Sulfur-Substituted Phosphatidylethanolamines

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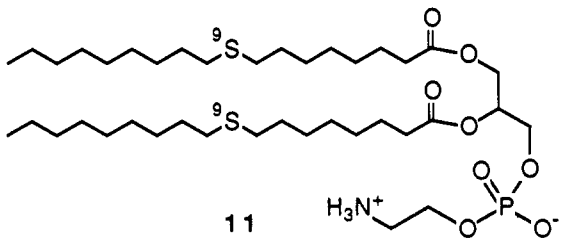
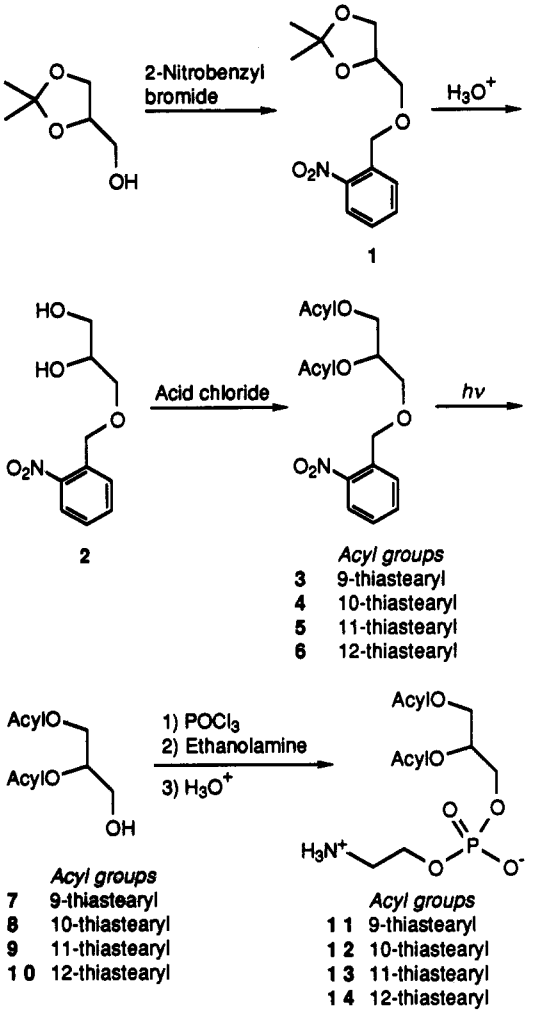
Cyclopropane fatty acids (CFAs) are common natural products which are found in esterified form as components of phospholipid molecules, particularly the phosphatidylethanolamines (PEs), in bacteria and protozoa.[1] The CFA synthases in these organisms utilize olefin-rich PEs as one substrate, and the second substrate is *S*-adenosylmethionine (SAM), which provides the extra carbon atom. In recent years we have shown that sulfur-substituted derivatives of stearic acid (thiastearic acids) are powerful inhibitors of CFA biosynthesis in a variety of protozoa, and we have proposed that these compounds are incorporated into the PEs of the protozoa, where they inhibit the CFA synthase.[2-4] In order to test this hypothesis, it has been necessary to prepare a variety of sulfur-substituted PEs for use as potential inhibitors of the CFA synthase[5] in cell-free systems. Dihydrosterculic acid (9,10-methyleneoctadecanoic acid) and lactobacillic acid (11,12-methyleneoctadecanoic acid) are among the most abundant CFAs, and they are derived from the corresponding olefinic acids (as part of PEs).[1] Obviously the SAM-dependent alkylations must occur on carbons 9–12 of the olefinic acids, so we chose to prepare a series of PEs in which the fatty acyl groups are analogs of octadecanoic acid containing sulfur atoms in place of the methylenes at positions 9, 10, 11, or 12 (e.g., compound **11**).[6]



11

Most syntheses of phospholipids make use of benzyl protecting groups which are removed when necessary by catalytic hydrogenation. However, the thioethers in our target molecules preclude hydrogenation, so we employed the photochemically removable 2-nitrobenzyl group instead. Apart from this modification, the general sequence (see Scheme I) used to prepare the sulfur-substituted diacylglycerols **7–10** was similar to that used by Bruzik et al.[7] The fully-protected glycerol **1** was prepared by alkylation of O^1,O^2-isopropylideneglycerol with 2-nitrobenzyl bromide, and then acid hydrolysis liberated the diol **2**. The appropriate thiastearic acids[3,8] were converted to the acid chlorides by treatment with oxalyl chloride in benzene, and the products were used immediately for the acylation of diol **2** to give compounds **3–6** in 80–99% yield. Photolysis of **3–6** in Pyrex vessels with a mercury vapor lamp gave the desired diacylglycerols **7–10** in 50–60% yield after chromatography.

Scheme I



For the final conversion of the diacylglycerols to PEs, we first attempted to use a reaction sequence in which an intermediate cyclic phosphoramidate could be purified by chromatography before hydrolysis to the PE (see Bruzik and Tsai[9] for an example of such a scheme). Unfortunately, the yields of the phosphoramidates were poor and the compounds themselves were sensitive to chromatography, and we were never able to obtain pure PEs by this route. Eventually we found that the simple three-step procedure of Eibl,[10] in which the intermediate cyclic phosphoramidate is isolated by crystallization and used immediately, provided good quality PEs from the diacylglycerols without chromatographic purification steps. One recrystallization

(1) Law, J. H. *Acc. Chem. Res.* **1971**, *4*, 199–203, and references cited therein.
(2) Pascal, R. A., Jr.; Mannarelli, S. J.; Ziering, D. L. *J. Biol. Chem.* **1986**, *261*, 12441–12443.
(3) Rahman, M. D.; Ziering, D. L.; Mannarelli, S. J.; Swartz, K. L.; Huang, D.-S.; Pascal, R. A., Jr. *J. Med. Chem.* **1988**, *31*, 1656–1659.
(4) Beach, D. H.; Pascal, R. A., Jr.; Holz, G. G., Jr. *Mol. Biochem. Parasitol.* **1989**, *35*, 57–66.
(5) Taylor, F. R.; Cronan, J. E., Jr. *Biochemistry* **1979**, *18*, 3292–3300.
(6) An outline of the synthesis of **11** has been reported in a preliminary communication: Li, R.; Ganguli, S.; Pascal, R. A., Jr. *Tetrahedron Lett. In press.*
(7) Bruzik, K.; Jiang, R. T.; Tsai, M.-D. *Biochemistry* **1983**, *22*, 2478–2486.
(8) Pascal, R. A., Jr.; Ziering, D. L. *J. Lipid Res.* **1986**, *27*, 221–224.
(9) Bruzik, K.; Tsai, M.-D. *J. Am. Chem. Soc.* **1984**, *106*, 747–754.
(10) Eibl, H. *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 4074–4077.

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of the products of this sequence from methylene chloride gave the analytically pure sulfur-substituted PEs 11–14 in 40% yield from the corresponding diacylglycerols.

To our knowledge, compounds 11–14 are the first PEs containing heteroatoms in the fatty acyl chains, and our synthesis should be easily extended to the preparation of other heteroatom-substituted PEs.

Experimental Section

(±)-O^1,O^2-Isopropylidene-O^3-(2-nitrobenzyl)glycerol (1). *n*-Butyllithium (52.20 mL, 1.6 M, 84.0 mmol) was added to a solution of O^1,O^2-isopropylideneglycerol (12.16 g, 84.0 mmol, Aldrich Chemical Co.) in anhydrous THF (200 mL) at room temperature under argon. After 30 min of stirring, 2-nitrobenzyl bromide (20 g, 84.0 mmol) was added to the reaction mixture, and it was refluxed for 46 h at 70 °C. The mixture was cooled, acidified with dilute HCl, and extracted three times with ether. After being dried over Na_2SO_4, the solvent was evaporated and the crude product was chromatographed on silica gel (solvent, toluene) to give compound 1 (9.8 g, 40%): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.37 (s, 3 H), 1.43 (s, 3H), 3.63 (m, 2 H), 3.78 (dd, 1 H, J = 8, 6 Hz), 4.08 (dd, 1 H, J = 8, 6 Hz), 4.35 (quintet, 1 H, J = 6 Hz), 4.94 (s, 2 H), 7.43 (dd, 1 H, J = 8, 8 Hz), 7.63 (dd, 1 H, J = 8, 8 Hz), 7.78 (d, 1 H, J = 8 Hz), 8.03 (d, 1 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 25.3, 26.7, 66.6, 70.0, 72.1, 74.6, 109.5, 124.6, 127.9, 128.7, 133.6, 134.8, 147.3; MS, m/z 267 (M^+, 2), 252 (54, M – CH_3), 136 (86), 101 (100), 78 (64); exact mass 252.0883 (M – CH_3 ion), calcd for $C_{12}H_{14}NO_5$ 252.0872.

(±)-O^1-(2-Nitrobenzyl)glycerol (2). Compound 1 (4.0 g, 15 mmol) was stirred in 10% aqueous acetic acid (200 mL) at 60 °C for 5 h. The reaction mixture was extracted three times with ethyl acetate, the extract was dried and concentrated, and the residue was chromatographed on silica gel (solvent, 1:3 ethyl acetate–hexane) to give compound 2 (2.2 g, 70%): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.68 (m, 4 H), 3.97 (tt, 1 H, J = 6, 4 Hz), 4.97 (s, 2 H), 7.46 (ddd, 1 H, J = 8, 8, 1 Hz), 7.65 (ddd, 1 H, J = 8, 8, 1 Hz), 7.72 (d, 1 H, J = 8 Hz), 8.04 (dd, 1 H, J = 8, 1 Hz); ^{13}C NMR ($CDCl_3$) δ 63.8, 70.0, 70.8, 72.4, 124.6, 128.2, 128.7, 133.5, 134.2, 147.4; MS, m/z 227 (M^+, 1.5), 136 (100), 120 (93), 92 (43), 78 (72); exact mass 227.0754, calcd for $C_{10}H_{13}NO_5$ 227.0794.

(±)-O^1,O^2-Bis(9-thiastearyl)-O^3-(2-nitrobenzyl)glycerol (3). Oxalyl chloride (2.0 M in CH_2Cl_2, 8.5 mL, 17 mmol) was added to a solution of 9-thiastearic acid[8] (3.3 g, 11.0 mmol) in benzene (70 mL) under argon. After being stirred for 15 min at room temperature, the reaction mixture was refluxed for 2 h. The benzene solvent and excess oxalyl chloride were distilled away, benzene was added, and the process was repeated three times. Benzene (40 mL) was then added, followed a solution of compound 2 (1 g, 4.4 mmol) in benzene (10 mL) and dry pyridine (2.6 g). The reaction mixture was stirred for 40 h at room temperature, diluted with water, and extracted three times with ether. The combined extracts were dried over Na_2SO_4, concentrated, and chromatographed on silica gel (solvent, 1:1 methylene chloride–hexane) to give compound 3 (3.2 g, 90%): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.85 (t, 6 H, J = 6 Hz), 1.24 (m, 36 H), 1.54 (m, 12 H), 2.29 (t, 2 H, J = 8 Hz), 2.31 (t, 2 H, J = 8 Hz), 2.46 (overlapping t's, 8 H), 3.71 (m, 2 H), 4.19 (dd, 1 H, J = 12, 6 Hz), 4.35 (dd, 1 H, J = 12, 4 Hz), 4.89 (d, 1 H, J = 15 Hz), 4.91 (d, 1 H, J = 15 Hz), 5.27 (quintet, 1 H, J = 6 Hz), 7.42 (ddd, 1 H, J = 8, 8, 1 Hz), 7.63 (ddd, 1 H, J = 8, 8, 1 Hz), 7.73 (dd, 1 H, J = 8, 1 Hz) 8.04 (dd, 1 H, J = 8, 1 Hz), ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.7, 24.8, 28.7, 28.81, 28.87, 28.92, 29.2, 29.4, 29.6, 29.7, 31.8, 32.0, 32.2, 33.9, 34.2, 62.4, 69.5, 69.9, 124.6, 128.0. 128.4, 133.6, 134.5, 147.0, 172.9, 173.2; MS, m/z 795 (M^+, 1), 643 (M – $OCH_2C_6H_4NO_2$, 10) 533 (33), 359 (34), 285 (100), 159 (45), 136 (51); exact mass 795.5152, calcd for $C_{44}H_{77}NO_7S_2$ 795.5141.

(±)-O^1,O^2-Bis(10-thiastearyl)-O^3-(2-nitrobenzyl)glycerol (4) was obtained from compound 2 (0.98 g, 4.3 mmol), 10-thiastearic acid[8] (2.6 g, 8.6 mmol), and oxalyl chloride (8.6 mmol) in 81% yield (2.8 g) by using the procedure described for compound 3. 4: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.85 (t, 6 H, J = 6 Hz), 1.25 (m, 36 H), 1.56 (m, 12 H), 2.28 (t, 2 H, J = 8 Hz), 2.31 (t, 2 H, J = 8 Hz), 2.48 (overlapping t's, 8 H), 3.73 (d, 2 H), 4.19 (dd, 1 H, J = 12, 6 Hz), 4.37 (dd, 1 H, J = 12, 4 Hz), 4.87 (d, 1 H, J = 13 Hz), 4.92 (d, 1 H, J = 13 Hz), 5.30 (quintet, 1 H, J = 6 Hz), 7.44 (ddd, 1 H, J = 7, 7, 1 Hz), 7.63 (ddd, 1 H, J = 7, 7, 1 Hz), 7.74 (dd, 1 H, J = 7, 1 Hz), 8.07 (dd, 1 H, J = 7, 1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.77, 24.83, 28.80, 28.88, 28.95, 28.97, 29.00, 29.09, 29.12, 29.15, 29.6, 29.7, 31.8, 32.11, 32.15, 34.0, 34.2, 62.4, 69.5, 69.9, 124.6, 128.0, 128.4, 133.6, 134.5, 147.1, 172.9, 173.2; MS, m/z 795 (M^+, 0.8), 643 (9), 547 (28), 359 (30), 285 (100), 136 (48); exact mass 795.5136, calcd for $C_{44}H_{77}NO_7S_2$ 795.5141.

(±)-O^1,O^2-Bis(11-thiastearyl)-O^3-(2-nitrobenzyl)glycerol (5) was obtained from compound 2 (0.95 g, 4.19 mmol), 11-thiastearic acid[3] (3.30 g, 10.90 mmol), and oxalyl chloride (17.0 mmol) in 90.5% yield (3.01 g) by using the procedure described for compound 3. 5: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.86 (t, 6 H, J = 6 Hz), 1.27 (m, 36 H), 1.56 (m, 12 H), 2.30 (t, 2 H, J = 8 Hz), 2.32 (t, 2 H, J = 8 Hz), 2.48 (overlapping t's, 8 H), 3.72 (m, 2 H), 4.19 (dd, 1 H, J = 12, 6 Hz), 4.37 (dd, 1 H, J = 12, 4 Hz), 4.88 (d, 1 H, J = 11 Hz), 4.92 (d, 1 H, J = 11 Hz), 5.29 (quintet, 1 H, J = 6 Hz), 7.44 (ddd, 1 H, J = 8, 8, 1 Hz), 7.63 (ddd, 1 H, J = 8, 8, 1 Hz), 7.73 (dd, 1 H, J = 8, 1 Hz), 8.07 (dd, 1 H, J = 8, 1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.82, 24.87, 28.7, 28.9, 29.00, 29.05, 29.17, 29.22, 29.30, 29.67, 29.71, 31.7, 32.1, 34.0, 34.2, 62.5, 69.6, 69.9, 124.7, 128.0, 128.4, 133.7, 134.6, 147.1, 173.0, 173.3; MS m/z 795 (M^+, 0.3), 561 (23), 359 (17), 302, (18), 285 (100), 131 (22); exact mass 795.5136, calcd for $C_{44}H_{77}NO_7S_2$ 795.5141.

(±)-O^1,O^2-Bis(12-thiastearyl)-O^3-(2-nitrobenzyl)glycerol (6) was obtained from compound 2 (0.88 g, 3.87 mmol), 12-thiastearic acid (2.70 g, 9.0 mmol), and oxalyl chloride (18.0 mmol) in 99% yield (3.08 g) by using the procedure described for compound 3. 6: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 6 H, J = 6 Hz), 1.26 (m, 36 H), 1.56 (m, 12 H), 2.30 (t, 2 H, J = 8 Hz), 2.33 (t, 2 H, J = 8 Hz), 2.49 (overlapping t's, 8 H), 3.73 (d, 2 H), 4.19 (dd, 1 H, J = 12, 6 Hz), 4.37 (dd, 1 H, J = 12, 4 Hz), 4.87 (d, 1 H, J = 12 Hz), 4.92 (d, 1 H, J = 12 Hz), 5.30 (quintet, 1 H, J = 6 Hz), 7.44 (ddd, 1 H, J = 8, 8, 1 Hz), 7.64 (ddd, 1 H, J = 8, 8, 1 Hz), 7.75 (dd, 1 H, J = 8, 1 Hz), 8.07 (dd, 1 H, J = 8, 1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 24.7, 24.8, 28.5, 28.8, 28.95, 28.98, 29.12, 29.20, 29.27, 29.4, 29.6, 31.3, 32.06, 32.09, 34.0, 34.2, 62.4, 69.5, 69.9, 124.6, 127.9, 128.4, 133.6, 134.5, 147.0, 172.9, 173.2; MS, m/z 795 (M^+, 3), 710 (16), 660 (26), 643 (41), 575 (68), 541 (17), 494 (19), 359 (72), 302 (44), 285 (100), 136 (92); exact mass 795.5128, calcd for $C_{44}H_{77}NO_7S_2$ 795.5141.

(±)-O^1,O^2-Bis(9-thiastearyl)glycerol (7). A solution of compound 3 (3.0 g, 3.8 mmol) in benzene (1200 mL) was flushed with argon for 5 min and then stirred and irradiated with a General Electric 275-W mercury vapor sun lamp for 48 h under argon in a Pyrex flask. The solvent was evaporated under reduced pressure, and the crude product was chromatographed on silica gel (solvent, 5:1 hexane–ethyl acetate) to give compound 7 (1.36 g, 55%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, 6 H, J = 7 Hz), 1.26 (m, 36 H), 1.60 (m, 12 H), 2.32 (t, 2 H, J = 8 Hz), 2.34 (t, 2 H, J = 8 Hz), 2.49 (t, 8 H, J = 7 Hz), 3.71 (m, 2 H), 4.22 (dd, 1 H, J = 12, 6 Hz), 4.31 (dd, 1 H, J = 12, 4 Hz), 5.08 (quintet, 1 H, J = 5 Hz), ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 24.7, 24.8, 28.7, 28.8, 29.2, 29.5, 29.6, 29.7, 31.8, 32.1, 32.2, 34.0, 34.2, 61.5, 62.0, 72.1, 173.2, 173.6; MS m/z 660 (M^+, 11), 533 (67), 483 (16), 359 (23), 302 (38), 285 (100), 199 (24), 159 (55); exact mass 660.4800, calcd for $C_{37}H_{72}O_8S_2$ 660.4821.

(±)-O^1,O^2-Bis(10-thiastearyl)glycerol (8) was obtained from compound 4 (1.86 g, 2.34 mmol) in 50% yield (0.77 g) by using the procedure described for 7. 8: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.87 (t, 6 H, J = 7 Hz), 1.26 (m, 36 H), 1.60 (m, 12 H), 2.32 (t, 2 H, J = 8 Hz), 2.34 (t, 2 H, J = 8 Hz), 2.49 (t, 8 H, J = 7 Hz), 3.71 (m, 2 H), 4.22 (dd, 1 H, J = 12, 6 Hz), 4.31 (dd, 1 H, J = 12, 4 Hz), 5.08 (quintet, 1 H, J = 5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.6, 24.8, 24.9, 28.86, 28.96, 29.03, 29.12, 29.20, 29.68, 29.74, 31.8, 32.18, 32.22, 34.0, 34.2, 61.6, 62.0, 72.1, 173.4, 173.7; MS m/z 660 (M^+, 6), 547 (38), 359 (14), 302 (24), 285 (100), 145 (26); exact mass 660.4842, calcd for $C_{37}H_{72}O_5S_2$ 660.4821.

(±)-O^1,O^2-Bis(11-thiastearyl)glycerol (9) was obtained from compound 5 (2.62 g, 3.29 mmol) in 55% yield (1.20 g) by using the procedure described for 7. 9: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.86 (t, 6 H, J = 7 Hz), 1.26 (m, 36 H), 1.55 (m, 12 H), 2.30 (t, 2 H, J = 8 Hz), 2.32 (t, 2 H, J = 8 Hz), 2.48 (t, 8 H, J = 7 Hz), 3.71 (m, 2 H), 4.22 (dd, 1 H, J = 12, 6 Hz), 4.31 (dd, 1 H, J = 12, 4 Hz), 5.08 (quintet, 1 H, J = 5 Hz); ^{13}C NMR ($CDCl_3$)

δ 14.0, 22.6, 24.81, 24.85, 28.87, 28.99, 29.02, 29.1, 29.3, 29.66, 29.69, 31.7, 32.1, 32.2, 34.0, 34.2, 61.5, 62.0, 72.1, 173.3, 173.7; MS *m/z* 660 (M^+, 12), 561 (59), 359 (25), 302 (41), 285 (100), 131 (30); exact mass 660.4818, calcd for $C_{37}H_{72}O_5S_2$ 660.4821.

(±)-*O*¹,*O*²-Bis(12-thiastearyl)glycerol (10) was obtained from compound **6** (2.8 g, 3.5 mmol) in 57% yield (1.32 g) by using the procedure described for compound **7**. **10**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.87 (t, 6 H, *J* = 7 Hz), 1.27 (m, 36 H), 1.57 (m, 12 H), 2.31 (t, 2 H, *J* = 8 Hz), 2.34 (t, 2 H, *J* = 8 Hz), 2.49 (t, 8 H, *J* = 7 Hz), 3.71 (m, 2 H), 4.22 (dd, 1 H, *J* = 12, 6 Hz), 4.31 (dd, 1 H, *J* = 12, 4 Hz), 5.08 (quintet, 1 H, *J* = 5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 24.86, 24.91, 28.6, 28.9, 29.05, 29.08, 29.2, 29.37, 29.44, 29.52, 29.7, 31.5, 32.2, 34.1, 34.3, 61.5, 62.0, 72.1, 173.4, 173.7; MS *m/z* 660 (M^+, 6), 575 (39), 359 (15), 302 (30), 285 (100), 199 (23); exact mass 660.4823, calcd for $C_{37}H_{72}O_5S_2$ 660.4821.

(±)-9-Thiaphosphatidylethanolamine 11. Triethylamine (0.32 mL, 2.2 mmol) in trichloroethylene (1.5 mL) was added to a solution of phosphorus oxychloride (0.212 mL, 2.2 mmol) in hexane (0.74 mL) at 0 °C. After 5 min of stirring, compound **7** (1 g, 1.51 mmol) in trichloroethylene (6.0 mL) was added dropwise to the mixture over 20 min at 5 °C under argon. A white precipitate appeared, and after being stirred for 30 min at 5 °C, the reaction mixture was filtered by suction to remove this precipitated triethylammonium chloride. Toluene (1.52 mL) was added to the filtrate, the solvent was removed under reduced pressure, and the oily residue (crude phosphatidic acid dichloride) was dissolved in THF (3.8 mL).

A solution of ethanolamine (0.11 g, 1.82 mmol) and triethylamine (0.96 mL, 6.8 mmol) in THF (3.6 mL) was added dropwise to the THF solution of phosphatidic acid dichloride. The reaction mixture was stirred for 10 min at 10 °C and then filtered by suction to remove precipitated triethylammonium chloride. The solvent was removed under reduced pressure, and the product was crystallized from hexane. The collected crystals were mixed with a solution of 2-propanol, water, and acetic acid (10:4:1, 60 mL) and stirred for 3 h at room temperature. Filtration of the reaction mixture gave crude (~90% pure) compound **11** (1.0 g, 87%); recrystallization from methlene chloride gave material of at least 97% purity as judged by NMR (0.42 g, 40%): ^{1}H NMR ($CDCl_3$ and CD_3OD, 500 MHz) δ 0.85 (t, 6 H, *J* = 7 Hz), 1.24 (m, 36 H), 1.56 (m, 12 H), 2.27 (t, 2 H, *J* = 8 Hz), 2.29 (t, 2 H, *J* = 8 Hz), 2.47 (t, 8 H, *J* = 7 Hz), 3.12 (br s, 2 H), 3.93 (t, 2 H, *J* = 6 Hz), 4.06 (br s, 2 H), 4.12 (dd, 1 H, *J* = 12, 7 Hz), 4.36 (dd, 1 H, *J* = 12, 4 Hz), 5.18 (m, 1 H); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 13.7, 22.4, 24.5, 28.5, 28.65, 28.71, 29.0, 29.2, 29.35, 29.43, 31.6, 31.8, 31.9, 33.7, 33.9, 40.3, 61.5, 62.3, 63.6, 70.0, 173.2, 173.5. Anal. Found for $C_{39}H_{78}NO_8PS_2$: C, 59.3; H, 9.6. Calcd: C, 59.7; H, 10.0.

(±)-10-Thiaphosphatidylethanolamine 12 was obtained from compound **8** (0.40 g, 0.61 mmol) in 42% yield (0.20 g) by using the procedure described for compound **11**. **12**: ^{1}H NMR ($CDCl_3$ and CD_3OD, 500 MHz) δ 0.86 (t, 6 H, *J* = 7 Hz), 1.25 (m, 36 H), 1.55 (m, 12 H), 2.26 (t, 2 H, *J* = 8 Hz), 2.27 (t, 2 H, *J* = 8 Hz), 2.47 (t, 8 H, *J* = 7 Hz), 3.13 (br s, 2 H), 3.91 (t, 2 H, *J* = 6 Hz), 4.06 (br s, 2 H), 4.10 (dd, 1 H, *J* = 12, 7 Hz), 4.33 (dd, 1 H, *J* = 12, 3 Hz), 5.18 (m, 1 H); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 14.0, 22.6, 24.77, 24.83, 28.88, 28.93, 29.03, 29.11, 29.15, 29.18, 29.7, 31.8, 32.15, 32.19, 34.0, 34.2, 40.3, 61.9, 62.5, 63.8, 70.2, 173.2, 173.5. Anal. Found for $C_{39}H_{78}NO_8PS_2$: C, 59.4; H, 9.6. Calcd: C, 59.7; H, 10.0.

(±)-11-Thiaphosphatidylethanolamine 13 was obtained from compound **9** (0.93 g, 1.4 mmol) in 39% yield (0.43 g) by using the procedure described for **11**. **13**: ^{1}H NMR ($CDCl_3$ and CD_3OD, 500 MHz) δ 0.84 (t, 6 H, *J* = 7 Hz), 1.24 (m, 36 H), 1.53 (m, 12 H), 2.25 (t, 2 H, *J* = 8 Hz), 2.27 (t, 2 H, *J* = 8 Hz), 2.46 (t, 8 H, *J* = 7 Hz), 3.11 (br s, 2 H), 3.91 (t, 2 H, *J* = 6 Hz), 4.06 (br s, 2 H), 4.10 (dd, 1 H, *J* = 12, 7 Hz), 4.33 (dd, 1 H, *J* = 12, 3 Hz), 5.18 (m, 1 H); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 14.0, 22.5, 24.76, 24.81, 28.8, 29.04, 29.08, 29.2, 29.3, 29.7, 31.7, 32.1, 34.0, 34.2, 40.3, 61.9, 62.5, 63.8, 70.2, 173.2, 173.5. Anal. Found for $C_{39}H_{78}NO_8PS_2 \cdot H_2O$: C, 58.3; H, 9.9. Calcd: C, 58.4; H, 10.1.

(±)-12-Thiaphosphatidylethanolamine 14 was obtained from compound **10** (0.95 g, 1.43 mmol) in 37% yield (0.37 g) by using the procedure described for compound **11**. **14**: ^{1}H NMR ($CDCl_3$ and CD_3OD, 500 MHz) δ 0.87 (t, 6 H, *J* = 7 Hz), 1.25 (m, 36 H), 1.56 (m, 12 H), 2.27 (t, 2 H, *J* = 8 Hz), 2.29 (t, 2 H, *J* = 8 Hz), 2.48 (t, 8 H, *J* = 7 Hz), 3.12 (br s, 2 H), 3.93 (t, 2 H, *J* = 6 Hz), 4.05 (br s, 2 H), 4.12 (dd, 1 H, *J* = 12, 7 Hz), 4.34 (dd, 1 H, *J* = 12, 4 Hz), 5.18 (m, 1 H); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 14.0, 22.4, 24.73, 24.79, 28.5, 28.9, 29.03, 29.06, 29.18, 29.22, 29.37, 29.43, 29.59, 29.63, 31.4, 32.1, 32.2, 33.9, 34.1, 40.2, 61.9, 62.5, 63.8, 70.2, 173.2, 173.5. Anal. Found for $C_{39}H_{78}NO_8PS_2 \cdot H_2O$: C, 58.4; H, 10.1. Calcd: C, 58.4; H, 10.1.

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Supplementary Material Available: ^{1}H NMR spectra of 1–14 (14 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.