol derivatives.[37,38] Thus, selective *O*-benzoylation of **39** gave **40** in 81% yield (Scheme 9). Fluorination of **40** with DAST proceeded with inversion to give **41**, which was converted by hydrolysis of the benzoate ester into the 2-deoxy-2-fluoro *scyllo*-inositol **44** in 69% overall yield from **40**. The transformation of **40** into the 2-deoxy analogue **45** proceeded in 80% overall yield and featured the radical dehalogenation of **42**.

Some *scyllo*-inositol derivatives may be prepared by reducing the corresponding ketones with aluminum and boron hydrides or by nucleophilic displacement of a suitable axial leaving group at C-2. Unfortunately, neither of these tactics produces the *scyllo*-inositol in good yield. Since *n*-$Bu_2Sn(H)Cl$ reduces cyclic α-alkoxy ke-

(32) (a) Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *Carbohydr. Res.* **1985**, *142*, 132. (b) Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *J. Chem. Soc., Perkin Trans. I* **1987**, 423.

(33) Ozaki, S.; Kondo, Y.; Nakahira, H.; Yamaoka, S.; Watanabe, Y. *Tetrahedron Lett.* **1987**, *28*, 4691.

(34) For examples of similar resolutions, see: (a) Vacca, J. P.; deSolms, S. J.; Huff, J. R.; Billington, D. C.; Baker, R.; Kulagowski, J. J.; Mawer, I. M. *Tetrahedron* **1989**, *45*, 5679 and previous work. (b) Reference 30b.

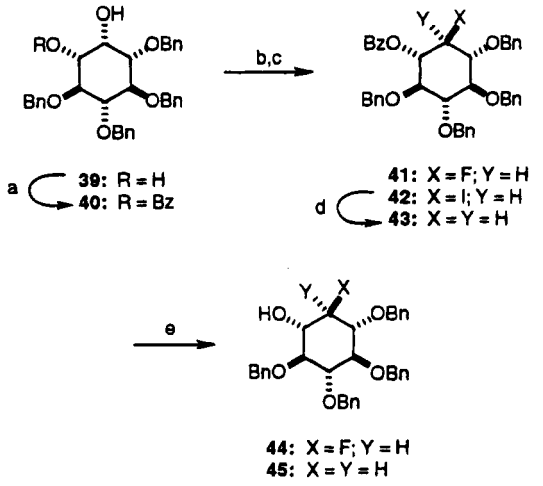
(35) Josey, J. A. Ph.D. Dissertation, The University of Texas, 1989.

(36) (a) Bruzik, K. S.; Salamonczyk, G. M. *Carbohydr. Res.* **1989**, *195*, 67. (b) Pietrusiewicz, K. M.; Salamonczyk, G. M. *Tetrahedron Lett.* **1991**, *32*, 4031. We thank Professor Pietrusiewic for providing the details of this procedure.

(37) Yang, S. S.; Beattie, T. R.; Durette, P. L.; Gallagher, T. F.; Shen, T. Y. U.S. Patent 4 515 722, 1986.

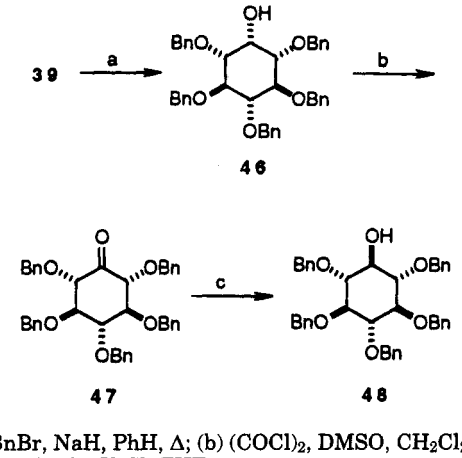
(38) Baker, R.; Kulagowski, J. J.; Billington, D. C.; Leeson, P. D.; Lennon, I. C.; Liverton, N. *J. Chem. Soc., Chem. Commun.* **1989**, 1383.

Scheme 9[a]



[a] (a) Bz-Cl, Et_3N, DMF; (b) DAST, CH_2Cl_2, 0 °C; (c) Ph_3P, I_2, imidazole, PhMe; (d) Bu_3SnH, AIBN, PhMe, Δ; (e) KOH, MeOH, THF.

Scheme 10[a]



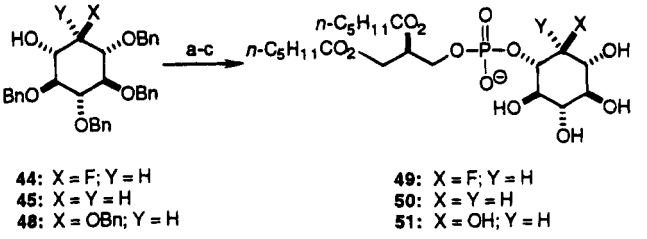
[a] (a) BnBr, NaH, PhH, Δ; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N; (c) n-$Bu_2Sn(H)Cl$, THF, Δ.

tones preferentially from the axial face,[39] we reasoned that it might be exploited for the stereoselective reduction of the C-2 carbonyl group of a protected *myo*-inositol derivative. Selective benzylation of the equatorial hydroxyl group of **39** using benzyl bromide in the presence of sodium hydride[40] followed by Swern oxidation[41] gave the ketone **47**. Subsequent reaction of **47** with n-$Bu_2Sn(H)Cl$ in refluxing THF afforded a readily separable mixture (8:1) of the protected *scyllo*-inositol **48** and the *myo*-inositol **46** (Scheme 10).

Coupling of the enantiomerically pure inositols **44**, **45**, and **48** with 1,2-*O*-dihexanoyl-*sn*-glycerol (**10c**) using (trimethylsilyl)ethyl dichlorophosphite followed by oxidation of the intermediate phosphite triesters with *tert*-butyl hydroperoxide gave the corresponding phosphate triesters, which were treated with dilute aqueous hydrofluoric acid at room temperature to provide **49**−**51** in good overall yields (Scheme 11). The biological activity of these phosphatidylinositol derivatives as inhibitors of PI-PLC is being evaluated, and the results of these studies will be reported independently.

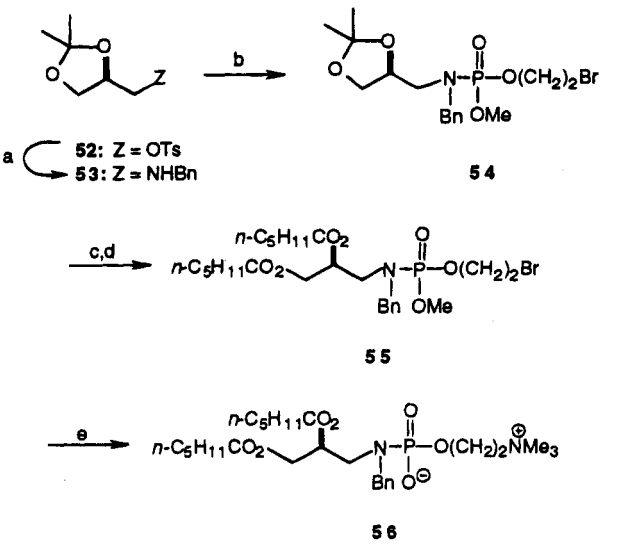
(39) Shibata, I.; Yoshida, T.; Kawakami, T.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 4049.
(40) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(41) See also: Yang, S. S.; Beattie, R. R. *J. Org. Chem.* **1981**, *46*, 1718.

Scheme 11[a]



[a] (a) $TMSCH_2CH_2OPCl_2$, $(i\text{-Pr})_2NEt$, PhMe, 0 °C; **10c**, PhMe, 0 °C; t-BuOOH, CH_2Cl_2, 0 °C; (b) H_2 (50 psi), 20% $Pd(OH)_2/C$, EtOH, cat. HOAc, rt; (c) HF, MeCN/THF (2:1), rt.

Scheme 12[a]



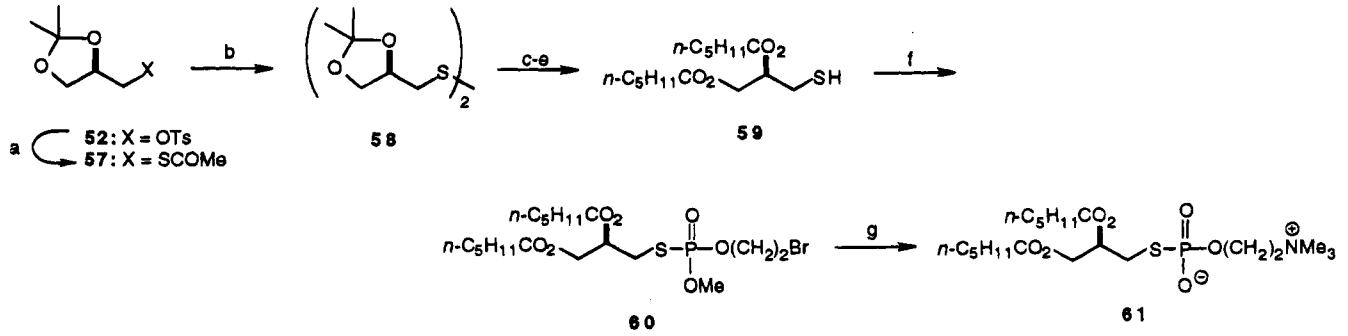
[a] (a) $BnNH_2$, cat. NaI, DMSO, 80 °C. (b) $MeOPCl_2$, $(i\text{-Pr})_2NEt$, THF, −78 °C; $HO(CH_2)_2Br$; aqueous H_2O_2, THF; (c) p-TsOH, MeOH; (d) hexanoic acid, DCC, DMAP; (e) Me_3N, PhMe, 50 °C.

3. Synthesis of Analogues of Phospholipids Derived from Modified Diacylglycerols. The work described thus far convincingly establishes this alkyl dichlorophosphite coupling and oxidation or sulfurization procedure for the synthesis of a number of diacylglycerol-derived phospholipids. However, in connection with preparing inhibitors of phospholipase C isoenzymes, we queried whether such phosphite couplings might also be extended to the synthesis of other phospholipid analogues including phosphoramidates and thiophosphates in which the oxygen at the *sn*-3 position of the glycerol moiety is replaced with a nitrogen or sulfur atom. To explore this important question, we set to the task of preparing the phosphoramidate **56** and the thiophosphate **61**.

The synthesis of **56** commenced by converting the known enantiomerically pure tosylate **52**[42] into the *N*-benzyl glycerol **53** in 69% yield (Scheme 12). Subjection of **53** to the phosphite coupling and oxidation protocol using methyl dichlorophosphite and 2-bromoethanol afforded **54** in 78% yield. Subsequent removal of the acetonide protecting group and acylation of the intermediate diol with n-hexanoic acid in the presence of DCC and DMAP gave the phosphoramidate **55**; treatment of **55** with trimethylamine then delivered **56**. In preliminary experiments, we were unable to prepare the NH analogue of **55** by a similar procedure, since attempted acid-catalyzed removal of the acetonide moiety from the

(42) Baer, E.; Fischer, H. O. L. *J. Chem. Soc.* **1948**, *70*, 609.

Scheme 13[a]



[a] (a) KSC(O)Me, 18-crown-6, MeCN; (b) NaOH, MeOH; (c) *p*-TsOH, MeOH; (d) hexanoyl chloride, Py, DMAP; (e) dithiothreitol, aqueous NH_4OH, EtOH; (f) $MeOPCl_2$, $HO(CH_2)_2Br$, $(i\text{-}Pr)_2NEt$, THF, −78 °C; **59**, -78 → 20 °C; 30% aqueous H_2O_2, THF, 0 °C; (g) Me_3N, PhMe, rt.

NH analogue of **54** led to decomposition. The enhanced stability of the *N*-benzyl derivative **54** may arise from the inability of the *N*-benzyl group to assume an apical orientation via pseudorotation on the pentacoordinate phosphorane intermediate.[43] Debenzylation of **56** by catalytic hydrogenolysis was examined in a few preliminary experiments without success.

The synthesis of the thiophospholipid **61** followed similar lines. Reaction of **52** with potassium thioacetate afforded **57** in 97% yield (Scheme 13).[44] Hydrolysis of the thioacetate **57** and aerial oxidation of the intermediate thiol gave **58**, which was converted into **59** in about 40% overall yield from **57** by sequential ketal hydrolysis, acylation, and reductive cleavage of the disulfide moiety using Cleland's reagent.[45] The diacylglyceryl thiol **59** was then coupled with bromoethanol using methyl dichlorophosphite, and the thiophosphite triester thus formed was oxidized to give the thiophosphate triester **60.** Treatment of **60** with trimethylamine provided the thiophosphate **61** in 35% overall yield.

Conclusions

The experiments outlined herein convincingly establish the generality and utility of this alkyl dichlorophosphite coupling and oxidation (or sulfurization) protocol for the efficient synthesis of the major classes of diacylglycerol-derived phospholipids and their analogues. Significantly *only equimolar quantities of the two alcohol components are required.* The starting alkyl (or aryl) dichlorophosphites are either commercially available or may be conveniently prepared in one step from phosphoros trichloride. These alkyl dichlorophosphites react smoothly at −78 °C with a variety of acylated *sn*-glyceryl derivatives bearing hydroxyl, thiol, and amino groups at the *sn*-3 position. Under the conditions employed, only small quantitites of undesired phosphite triesters resulting from the reaction of the initially formed dialkyl chlorophosphite with a second equivalent of the same alcohol were ever detected, and these could be readily removed by chromatography. The reactivity of the intermediate dialkyl chlorophosphites ensures that sterically hindered alcohols may be used as the second alcoholic reactant in the one-pot sequence. Oxidation or sulfurization of the intermediate phosphite triesters followed by global deprotection then led to the desired phosphate or phosphorothioate diesters in excellent overall yield. These synthetic procedures may be applied to the preparation of a diversity of phospholipid analogues bearing a variety of different glyceryl and head groups combinations. Such phospholipid derivatives are being used to study the mechanism of phosphodiester hydrolysis by enzymes of the phospholipase C and phospholipase D classes, and the results of these investigations will be reported in due course.[24]

Experimental Section

General. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from potassium/benzophenone ketyl under nitrogen and dichloromethane (CH_2Cl_2) was distilled from calcium hydride under nitrogen immediately prior to use. Diisopropylamine, triethylamine, and diisopropylethylamine were distilled from pulverized calcium hydride and stored over 4-Å molecular sieves under argon. *N,N*-Dimethylformamide (DMF) was distilled under reduced pressure from barium oxide and stored over 4-Å molecular sieves under argon. Reactions involving air- and/or moisture-sensitive reagents were executed under an inert atmosphere of dry argon, and the glassware was flamed dried under vacuum. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM). Percent yields are given for compounds that were ≥95% pure as judged by NMR, HPLC, or combustion analyses. Melting points are uncorrected. Infrared (IR) spectra were recorded as solutions in $CHCl_3$ unless noted otherwise. All spectra are reported in wavenumbers (cm^{-1}) and referenced to the 1601.8 cm^{-1} absorption of a polystyrene film. ^1H, ^{13}C, and ^{31}P NMR spectra were obtained at the indicated field for each compound as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts for ^1H and ^{13}C NMR spectra are reported in parts per million (ppm, δ) downfield relative to the internal standard tetramethylsilane (TMS); for the ^{13}C spectra TMS was referenced to the center line of the $CDCl_3$ triplet (δ 77.0). The ^{31}P chemical shifts are reported in parts per million (ppm, δ) downfield relative to the external standard phosphoric acid. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; and br, broad.

Quantitative gas chromatographic analyses (GLC) of the triacylglycerols were performed using a capillary DB-1 column (15 m, 0.25 mm i.d., 1 μm film) at 325 °C (oven temperature).

(43) For example, see: Lemmen, P.; Buchweitz, K. M.; Stumpf, R. *Chem. Phys. Lipids* **1990**, *53*, 65.

(44) For other methods of preparing related thiophospholipids, see: (a) Snyder, W. R. *J. Lipid Res.* **1987**, *28*, 949. (a) Moroder, L.; Musiol, H.-J.; Siglmüller, G. *Synthesis* **1990**, 889. (b) Mlotkowska, B.; Markowska, A. *Liebigs Ann. Chem.* **1990**, 923. (c) Alisi, M. A.; Brufani, M.; Filocamo, L.; Gostoli, G.; Lappa, S.; Maiorana, S.; Cesta, M. C.; Ferarri, E.; Pagella, P. G. *Tetrahedron Lett.* **1992**, *33*, 3891. (d) Alisi, M. A.; Brufani, M.; Filocamo, L.; Gostoli, G.; Maiorana, S.; Cesta, M. C.; Ferarri, E.; Lappa, S.; Pagella, P. *Tetrahedron Lett.* **1992**, *33*, 7793.

(45) (a) Cleland, W. W. *Biochemistry* **1964**, *3*, 480. (b) Cox, J. W.; Snyder, W. R.; Horrocks, L. A. *Chem. Phys. Lipids* **1979**, *25*, 369.

Quantitative ^{13}C NMR analyses were performed using samples of the appropriate acyl glyceride at a concentration of approximately 100 mg/650 μL of solution; the spectrum was acquired with 3072 scans. Copies of the analytical data are available in the supplementary material.

General Procedure for Preparing 1-*O*-Acyl-3-*O*-benzyl-*sn*-glycerols (8a,b). To a solution of 3-*O*-benzyl-*sn*-glycerol (**7**) (4.46 g, 24.5 mmol), DMAP (150 mg, 1.2 mmol), and the requisite carboxylic acid (25.7 mmol) in dry CH_2Cl_2 (170 mL) at 0 °C was added dropwise over 45 min a solution of dicyclohexylcarbodiimide (DCC) (9.64 g, 46.8 mmol) in dry CH_2Cl_2 (20 mL). A precipitate began to form immediately upon the addition of the DCC solution. The resulting suspension was stirred for an additional 1 h at 0 °C, the cooling bath was removed, and the mixture was stirred an additional 12 h. The mixture was filtered through Celite and evaporated to dryness under reduced pressure. The product was purified by either Kugelrohr distillation or flash chromatography eluting with the solvent indicated.

3-*O*-Benzyl-1-*O*-propionyl-*sn*-glycerol (8a): obtained as a clear, colorless viscous oil in 76% yield from **7** by Kugelrohr distillation (170 °C oven temp, 0.20 mmHg); IR (neat) ν 3460, 1750 cm^{-1}; ^1H NMR (300 MHz) δ 7.34–7.29 (comp, 5 H), 4.54 (s, 2 H), 4.16–4.13 (comp, 2 H), 4.01 (br s, 1 H), 3.56–3.45 (comp, 2 H), 2.95 (br s, 1 H), 2.33 (q, 2 H, J = 7.6 Hz), 1.12 (t, 3 H, J = 7.6 Hz); ^{13}C NMR (75 MHz) δ 174.4, 137.8 , 128.4, 127.8, 127.7, 73.5, 71.0, 68.9, 65.4, 27.4, 9.0; mass spectrum, m/z 238.1212 ($C_{13}H_{18}O_4$ requires 238.1205), 221, 181, 163, 146, 131, 91 (base).

3-*O*-Benzyl-1-*O*-palmitoyl-*sn*-glycerol (8b): obtained as a low melting white solid in 69% yield from **7** by HPLC eluting with hexanes/EtOAc (5:1); IR (KBr) ν 3460, 1750 cm^{-1}; ^1H NMR (300 MHz) δ 7.36–7.28 (comp, 5 H), 4.56 (s, 2 H), 4.18–4.14 (comp, 2 H), 4.03 (dd, 1 H, J = 10.5, 5.7 Hz), 3.58–3.47 (comp, 2 H), 2.51 (d, 1 H, J = 4.8 Hz), 2.32 (t, 2 H, J = 7.5 Hz), 1.63–1.58 (comp, 2 H), 1.27–1.24 (comp, 24 H), 0.88 (t, 3 H, J = 6.6 Hz); ^{13}C NMR (91 MHz) δ 173.8, 137.6, 128.4, 127.8, 127.7, 73.4, 70.9, 68.9, 65.3, 34.1, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 24.9, 22.6, 14.0; mass spectrum, m/z 420.3237 ($C_{26}H_{44}O_4$ requires 420.3240), 313, 257, 239, 181, 164, 107, 91 (base).

General Procedure for Preparing Mixed 1,2-*O*-Diacyl-3-*O*-benzyl-*sn*-glycerols (9a,b, $m \neq n$). To a solution of the appropriate 1-acyl-3-*O*-benzyl-*sn*-glycerol **8a,b** (4.7 mmol), DMAP (57 mg, 0.5 mmol), and the appropriate carboxylic acid (5.6 mmol) in dry CH_2Cl_2 (20 mL) at room temperature was added dropwise over 20 min a solution of DCC (1.26 g, 6.1 mmol) in dry CH_2Cl_2 (10 mL). The resulting suspension was stirred for 12 h at room temperature, the mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The product was purified by flash chromatography eluting with the indicated solvent as eluent.

3-*O*-Benzyl-2-*O*-palmitoyl-1-*O*-propionyl-*sn*-glycerol (9a): obtained as an opaque oil in 93% yield by flash chromatography eluting with hexanes/EtOAc (5:1): IR (neat) ν 1750 cm^{-1}; ^1H NMR (360 MHz) δ 7.36–7.27 (comp, 5 H), 5.26–5.23 (m, 1 H), 4.56 (d, 1 H, J = 12.1 Hz), 4.52 (d, 1 H, J = 12.1 Hz), 4.35 (dd, 1 H, J = 11.9, 3.9 Hz), 4.19 (dd, 1 H, J = 11.9, 6.5 Hz), 3.59 (d, 2 H, J = 5.0 Hz), 2.36–2.26 (comp, 4 H), 1.65–1.59 (comp, 2H), 1.27–1.24 (comp, 24 H), 1.11 (t, 3 H, J = 7.7 Hz), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (91 MHz) δ 173.9, 173.0, 137.9, 128.4, 127.8, 127.6, 73.4, 70.1, 68.4 , 62.8, 34.4, 31.9, 29.7, 29.5, 29.3, 29.1, 27.4, 25.0, 22.7, 14.0, 9.0; mass spectrum, m/z 476.3507 ($C_{29}H_{48}O_5$ requires 476.3502), 369, 313, 329, 237, 146, 131 (base) 114, 105, 91.

3-*O*-Benzyl-1-*O*-palmitoyl-2-*O*-propionyl-*sn*-glycerol (9b): obtained as an opaque viscous oil in 96% yield by flash chromatography eluting with hexanes/EtOAc (5:1); IR (neat) ν 1750 cm^{-1}; ^1H NMR (360 MHz) δ 7.37–7.27 (comp, 5 H), 5.25–5.23 (m, 1 H), 4.56 (d, 1 H, J = 12.1 Hz), 4.52 (d, 1 H, J = 12.1 Hz), 4.35 (dd, 1 H, J = 11.9, 3.8 Hz), 4.20 (dd, 1 H, J = 11.9, 6.3 Hz), 3.59 (d, 2 H, J = 5.2 Hz), 2.35 (q, 2 H, J = 7.6 Hz), 2.28 (t, 2 H, J = 7.4 Hz), 1.64–1.57 (comp, 2 H), 1.27–1.24 (comp, 24 H), 1.14 (t, 3 H, J = 7.6 Hz), 0.88 (t, 3 H, J = 6.9 Hz); ^{13}C NMR (91 MHz) δ 173.6, 173.3, 137.9, 128.4, 127.8, 127.6, 73.4, 70.3, 68.4, 62.6, 34.2, 31.9, 29.7, 29.5, 29.3, 29.2, 29.1, 27.6, 24.9, 22.7, 14.0, 9.0; mass spectrum, m/z 476.3507 ($C_{29}H_{48}O_5$ requires 476.3502), 369, 313 (base), 239, 146, 131, 114, 105, 91.

General Procedure for Preparing 1,2-*O*-Diacyl-3-*O*-benzyl-*sn*-glycerols (9c,d, $m = n$). To a solution of 3-*O*-benzyl-*sn*-glycerol (**7**) (2.84 g, 15.6 mmol), DMAP (190 mg, 1.6 mmol), and the carboxylic acid (39.0 mmol) in dry CH_2Cl_2 (50 mL) at room temperature was added dropwise over 30 min a solution of DCC (9.64 g, 46.8 mmol) in dry CH_2Cl_2 (40 mL), and the resulting suspension was stirred for 10 h. The solid was removed by filtration through Celite, the filtrate was concentrated under reduced pressure, and the product was purified by Kugelrohr distillation or either flash chromatography or HPLC using the solvent indicated as the eluent.

3-*O*-Benzyl-1,2-*O*-di-*n*-hexanoyl-*sn*-3-glycerol (9c): obtained as a colorless oil in 86% yield by purification by flash chromatography eluting with hexanes/EtOAc (10:1); IR ν 2920, 1730, 1160, 1100 cm^{-1}; ^1H NMR (300 MHz) δ 7.34–7.23 (comp, 5 H), 5.25–5.18 (comp, 1 H), 4.53 (d, 1 H, J = 12.1 Hz), 4.48 (d, 1 H, J = 12.1 Hz), 4.32 (dd, 1 H, J = 11.9, 3.8 Hz), 4.16 (dd, 1 H, J = 11.9, 6.5 Hz), 3.56 (d, 2 H, J = 5.1 Hz), 2.29 (t, 2 H, J = 7.5 Hz), 2.25 (t, 2 H, J = 7.5 Hz), 1.64–1.52 (comp, 4 H), 1.35–1.20 (comp, 8 H), 0.86 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 173.0, 172.7, 137.5, 128.1, 127.5, 127.3, 73.0, 69.7, 67.9, 62.3, 33.9, 33.7, 30.9, 24.34, 24.28, 22.0, 13.6; mass spectrum (CI, methane) m/z 378.2396 ($C_{22}H_{34}O_5$ requires 378.2406), 379 (M + H), 271, 263 (base), 173.

3-*O*-Benzyl-1,2-*O*-dipalmitoyl-*sn*-3-glycerol (9d): obtained as a white solid in 98% yield by flash chromatography eluting with hexanes/EtOAc (10:1); mp 64–65.5 °C; IR (KBr) ν 1750 cm^{-1}; ^1H NMR (300 MHz) δ 7.35–7.26 (comp, 5 H), 5.26–5.23 (m, 1 H), 4.55–4.52 (comp, 2 H), 4.35 (dd, 1 H, J = 11.9, 3.9 Hz), 4.18 (dd, 1 H, J = 11.9, 6.4 Hz), 3.58 (d, 1 H, J = 5.2 Hz), 2.33–2.24 (comp, 4 H), 1.61-1.56 (comp, 4 H), 1.28–1.24 (comp, 48 H), 0.88 (t, 6 H, J = 6.6 Hz); ^{13}C NMR (91 MHz) δ 173.3, 173.1, 137.9, 128.4, 127.8, 127.7, 73.4, 70.2, 68.5, 62.8, 34.4, 32.4, 31.9, 29.7, 29.5, 29.3, 29.2, 25.0, 22.7, 14.1; mass spectrum, m/z 658, 551, 419, 314, 313 (base), 296, 239, 219, 146, 91. Anal. Calcd for $C_{42}H_{74}O_5$: C, 76.54; H, 11.32. Found: C, 76.19; H, 12.03.

General Procedure for Preparing 1,2-*O*-Diacyl-*sn*-glycerols (10a–d) from 1,2-*O*-Diacyl-*O*-benzyl-*sn*-glycerols (9a–d). The appropriate 1,2-*O*-diacyl-3-*O*-benzyl-*sn*-glycerol **9a–d** (3.0 mmol) was dissolved in a mixture of absolute ethanol (50 mL) and glacial acetic acid (5 mL) containing 10% Pd/C (50–75 mg), and the mixture was stirred under an atmosphere of H_2 at room temperature. As soon as the reaction was complete as judged by TLC, the mixture was diluted with CH_2Cl_2 (50 mL). Celite was added, the mixture was filtered, and the filtrate was evaporated under reduced pressure and ≤25 °C (water bath) to afford the crude product that was purified by flash chromatography eluting with the solvent indicated. These 1,2-*O*-diacyl-*sn*-glycerols exhibit varying propensities to undergo 2,3-acyl migration on storage to deliver the corresponding 1,3-*O*-diacylglycerols, and some caution should be exercised. For example, whereas 1,2-*O*-dihexanoylglycerol appears reasonably stable on storage in the freezer (−20 °C), 1,2-*O*-dipalmitoylglycerol isomerizes to form significant amounts of 1,3-*O*-dipalmitoylglycerol under the same conditions.

2-*O*-Palmitoyl-1-*O*-propionyl-*sn*-glycerol (10a): obtained as a white solid in 91% yield by flash chromatography eluting with hexanes/EtOAc (4:1); mp 37.5–39 °C; IR (neat) ν 3480, 1760 cm^{-1}; ^1H NMR (250 MHz) δ 5.10 (comp, 1 H), 4.33 (dd, 1 H, J = 11.9, 4.4 Hz), 4.24 (dd, 1 H, J = 11.9, 5.9 Hz), 3.74 (d, 2 H, J = 5.1 Hz), 2.68 (br s, 1 H), 2.39–2.30 (comp, 4 H), 1.69–1.55 (comp, 2 H), 1.35–1.21 (comp, 24 H), 1.15 (t, 3 H, J = 7.5 Hz), 0.88 (t, 3 H, J = 6.7 Hz); ^{13}C NMR (63 MHz) δ 174.3, 173.4, 72.0, 62.2, 61.3, 34.2, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 27.3, 24.9, 22.6, 14.0, 8.9; mass spectrum (CI, methane) m/z 387.3118 ($C_{22}H_{42}O_5$ + H requires 387.3111), 369, 313, 131, 121.

1-*O*-Palmitoyl-2-*O*-propionyl-*sn*-glycerol (10b): obtained as a white solid in 99% yield by flash chromatography eluting with hexanes/EtOAc (4:1); mp 43–44.5 °C; IR (neat) ν 3480, 1765 cm^{-1}; ^1H NMR (250 MHz) δ 5.15–5.02 (comp, 1 H), 4.33 (dd, 1 H, J = 11.9, 4.4 Hz), 4.23 (dd, 1 H, J = 11.9,

5.7 Hz), 3.73 (d, 2 H, J = 5.1 Hz), 2.6 (br s, 1 H), 2.43–2.29 (comp, 4 H), 1.63–1.59 (comp, 2 H), 1.28–1.24 (comp, 24 H), 1.16 (t, 3 H, J = 7.5 Hz), 0.88 (t, 3 H, J = 6.7 Hz); ^{13}C NMR (63 MHz) δ 174.0, 173.7, 72.1, 62.0, 61.3, 34.0, 31.8, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 27.5, 24.8, 22.6, 14.0, 8.9; mass spectrum (CI, methane) m/z 387.3124 ($C_{22}H_{42}O_5$ + H requires 387.3111), 369, 313, 131.

1,2-*O*-Di-*n*-hexanoyl-*sn*-glycerol (10c): obtained as a colorless oil in 87% yield by flash chromatography eluting with hexanes/EtOAc (2:1); IR ν 3440, 2900, 1720 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.10–5.03 (m, 1 H), 4.31 (dd, 1 H, J = 11.9, 4.3 Hz), 4.20 (dd, 1 H, J = 11.9, 5.8 Hz), 3.70 (t, 1 H, J = 5.8 Hz), 2.42 (t, 1 H, J = 6.4 Hz), 2.32 (t, 2 H, J = 7.2 Hz), 2.30 (t, 2 H, J = 7.3 Hz), 1.65–1.50 (comp, 4 H), 1.40–1.20 (comp, 8 H), 0.87 (t, 6 H, J = 6.7 Hz); ^{13}C NMR (75 MHz) δ 173.6, 173.3, 71.8, 62.1, 60.9, 34.0, 33.8, 31.0, 24.3, 22.0, 13.6; mass spectrum (CI, methane) m/z 289.2001 ($C_{15}H_{28}O_5$ requires 289.2015), 271, 173 (base), 154.

1,2-*O*-Dipalmitoyl-*sn*-3-glycerol (10d): obtained as a white solid in 93% yield from 3-benzyl-1,2-dipalmitoyl-*sn*-glycerol (**6**, $m = n = 14$) by flash chromatography eluting with hexanes/EtOAc (5:1); mp 64.5–66.5 °C; IR ($CHCl_3$) ν 1735 cm^{-1}; ^{1}H NMR (360 MHz) δ 5.08 (p, 1 H, J = 5.0 Hz), 4.32 (dd, 1 H, J = 11.9, 4.5 Hz), 4.23 (dd, 1 H, J = 11.9, 5.7 Hz), 3.73 (t, 2 H, J = 5.2 Hz), 2.33 (q, 4 H, J = 7.7 Hz), 2.08 (br s, 1 H), 1.67–1.59 (comp, 4 H), 1.28–1.25 (comp, 48 H), 0.88 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 173.6, 173.3, 72.3, 62.1, 61.6, 34.3, 34.1, 31.9, 29.8, 29.7, 29.4, 29.3, 29.1, 24.9, 22.7, 14.0; mass spectrum, m/z 551.5013 (M^+ − OH) ($C_{35}H_{67}O_4$ requires 551.5022), 313, 239 (base), 129, 116, 98.

General Procedure for Alkyl Dichlorophosphite Coupling Followed by Oxidation or Sulfurization. A solution of the first alcohol, ROH (1.90 mmol), which was usually the more hindered one, in a minimum volume of solvent (indicated) was added dropwise to a vigorously stirred solution of alkyl dichlorophosphite (indicated) (1.90 mmol) and *N,N*-diisopropylethylamine (0.61 g, 4.74 mmol) in dry, deoxygenated solvent (5 mL) at the temperature indicated. After 30–45 min of stirring, a solution of the second reactant nucleophile R'OH, R'SH, or R'NHR'' (1.90 mmol) in a minimum amount of the same solvent was added slowly, and the resulting suspension was stirred for 2 h at the same temperature. *The reactant nucleophiles are listed in the order of their addition.* The cooling bath was then removed, and stirring was continued for an additional 1 h at room temperature. The solvent was removed under reduced pressure, and the residue was suspended in EtOAc. The solids were removed by vacuum filtration through Celite, and the filtrate was concentrated under reduced pressure to provide the crude phosphite triester. The crude phosphite triester thus obtained was then dissolved in CH_2Cl_2 (about 10 mL) at 0 °C, the indicated oxidizing agent (4.40 mmol) was added, and the mixture was stirred vigorously for 1 h at 0 °C. The excess oxidizing agent was destroyed by the addition of trimethyl phosphite (0.5 mL). The mixture was diluted with CH_2Cl_2 (30 mL), saturated NaCl (25 mL) was added, and the layers were separated. The organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield the crude phosphate triester, which was purified by flash chromatography eluting with the solvent indicated. Alternately, the intermediate phosphite triester can be sulfurated by stirring it with sublimed elemental sulfur, S_8 (0.61 g, 19.0 mmol), in degassed toluene (15 mL) or carbon disulfide/pyridine (2:1, 15 mL). After 1 h the solvent was removed under reduced pressure, and the residue was suspended in ethyl acetate. The solids were removed by filtration through a plug of Celite, and the filtrate was concentrated under reduced pressure to yield the crude phosphorothioate triester, which was purified by flash chromatography eluting with the solvent indicated.

***O*-(2-Bromoethyl) *O*-(1',2'-*O*-di-*n*-hexanoyl-*sn*-3'-glyceryl) *O*-methyl Phosphate (13):** obtained by the general coupling/oxidation procedure (methyl dichlorophosphite, **10c**, and 2-bromoethanol in THF at −78 °C; 30% H_2O_2) as a colorless oil in 71% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (1:2): IR (CCl_4) ν 2940, 1750, 1295, 1175 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.22–5.15 (m, 1 H), 4.30–4.22 (comp, 3 H), 4.20–4.08 (comp, 3 H), 3.74 (d, 1.5 H, J = 11.1 Hz), 3.73 (d, 1.5 H, J = 11.2 Hz), 3.48 (t, 2 H, J = 6.0 Hz), 2.28 (t, 2 H, J = 7.5 Hz), 2.25 (t, 2 H, J = 7.6 Hz), 1.61–1.50 (comp, 4 H), 1.31–1.17 (comp, 8 H), 0.83 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 172.5, 172.1, 68.8 (d, J_{CP} = 6.7 Hz), 66.4 (d, J_{CP} = 5.2 Hz), 65.2, 61.0, 54.1 (d, J_{CP} = 5.1 Hz), 33.5, 33.3, 30.6, 23.9, 21.7, 29.1 (d, J_{CP} = 7.3 Hz), 13.3; ^{31}P NMR (90 MHz) δ −0.64; mass spectrum (CI, methane) m/z 489.1213 ($C_{18}H_{34}BrO_8P$+H requires 489.1253), 375, 373, 272, 271 (base), 255.

***O*-(2-Bromoethyl) *O*-(1',2'-*O*-di-*n*-hexanoyl-*sn*-3'-glyceryl) *O*-methyl phosphorothioate (14):** obtained by the general coupling/sulfurization procedure (methyl dichlorophosphite, **10c**, and 2-bromoethanol in THF at −78 °C; S_8) as a colorless oil in 65% overall yield after purification by flash chromatography (hexanes/EtOAc, 3:1); IR ν 2920, 1730 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.21–5.28 (m, 1 H), 4.36–4.14 (comp, 6 H), 3.77 (d, 3 H, J = 13.7 Hz), 3.52 (t, 2 H, J = 6.2 Hz), 2.36–2.29 (comp, 4 H), 1.67–1.58 (comp, 4 H), 1.40–1.26 (comp, 8 H), 0.89 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 171.0, 172.6, 69.2 (d, J_{CP} = 7.4 Hz), 67.2 (d, J_{CP} = 4.8 Hz), 65.9, 61.5, 54.8 (d, J_{CP} = 6.3 Hz), 34.0, 33.9, 31.1, 29.2, 24.4, 22.1, 29.1, 13.8; ^{31}P NMR (146 MHz) δ +69.97; mass spectrum (CI, methane) m/z 504.0902 ($C_{18}H_{34}BrO_7PS$ requires 504.0946), 505 (M^+ + H), 407, 391, 389, 271 (base).

***O*-(2-Bromoethyl) *O*-(1',2'-*O*-di-*n*-hexanoyl-*sn*-3'-glyceryl) *O*-(2''-(trimethylsilyl)ethyl) phosphorothioate (15):** obtained by the general coupling/sulfurization procedure (2-(trimethylsilyl)ethyl dichlorophosphite, **10c**, and 2-bromoethanol in THF at −78 °C; S_8) as a colorless oil in 53% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (2:1); IR ν 2958, 1738 cm^{-1}; ^{1}H NMR (250 MHz) δ 5.21–5.28 (m, 1 H), 4.36–4.14 (comp, 8 H), 3.52 (t, 2 H, J = 6.2 Hz), 2.32–2.25 (comp, 4 H), 1.67–1.55 (comp, 4 H), 1.35–1.20 (comp, 8 H), 1.08 (t, 2 H, J = 8.4 Hz), 0.85 (t, 6 H, J = 6.8 Hz), 0.03 (s, 9 H); ^{13}C NMR (62 MHz) δ 173.2, 172.7, 69.2 (d, J_{CP} = 11.4 Hz), 67.6 (d, J_{CP} = 6.4 Hz), 67.0 (d, J_{CP} = 4.5 Hz), 65.6, 61.7, 34.1, 34.0, 31.2, 31.1, 29.2 (d, J_{CP} = 8.5 Hz), 24.5, 22.2, 19.2 (d, J_{CP} = 6.3 Hz), 13.8, −1.6; ^{31}P NMR (146 MHz) δ +68.21; mass spectrum (CI, methane) m/z 591.1576 ($C_{22}H_{44}BrO_7PSSi$ + H requires 591.1576), 563 , 449, 377, 271 (base).

1,2-*O*-Di-*n*-hexanoyl-*sn*-glycero-3-phosphocholine (16). Trimethylamine was passed into a solution of methyl phosphate triester **13** (330 mg, 0.67 mmol) in dry toluene (4 mL) in a heavy-walled vessel at −40 °C until the volume of the reaction mixture was approximately doubled. The vessel was closed tightly, and the reaction mixture was stirred at 40–60 °C for 24 h. The vessel was then cooled and opened, and the excess trimethylamine was evaporated under a stream of N_2. The remaining solvent was removed *in vacuo*, the residue was triturated with $CHCl_3$ (5 mL), and the solid was removed by filtration through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with $CHCl_3/CH_3OH/H_2O$ (2:1:0.2) to give 254 mg (83% yield) of **16** as a white solid foam: IR ν 2900, 1720, 1230, 1160 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.01–4.91 (comp, 1 H), 4.19 (d, 1 H, J = 11.8 Hz), 4.12–3.95 (comp, 2 H), 3.19 (dd, 1 H, J = 11.8, 7.3 Hz), 3.75–3.63 (comp, 2 H), 3.63–3.53 (comp, 2 H), 3.18 (s, 9 H), 2.10–2.03 (comp, 4 H), 1.45–1.25 (comp, 4 H), 1.18–0.97 (comp, 8 H), 0.67 (t, 6 H, J = 6.4 Hz); ^{13}C NMR (75 MHz) δ 173.0, 172.6, 70.4 (d, J = 6.9 Hz), 66.1 (d, J = 3.5 Hz), 63.0 (d, J = 4.5 Hz), 62.7, 58.9 (d, J = 4.0 Hz), 54.0, 33.9, 33.7, 30.8, 24.24, 24.17, 21.8, 13.4; ^{31}P NMR (90 MHz) δ −0.28; mass spectrum (CI, methane) m/z 454.2592 ($C_{20}H_{40}NO_8P$ + H requires 454.2570), 271, 173, 139.

1,2-*O*-Di-*n*-hexanoyl-*sn*-glycero-3(R_P/S_P)-phosphothiocholine (17). Trimethylamine was passed into a solution of phosphorothioate triester **15** (0.57 g, 0.96 mmol) in dry toluene (5 mL) in a heavy-walled vessel at −78 °C until the volume of the reaction mixture was approximately doubled. The vessel was closed tightly, and the reaction mixture was stirred at 40–45 °C for 48 h. The vessel was then cooled and opened, and the excess trimethylamine was evaporated under a stream of Ar. The remaining solvent was removed *in vacuo*, and the residue was mostly dissolved in chloroform (5 mL); the remaining solids were removed by filtration through Celite.

The filtrate was concentrated under reduced pressure, and the residue was dissolved in acetonitrile (15 mL) containing (13 μL) of 49% aqueous HF. The reaction mixture was stirred at room temperature for 15 min and then concentrated under reduced pressure. The product was purified by flash chromatography eluting with $CHCl_3/CH_3OH/H_2O$ (2.2:1.0:0.15) to give 0.28 g (64% yield) of **17** as a white solid foam: ^1H NMR (300 MHz) δ 5.24–5.19 (m, 1 H), 4.46–4.33 (comp, 3 H), 4.18–3.95 (comp, 3 H), 3.91–3.75 (comp, 2 H), 3.37 (s, 9 H), 2.31 (t, 2 H, J = 7.4 Hz), 2.28 (t, 2 H, J = 7.6 Hz), 1.64–1.53 (comp, 4 H), 1.37–1.20 (comp, 8 H), 0.88 (t, 6 H, J = 6.7 Hz); ^{13}C NMR (75 MHz) δ 173.4, 173.0, 70.2 (d, J_{CP} = 10.5 Hz), 66.0 (d, J_{CP} = 6.7 Hz), 63.8, 62.8, 59.5 (d, J_{CP} = 3.6 Hz), 54.6, 34.2, 34.0, 31.2, 31.1, 24.5, 24.4, 22.3, 13.9; ^{31}P NMR (146 MHz) δ 55.17, 55.13; IR ν 3365, 2960, 1733 cm^{-1}; mass spectrum (CI, methane) m/z 470.2347 ($C_{20}H_{40}NO_7PS$ + H requires 470.2341), 271 (base), 227.

***O*-(1,2-*O*-Di-*n*-hexanoyl-*sn*-3-glyceryl) *O*-[2′-((*N*-*tert*-butyloxycarbonyl)amino)ethyl] *O*-(2″-(trimethylsilyl)-ethyl) phosphate (19):** obtained by the general coupling/oxidation procedure (2-(trimethylsilyl)ethyl dichlorophosphite, **10c**, and *N*-Boc-ethanolamine in THF at −78 °C; *tert*-butyl hydroperoxide) as a colorless oil in 68% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (7:1); ^1H NMR (250 MHz) δ 5.20–5.08 (m, 2 H), 4.22 (dd, 1 H, J = 11.7, 4.3 Hz), 4.13–3.89 (comp, 7 H), 3.34–3.21 (m, 2 H), 2.27–2.13 (comp, 4 H), 1.59–1.42 (m, 4 H), 1.32 (s, 9 H), 1.26–1.11 (m, 8 H), 1.03–0.97 (comp, 2 H), 0.76 (comp, 6 H), −0.08 (s, 9 H); ^{13}C NMR (62 MHz) δ 172.9, 172.5, 155.6, 79.1, 69.2, 69.1, 66.8, 66.7, 65.1, 65.0, 61.4, 40.7, 33.8, 33.7, 31.0, 30.9, 28.1, 24.3, 22.0, 19.4, 19.3, 13.6, −1.8; mass spectrum (CI, methane) m/z 612.3331 ($C_{27}H_{54}NO_{10}PSi$ + H requires 612.3333), 584, 528, 513, 425, 631, 271, 237, 173, 135, 119.

1,2-*O*-Di-*n*-hexanoyl-*sn*-glycero-3-phosphoethanolamine (20). To a stirred solution of **19** (0.34 g, 0.55 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added CF_3CO_2H (1.5 mL). After stirring at 0 °C for 30 min, the mixture was warmed to room temperature, and the solvents were removed under reduced pressure. The crude phosphatidyl ethanolamine was then repeatedly taken up in benzene (5 mL) and the solvent evaporated under reduced pressure to remove the last traces of CF_3CO_2H before being dried under high vacuum. The product was purified by flash chromatography eluting with 2-propanol/water (88:12) to afford 0.22 g (95%) as a clear colorless oil: ^1H NMR (250 MHz) δ 5.25–5.13 (m, 1 H), 4.92–4.89 (m, 1 H), 4.19–4.03, (m, 3 H), 3.99–3.87 (m, 2 H), 3.41–3.27 (m, 2 H), 2.36–2.30 (m, 4 H), 1.66–1.48 (m, 4 H), 1.39–1.17 (m, 8 H), 0.76 (t, 6 H, J = 9.0 Hz); ^{13}C NMR (63 MHz) δ 173.3, 173.1, 77.2, 70.0, 64.1, 62.3, 40.2, 34.1, 33.9, 31.2, 31.1, 24.5, 24.4, 22.0, 13.7; ^{31}P NMR (146 MHz) δ −2.31; mass spectrum (FAB(−)) m/z 410.1924 ($C_{17}H_{34}NO_8P$ − H requires 410.1944), 367, 227, 153, 113.

3-*O*-(*p*-Methoxybenzyl)-*sn*-glycerol (21). To a mixture of 1,2-*O*-isopropylidene-*sn*-glycerol[26] (4.00 g, 30.3 mmol) and potassium *tert*-butoxide (3.39 g, 30.3 mmol) in dry *tert*-butyl alcohol (10 mL) at reflux was added *p*-methoxybenzyl chloride (7.11 g, 45.5 mmol) dropwise over 20 min. The resulting mixture was heated at reflux for an additional 40 min. The mixture was allowed to cool to room temperature and poured into 50% aqueous acetic acid (100 mL). The mixture was adjusted to pH 4 by careful addition of glacial acetic acid (*ca.* 8 mL) and stirred for 16 h. The solvent was removed under vacuum, and the residue was filtered through a plug of glass wool and distilled through a 15-cm Vigreux column under vacuum to provide 5.90 g (92%) of **21** as a clear, colorless, viscous oil: bp 152–155 °C (0.25 mmHg); IR (neat) ν 3420 cm^{-1}; ^1H NMR (300 MHz) δ 7.23 (d, 2 H, J = 8.3 Hz), 6.87 (d, 2 H, J = 8.3 Hz), 4.45 (s, 2 H), 3.87–3.83 (m, 1 H), 3.79 (s, 3 H), 3.64–3.48 (comp, 4 H), 2.75 (br s, 2 H); ^{13}C NMR (75 MHz) δ 159.3, 129.8, 129.4, 113.8, 73.1, 71.4, 70.7, 64.0, 55.2; mass spectrum, m/z 212.1048 ($C_{11}H_{16}O_4$ requires 212.1049), 137, 121 (base), 107, 91. Anal. Calcd for $C_{11}H_{16}O_6$: C, 62.25; H, 7.60. Found: C, 61.75; H, 7.44.

3-*O*-(*p*-Methoxybenzyl)-1-*O*-palmitoyl-*sn*-glycerol: obtained as a low melting white solid in 54% yield from **21** by HPLC eluting with hexanes/EtOAc (5:1) employing the standard procedure for preparing 1-*O*-acyl-3-*O*-benzyl-*sn*-glycerols (*vide supra*); IR (neat) ν 3290, 1740 cm^{-1}; ^1H NMR (300 MHz) δ 7.25 (d, 2 H, J = 8.4 Hz), 6.88 (d, 2 H, J = 8.4 Hz), 4.48 (s, 2 H), 4.20–4.08 (comp, 2 H), 4.02–4.00 (m, 1 H), 3.81 (s, 3 H), 3.52 (dd, 1 H, J = 9.5, 4.3 Hz), 3.45 (dd, 1 H, J = 9.5, 6.1 Hz), 2.49 (br s, 1 H), 2.32 (t, 2 H, J = 7.5 Hz), 1.63–1.58 (comp, 2 H), 1.27–1.24 (comp, 26 H), 0.88 (t, 3 H, J = 6.6 Hz); ^{13}C NMR (75 MHz) δ 173.9, 159.3, 129.7, 129.4, 113.8, 73.1, 70.6, 68.9, 65.3, 55.2, 34.1, 31.9, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 24.9, 22.7, 14.1; mass spectrum, m/z 450.3336 ($C_{27}H_{46}O_5$ requires 450.3345), 313, 239, 211, 194, 163, 137, 121 (base).

2-*O*-(Benzyloxymethyl)-3-*O*-(*p*-methoxybenzyl)-1-*O*-palmitoyl-*sn*-glycerol. To a solution of 3-*O*-(*p*-methoxybenzyl)-1-palmitoyl-*sn*-glycerol (1.50 g, 3.3 mmol) from the preceding experiment and *i*-Pr_2NEt (950 mg, 7.3 mmol) in dry CH_2Cl_2 (10 mL) at room temperature was added dropwise freshly distilled chloromethyl benzyl ether (1.05 g, 6.7 mmol). The resulting mixture was stirred for 22 h at room temperature. The mixture was then diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous NH_4Cl (1 × 15 mL) and H_2O (1 × 15 mL), dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The crude mixture was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to afford 1.79 g (94%) of the product as a clear viscous oil: IR (neat) ν 1740, 1530 cm^{-1}; ^1H NMR (300 MHz) δ 7.33–7.29 (comp, 5 H), 7.23 (d, 2 H, J = 8.5 Hz), 6.85 (d, 2 H, J = 8.5 Hz), 4.85 (s, 2 H), 4.63 (s, 2 H), 4.46 (s, 2 H), 4.28 (dd, 1 H, J = 11.6, 4.2 Hz), 4.17 (dd, 1 H, J = 11.6, 5.9 Hz), 4.08–4.04 (m, 1 H), 3.77 (s, 3 H), 3.54 (d, 2 H, J = 5.2 Hz), 2.26 (t, 2 H, J = 7.5 Hz), 1.74–1.56 (comp, 2 H), 1.32–1.22 (comp, 26 H), 0.88 (t, 3 H, J = 6.6 Hz); ^{13}C NMR (75 MHz) δ 173.3, 159.4, 137.9, 130.2, 129.1, 128.3, 127.7, 127.5, 113.9, 94.1, 74.1, 73.1, 69.9, 69.5, 64.0, 55.2, 34.2, 31.9, 29.6, 29.4, 29.3, 24.9, 22.6, 13.9; mass spectrum, m/z 539 (M^+ − OCH_3), 449, 343, 313 (base), 211, 121, 91. Anal. Calcd for $C_{35}H_{54}O_6$: C, 73.65; H, 9.54. Found: C, 73.65; H, 9.86.

2-*O*-(Benzyloxymethyl)-1-*O*-palmitoyl-*sn*-glycerol (22). To a solution of 2-*O*-(benzyloxymethyl)-3-*O*-(*p*-methoxybenzyl)-1-palmitoyl-*sn*-glycerol (1.1 g, 1.9 mmol) from the preceding experiment in CH_2Cl_2/H_2O (20:1) (10.5 mL) at room temperature was added in one portion DDQ (570 mg, 2.5 mmol). After stirring for 30 min, the mixture was decanted, and the precipitate was washed with CH_2Cl_2 (20 mL). The organic solution was washed with saturated $NaHCO_3$ (1 × 5 mL). The aqueous phase was back-extracted with CH_2Cl_2 (2 × 5 mL), and the combined organics were washed with saturated aqueous $NaHCO_3$ (1 × 10 mL) and saturated aqueous NaCl (1 × 10 mL), dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The crude mixture was separated by flash chromatography eluting with hexanes/EtOAc (3:1) to afford 764 mg (88%) of **22** as an opaque viscous oil: IR (neat) ν 3420, 1730 cm^{-1}; ^1H NMR (300 MHz) δ 7.39–7.28 (comp, 5 H), 4.90 (d, 1 H, J = 7.1 Hz), 4.85 (d, 1 H, J = 7.1 Hz), 4.67 (d, 1 H, J = 11.8 Hz), 4.65 (d, 1 H, J = 11.8 Hz), 4.24 (dd, 1 H, J = 11.8, 5.7 Hz), 4.19 (dd, 1 H, J = 11.8, 5.0 Hz), 3.92–3.88 (m, 1 H), 3.70–3.63 (comp, 2 H), 2.55–2.53 (m, 1 H), 2.52–2.50 (comp, 2 H), 2.33–2.28 (comp, 2 H), 1.27–1.23 (comp, 24 H), 0.88 (t, 3 H, J = 6.7 Hz); ^{13}C NMR 75 MHz) δ 173.6, 137.2, 128.4, 127.8, 94.4, 77.3, 69.9, 63.2, 62.4, 34.1, 31.8, 29.6, 29.3, 29.2, 24.8, 22.6, 14.0; mass spectrum (FAB), m/z 369, 313, 154, 131 (base). Anal. Calcd for $C_{27}H_{46}O_5$: C, 71.96; H, 10.29. Found: C, 71.75; H, 10.25.

***O*-[2-(*N*-(*tert*-Butyloxycarbonyl)amino)ethyl] *O*-methyl *O*-(1′-*O*-palmitoyl-2′-*O*-(benzyloxymethyl)-*sn*-3′-glyceryl) phosphate (23):** obtained by the general coupling/oxidation procedure (methyl dichlorophosphite, **22**, and *N*-Boc-ethanolamine in THF at −78 °C; 30% H_2O_2) as an opaque viscous oil in 81% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (1:1): IR (neat) ν 1740, 1550, 1305, 1080 cm^{-1}; ^1H NMR (300 MHz) δ 7.36–7.29 (comp, 5 H), 5.10 (br s, 1 H), 4.86 (s, 2 H), 4.66 (s, 2 H), 4.28 (dd, 1 H, J = 11.6, 4.3 Hz), 4.19–4.08 (comp, 6 H), 3.79 and 3.76 (overlapping d, J = 11.2 Hz), 3.49–3.38 (m, 1 H). 2.30 (t, 2 H, J = 7.6 Hz), 1.63–1.60 (comp, 2 H), 1.44 (s, 9 H), 1.30–1.22 (comp, 24 H), 0.88 (t, 3 H, J = 6.6 Hz); ^{13}C NMR

(75 MHz) δ 173.3, 156.7, 137.3, 128.4, 127.8, 93.9, 73.4, 73.3, 60.7, 67.1, 66.6, 62.7, 54.4, 40.9, 34.0, 31.8, 29.6, 29.4, 29.3, 29.2, 29.1, 28.3, 24.8, 22.6, 14.0; ^{31}P NMR (146 MHz) δ 0.87; mass spectrum (CI, methane), *m/z* 688 (M^+ + H), 632, 588 (base), 524, 391, 371, 313, 296, 106. Anal. Calcd for $C_{35}H_{62}NO_{10}P$: C, 61.12; H, 9.09; N, 2.04. Found: C, 61.39; H, 9.04; N, 1.94.

***O*-[2-(*N*-(*tert*-Butyloxycarbonyl)amino)ethyl] *O*-Methyl *O*-(1′-*O*-Palmitoyl-*sn*-3′-glyceryl) Phosphate (24).** To a solution of **23** (1.08 g, 1.6 mmol) in absolute EtOH (215 mL) at room temperature was added freshly prepared W-4 Raney nickel (*ca.* 1.5 g), and the resulting suspension was stirred under an atmosphere of H_2 for 16 h. The H_2 was displaced with Ar, Celite (500 mg) was added, and the mixture was stirred an additional 10 min. The mixture was then filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude mixture was purified by flash chromatography eluting with hexanes/acetone (2:1) to afford 792 mg (89%) of **24** as an opaque oil: IR (neat) ν 3380, 1730 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.18 (br s, 1 H), 4.20–4.08 (comp, 7 H), 3.82 and 3.78 (overlapping d, 3 H, *J* = 11.3 Hz), 3.43–3.41 (comp, 2 H), 2.37–2.32 (comp, 2 H), 1.66–1.51 (comp, 2 H), 1.45 (s, 9 H), 1.27–1.23 (comp, 24 H), 0.88 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz) δ 173.8, 155.8, 79.7, 68.9, 68.7, 67.3, 67.2, 64.3, 64.2, 54.7, 54.6, 40.8, 34.0, 31.9, 29.7, 29.4, 29.3, 29.2, 29.1, 28.3, 24.8, 22.6, 14.1; ^{31}P NMR (146 MHz) δ 1.30; mass spectrum (CI, methane), *m/z* 568.3632 (M + H) ($C_{27}H_{55}NO_9P$ requires 568.3600), 512, 494, 468, 433, 419, 391, 162, 106 (base). Anal. Calcd for $C_{27}H_{54}NO_9P$: C, 57.12; H, 9.59; N, 2.47. Found: C, 57.65; H, 9.66; N, 2.41.

***O*-[2-(*N*-(*tert*-Butyloxycarbonyl)amino)ethyl] *O*-(2′-*O*-Linoleoyl-1′-*O*-palmitoyl-*sn*-3′-glyceryl) *O*-Methyl Phosphate (25).** To a solution of **24** (400 mg, 0.71 mmol), linoleic acid (217 mg, 0.78 mmol), and DMAP (9 mg, 70 μmol) in dry CH_2Cl_2 (10 mL) at room temperature was added dropwise over 30 min a solution of DCC (167 mg, 0.81 mmol) in CH_2Cl_2 (5 mL). The resulting suspension was stirred for 6 h at room temperature at which time the mixture was filtered through Celite and the filtrate evaporated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to afford 526 mg (91%) of **25** as an opaque viscous oil: ^{1}H NMR (500 MHz) δ 5.40–5.30 (comp, 4 H), 5.26–5.23 (m, 1 H), 5.08 (br s, 1 H), 4.33 (dd, 1 H, *J* = 12.0, 4.4 Hz), 4.22–4.15 (comp, 3 H), 4.12–4.08 (comp, 2 H), 3.79 and 3.77 (overlapping d, 3 H, *J* = 11.2 Hz), 3.42–3.40 (comp, 2 H), 2.77 (t, 2 H, *J* ≈ 6.6 Hz), 2.34 (t, 2 H, *J* = 7.6 Hz), 2.32 (t, 2 H, *J* = 7.6 Hz), 2.07–2.03 (comp, 4 H), 1.64–1.58 (comp, 8 H), 1.46 (s, 9 H), 1.40–1.20 (comp, 34 H), 0.90–0.87 (comp, 6 H); ^{13}C NMR (75 MHz) δ 173.2, 172.8, 155.8, 130.2, 129.9, 128.1, 127.8, 79.5, 69.4, 69.3, 67.3, 67.2, 65.5, 61.5, 54.6, 54.5, 40.9, 40.8, 34.1, 34.0, 31.9, 31.5, 29.7, 29.4, 29.3, 29.2, 29.1, 28.3, 27.2, 25.6, 24.8, 22.6, 22.5, 14.1; mass spectrum (FAB), *m/z* 730, 576, 333, 241, 185, 149 (base).

2-*O*-Linoleoyl-1-*O*-palmitoyl-*sn*-glycero-3-phosphoethanolamine (26): obtained as a clear, viscous oil in 90% yield from **25** by sequential treatment with NaI in warm 2-butanone and then with cold TFA/CH_2Cl_2 (1:1). The **26** thus obtained was spectroscopically (^{1}H and ^{13}C NMR) identical to an authentic sample purchased from Sigma. ^{1}H NMR (300 MHz): δ 5.37–5.32 (comp, 4 H), 5.26–5.22 (m, 1 H), 4.37–4.00 (comp, 6 H), 3.42–3.38 (comp, 2 H), 2.77 (t, 2 H, *J* = 5.9 Hz), 2.36–2.27 (comp, 4 H), 2.10–1.95 (comp, 4 H), 1.61–1.57 (comp, 8 H), 1.25 (comp, 34 H), 0.90–0.86 (comp, 6 H).

***O*-(1,2-*O*-Dipalmitoyl-*sn*-3-glyceryl *O*-[*N*-(carbobenzyloxy)-L-serine benzyl ester] *O*-phenyl phosphate (27):** obtained by the general coupling/oxidation procedure (methyl dichlorophosphite, **10d**, and *N*-(carbobenzyloxy)-L-serine benzyl ester in THF at −78 °C; 30% H_2O_2) as a white solid in 91% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (5:1); mp 47–48 °C; IR (neat) ν 1750, 1725, 1550, 1275, 1100 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.38–7.27 (comp, 10 H), 7.19–7.12 (comp, 5 H), 5.90–5.75 (m, 1 H), 5.25–5.08 (comp, 4 H), 4.66–4.62 (m, 1 H), 4.61–4.52 (m, 1 H), 4.50–4.42 (m, 1 H), 4.27-4.13 (comp, 3 H), 4.09 (d, 1 H, *J* = 5.8 Hz), 4.08 (d, 1 H, *J* ≈ 5.8 Hz), 2.29–2.23 (comp, 4 H), 1.63–1.53 (comp, 4 H), 1.30–1.21 (comp, 48 H), 0.88 (t, 6 H, *J* = 7.0 Hz); ^{13}C NMR (91 MHz) δ 173.0, 172.6, 168.5, 155.7, 150.9, 136.0, 135.0, 129.8, 128.6, 128.5, 128.2, 128.1, 128.0, 125.4, 119.9, 69.3, 68.0, 67.7, 67.2, 66.4, 61.5, 54.7, 54.6, 34.0, 33.9, 31.6, 29.7, 29.4, 29.3, 29.0, 28.8, 24.8, 22.5, 13.9; mass spectrum (FAB), *m/z* 661, 552, 367, 313, 255, 153. Anal. Calcd for $C_{59}H_{90}NO_{12}P$: C, 68.38; H, 8.75; N, 1.35. Found: C, 67.50; H, 8.48; N, 1.46.

1,2-*O*-Dipalmitoyl-*sn*-glycero-3-phosphoserine (28): obtained in 71% yield from **27** by deprotection via hydrogenolysis over a mixture of platinum oxide and palladium black in glacial acetic acid;[27] as a white solid recrystallized from glacial acetic acid; mp 166 °C dec. The material thus obtained was spectroscopically (^{1}H and ^{13}C NMR) identical to an authentic sample purchased from Sigma; mass spectrum (FAB), *m/z* 736.5122 (M^++ H) ($C_{38}H_{74}NO_{10}P$ requires 736.5109), 718, 648 (base), 410, 392, 289, 256.

1,2:4,5-*O*-Diisosopropylidene-3-*O*-camphanoyl-L-*myo*-inositol (30a) and 1-*O*-Camphanoyl-2,3:5,6-*O*-diisopropylidene-D-*myo*-inositol (31a). (1*S*)-(−)-Camphanoyl chloride (5.35 g, 24.7 mmol) in anhydrous DMF (20 mL) was added dropwise, *via* syringe drive, over a period of 3 h to a solution of **29**[31b] (7.39 g, 28.4 mmol) and imidazole (1.97 g, 28.0 mmol) in anhydrous DMF (75 mL) cooled to 0 °C. When the addition was complete the resulting mixture was stirred at 0 °C for an additional 3 h at which time the cooling bath was removed. The mixture was stirred at room temperature for 18 h, whereupon the solvent was removed *in vacuo*. The residue dissolved in CH_2Cl_2 (100 mL), and the resulting solution was washed successively with saturated aqueous sodium bicarbonate (30 mL), water (2 × 30 mL), and brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was subjected to flash chromatography eluting with hexanes/EtOAc (1:1) to afford 9.31 g (75%) of a mixture of the desired diastereomeric monocamphanate esters **30a** and **31a** suitable for use in the next step. The diastereomeric esters were separated by HPLC eluting with hexanes/acetone (20:1) for partial spectroscopic characterization.

For the less polar diastereomer **30a:** ^{1}H NMR (300 MHz) δ 5.18 (dd, 1 H, *J* = 10.5, 4.6 Hz), 4.61 (t, 1 H, *J* = 4.6 Hz), 4.08–4.00 (comp, 2 H), 3.92–3.84 (m, 1 H), 3.38 (dd, 1 H, *J* = 10.5, 9.6 Hz), 2.85 (d, 1 H, *J* = 3.0 Hz), 2.45 (ddd, 1 H, *J* = 13.3, 10.8, 4.2 Hz), 2.05 (ddd, 1 H, *J* = 13.4, 9.2, 4.5 Hz), 1.90 (ddd, 1 H, *J* = 13.2, 10.8, 4.5 Hz), 1.72 (ddd, 1 H, *J* = 13.3, 9.2, 4.2 Hz), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.26 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz) δ 178.1, 167.0, 112.8, 110.2, 90.9, 81.8, 78.1, 74.5, 74.4, 74.1, 72.0, 54.8, 54.6, 30.4, 28.8, 28.0, 26.8, 25.7, 16.6, 16.4, 9.6.

For the more polar diastereomer **31a:** ^{1}H NMR (300 MHz) δ 5.16 (dd, 1 H, *J* = 10.5, 4.6 Hz), 4.65 (t, 1 H, *J* = 4.6 Hz), 4.07 (t, 1 H, *J* = 5.8 Hz), 3.97 (t, 1 H, *J* = 10.0 Hz), 3.86 (ddd, 1 H, *J* = 10.4, 6.9, 3.2 Hz), 3.38 (t, 1 H, *J* = 10.2 Hz), 3.14 (d, 1 H, *J* = 2.8 Hz), 2.46 (ddd, 1 H, *J* = 13.3, 10.8, 4.2 Hz), 2.06 (ddd, 1 H, *J* = 13.4, 9.2, 4.5 Hz), 1.91 (ddd, 1 H, *J* = 13.2, 10.8, 4.5 Hz), 1.66 (ddd, 1 H, *J* = 13.3, 9.2, 4.2 Hz), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.26 (s, 3 H), 1.08 (s, 3 H), 1.02 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz) δ 177.8, 166.7, 112.8, 110.2, 91.0, 81.8, 78.1, 74.5, 74.3, 72.2, 54.8, 54.5, 30.5, 29.1, 28.0, 26.9, 26.8, 25.7, 16.4, 16.3, 9.6.

1,2:4,5-*O*-Diisopropylidene-3-*O*-camphanoyl-6-*O*-(*tert*-butyldimethylsilyl)-L-*myo*-inositol (30b) and 1-*O*-Camphanoyl-2,3:5,6-*O*-diisopropylidene-4-*O*-(*tert*-butyldimethylsilyl)-D-*myo*-inositol (31b). A solution of a mixture of the diastereomeric camphanate esters **30a** and **31a** (4.01 g, 9.10 mmol) and imidazole (0.75 g, 10.9 mmol) in DMF (25 mL) was cooled to 0 °C, and *tert*-butyldimethylsilyl chloride (1.52 g, 10.1 mmol) was added in a single portion. The mixture was stirred at 0 °C for 2 h and then at room temperature for 20 h. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (50 mL), and the resulting solution was washed successively with saturated aqueous sodium bicarbonate (15 mL), water (2 × 15 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated. The residue was separated by flash chromatography eluting with CH_2Cl_2/acetone (97:3) to afford 2.41 g (47%) of **30b** and 2.45 g (48%) of **31b**.

For the less polar diastereomer **30b**: IR ν 1810, 1760 cm^{-1};

^{1}H NMR (300 MHz) δ 5.16 (dd, 1 H, J = 10.5, 4.6 Hz), 4.56 (t, 1 H, J = 4.6 Hz), 4.01–3.94 (comp, 2 H), 3.77 (dd, 1 H, J = 10.5, 6.3 Hz), 3.30 (t, 1 H, J = 10.0 Hz), 2.45 (ddd, 1 H, J = 13.3, 10.8, 4.2 Hz), 2.04 (ddd, 1 H, J = 13.4, 9.2, 4.5 Hz), 1.89 (ddd, 1 H, J = 13.2, 10.8, 4.5 Hz), 1.66 (ddd, 1 H, J = 13.3, 9.2, 4.2 Hz), 1.44 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.24 (s, 3 H), 1.08 (s, 3 H), 1.02 (s, 3 H), 0.96 (s, 3 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz) δ 178.2, 167.1, 112.0, 109.7, 91.0, 82.9, 78.9, 75.2, 74.5, 74.1, 72.4, 54.8, 54.5, 30.5, 28.9, 28.0, 26.9, 26.8, 25.8, 25.7, 18.2, 16.6, 16.4, 9.7, −4.6, −4.7; mass spectrum (CI, methane) m/z 555.2963 ($C_{28}H_{46}O_9Si$ + H requires 555.2976), 497, 489, 365, 337 (base).

For the more polar diastereomer **31b**: IR ν 1790, 1760 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.11 (dd, 1 H, J = 10.5, 4.6 Hz), 4.61 (t, 1 H, J = 4.6 Hz), 4.00 (t, 1 H, J = 5.7 Hz), 3.92 (t, 1 H, J = 10.0 Hz), 3.77 (dd, 1 H, J = 10.5, 6.3 Hz), 3.30 (t, 1 H, J = 10.0 Hz), 2.47 (ddd, 1 H, J = 13.3, 10.8, 4.2 Hz), 2.06 (ddd, 1 H, J = 13.4, 9.2, 4.5 Hz), 1.91 (ddd, 1 H, J = 13.2, 10.8, 4.5 Hz), 1.67 (ddd, 1 H, J = 13.3, 9.2, 4.2 Hz), 1.45 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 1.25 (s, 3 H), 1.08 (s, 3 H), 1.00 (s, 3 H), 0.92 (s, 3 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz) δ 177.9, 166.7, 112.1, 109.6, 91.1, 82.8, 78.8, 75.3, 74.2, 72.5, 54.7, 54.5, 30.5, 29.1, 28.1, 27.0, 26.8, 25.9, 25.7, 18.2, 16.3, 16.2, 9.7, −4.6, −4.7; mass spectrum (CI methane) m/z 555.2970 ($C_{28}H_{46}O_9Si$ + H requires 555.2976), 497, 489, 365, 337 (base).

2,3:5,6-*O*-Diisopropylidene-4-*O*-(*tert*-butyldimethylsilyl)-D-*myo*-inositol (33). Compound **31b** (1.02 g, 1.84 mmol) was suspended in methanol (100 mL) containing potassium hydroxide (0.52 g, 9.2 mmol), and the resulting mixture was stirred at room temperature until it became homogeneous (approximately 20 min), whereupon the solvent was removed under reduced pressure. The residue was suspended in saturated aqueous NH_4Cl (60 mL) and extracted with $CHCl_3$ (100 mL), and the organic phase was washed successively with water (2 × 30 mL) and brine (30 mL) and dried ($MgSO_4$). The excess solvents were removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (7:3) to afford 0.65 g (94%) of **33** as a colorless glass: ^{1}H NMR (300 MHz) δ 4.38 (t, 1 H, J = 4.8 Hz), 3.99–3.92 (comp, 2 H), 3.78–3.71 (comp, 2 H), 3.22 (t, 1 H, J = 9.9 Hz), 2.58 (d, 1 H, J = 9.8 Hz), 1.47 (s, 3 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz) δ 111.7, 109.6, 82.9, 78.7, 77.6, 75.7, 69.7, 28.0, 26.9, 26.8, 25.9, 25.6, 18.2, −4.6, −4.8; mass spectrum m/z 375.2205 ($C_{18}H_{34}O_6Si$ + H requires 375.2203), 359, 317, 259, 183, 129 (base).

***O*-(1,2-*O*-Di-*n*-hexanoyl-*sn*-3-glyceryl *O*-(D-2′,3′:5′,6′-*O*-diisopropylidene-4′-*O*-(*tert*-butyldimethylsilyl)-*myo*-inositol) *O*-methyl phosphate (34):** obtained by the general coupling/oxidation procedure (methyl dichlorophosphite, **33**, and **10c** in THF at −78 °C; *tert*-butyl hydroperoxide) as a colorless oil in 75% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (2:1); IR ν 1735, 1460, 1375, 1240, 1163 cm^{-1}; ^{1}H NMR (250 MHz) δ 5.29–5.21 (comp, 1 H), 4.72–4.59 (comp, 1 H), 4.55–4.49 (comp, 1 H), 4.39–4.31 (comp, 1 H), 4.26–4.12 (comp, 3 H), 3.99–3.90 (comp, 2 H), 3.81–3.74 (comp, 4 H), 3.29–3.21 (comp, 1 H), 2.30 (q, 4 H, J = 7.66 Hz), 1.68–1.54 (comp, 4 H), 1.50 (s, 3 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.22 (s, 3 H), 1.31–1.22 (comp, 8 H), 0.95–0.86 (comp, 15 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (63 MHz) δ 173.1, 172.7, 112.1, 109.8, 82.7, 78.7, 75.2, 74.9, 69.4, 69.2, 65.7, 65.6, 61.8, 61.7, 54.5, 54.4, 34.0, 33.9, 31.1, 28.0, 26.8, 26.7, 25.9, 25.6, 24.4, 22.2, 18.1, 15.2, 13.8, −4.6, -4.8; ^{31}P NMR (125.8 MHz, benzene-d$_6$) δ −1.70, −1.75; mass spectrum (CI(+)) m/z 739.3846 ($C_{34}H_{63}O_{13}PSi$ + H requires 739.3854), 525, 375, 221.

***O*-(1,2-*O*-Di-*n*-hexanoyl-*sn*-3-glyceryl) *O*-(D-2′,3′:5′,6′-*O*-diisopropylidene-4′-*O*-(*tert*-butyldimethylsilyl)-*myo*-inositol) *O*-(2″-(trimethylsilyl)ethyl) phosphate (35):** obtained by the general coupling/oxidation procedure (2-(trimethylsilyl)-ethyl dichlorophosphite, **33**, and **10c** in THF at −78 °C; *tert*-butyl hydroperoxide) as a colorless oil in 79% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (2:1): IR ν 2945, 1735, 1460, 1380, 1260, 1170 cm^{-1}; ^{1}H NMR (250 MHz) δ 5.30 (m, 1 H), 4.69–4.60 (m, 1 H), 4.50 (t, 1 H, J = 4.6 Hz), 4.35 (dd, 1 H, J = 12.0, 4.6 Hz), 4.23–4.13 (comp, 5 H), 3.99–3.89 (comp, 2 H), 3.81–3.72 (m, 1 H), 3.25 (t, 1 H, J = 10.5 Hz), 2.38–2.19 (comp, 4 H), 1.63–1.54 (comp, 4 H), 1.49 (s, 3 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.32–1.21 (comp, 8 H), 1.16–1.07 (comp, 2 H), 0.91–0.80 (comp, 15 H), 0.08 (s, 3 H), 0.07 (s, 3 H), −0.01 (s, 9 H); ^{13}C NMR (63 MHz) δ 173.1, 172.7, 112.0, 109.7, 82.7, 78.7, 76.5, 75.2 (d, J_{CP} = 7.8 Hz), 75.0, 74.7, 74.6, 69.4 (d, J_{CP} = 8.4 Hz), 67.0 (d, J_{CP} = 6.2 Hz), 65.4, 61.9, 34.1, 33.9, 31.1, 28.0, 26.8, 26.7, 26.0, 25.6, 24.4, 22.2, 19.4, 19.3, 18.1, 13.8, −1.6, −4.6, −4.8; ^{31}P NMR (146 MHz) δ −1.3, -1.5; mass spectrum (CI) m/z 823.4249 ($C_{38}H_{73}O_{13}PSi_2$ − H requires 823.4248), 723, 633, 298, 240, 196, 108.

***O*-(1,2-*O*-Di-*n*-hexanoyl-*sn*-3-glyceryl) *O*-(D-2′,3′:5′,6′-*O*-diisopropylidene-4′-*O*-(*tert*-butyldimethylsilyl)-*myo*-inositol) *O*-(2-(trimethylsilyl)ethyl) phosphorothioate (36):** obtained by the general coupling/sulfurization procedure (2-(trimethylsilyl)ethyl dichlorophosphite, **33**, and **10c** in THF at −78 °C; S_8) as a colorless oil in 75% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (2:1): IR ν 1735, 1460, 1380, 1255, 1165 cm^{-1}; ^{1}H NMR (250 MHz) δ 5.30 (m, 1 H), 4.69–4.60 (m, 1 H), 4.50 (t, 1 H, J = 4.6 Hz), 4.35 (dd, 1 H, J = 12.0, 4.6 Hz), 4.23–4.13 (comp, 5 H), 3.99–3.89 (comp, 2 H), 3.81–3.72 (m, 1 H), 3.25 (t, 1 H, J = 10.5 Hz), 2.38–2.19 (comp, 4 H), 1.63-1.54 (comp, 4 H), 1.49 (s, 3 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.32–1.21 (comp, 8 H), 1.16–1.07 (comp, 2 H), 0.91–0.80 (comp, 15 H), 0.08 (s, 3 H), 0.07 (s, 3 H), −0.01 (s, 9 H); ^{13}C NMR (63 MHz) δ 173.1, 172.7, 112.0, 109.7, 82.7, 78.7, 76.5, 75.2 (d, J_{CP} = 8.4 Hz), 75.0, 74.7, 74.6, 69.4 (d, J_{CP} = 8.4 Hz), 67.0, 66.9 (d, J_{CP} = 6.2 Hz), 65.4, 61.9, 34.1, 33.9, 31.1, 28.0, 26.8, 26.7, 26.0, 25.6, 24.4, 22.2, 19.4, 19.3, 18.1, 13.8, −1.6, −4.6, −4.8; ^{31}P NMR (146 MHz) δ 70.9, 70.8; mass spectrum (CI) m/z 839.4012 ($C_{38}H_{73}O_{12}PSSi_2$ − H requires 839.4021), 739, 569, 240, 223, 184.

General Procedure for Removal of Acetonide Group from Phosphatidyl Inositol Derivatives. To a solution of the protected phosphatidyl inositol derivative **35** or **36** (0.08 mmol) in CH_3CN/THF (2:1) (1.5 mL) was added aqueous HF (80 μL, 2.45 N), and the resulting solution was stirred at room temperature for 2 h. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography eluting with the indicated solvent.

1,2-*O*-Di-*n*-hexanoyl-*sn*-glycero-3-phospho-*myo*-inositol (37): obtained as a colorless solid in 70% yield using the general deprotection procedure and flash chromatography eluting with 2-propanol/water (88:12); IR ν 3455, 1735, 1460, 1375, 1245, 1165 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 5.14–5.11 (m, 1 H), 4.39 (dd, 1 H, J = 9.6, 2.2 Hz), 4.12–4.02 (comp, 2 H), 3.98–3.61 (comp, 3 H), 3.61–3.39 (comp, 2 H), 3.36 (t, 1 H, J = 9.3 Hz), 3.11 (dd, 1 H, J = 9.6, 2.2 Hz), 2.93 (t, 1 H, J = 9.0 Hz), 2.31–2.23 (comp, 4 H), 1.51–1.44 (comp, 4 H), 1.27–1.15 (comp, 8 H), 0.84 (t, 6 H, J = 7.1 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 172.6, 172.4, 75.9, 75.2, 72.3, 71.5, 70.2, 63.0, 62.4, 33.5, 33.3, 30.6, 24.1, 24.0, 21.8, 13.7; ^{31}P NMR (146 MHz, DMSO-d_6) δ −2.03; mass spectrum (FAB(−)) m/z 530.2166 ($C_{21}H_{39}O_{13}P$ requires 530.2128), 413, 367, 251, 153, 115.

1,2-*O*-Di-*n*-hexanoyl-*sn*-glycero-3(R_P/S_P)-phosphothio-*myo*-inositol (38): obtained as a colorless solid in 66% yield using the general deprotection procedure and flash chromatography eluting with 2-propanol/water (88:12); IR ν 3455, 1735, 1460, 1375, 1245, 1165 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.14–5.11 (m, 1 H), 4.19 (dd, 1 H, J = 9.6, 2.2 Hz), 4.02 (dd, 1 H, J = 9.5, 8.9 Hz), 3.89–3.37 (comp, 3 H), 3.61–3.39 (comp, 2 H), 3.36 (t, 1 H, J = 9.3 Hz), 3.11 (dd, 1 H, J = 9.6, 2.2 Hz), 2.93 (t, 1 H, J = 9.0 Hz), 2.31–2.23 (comp, 4 H), 1.51–1.44 (comp, 4 H), 1.27–1.15 (comp, 8 H), 0.84 (t, 6 H, J = 7.1 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 172.6, 172.4, 75.9, 75.2, 72.3, 71.5, 70.2, 63.0, 62.4, 33.5, 33.3, 30.6, 24.1, 24.0, 21.8, 13.7; ^{31}P NMR (146 MHz, DMSO-d_6) δ 57.6, 56.9; mass spectrum (FAB(−)) m/z 545.1850 ($C_{21}H_{39}O_{12}PS$ − H requires 545.1822), 529, 483, 153, 115.

***meso*-2,3,4,5,6-*O*-Pentabenzyl-*scyllo*-ionose (47).** A solution of dimethyl sulfoxide (2.90 mL, 41.2 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a stirred solution of oxalyl chloride (1.80 mL, 20.6 mmol) in CH_2Cl_2 (25 mL) at -78 °C,

over 15 min. The mixture was stirred for an additional 5 min whereupon a solution of **46** (3.27 g, 5.18 mmol) in CH_2Cl_2 (25 mL) was added. The resulting mixture was stirred for an additional 2 h. At this time triethylamine (1.40 mL, 10.3 mmol) was added and the mixture allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2 (75 mL), and the organic layer was washed successively with 50% saturated NH_4Cl (50 mL), water (2 × 50 mL), 5% $CuSO_4$ (3 × 50 mL), and water (50 mL). The combined organics werre dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography eluting with hexane/EtOAc (4:1) to afford 2.75 g (84%) of **47** as a white solid. This material had physical characteristics identical to those reported in the literature:[46] ^{1}H NMR (250 MHz) δ 7.40–7.21 (comp, 25 H), 4.92 (s, 2 H), 4.88 (s, 4 H), 4.75 (d, 2 H, J = 10.7 Hz), 4.55 (d, 2 H, J = 11.5 Hz), 4.15 (d, 2 H, J = 9.7 Hz), 3.87 (t, 1 H, J = 9.2 Hz), 3.62 (t, 2 H, J = 9.5 Hz); ^{13}C NMR (63 MHz) δ 202.1, 138.1, 138.0, 137.2, 128.4, 128.3, 128.2, 128.0, 127.0, 127.8, 127.7, 127.6, 83.7, 82.1, 81.4, 76.0, 75.9, 73.3; mass spectrum (CI(+)) m/z 628.2807 ($C_{41}H_{40}O_6$ requires 628.2825).

***meso*-2,3,4,5,6-*O*-Pentabenzyl-*scyllo*-inositol (48).** A solution of n-Bu_2Cl_2 (3.32 g, 10.9 mmol) in THF (10 mL) was added dropwise to a solution of n-Bu_2SnH_2 (2.57 g, 10.9 mmol) and the mixture stirred at room temperature for 10 min. A solution of **47** (2.75 g, 4.37 mmol) was added, and the mixture was heated at reflux for 18 h. After the solution was cooled to room temperature, methanol (8 mL) was added, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography eluting with hexane/EtOAc (4:1) to afford 2.36 g (86%) of **48** as a colorless solid: mp 105–106 °C; ^{1}H NMR (250 MHz) δ 7.35–7.25 (comp, 25 H), 4.93–4.79 (m, 10 H), 3.66–3.54 (comp, 4 H), 3.47–3.40 (comp, 2 H), 2.58 (br s, 1 H); ^{13}C NMR (63 MHz) δ 138.4, 138.3, 128.4, 128.3, 127.8, 127.7, 127.6, 83.1, 82.7, 82.4, 75.8, 75.7, 75.4, 74.3; mass spectrum (CI, methane) m/z 631.3049 ($C_{41}H_{42}O_6$ + H requires 631.3060), 540, 449, 359, 271,181.

***O*-(1,2-*O*-Di-*n*-hexanoyl-*sn*-3-glyceryl) *O*-(D-2′-deoxy-2′-fluoro-3′,4′,5′,6′-tetra-*O*-benzyl-*scyllo*-inositol) *O*-(2″-(trimethylsilyl)ethyl) phosphate**: obtained by the general coupling/oxidation procedure (2-(trimethylsilyl)ethyl dichlorophosphite, **44**, and **10c** in toluene at 0 °C; *tert*-butyl hydroperoxide) as a colorless oil in 74% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (2:1); IR ν 2960, 1735, 1500, 1455, 1360, 1250 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.43–7.20 (comp, 20 H), 5.30–5.27 (m, 0.66 H), 5.11–5.07 (m, 0.33 H), 4.96–4.67 (comp, 8.5 H), 4.62 (t, 0.5 H, J = 9.0 Hz), 4.49–4.34 (comp, 1 H), 4.27–4.04 (comp, 3 H), 4.01–3.72 (comp, 4 H), 3.69–3.53 (comp, 3 H), 2.38–2.25 (comp, 4 H), 1.69–1.59 (comp, 4 H), 1.38–1.26 (comp, 6 H), 1.17–1.12 (m, 2 H), 0.93 (t, 6 H, J = 7.3 Hz), −0.02 (s, 3 H), −0.05 (s, 6 H); ^{13}C NMR (75 MHz) δ 173.0, 172.8, 172.5, 137.9, 137.9, 137.7, 137.7, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 126.9, 93.5 (d, J_{CF} = 186.7 Hz), 81.7, 80.9, 80.8, 80.2, 79.9, 79.3, 78.0, 75.8, 75.3, 75.0, 74.9 (d, J_{CP} = 6.9 Hz), 69.3 (d, J_{CP} = 8.9 Hz), 69.2, 66.8 (d, J_{CP} = 6.8 Hz), 65.0, 61.6, 61.4, 33.9, 33.8, 33.7, 31.0, 24.3, 22.1, 19.6, 19.1, 13.7, −1.7, −1.8; ^{31}P NMR (146 MHz) δ −1.92, −2.15; mass spectrum (CI(+)) m/z 991.4594 ($C_{54}H_{74}FO_{12}PSi$ − H requires 991.4593), 966, 767, 433, 415, 343, 271.

***O*-(1,2-*O*-Di-*n*-hexanoyl-*sn*-3-glyceryl, *O*-(D-2′-deoxy-3′,4′,5′,6′-*O*-tetrabenzyl-*scyllo*-inositol) *O*-(2″-(trimethylsilyl)ethyl) phosphate:** obtained by the general coupling/oxidation procedure (2-(trimethylsilyl)ethyl dichlorophosphite, **45**, and **10c** in toluene at 0 °C; *tert*-butyl hydroperoxide) as a colorless oil in 71% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (2:1); IR ν 2960, 1735, 1500, 1455, 1380, 1360, 1250 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.34–7.16 (comp, 20 H), 5.23–5.20 (m, 0.5 H), 5.09–5.06 (m, 0.5 H), 4.96–4.73 (comp, 8 H), 4.70–4.57 (comp, 1 H), 4.33–4.24 (comp, 1 H), 4.19–3.92 (comp, 5 H), 3.56–3.39 (comp, 4 H), 2.70–2.62 (comp, 1 H), 2.35–2.24 (comp, 4 H), 1.71–1.57 (comp, 4 H), 1.38–1.21 (comp, 8 H), 1.09 (br t, 2 H, J = 9.0 Hz), 1.06–0.98 (comp, 1 H), 0.96–0.82 (comp, 6 H), 0.04 (s, 4.5 H), −0.02 (s, 4.5 H); ^{13}C NMR (75 MHz) δ 173.0, 172.6, 138.5, 138.4, 138.2, 138.0, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 127.2, 85.0, 83.8, 83.7, 82.5, 76.0, 75.8, 75.7, 75.3, 72.6, 69.3, 69.2, 66.9, 66.8, 66.7, 66.6, 65.3, 65.2, 64.9, 61.6, 61.5, 33.9, 33.8, 31.1, 24.4, 22.2, 19.5, 19.4, 13.8, −1.6, −1.7; ^{31}P NMR (146 MHz) δ −2.03, −2.17; mass spectrum (FAB(+)) m/z 973.4699 ($C_{54}H_{75}O_{12}PSi$ − H requires 973.4687), 948, 677, 570, 433, 416, 343, 271, 181.

***O*-(1,2-*O*-Di-*n*-hexanoyl-*sn*-3-glyceryl) *O*-(D-2′,3′,4′,5′,6′-*O*-pentabenzyl-*scyllo*-inositol) *O*-(2″-(trimethylsilyl)ethyl) phosphate**: obtained by the general coupling/oxidation procedure (2-(trimethylsilyl)ethyl dichlorophosphite, **48**, and **10c** in toluene at 0 °C; *tert*-butyl hydroperoxide) as a colorless oil in 71% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (2:1); IR ν 2960, 1735, 1500, 1455, 1380, 1360, 1250 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.43–7.29 (m, 25 H), 5.01–4.78 (comp, 11 H), 4.59–4.42 (m, 1 H), 4.13–3.84 (comp, 5 H), 3.72–3.49 (comp, 6 H), 2.21 (q, 4 H, J = 7.2 Hz), 1.68–1.55 (m, 4 H), 1.38–1.24 (m, 8 H), 0.95–0.89 (m, 8 H), −0.02 (s, 9 H); ^{13}C NMR (63 MHz) δ 173.0, 172.7, 138.4, 138.3, 138.1, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.3, 127.2, 127.1, 82.6, 82.3, 80.8, 80.7, 79.9 (d, J_{CP} = 7.0 Hz), 75.9, 74.9, 74.8, 69.4 (d, J_{CP} = 8.9 Hz), 66.8 (d, J_{CP} = 6.9 Hz), 65.3, 65.2, 61.7, 34.0, 33.8, 31.2, 31.1, 24.4, 22.2, 19.4, 13.9, −1.7; ^{31}P NMR (146 MHz) δ −2.2; mass spectrum (FAB(+)) m/z 1079.5118 ($C_{61}H_{81}O_{13}PSi$ − H requires 1079.5406), 1039, 948, 677, 570, 433, 416, 343, 271, 181.

General Procedure for Deprotecting Phosphatidylinositol Derivatives To Give 49–51. To a solution of the appropriate protected phosphatidyl inositol derivative obtained from the preceding experiments (0.08 mmol) in absolute ethanol (90 mL) was added 20% $Pd(OH)_2$ on carbon (0.24 g). The resulting suspension was shaken under an atmosphere of hydrogen (50 psi) for 6 h. The catalyst was removed by filtration through a 45-μm nylon filter, and the solvent was removed under reduced pressure. The residue was dissolved in CH_3CN/THF (2:1) (1.5 mL), and aqueous HF (80 μL, 2.45 N) was added. After stirring the mixture at room temperature for 1 h, the volatiles were removed under reduced pressure, and the residue was purified by flash chromatography eluting with 2-propanol/water (88:12).

1,2-*O*-Di-*n*-hexanoyl-*sn*-glycero-3-phospho(2′-deoxy-2′-fluoro-*scyllo*-inositol (49): obtained as a colorless solid foam in 82% yield; IR ν 3370, 1735, 1240, 1170, cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.31–5.28 (m, 1 H), 5.16–4.89 (comp, 4 H), 4.37–4.21 (m, 1 H), 4.19–4.05 (m, 2 H), 4.02–3.80 (m, 4 H), 3.49–3.38 (m, 2 H), 3.07 (t, 2 H, J = 7.5 Hz), 2.35–2.19 (m, 4 H), 1.60–1.47 (m, 4 H), 1.38–1.15 (m 8), 0.83 (t, 6 H, J = 9.1 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 172.7, 172.3, 93.8 (d, J_{CF} = 177.9 Hz), 76.1, 73.9, 72.9, 72.7, 72.1, 71.9, 70.3 (d, J_{CP} = 8.0 Hz), 33.6, 33.4, 30.6, 25.5, 24.2, 24.1, 21.8, 13.9; ^{31}P NMR (146 MHz, DMSO-d_6) δ −2.57; mass spectrum (FAB(−)) m/z 531.1990 ($C_{21}H_{39}O_{12}FP$ − H requires 531.2007), 433, 367, 251, 153, 115.

1,2-*O*-Di-*n*-hexanoyl-*sn*-glycero-3-phospho-2′-deoxy-*scyllo*-inositol (50): obtained as a colorless solid foam in 85% yield; IR ν 3380, 1735, 1460, 1245, 1165, cm^{-1}; ^{1}H NMR (500 MHz, CH_3OH-d_6) δ 5.22–5.21 (m, 1 H), 4.41 (dd, 1 H, J = 12.0, 3.3 Hz), 4.18 (dd, 1 H, J = 12.0, 6.6 Hz), 4.07–4.03 (m, 1 H), 4.02–3.95 (comp, 2 H), 3.44–3.39 (m, 1 H), 3.36–3.31 (m, 1 H), 3.20–3.15 (comp, 2 H), 2.37–2.29 (comp, 5 H), 1.98–1.57 (comp, 4 H), 1.47 (q, 1 H, J = 12.1 Hz), 1.36–1.27 (comp, 8 H), 0.84 (t, 6 H, J = 6.9 Hz); ^{13}C NMR (63 MHz, DMSO-d_6) δ 172.6, 172.3, 77.0, 76.9, 74.9, 72.4, 70.4, 70.3 (d, J_{CP} = 7.9 Hz), 68.4, 62.3, 37.3, 33.5, 33.3, 30.6, 30.5, 24.1, 24.0, 21.7, 13.7; ^{31}P NMR (146 MHz, DMSO-d_6) δ −2.15; mass spectrum (FAB(−)) m/z 513.2090 ($C_{21}H_{39}O_{12}P$ − H requires 513.2101), 415, 367, 251, 153, 115.

1,2-*O*-Di-*n*-hexanoyl-*sn*-glycero-3-phospho-*scyllo*-inositol (51): obtained as a colorless solid foam in 81% yield; IR ν 3380, 1735, 1460, 1245, 1165, cm^{-1}; ^{1}H NMR (250 MHz, CH_3OH-d_4) δ 5.31–5.19 (m, 1 H), 4.45 (dd, 1 H, J = 10.0, 3.1 Hz), 4.23–4.05 (m, 3 H), 3.91–3.74 (m, 1 H), 3.28–3.3.24 (m, 1 H), 3.22–3.05 (m, 4 H), 2.48–2.25 (m, 4 H), 1.69–1.52 (m, 4 H), 1.47–1.23 (m, 8 H), 0.88 (t, J = 6.3 Hz, 6 H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 172.6, 172.3, 78.2, 74.2, 73.6 (d, J_{CP} = 9.3

(46) Lowe, G.; McPhee, F. *J. Chem. Soc., Perkin Trans. I* **1991**, 1249.

Hz), 70.6 (d, J_{CP} = 8.8 Hz), 63.1, 62.6, 62.0, 33.6, 33.3, 30.6, 25.5, 24.1, 24.0, 21.8, 13.7; ^{31}P NMR (146 MHz, DMSO-d_6) δ −2.05; mass spectrum (FAB(−)) m/z 530.2143 ($C_{21}H_{39}O_{13}P$ − H requires 530.2128), 529, 459, 367, 305, 199, 168, 153, 122, 115.

***N*-Benzyl-*N*-[*O*-2,3-isopropylidene-2(*S*),3-dihydroxypropyl]amine (53).** A solution of tosylate **52**[42] (2.10 g, 7.34 mmol), benzylamine (2.0 mL, 18.31 mmol), and NaI (0.16 g, 1.07 mmol) in DMSO (3 mL) was stirred at 80 °C overnight. Water (50 mL) was added, and the aqueous solution was extracted with ether (2 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL) and saturated brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford 1.10 g (69%) of **53** as a colorless liquid: ^{1}H NMR (300 MHz) δ 7.33−7.24 (comp, 5 H), 4.26 (m, 1 H), 4.03 (dd, 1 H, J = 7.9, 6.5 Hz), 3.83 (s, 2 H), 3.69 (t, 1 H, J = 7.4 Hz), 2.74 (d, 2 H, J = 5.6 Hz), 1.78 (s, 1 H), 1.41 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (75 MHz) δ 140.0, 128.2, 127.9, 126.7, 108.9, 75.2, 67.3, 53.7, 51.5, 26.7, 25.2; mass spectrum (CI, methane) m/z 222.1476 ($C_{13}H_{19}NO_2$ + H requires 222.1494) (base), 192, 164, 120.

***O*-(2-Bromoethyl) *O*-methyl *N*-[1′,2′-*O*-isopropylidene-*sn*-glycero-(3′-*N*-benzylamino)]phosphoramidate (54):** obtained in 78% yield as a colorless oil using the amine **53** and the general coupling/oxidation procedure (method A) after purification by flash chromatography eluting with EtOAc; IR ν 1260, 1150, 1050 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.40−7.23 (comp, 5 H), 4.37−4.22 (comp, 5 H), 3.98 (dd, 1 H, J = 8.3, 6.5 Hz), 3.75 (d, 1.5 H, J = 11.2 Hz), 3.73 (d, 1.5 H, J = 11.2 Hz), 3.55−3.50 (comp, 1 H), 3.53 (t, 2 H, J = 6.2 Hz), 3.15−2.93 (comp, 2 H), 1.39 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (75 MHz) δ 137.2, 128.3, 127.3, 109.3, 75.0, 74.9, 67.2, 65.4 (d, J_{CP} = 14.8 Hz), 65.3 (d, J_{CP} = 14.6 Hz), 53.3, 53.0, 50.0 (d, J_{CP} = 17.1 Hz), 49.9 (d, J_{CP} = 16.8 Hz), 47.8, 29.9 (d, J_{CP} = 8.3 Hz), 29.8 (d, J_{CP} = 7.3 Hz), 26.6, 25.2; mass spectrum (CI, methane) m/z 422.0716 ($C_{16}H_{26}BrO_5NP$ + H requires 422.0732), 366, 364 (base), 342, 329, 327, 91.

***O*-(2-Bromoethyl) *O*-Methyl *N*-Benzyl-*N*-[2′(*S*),3′-dihydroxypropyl]phosphoramidate.** A solution of **54** (0.62 g, 1.48 mmol) and *p*-TsOH·H_2O (160 mg, 0.84 mmol) in CH_3OH (40 mL) was stirred at room temperature overnight, whereupon solid $NaHCO_3$ (200 mg) was added. The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure to give an oil, which was mostly dissolved in $CHCl_3$ (5 mL). The remaining solid was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with $CHCl_3$/CH_3OH (5:1) to afford 78 mg (13%) of starting material and 370 mg (66%; 76% based on the recovered **54**) of diol as a viscous colorless oil: IR (CCl_4) ν 3360 (br), 1240, 1040 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.34−7.28 (comp, 5 H), 4.16 (dd, 1 H, J = 9.2, 6.0 Hz), 4.38−4.23 (comp, 4 H), 3.87−3.72 (comp, 1 H), 3.78 (d, 1.5 H, J = 11.1 Hz), 3.77 (d, 1.5 H, J = 11.1 Hz), 3.69−3.56 (comp, 1 H), 3.55 (t, 2 H, J = 6.0 Hz), 3.19−2.92 (comp, 2 H), 2.97 (s, 2 H); ^{13}C NMR (75 MHz) δ 136.8, 128.4, 128.2, 127.4, 69.6 (d, J_{CP} = 9.0 Hz), 65.7 (d, J_{CP} = 6.1 Hz), 63.7, 53.4 (d, J_{CP} = 7.5 Hz), 50.1 (d, J_{CP} = 4.7 Hz), 50.0 (d, J_{CP} = 6.2 Hz), 47.6 (d, J_{CP} = 4.4 Hz), 30.1 (d, J_{CP} = 9.4 Hz), 29.4 (d, J_{CP} = 7.6 Hz); mass spectrum (CI, methane) m/z 384 (base), 382.0452 ($C_{13}H_{21}BrNO_5P$ + H requires 382.0419), 327, 325, 233, 231, 91.

***O*-(2-Bromoethyl) *O*-Methyl *N*-benzyl-*N*-[2′(*S*),3′-bis(*n*-hexanoyloxy)propyl]phosphoramidate (55).** To a solution of the diol from the preceding experiment (140 mg, 0.37 mmol), hexanoic acid (87 mg, 0.75 mmol), and DMAP (6 mg, 0.049 mmol) in CH_2Cl_2 (2 mL) was added dropwise a solution of DCC (180 mg, 0.87 mmol) in CH_2Cl_2 (1 mL); the mixture was stirred at room temperature for 6 h. The white solid was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to afford 150 mg (71%) of **55** as a colorless oil: IR (CCl_4) ν 1260, 1020 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.43−7.28 (comp, 5 H), 5.32−5.25 (comp, 1 H), 4.34−4.15 (comp, 5 H), 3.97 (dd, 1 H, J = 12.0, 5.9 Hz), 3.73 (d, 3 H, J = 11.2 Hz), 3.53 (t, 2 H, J = 6.2 Hz), 3.22−3.04 (comp, 2 H), 2.33−2.23 (comp, 4 H), 1.66−1.52 (comp, 4 H), 1.40−1.20 (comp, 8 H), 0.91−0.86 (comp, 6 H); ^{13}C NMR (75 MHz) δ 173.1, 172.9, 136.6, 128.5, 128.4, 127.6, 68.9, 68.7, 65.6 (d, J_{CP} = 4.7 Hz), 65.5 (d, J_{CP} = 4.7 Hz), 62.95, 62.90, 53.4 (d, J_{CP} = 5.5 Hz), 53.3 (d, J_{CP} = 6.6 Hz), 49.9, 44.9, 34.1, 33.8, 31.1, 24.3, 22.2, 29.9 (d, J_{CP} = 7.8 Hz), 29.8 (d, J_{CP} = 11.5 Hz), 13.7; ^{31}P NMR (146 MHz) δ 11.46; mass spectrum (CI, methane) m/z 578.1891 ($C_{25}H_{41}BrO_7NP$ + H requires 578.1882), 580, 579, 498, 464, 462.

1,2-*O*-Di-*n*-hexanoyl-*sn*-(3-(*N*-benzylamino)glyceryl) phosphoramidocholine (56): obtained as a white solid foam from **55** in 53% yield (based upon 17% recovered **55**) according to the deprotection procedure described for the preparation of **17** and purifying by flask chromatography eluting with $CHCl_3$/CH_3OH/H_2O (2.5:1:0.1); IR ν 1210, 1060 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.27 (d, 2 H, J = 7.4 Hz), 7.15 (t, 2 H, J = 7.3 Hz), 7.07 (t, 1 H, J = 7.1 Hz), 5.19−5.12 (m, 1 H), 4.42−4.38 (m, 1 H), 4.23−4.16 (comp, 2 H), 4.15−4.00 (comp, 2 H), 3.87 (dd, 1 H, J = 12.1, 7.9 Hz), 3.63−3.58 (comp, 2 H), 3.22 (s, 9 H), 3.34−3.12 (comp, 1 H), 2.97−2.86 (comp, 1 H), 2.14−2.08 (comp, 4 H), 1.50−1.40 (comp, 4 H), 1.26−1.14 (comp, 8 H), 0.78 (t, 6 H, J = 6.5 Hz); ^{13}C NMR (75 MHz) δ 173.3, 172.8, 140.5, 128.1, 127.9, 126.3, 71.4, 66.6), 64.3, 58.3 (d, J_{CP} = 4.0 Hz), 54.1, 51.9, 46.9, 34.2, 33.9, 31.0, 24.4, 24.3, 22.0, 13.6; ^{31}P NMR (146 MHz) δ 7.85; mass spectrum (CI, methane) m/z 543.3200 ($C_{27}H_{47}N_2O_7P$ + H requires 543.3199), 484, 378 (base), 368, 356, 262, 117, 100, 91.

***S*-[*O*-2,3-Isopropylidene-2(*S*),3-dihydroxypropyl] Ethanethioate (57).** A mixture of tosylate **52** (51.8 g, 181 mmol), potassium thioacetate (31.0 g, 271 mmol), and dry 18-crown-6 (1.6 g, 6.1 mmol) in CH_3CN (500 mL) was heated at reflux for 2 h. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. The residual liquid was purified by vacuum distillation (bp 95−98 °C, 0.2 mmHg) to afford 33.2 g (97%) of **57**: IR (CCl_4) ν 1680 cm^{-1}; ^{1}H NMR (300 MHz) δ 4.23 (p, 1 H, J = 6.1 Hz), 4.06 (dd, 1 H, J = 8.4, 6.1 Hz), 3.64 (dd, 1 H, J = 8.4, 6.1 Hz), 3.12 (dd, 1 H, J = 13.7, 5.7 Hz), 3.06 (dd, 1 H, J = 13.7, 6.1 Hz), 2.36 (s, 3 H), 1.43 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (75 MHz) δ 194.9, 109.5, 74.4, 68.2, 32.0, 30.4, 26.7, 25.3; mass spectrum (CI, methane) m/z 191.0756 ($C_8H_{14}O_3S$ + H requires 191.0742), 175, 133 (base).

3,3′-Dithiobis[*O*-1,2-isopropylidene-1,2(*S*)-propanediol] (58). A solution of **57** (1.90 g, 9.99 mmol) in CH_3OH (25 mL) containing NaOH (1.50 g, 37.50 mmol) was stirred at room temperature for 4 h, whereupon I_2 (1.30 g, 5.12 mmol) was added and stirring continued at room temperature overnight. The solvent was removed under reduced pressure, the residue was dissolved in H_2O (25 mL), and the mixture was extracted with ether (2 × 30 mL). The combined ethereal extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to afford 1.21 g (82%) of **58** as a colorless liquid: IR ν 2990, 2940, 2880, 1385 cm^{-1}; ^{1}H NMR (300 MHz) δ 4.25−4.17 (m, 1 H), 3.98 (dd, 1 H, J = 8.2, 6.2 Hz), 3.60 (dd, 1 H, J = 8.2, 6.2 Hz), 2.85 (dd, 1 H, J = 13.5, 5.6 Hz), 2.70 (dd, 1 H, J = 13.5, 7.0 Hz), 1.28 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (75 MHz) δ 109.2, 74.5, 68.3, 42.2, 26.7, 25.2; mass spectrum (CI, methane) m/z 294.0953 ($C_{12}H_{22}NO_4S_2$ requires 294.0959), 279, 237 (base), 179.

3,3′-Dithiobis[1,2(*S*)-propanediol]. A mixture of **58** (1.30 g, 4.42 mmol) and *p*-TsOH·H_2O (100 mg, 0.64 mmol) in CH_3OH (20 mL) was stirred at room temperature overnight, whereupon solid Na_2CO_3 was added. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was washed with hot EtOAc to afford 0.91 g (96%) of the tetrol: ^{1}H NMR (300 MHz) δ 4.78 (s, 2 H), 3.82−3.75 (m, 1 H), 3.51 (dd, 1 H, J = 11.3, 4.6 Hz), 3.46 (dd, 1 H, J = 11.3, 5.6 Hz), 2.87 (dd, 1 H, J = 13.4, 5.0 Hz), 2.68 (dd, 1 H, J = 13.4, 7.4 Hz); ^{13}C NMR (75 MHz) δ 71.9, 65.9, 43.6; mass spectrum (CI, methane) m/z 214.0340 ($C_6H_{14}O_4S_2$ requires 214.0333), 197 (base), 179, 123, 105.

3,3′-Dithiobis[1,2(*S*)-bis(*n*-hexanoyloxy)propane]. To a solution of the tetrol obtained from the preceding experiment (120 mg, 0.56 mmol) and DMAP (7 mg, 0.06 mmol) in dry pyridine (1 mL) was added slowly *n*-hexanoyl chloride (0.36

mL, 2.41 mmol) at 0 °C, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (5 mL), and the organic mixture was washed with saturated $NaHCO_3$ (5 mL), 0.5 N HCl (5 mL), and H_2O (5 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography eluting with hexanes/EtOAc (8:1) to afford 176 mg (52%) of tetraester as a colorless oil: IR ν 1740 cm^{-1}; ^1H NMR (300 MHz) δ 5.33–5.25 (m, 1 H), 4.36 (dd, 1 H, J = 11.9, 3.4 Hz), 4.15 (dd, 1 H, J = 11.9, 5.7 Hz), 2.91 (d, 2 H, J = 6.5 Hz), 2.30 (t, 4 H, J = 7.2 Hz), 1.66–1.55 (comp, 4 H), 1.36–1.22 (comp, 6 H), 0.88 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 173.2, 172.8, 69.6, 63.4, 39.2, 34.1, 34.0, 31.2, 24.5, 22.2, 13.8; mass spectrum (CI, methane) m/z 606.3269 ($C_{30}H_{54}O_8S_2$ requires 606.3260), 491 (base), 271.

1,2(*S*)-Bis(*n*-hexanoyloxy)-3-propanethiol (59). To a solution of tetraester from the preceding experiment (5.00 g, 8.24 mmol) and dithiothreitol (2.04 g, 13.23 mmol) in absolute ethanol (120 mL) was added 30% aqueous NH_4OH (280 μL) to pH $\approx$ 9.5 with stirring at room temperature. After 30 min the solvent was remoed under reduced pressure, and the residue was taken up in CH_2Cl_2 (100 mL). The combined organics were washed with H_2O (4 × 10 mL) and saturated aqueous NaCl (1 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography eluting with hexanes/EtOAc (5:1) to afford 4.83 g (97%) of **59** as a colorless oil: IR ν 1740, 1170 cm^{-1}; ^1H NMR (300 MHz) δ 5.04–4.97 (m, 1 H), 4.28 (dd, 1 H, J = 11.9, 4.0 Hz), 4.15 (dd, 1 H, J = 11.9, 5.7 Hz), 2.69–2.64 (comp, 2 H), 2.26 (t, 2 H, J = 7.5 Hz), 2.24 (t, 2 H, J = 7.5 Hz), 1.61–1.50 (comp, 4 H), 1.42 (t, 1 H, J = 8.8 Hz), 1.36–1.16 (comp, 8 H), 0.82 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 172.4, 172.1, 71.6, 62.4, 33.6, 33.4, 30.7, 24.3, 24.1, 21.8, 13.4; mass spectrum (CI, methane) m/z 305.1732 ($C_{15}H_{28}O_4S$ + H requires 305.1786), 287, 261, 189 (base).

***O*-(2-Bromoethyl) *S*-(1′,2′-*O*-di-*n*-hexanoyl-*sn*-3′-glyceryl) *O*-methyl thiophosphate (60):** obtained by the general coupling/oxidation procedure (methyl dichlorophosphite, **59**, and bromoethanol in THF at −78 °C; 30% H_2O_2) as a colorless oil in 38% overall yield after purification by flash chromatography eluting with hexanes/EtOAc (1:1); IR ν 1730, 1160 cm^{-1}; ^1H NMR (300 MHz) δ 5.26–5.18 (m, 1 H), 4.43–4.25 (comp, 3 H), 4.12 (dd, 1 H, J = 11.9, 5.7 Hz), 3.80 (d, 3 H), 3.54 (t, 2 H, J = 6.2 Hz), 3.19–2.96 (comp, 2 H), 2.30 (t, 2 H, J = 7.5 Hz), 2.29 (t, 2 H, J = 7.5 Hz), 1.65–1.54 (comp, 4 H), 1.33–1.23 (comp, 8 H), 0.87 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 173.1, 172.7, 69.9, 66.4 (d, J_{CP} = 5.0 Hz), 63.1, 54.2 (d, J_{CP} = 7.1 Hz), 34.0, 33.9, 31.1, 24.4, 22.2, 29.2 (d, J_{CP} = 9.2 Hz), 13.8; ^{31}P NMR δ +28.38; mass spectrum (CI, methane) m/z 505.1011 ($C_{18}H_{34}BrO_7PS$ + H requires 505.1024), 391 (base), 390, 271.

1,2-*O*-Di-*n*-hexanoyl-*sn*-3-glycerylphosphothiocholine (61): obtained from **60** in 82% yield as a white solid foam according to the deprotection procedure described for the preparation of **17** followed by flash chromatography eluting with $CHCl_3/CH_3OH/H_2O$ (2:1:0.1); IR ν 1720, 1160 cm^{-1}; ^1H NMR (300 MHz) δ 5.29–5.18 (m, 1 H), 4.29–5.37 (m, 1 H), 4.37–4.21 (comp, 2 H), 4.05 (dd, 1 H, J = 11.9, 5.7 Hz), 3.84–3.75 (comp, 2 H), 3.34 (s, 9 H), 2.96–2.84 (comp, 2 H), 2.26 (t, 1 H, J = 7.5 Hz), 2.24 (t, 1 H, J = 7.5 Hz), 1.65–1.48 (comp, 4 H), 1.38–1.18 (comp, 8 H), 0.87 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 173.5, 173.2, 71.3, 66.1 (d, J_{CP} = 6.7 Hz), 64.1, 59.2 (d, J_{CP} = 3.7 Hz), 54.3, 34.3, 34.0, 31.2, 24.6, 24.5, 22.2, 31.0, 13.9; ^{31}P NMR δ +16.85; mass spectrum (CI, methane) m/z 470.2371 ($C_{20}H_{40}NO_7PS$ + H requires 470.2341), 287, 261, 203 (base), 189.

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Supplementary Material Available: Experimental and spectral details for compounds **11a,b**, **12a,b**, (+)- and (−)-**32**, **42**, **43**, and **45**, copies of ^1H NMR spectra of all new compounds, copies of ^{31}P of selected intermediates and final products, and copies of the ^{13}C NMR spectra or GLC traces for the diacylglycerols **10a,b** and the triacylglycerols **11a,b** and **12a,b** (93 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.