Synthesis of Defective Phospholipids

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Phospholipids have been synthesized that possess a normal 16-carbon chain plus a "defective" chain only 8 or 12 carbons long and terminated with methoxyl, hydroxyl, or carboxyl groups. In addition, dimeric phospholipids have been prepared in which two phospholipid units are joined at position-1 with chains of 22 or 32 carbons while unconnected chains at position-2 are, once again, short and functionalized. These phospholipids are potentially useful for constructing membranes that contain cavities or irregularities and, therefore, are capable of serving as self-assembled host systems in which drugs and other guest molecules are retained and, perhaps, eventually released.

The premise for this membrane study is straightforward: It should be possible, with specially designed phospholipids, to create bilayer membranes that contain defects or water-filled cavities. Cavity-bearing membranes could function as self-assembled "host" systems within which guest molecules are retained. In this manner, water-soluble drugs and other compounds could be stored and perhaps eventually released. The challenge, therefore, was to design and synthesize appropriate phospholipids and, ultimately, to examine their membranes for the presence of transient or permanent voids.

Addition of channel compounds to membrane bilayers has been widely investigated in recent years.[1] We ourselves discovered a simple synthetic compound that exceeds gramicidin in its ability to guide ions through bilayers.[2] The goals of the present program are, however, quite different. We are not seeking membrane-spanning channels so much as enclosed cavities into which ions and polar molecules can reside for reasonably long time periods. This is best achieved, in our view, by manipulating the phospholipid structure rather than by inserting external host compounds into the membrane.

Eight phospholipids were selected for study (Figure 1). All but the three dimeric lipids possess a "normal" 16-carbon chain plus a shorter chain of 8 or 12 carbons terminated by a functional group (OCH_3, OTBS, OH, or COOH). Owing to the asymmetry of the chains, voids in the membrane are possible depending on exactly how the molecules arrange themselves in the bilayer. One could imagine, for example, a set of short chains alligned on the periphery of a cylinder to encompass, with their terminal methoxyls, a crown ether-like cavity (Figure 2). Of course, cavity formation is a dynamic process. Voids of different sizes could close and reopen rapidly as the lipid molecules interdigitate or otherwise diffuse through the bilayer. Alternatively, space-filling but metastable lipid configurations might seize the opportunity to rearrange themselves in order to accommodate the spatial needs of a guest molecule. In other words, upon entering a partially disordered membrane, a guest might induce a cavity that, in the absence of the guest, forms only transiently or not at all.

Note that there was no certainty that our new phospholipids could even form bilayers. This was especially true for the ones terminated with OH and COOH groups where "looping" to the aqueous surface[3] could badly disrupt normal lipid packing. Uncertainties notwithstanding, it seemed that an examination of the phospholipids, and their ability to incorporate guests *via* "defective" membranes, were a worthwhile undertaking. In this paper, the syntheses of all eight phospholipids in Figure 1 are described. Biophysical properties of the lipids will be recounted at a later date.

Much of what is known about phospholipids with two short chains originates from one particular group.[4−8] The following cites some of their key observations (in which, for example, C_6-C_7-PC represents 1-hexanoyl-2-heptanoyl-*sn*-3-phosphocholine): (a) Phospholipids with 6−8 carbons in each fatty acyl chain form micelles, not bilayers. In this sense they resemble phospholipids having only a single long chain (although the latter have much lower critical micelle concentrations for an equal number of carbons). (b) Micelles of the di-C_7 or di-C_8 lipids grow dramatically with concentration into capsule-shaped structures. Growth occurs by insertion of the lipid into the shaft of the capsul to create, ultimately, long rigid rods. (c) $C_{16}-C_{16}-PC$ (20 mM) mixed with C_7-C_7-PC (5 mM) forms a disk with a rounded periphery (radius = 86 Å; diameter = 45 Å). The disk consists of a circular bilayer of long-chained lipids whose edge is "capped" by hemicircular short-chained lipids. These observations apply rather peripherally to our own systems in which one chain is long (16 carbons) whereas the other is short to medium (8 or 12 carbons) and terminated with a heteroatom.

Phospholipids with one hydrocarbon chain shorter than the other have also been intensively studied, and we now summarize some of their important properties: (a) For modest differences in chain asymmetry, the main transition temperature (T_m) and the transition enthalpy (ΔH) both decrease with increasing asymmetry.[9] For example, $C_{14}-C_{14}-PC$, $C_{15}-C_{13}-PC$, and $C_{16}-C_{12}-PC$ have T_m values of 24.1, 18.8, and 11.3 °C, respectively. The trends

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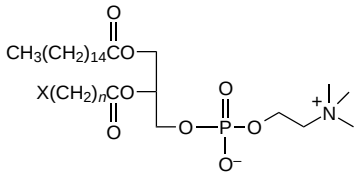

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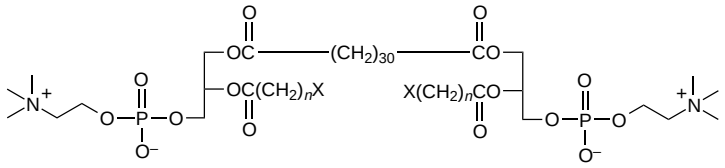

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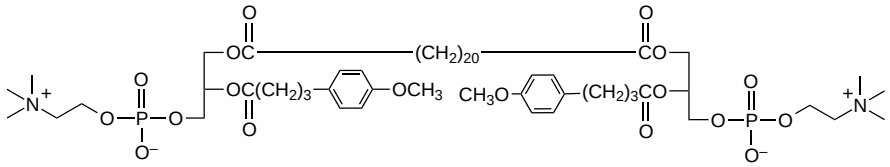


3

compd	X	*n*
1a	OCH_3	7
1b	OCH_3	11
1c	OTBS	11
1d	OH	11
1e	CO_2H	10
2a	OCH_3	7
2b	OCH_3	11

Figure 1. Phospholipids synthesized in this work.

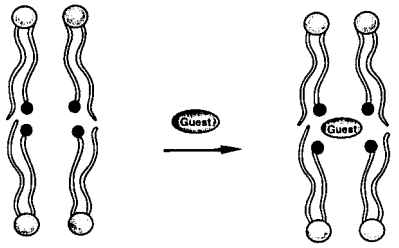
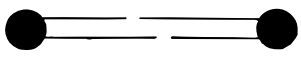
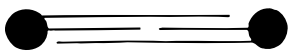


Figure 2. Schematic representation of a guest molecule entering a defect within a membrane host.

are reversed (as will be explained momentarily) with highly asymmetric lipids, *e.g.*, $C_{18}-C_{10}-PC$ has a $T_m = 18.7$ °C and a $\Delta H = 9.0$ kcal/mol. (b) A structural model, applicable to modestly asymmetric lipids in the gel state ($T < T_m$), incorporates two lipid molecules with their long and short chains opposing each other:[10]



Such chain "interdigitation" becomes more pronounced[11] as the asymmetry increases from, say, $C_{18}-C_{16}-PC$ to $C_{18}-C_{14}-PC$ to $C_{18}-C_{12}-PC$. (c) When one chain is roughly half the length of the other, a so-called "mixed interdigitated" arrangement is believed to exist in the gel state with excess water.[12]



Such an arrangement, as occurs with $C_{18}-C_{10}-PC$, is consistent with X-ray data showing a membrane thickness approximating the length of a single long chain. In the liquid crystalline state ($T > T_m$), membrane thickness becomes "normal" (*i.e.*, $C_{18}-C_{10}-PC \approx C_{14}-C_{14}-PC$). The mixed interdigitated mode explains the reversal in the thermotropic properties mentioned above. (d) Experiments with a spin label (16-doxylstearate) seem to show restricted motion in $C_{18}-C_{10}-PC$, but enhanced motional freedom in $C_{18}-C_{14}-PC$, relative to the symmetrical forms of the lipid in the gel state.[13] (e) Both ^1H and ^{13}C spin−lattice relaxation times at $T > T_m$ indicate inhibited segmental motion at megahertz frequencies for $C_{18}-C_{10}-PC$ compared to those for a symmetrical lipid.[14] (f) Mixtures of symmetrical and asymmetrical lipids can become immiscible at $T < T_m$. (g) Finally, we should caution that the study of asymmetrical lipids is not a simple business. Their degree of hydration,[11] liposomal size,[15] and even the bilayer's thermal history[16] are all known to affect the membrane properties.

It has recently been written: "There have been few studies related to the solubilization of organic solutes by vesicles and the removal of these solutes from water".[17] This, plus the complexity of our lipid structures, made predictions difficult. In any event, the first task at hand was to synthesize the necessary materials, and this is the subject of the current paper.

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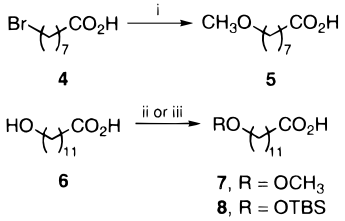
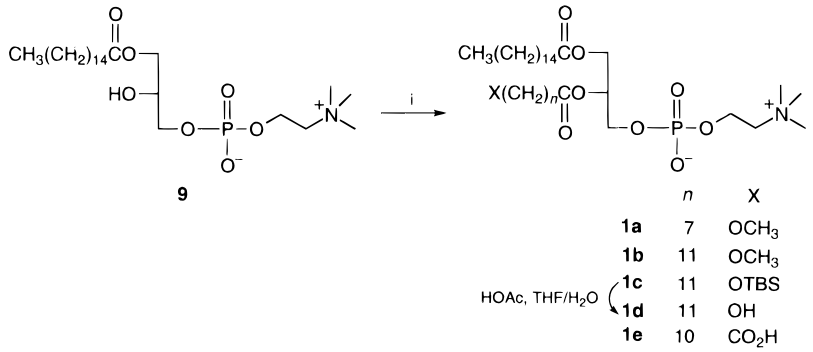
Scheme I



(i) $NaOCH_3$, CH_3OH, Δ; (ii) (a) NaH, DMF/THF, (b) CH_3I, Δ, (c) NaOH(aq), Δ; (iii) (a) TBSCl, imidazole, DMF, (b) K_2CO_3, CH_3OH/H_2O

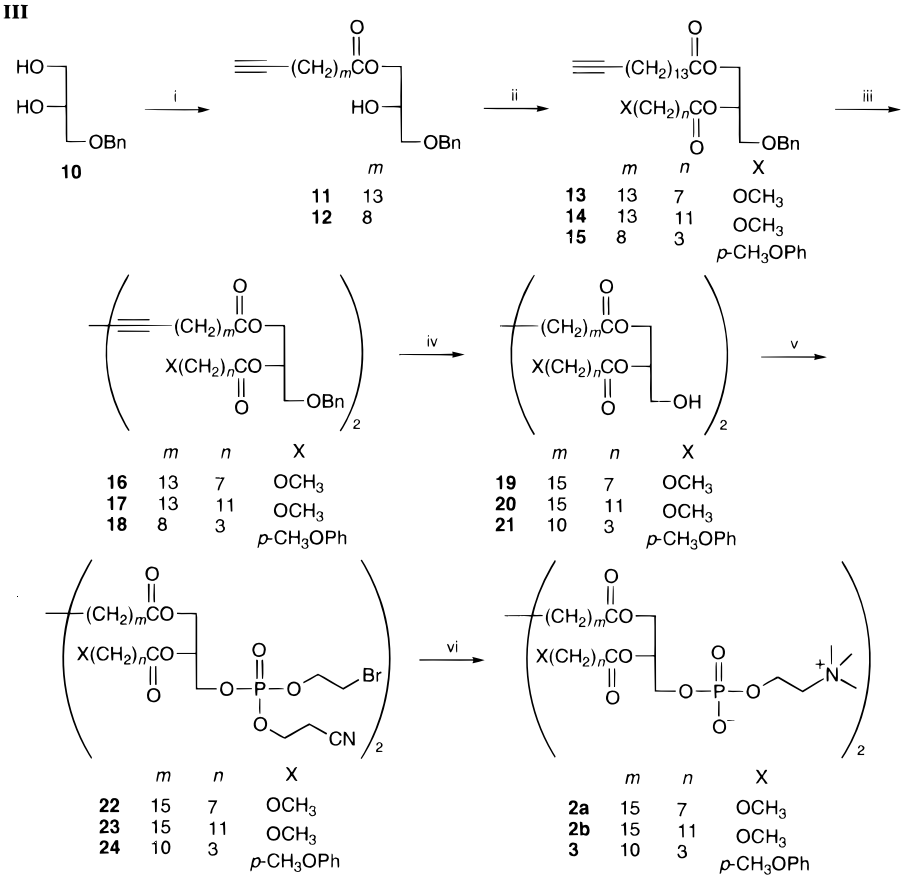
Scheme II



	n	X
1a	7	OCH_3
1b	11	OCH_3
1c	11	OTBS
1d	11	OH
1e	10	CO_2H

(i) carboxylic acid, DCC, DMAP, CH_2Cl_2

Scheme III



(i) $CH{\equiv}C(CH_2)_mCO_2H$, DCC, DMAP, CH_2Cl_2; (ii) $X(CH_2)_nCO_2H$, DCC, DMAP, CH_2Cl_2; (iii) CuCl, O_2, TMEDA, xylenes, 140-150 °C; (iv) H_2, 10% Pd/C; (v) *i*-$Pr_2NP(OCH_2CH_2Br)(OCH_2CH_2CN)$, tetrazole, THF; (vi) $(CH_3)_3N$

Figure 3. Schemes for the synthesis of the phospholipids.

Results and Discussion

Figure 3, subdivided into three schemes, describes the synthetic routes to our eight new phospholipids. Scheme I shows the two ways in which "short" fatty acids were terminated with either an OCH_3 or OTBS group (where OTBS signifies *tert*-butyldimethylsiloxy). Thus, the bromine of an ω-bromo acid was displaced with methoxide or, alternatively, an ω-hydroxy acid was derivatized with methyl iodide or TBSCl. Scheme II shows how a lysophospholipid was acylated with one of the carboxylic acids using dicyclohexylcarbodiimide (DCC) and (dimethylamino)pyridine (DMAP) in CH_2Cl_2. These standard proce-

dures, detailed in the Experimental Section, gave lipids **1a**−**e** that were identified, usually after column chromatography, by NMR, mass spectrometry, and elemental analysis.

It should be pointed out that our synthetic procedures are all written in "recipe format" as described in a recent publication.[18] This new format provides all the necessary information, saves considerable space, and avoids overuse of the passive voice.

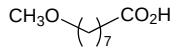
Scheme III outlines the steps used to prepared the dimeric phospholipids **2** and **3**. The strategy involved inserting the phosphatidylcholine group at the very end of the sequence when the dimeric skeleton was already in place (*i.e.*, **19**−**21** to **2** and **3**). This aided in the purification of intermediates which were uncharged throughout. A high-temperature Glaser coupling, developed previously by us for constructing macrocyclic lipids,[19,20] was key to the synthesis. Thus, ω-acetylenes **13**−**15** were joined to form diacetylenes **16**−**18** *via* the following general procedure (recipe format): Bubble O_2 into a suspension of CuCl (1.5 equiv) and TMEDA (1.6 equiv) in xylene (3−6 mL) at 140 °C for 15 min. Add a solution of the mixed-chain diacyl-3-benzyl-*sn*-glycerol (0.2−0.7 mmol) in xylene (1−3 mL). Stir at 140−150 °C for 30 min, cool to rt, dilute with EtOAc (30−60 mL), and wash with brine (30−60 mL). Dry organic layer over Na_2SO_4, filter, and rotoevaporate. Purify by flash chromatography, eluting with hexanes/EtOAc (2:1) to give the bis(diacyl-3-benzylglycerol). Note that subsequent hydrogenation (10% Pd/C), in which **16**−**18** were converted into **19**−**21**, served two purposes: removal of the benzyl protecting group and saturation of the diacetylenic unit.

Only one other synthetic detail needs mentioning. Mixed-chain intermediates **13**−**15** were prepared by first acylating position-1 of (*R*)-3-(benzyloxy)-1,2-propanediol with slightly less than an equivalent of fatty acid (DCC and DMAP in CH_2Cl_2 at 20 °C). The second fatty acid was then placed at position-2 using much the same conditions. Success of the procedure rests solely upon the greater reactivity of the primary hydroxyl over the secondary hydroxyl.

Experimental Section

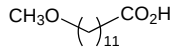
15-Hexadecynoic acid was synthesized from 7-hexadecyn-1-ol (Lancaster) according to the known procedure.[21] 10-Undecynoic acid was pruchased from Lancaster, (*R*)-3-(benzyloxy)-1,2-propanediol from Fluka, and (4-methoxyphenyl)butyric acid from Aldrich. 1-Palmitoyl-2-hydroxy-*sn*-glycero-3-phosphocholine was obtained from Avanti Polar Lipids. This L-α-lysophosphatidylcholine was reported to be 99% pure; acylation of the alcohol should not affect its enantiomeric purity. Chloroform, methanol, ethyl acetate, hexane, and acetone were either reagent or HPLC grade.

8-Methoxyoctanoic Acid (5). Add 8-bromooctanoic acid (1.24 g, 5.57 mmol) to a suspension of CH_3ONa (3.43 g, 63.42 mmol) in CH_3OH (25 mL). Heat to reflux overnight. Add 2 M of HCl(aq) (*ca.* 5 mL) to neutralize the reaction mixture. Rotoevaporate the solution. Add 1 M HCl(aq) (50 mL). Extract with EtOAc (2 × 25 mL). Wash the combined extracts with brine (50 mL). Dry over Na_2SO_4, filter, and rotoevaporate. Purify by flash chromatography (1:1 hexanes/EtOAc) to give 0.76 g (78%) of **5** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (t, 2 H, J = 6.6 Hz, OCH_2), 3.31 (s, 3 H, CH_3O), 2.31 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 1.50−1.63 (comp, 4 H, $(CH_2)_2$), 1.28−1.40 (comp, 6 H, $(CH_2)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6 (*C*=O), 72.8 (OCH_2), 58.3 (OCH_3), 34.0, 29.4, 29.0, 28.9, 25.8, 24.5 ($(CH_2)_6CO_2H$); mass spectrum (FAB) *m*/*z* 175.1330 ($C_9H_{18}O_3$ + H requires 175.1334).



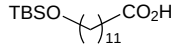
5

12-Methoxydodecanoic Acid (7). Add a solution of 12-hydroxydodecanoic acid (1.70 g, 7.86 mmol) in THF/DMF (5 mL/2 mL) to a suspension of NaH (1.81 g, 75.42 mmol). Stir at rt overnight. Add CH_3I (9 mL). Heat to reflux overnight. Cool the reaction mixture to rt. Add H_2O (15 mL) and NaOH (0.4 g). Heat to reflux for 3 h. Add 2 N HCl (25 mL) and extract with ether (2 × 25 mL). Wash with brine (30 mL). Dry over Na_2SO_4, filter, and rotoevaporate. Purify by flash chromatography (1:1 hexanes/EtOAc) to give 1.20 g (66%) of **7** as a white solid: ^{1}H NMR (75 MHz, $CDCl_3$) δ 3.36 (t, 2 H, J = 6.7 Hz, CH_3OCH_2), 3.33 (s, 3 H, CH_3OCH_2), 2.33 (t, 2 H, J = 7.5 Hz, CH_2CO_2H), 1.51−1.67 (comp, 4 H, $(CH_2)_2CH_2CO_2H$), 1.26 (s, 14 H, $CH_3(CH_2)_7$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 179.7 (*C*=O), 72.9 (CH_2OCH_3), 58.4 (CH_3OCH_2), 34.0 (CH_2CO_2H), 29.55, 29.49, 29.4, 29.3, 29.2, 29.0, 26.1, 24.7 (fatty CH_2); mass spectrum (FAB) *m*/*z* 231.1951 ($C_{13}H_{26}O_3$ + H requires 231.1960).



7

12-((*tert*-Butyldimethylsilyl)oxy)dodecanoic Acid (8). Add TBSCl (2.87 g, 19.04 mmol) to a solution of 12-hydroxydodecanoic acid (1.51 g, 6.98 mmol) and imidazole (1.23 g, 18.07 mmol) in DMF (10 mL). Stir at rt overnight. Add brine (50 mL). Extract with ether (2 × 50 mL). Wash with saturated $NaHCO_3$ (50 mL) and then brine (50 mL). Dry the ether solution over Na_2SO_4, filter, and rotoevaporate. Dry *in vacuo* overnight to give *tert*-butyldimethylsilyl 12-((*tert*-butyldimethylsilyl)oxy)dodecanoate as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (t, 2 H, J = 6.6 Hz, CH_2OSi), 2.27 (t, 2 H, J = 7.4 Hz, CH_2CO_2Si), 1.46−1.59 (comp, 4 H, $(CH_2)_2CH_2OSi$), 1.25 (s, 14 H, $(CH_2)_7CH_2CO_2H$), 0.90 (s, 9 H, $(CH_3)_3CSiOC(O)$), 0.87 (s, 9 H, $(CH_3)_3CSiOCH_2$), 0.23 (s, 6 H, $(CH_3)_2SiOCH_2$), 0.02 (s, 6 H, $(CH_3)_2SiOC(O)$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (CO_2Si), 63.2 (CH_2OSi), 36.0, 32.9, 29.6, 29.5, 29.44, 29.40, 29.3, 29.1, 25.8, 25.1 (fatty CH_2), 25.9 ($(CH_3)_3SiOCH_2$), 25.5 ($(CH_3)_3CSiOC(O)$), 18.3 ($(CH_3)_3CSiOCH_2$), 17.5 ($(CH_3)_3CHSiOC(O)$), −4.8 ($(CH_3)_2Si$), −5.3 ($(CH_3)_2Si$); mass spectrum (LSIMS) *m*/*z* 445.3529 ($C_{24}H_{52}O_3Si_2$ + H requires 445.3533), 387.



8

Dissolve in CH_3OH (125 mL) and a solution of K_2CO_3 (1.82 g, 18.36 mmol) in H_2O (25 mL). Stir for 30 min. Add pH 2.0 buffer (50 mL) and then 2 N HCl (*ca.* 10 mL) until pH 7−8. Rotoevaporate. Cool in the ice bath and add 2 N HCl dropwise while stirring until pH 6−7. Saturate the solution with NaCl. Extract with ether (3 × 75 mL). Wash the combined extracts with brine (50 mL). Dry over Na_2SO_4, filter, and rotoevaporate. Purify by flash chromatography (2:1 hexanes/EtOAc) to give 1.85 g (80%) of **8** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.1 (s, br, 1 H, CO_2H), 3.59 (t, 2 H, J = 6.6 Hz, CH_2OSi), 2.33 (t, 2 H, J = 7.4 Hz, CH_2CO_2H), 1.46−1.64 (comp, 4 H, $(CH_2)_2CH_2CO_2H$), 1.26 (s, br, 14 H, $(CH_2)_7CH_2CO_2H$), 0.88 (s, 9 H, $(CH_3)_3CSi$), 0.39 (s, 6 H, $(CH_3)_2Si$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2 (CO_2H), 63.3 (CH_2OSi), 34.1, 32.8, 29.6, 29.5, 29.4, 29.2, 29.0, 25.8, 24.7 (fatty CH_2), 26.0 ($(CH_3)_3CSi$), 18.3 ($(CH_3)_3CSi$), −5.1 ($(CH_3)_2Si$); mass spectrum (LSIMS) *m*/*z* 331.2662 ($C_{18}H_{38}O_3Si$ + H requires 331.2668).

1-Palmitoyl-2-(8-methoxyoctanoyl)-*sn*-glycero-3-phosphocholine (1a). Dissolve 1-palmitoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (100 mg, 0.20 mmol), carboxylic acid **5** (77 mg, 0.44 mmol), and DMAP (60 mg, 0.49 mmol) in CH_2Cl_2 (2

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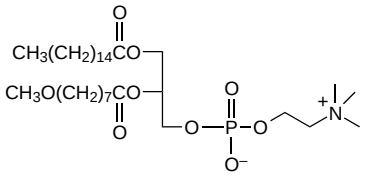
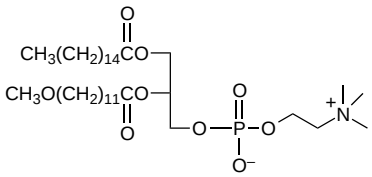
mL). Add 1,3-dicyclohexylcarbodiimide (100 mg, 0.48 mmol). Stir at rt for 2 days. Remove the white solid by filtration through a small cotton wool plug in a 6 in. pipet. Rotoevaporate the filtrate. Purify twice by column chromatography (65:35:4 $CHCl_3/CH_3OH/H_2O$; 1 in. diameter × 2 in. height flash silica gel; elution rate *ca*. 4 mL/min) to give 46 mg (35%) of **1a**. Lyophilize to give white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (m, 1 H, C^2*H*), 4.35 (dd, 1 H, J = 12.0, 2.6 Hz, C^1*H*), 4.26 (m, 2 H, POCH_2CH_2N), 4.08 (dd, 1 H, J = 12.0, 7.2 Hz, C^1*H*), 3.82−3.95 (comp, 2 H, C$^3H_2$), 3.77 (m, 2 H, CH_2N), 3.28−3.33 (comp, 14 H, CH_2OCH_3 and N(CH_3)$_3$), 2.26 (t, 2 H, J = 6.9 Hz, CH_2CO$_2$), 2.23 (t, 2 H, J = 6.9 Hz, CH_2CO$_2$), 1.45−1.56 (comp, 6 H, fatty CH_2), 1.16−1.32 (comp, 30 H, fatty CH_2), 0.84 (t, 3 H, J = 6.6 Hz, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 173.0 (*C*═O), 72.7 (*C*H$_2$OCH$_3$), 70.5 (d, J = 7.3 Hz, *C*^{2}), 66.2 (d, J = 5.9 Hz, *C*H$_2$N), 63.2 (d, J = 5.4 Hz, *C*^{3}), 62.9 (*C*^{1}), 59.2 (d, J = 5.3 Hz, POCH_2CH_2N), 58.4 (*C*H$_3$OCH$_2$), 54.2 (N(*C*H$_3$)$_3$), 34.2, 34.0, 31.8, 29.6, 29.52, 29.47, 29.3, 29.11, 29.06, 28.9, 25.9, 24.82, 24.78, 22.6 (fatty *C*H$_2$), 14.0 (*C*H$_3$CH$_2$); mass spectrum (FAB) *m*/*z* 652.4540 ($C_{33}H_{66}NO_9P$ + H requires 652.4553).



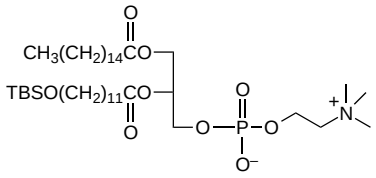
1a

1-Palmitoyl-2-(12-methoxydodecanoyl)-*sn*-glycero-3-phosphocholine (1b). Dissolve 1-palmitoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (156 mg, 0.315 mmol) and acid **7** (227 mg, 0.98 mmol) in CH_2Cl_2 (5 mL) (warming in a water bath at *ca*. 40 °C may be needed). Add DMAP (37 mg, 0.30 mmol) and a solution of 1,3-dicyclohexylcarbodiimide (204 mg, 0.99 mmol) in CH_2Cl_2 (2 mL). Stir at rt for 2 days. Remove the white solid by filtration through a small cotton wool plug in a 6 in. pipet. Rotoevaporate the filtrate. Purify twice by column chromatography (65:35:4 $CHCl_3/CH_3OH/H_2O$; 1 in. diameter × 2 in. height flash silica gel; elution rate *ca*. 4 mL/min) to give 165 mg (74%) of **1b**. Lyophilize to give white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (m, 1 H, C^2*H*), 4.34 (dd, 1 H, J = 12.0, 2.7 Hz, C^1*H*), 4.25 (m, 2 H, POCH_2CH_2N), 4.06 (dd, 1 H, J = 12.0, 7.3 Hz, C^1*H*), 3.88 (m, 2 H, C$^3H_2$), 3.78 (m, 2 H, CH_2N), 3.34 (s, 9 H, N(CH_3)$_3$), 3.30 (t, 2H, J = 6.7 Hz, CH_2-OCH$_3$), 3.27 (s, 3H, CH$_2$OCH_3), 2.23 (t, 2 H, J = 7.5 Hz, CH_2-CO$_2$), 2.21 (t, 2 H, J = 7.4 Hz, CH_2CO$_2$), 1.44−1.57 (comp, 6 H, fatty CH_2), 1.20 (s, 38 H, fatty CH_2), 0.82 (t, 3 H, J = 6.6 Hz, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 173.0 (*C*═O), 72.8 (*C*H$_2$OCH$_3$), 70.5 (d, J = 7.6 Hz, *C*^{2}), 66.2 (*C*H$_2$N), 63.2 (d, J = 4.5 Hz, *C*^{3}), 62.9 (*C*^{1}), 59.2 (POCH_2CH_2N), 58.4 (*C*H$_3$-OCH$_2$), 54.2 (N(*C*H$_3$)$_3$), 34.2, 34.0, 31.8, 29.6, 29.5, 29.46, 29.38, 29.3, 29.22, 29.20, 29.05, 29.02, 26.0, 24.85, 24.78, 22.5 (fatty *C*H$_2$), 14.0 (*C*H$_3$CH$_2$); mass spectrum (FAB) *m*/*z* 708.5184 ($C_{37}H_{74}NO_9P$ + H requires 708.5179). Anal. Calcd for $C_{37}H_{74}NO_9P\cdot1.5H_2O$: C, 60.46; H, 10.56; N, 1.91. Found: C, 60.41; H, 10.52; N, 1.91.



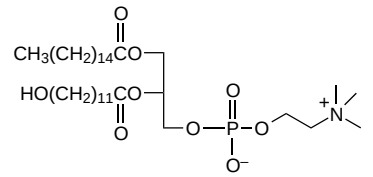
1b

1-Palmitoyl-2-[(12-((*tert*-butyldimethylsilyl)oxy)dodecanoyl]-*sn*-glycero-3-phosphocholine (1c). Dissolve 1-palmitoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (170 mg, 0.343 mmol) and **8** (0.58 g, 1.76 mmol) in CH_2Cl_2 (5 mL) (warming in a water bath at *ca*. 40 °C was needed). Add DMAP (41 mg, 0.336 mmol) and then a solution of 1,3-dicyclohexylcarbodiimide (0.49 g, 2.40 mmol) in CH_2Cl_2 (2 mL). Stir for 2 days. Filter through a small cotton wool plug in a 6 in. pipet. Rotoevaporate the filtrate. Purify twice by column chromatography (65:35:4 $CHCl_3/CH_3OH/H_2O$; 1 in. diameter × 2 in. height flash silica gel; elution rate *ca*. 4 mL/min) to give 225 mg (81%) of **1c**. Lyophilize to give a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (m, 1 H, C^2*H*), 4.38 (dd, 1 H, J = 12.0, 2.6 Hz, C^1*H*), 4.30 (m, 2 H, POCH_2CH_2N), 4.11 (dd, 1 H, J = 12.0, 7.3 Hz, C^1*H*), 3.85−3.97 (comp, 2 H, C$^3H_2$), 3.80 (m, 2 H, CH_2N), 3.58 (t, 2 H, J = 6.6 Hz, CH_2OSi), 3.36 (s, 9H, N(CH_3)$_3$), 2.28 (t, 2 H, J = 7.3 Hz, CH_2CO$_2$), 2.236 (t, 2 H, J = 7.3 Hz, CH_2CO$_2$), 1.45−1.58 (comp, 6 H, fatty CH_2), 1.24 (comp, 38 H, fatty CH_2), 0.88 (s, 9H, (CH_3)$_3$CSi), 0.87 (t, 3 H, J = 6.6 Hz, CH_3CH$_2$), 0.33 (s, 6H, (CH_3)$_2$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 173.1 (*C*═O), 70.5 (d, J = 7.6 Hz, *C*^{2}), 66.3 (d, J = 6.2 Hz, *C*H$_2$N), 63.4 (d, J = 5.40 Hz, *C*^{3}), 63.3 (*C*H$_2$OSi), 62.9 (*C*^{1}), 59.3 (d, J = 4.6 Hz, POCH_2CH_2N), 54.4 (N(*C*H$_3$)$_3$), 34.3, 34.1, 32.9, 31.9, 29.7, 29.6, 29.52, 29.46, 29.3, 29.2, 25.8, 25.0, 24.9, 22.6 (fatty *C*H$_2$), 26.0 ((*C*H$_3$)$_3$CSi), 18.3 ((CH$_3$)$_3$*C*Si), 14.1 (*C*H$_3$-CH$_2$), −5.3 ((*C*H$_3$)$_2$Si); mass spectrum (LSIMS) *m*/*z* 808.5888 ($C_{42}H_{86}NO_9PSi$ + H requires 808.5888).



1c

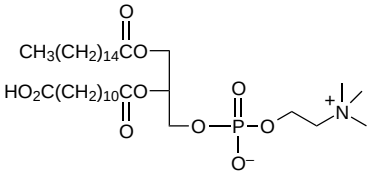
1-Palmitoyl-2-(12-hydroxydodecanoyl)-*sn*-glycero-3-phosphocholine (1d). Add a solution of 2 mL of HOAc/H_2O/THF (3:1:1) to **1c** (22 mg, 0.027 mmol). Stir at rt for 1 h. Dry *in vacuo*. Purify twice by column chromatography (65:35:4 $CHCl_3/CH_3OH/H_2O$; 1 in. diameter × 2 in. height flash silica gel; elution rate *ca*. 4 mL/min) to give 13 mg (70%) of **1d**. Lyophilize to give a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (m, 1 H, C^2*H*), 4.35 (dd, 1 H, J = 11.9, 2.4 Hz, C^1*H*), 4.24 (m, 2 H, POCH_2CH_2N), 4.09 (dd, 1 H, J = 11.9, 7.3 Hz, C^1*H*), 3.82−3.97 (comp, 2 H, C$^3H_2$), 3.73 (m, 2 H, CH_2N), 3.53 (t, 2H, J = 6.6 Hz, CH_2OH), 3.30 (s, 9 H, N(CH_3)$_3$), 2.26 (t, 2 H, J = 7.4 Hz, CH_2CO$_2$), 2.24 (t, 2 H, J = 7.6 Hz, CH_2CO$_2$), 1.45−1.55 (comp, 6 H, fatty CH_2), 1.22 (comp, 38 H, fatty CH_2), 0.84 (t, 3 H, J = 6.6 Hz, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 173.1 (*C*═O), 70.5 (d, J = 7.4 Hz, *C*^{2}), 66.2 (d, J = 5.5 Hz, *C*H$_2$N), 63.3 (d, J = 4.7 Hz, *C*^{3}), 62.9 (*C*^{1}), 62.4 (*C*H$_2$OH), 59.2 (d, J = 4.6 Hz, POCH_2CH_2N), 54.2 (N(*C*H$_3$)$_3$), 34.2, 34.1, 32.7, 31.8, 29.6, 29.5, 29.31, 29.26, 29.2, 29.1, 28.9, 28.8, 25.7, 24.8, 24.7, 22.6 (fatty *C*H$_2$), 14.0 (*C*H$_3$CH$_2$); mass spectrum (LSIMS) *m*/*z* 694.5031 ($C_{36}H_{72}O_9NP$ + H requires 694.5023). Anal. Calcd for $C_{36}H_{72}NO_9P$: C, 62.31; H, 10.46; N, 2.02. Found: C, 62.24; H, 10.49; N, 2.01.



1d

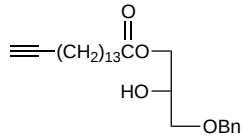
1-Palmitoyl-2-(11-carboxyundecanoyl)-*sn*-glycero-3-phosphocholine (1e). Warm a mixture of 1-palmitoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (104 mg, 0.210 mmol) and 1,10-decanedicarboxylic acid (0.47 g, 2.31 mmol) in CH_2Cl_2 (10 mL) at *ca*. 40 °C in a water bath until most of the diacid dissolved. Add DMAP (22 mg, 0.18 mmol) and then a solution of 1,3-dicyclohexylcarbodiimide (114 mg, 0.55 mmol) in CH_2Cl_2 (1 mL). Stir for 3 days. Filter through a small cotton wool plug in a 6 in. pipet. Rotoevaporate the filtrate. Purify twice by column chromatography (65:35:4 $CHCl_3/CH_3OH/H_2O$; 1 in. diameter × 2 in. height flash silica gel; elution rate *ca*. 4 mL/min) to give 31 mg (21%) of **1e**. Lyophilize to give white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (m, 1 H, C^2*H*), 4.26−4.40 (comp, 3 H, C^1*H* and POCH_2CH_2N), 4.11 (dd, 1 H, J = 11.5, 7.0 Hz, C^1*H*), 3.93 (m, 2 H, C$^3H_2$), 3.77 (m, 2 H, CH_2N), 3.31 (s, 9 H, N(CH_3)$_3$), 2.17−2.35 (comp, 6 H, CH_2CO$_2$), 1.50−

1.65 (comp, 6 H, J = 6.9 Hz, CH_2CH$_2$CO$_2$), 1.45−1.56 (comp, 6 H, fatty CH_2), 1.23 (comp, 36 H, fatty CH_2), 0.86 (t, 3 H, J = 6.6 Hz, CH_3CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.5 (*C*O$_2$H), 173.4, 173.1 (*C*=O), 70.5 (d, J = 7.3 Hz, *C*^{2}), 66.3 (d, J = 5.0 Hz, *C*H$_2$N), 63.5 (d, J = 3.6 Hz, *C*^{3}), 62.8 (*C*^{1}), 59.3 (d, J = 3.6 Hz, POCH$_2$CH$_2$N), 54.3 (N(*C*H$_3$)$_3$), 34.8, 34.1, 31.9, 29.7, 29.5, 29.3, 29.1, 28.9, 28.8, 28.6, 25.0, 24.8, 24.6, 22.6 (fatty *C*H$_2$), 14.1 (CH$_3$CH$_2$); mass spectrum (LSIMS) m/z 708.4825 (C$_{36}$H$_{70}$NO$_{10}$P + H requires 708.4816).



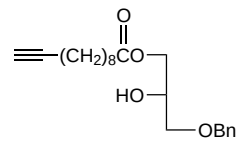
1e

1-(15-Hexadecynoyl)-3-benzyl-*sn*-glycerol (11). Add a solution of 1,3-dicyclohexylcarbodiimide (0.61 g, 2.98 mmol) in CH$_2$Cl$_2$ (1 mL) dropwise to a solution of (*R*)-3-(benzyloxy)-1,2-propanediol (0.52 g, 2.85 mmol), 15-hexadecynoic acid[2] (0.68 g, 2.68 mmol), and DMAP (30 mg, 0.25 mmol) in CH$_2$Cl$_2$ (4 mL) at 20 °C. Stir overnight. Filter through a small cotton wool plug in a 6 in. pipet. Rotoevaporate the filtrate. Purify by flash chromatography (first eluting with hexanes/EtOAc (3:1) to get rid of the diacylation product and then 1:1 hexanes/EtOAc to collect the desired monoacylated product) to afford 0.74 g (66%) of **11** as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.24−7.36 (comp, 5 H, Ar-*H*), 4.53 (s, 2 H, C*H*$_2$Ph), 4.10−4.19 (comp, 2 H, C^1*H*$_2$), 4.01 (m, 1 H, C^2*H*$_2$), 3.53 (dd, 1 H, J = 9.6, 4.4 Hz, C^3*H*), 3.47 (dd, 1 H, J = 9.6, 6.0 Hz, C^3*H*), 2.80 (d, 1 H, O*H*), 2.30 (t, 2 H, J = 7.5 Hz, C*H*$_2$CO$_2$), 2.16 (td, 2 H, J = 7.0, 2.6 Hz, C*H*$_2$C≡C), 1.93 (t, 1 H, J = 2.6 Hz, C≡C*H*), 1.46−1.61 (comp, 4 H, fatty C*H*$_2$), 1.07−1.42 (comp, 18 H, fatty C*H*$_2$); mass spectrum (LSIMS) m/z 417.3003 (C$_{26}$H$_{40}$O$_4$ + H requires 417.3005).



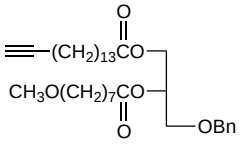
11

1-(10-Undecynoyl)-3-benzyl-*sn*-glycerol (12). Add a solution of 1,3-dicyclohexylcarbodiimide (111 mg, 0.54 mmol) in CH$_2$Cl$_2$ (1 mL) dropwise to a solution of (*R*)-3-(benzyloxy)-1,2-propanediol (105 mg, 0.57 mmol), 10-undecynoic acid (92 mg, 0.50 mmol), and DMAP (8 mg, 0.06 mmol) in CH$_2$Cl$_2$ (2 mL) at rt. Stir overnight. Filter through a small cotton wool in a 6 in. pipet. Rotoevaporate the filtrate. Purify by flash chromatography eluting with hexanes/EtOAc (3:1) to afford 110 mg (65%) of **12** as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.27−7.37 (comp, 5 H, Ar-*H*), 4.55 (s, 2 H, C*H*$_2$Ph), 4.09−4.21 (comp, 2 H, C^1*H*$_2$), 4.02 (m, 1 H, C^2*H*$_2$), 3.54 (dd, 1 H, J = 9.6, 4.4 Hz, C^3*H*), 3.48 (dd, 1 H, J = 9.6, 5.9 Hz, C^3*H*), 2.65 (d, 1 H, O*H*), 2.31 (t, 2 H, J = 7.5 Hz, C*H*$_2$CO$_2$), 2.17 (td, 2 H, J = 7.0, 2.6 Hz, C*H*$_2$C≡C), 1.93 (t, 1 H, J = 2.6 Hz, C≡C*H*), 1.46−1.62 (comp, 4 H, fatty C*H*$_2$), 1.29−1.42 (comp, 18 H, fatty C*H*$_2$); mass spectrum (LSIMS) m/z 347.2222 (C$_{21}$H$_{30}$O$_4$ + H requires 347.2222).



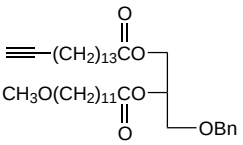
12

1-(15-Hexadecynoyl)-2-(8-methoxyoctanoyl)-3-benzyl-*sn*-glycerol (13). Add a solution of 1,3-dicyclohexylcarbodiimide (0.42 g, 2.04 mmol) in CH$_2$Cl$_2$ (1.5 mL) to a solution of **11** (0.74 g, 1.77 mmol), carboxylic acid **5** (0.31 g, 1.78 mmol), and DMAP (20 mg, 0.16 mmol) in CH$_2$Cl$_2$ (4 mL). Stir at rt overnight. Filter through a small cotton wool plug in a 6 in. pipet. Purify by flash chromatography eluting with hexanes/EtOAc (3:1) to afford 0.79 g (78%) of **13** as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.21−7.33 (comp, 5 H, Ar-*H*), 5.21 (m, 1 H, C^2*H*), 4.52 (d, 1 H, J = 12.2 Hz, C*H*Ph), 4.47 (d, 1 H, J = 12.2 Hz, C*H*Ph), 4.31 (dd, 1 H, J = 11.8, 3.7 Hz, C^1*H*), 4.15 (dd, 1 H, J = 11.8, 6.3 Hz, C^1*H*), 3.55 (d, 2 H, J = 5.2 Hz, C^3*H*$_2$), 3.31 (t, 2 H, J = 6.6 Hz, CH$_3$OC*H*$_2$), 3.28 (s, 3 H, OC*H*$_3$), 2.28 (t, 2 H, J = 7.5 Hz, C*H*$_2$CO$_2$), 2.24 (t, 2 H, J = 7.5 Hz, C*H*$_2$CO$_2$), 2.13 (td, 2 H, J = 7.0, 2.6 Hz, C*H*$_2$C≡C), 1.90 (t, 1 H, J = 2.6 Hz, C≡C*H*), 1.44−1.58 (comp, 8 H, fatty C*H*$_2$), 1.04−1.40 (comp, 24 H, fatty C*H*$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.1, 172.8 (*C*=O), 137.5, 128.2, 127.6, 127.4 (Ar*C*), 84.5 (*C*≡CH), 73.1 (*C*H$_2$Ph), 72.6 (*C*H$_2$OCH$_3$), 69.8 (*C*^{2}), 68.1, 68.0 (*C*^{3}, *C*≡CH), 62.4 (*C*^{1}), 58.3 (*C*H$_3$O), 34.1, 33.9, 29.4, 29.32, 29.29, 29.1, 28.9, 28.8, 28.6, 28.3, 25.8, 24.7 (fatty *C*H$_2$), 18.2 (*C*H$_2$C≡CH); mass spectrum (LSIMS) m/z 573.4153 (C$_{35}$H$_{56}$O$_6$ + H requires 573.4155).



13

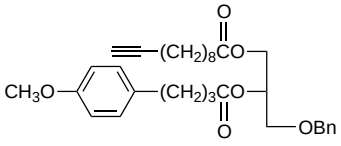
1-(15-Hexadecynoyl)-2-(12-methoxydodecanoyl)-3-benzyl-*sn*-glycerol (14). Add a solution of 1,3-dicyclohexylcarbodiimide (0.22 g, 1.08 mmol) in CH$_2$Cl$_2$ (1 mL) to a solution of **11** (0.39 g, 0.93 mmol), carboxylic acid **7** (0.22 g, 0.96 mmol), and DMAP (10 mg, 0.08 mmol) in CH$_2$Cl$_2$ (5 mL). Stir at rt overnight. Filter through a small cotton wool plug in a 6 in. pipet. Purify by flash chromatography eluting with hexanes/EtOAc (4:1) to afford 0.42 g (72%) of **14** as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.17−7.29 (comp, 5 H, Ar-*H*), 5.18 (m, 1 H, C^2*H*), 4.49 (d, 1 H, J = 12.1 Hz, C*H*Ph), 4.44 (d, 1 H, J = 12.1 Hz, C*H*Ph), 4.29 (dd, 1 H, J = 11.8, 3.7 Hz, C^1*H*), 4.12 (dd, 1 H, J = 11.8, 6.4 Hz, C^1*H*), 3.52 (d, 2 H, J = 5.2 Hz, C^3*H*$_2$), 3.28 (t, 2 H, J = 6.5 Hz, CH$_3$OC*H*$_2$), 3.24 (s, 3 H, OC*H*$_3$), 2.25 (t, 2 H, J = 7.4 Hz, C*H*$_2$CO$_2$), 2.21 (t, 2 H, J = 7.5 Hz, C*H*$_2$CO$_2$), 2.09 (td, 2 H, J = 7.0, 2.6 Hz, C*H*$_2$C≡C), 1.88 (t, 1 H, J = 2.6 Hz, C≡C*H*), 1.40−1.57 (comp, 8 H, fatty C*H*$_2$), 1.21 (s, 32 H, fatty C*H*$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 172.7, 172.5 (*C*=O), 137.4, 128.0, 127.4, 127.2 (Ar*C*), 84.2 (*C*≡CH), 72.9 (*C*H$_2$Ph), 72.5 (*C*H$_2$OCH$_3$), 69.7 (*C*^{2}), 67.9 (*C*^{3}, *C*≡CH), 62.3 (*C*^{1}), 58.1 (*C*H$_3$O), 33.9, 33.7, 29.4, 29.3, 29.2, 29.1, 29.0, 28.8, 28.7, 28.4, 28.2, 25.9, 24.6, 24.5 (fatty *C*H$_2$), 18.0 (*C*H$_2$C≡CH); mass spectrum (FAB) m/z 629.4758 (C$_{39}$H$_{64}$O$_6$ + H requires 629.4781).



14

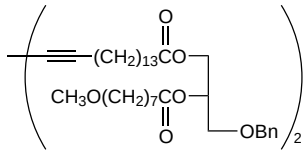
1-(10-Undecynoyl)-2-[4-(4′-methoxyphenyl)butyroyl]-3-benzyl-*sn*-glycerol (15). Add a solution of 1,3-dicyclohexylcarbodiimide (72 mg, 0.349 mmol) in CH$_2$Cl$_2$ (1 mL) to a solution of **12** (110 mg, 0.317 mmol), (4-methoxyphenyl)butyric acid acid (64 mg, 0.329 mmol), and DMAP (4 mg, 0.033 mmol) in CH$_2$Cl$_2$ (4 mL). Stir at rt overnight. Filter through a small cotton wool plug in a 6 in. pipet. Purify by flash chromatography eluting with hexanes/EtOAc (4:1) to afford 127 mg (76%) of **15** as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.27−7.34 (comp, 5 H, OCH$_2$Ar-*H*), 7.09 (d, 2 H, J = 8.5 Hz, CH$_3$O-Ar-*H*), 6.83 (d, 2 H, J = 8.5 Hz, CH$_3$O-Ar-*H*), 5.28 (m, 1 H, C^2*H*), 4.57 (d, 1 H, J = 12.2 Hz, OC*H*Ph), 4.52 (d, 1 H, J = 12.2 Hz, OC*H*Ph), 4.38 (dd, 1 H, J = 11.9, 3.8 Hz, C^1*H*), 4.21 (dd, 1 H, J = 11.9, 6.4 Hz, C^1*H*), 3.78 (s, 3 H, OC*H*$_3$), 3.61 (d, 2 H, J = 5.1 Hz, C^3*H*$_2$), 2.61 (t, 2 H, J = 7.5 Hz, CH$_2$C*H*$_2$Ar), 2.35 (t, 2 H, J = 7.4 Hz, C*H*$_2$CO$_2$), 2.29 (t, 2 H, J = 7.5 Hz, C*H*$_2$CO$_2$), 2.18 (td, 2 H, J = 7.0, 2.5 Hz, C*H*$_2$C≡C), 1.88−1.98

(comp, 3 H, C≡C*H* and CH_2CH$_2$Ar), 1.48−1.62 (comp, 4 H, fatty CH_2), 1.24−1.48 (comp, 8 H, fatty CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.6 (*C*═O), 157.7, 137.5, 133.2, 129.2, 128.2, 127.6, 127.4, 113.6 (Ar*C*), 84.5 (*C*≡CH), 73.1 (*C*H$_2$Ph), 70.0 (*C*^{2}), 68.1 (*C*^{3}, *C*≡CH), 62.5, (*C*^{1}), 55.0 (*C*H$_3$OAr), 33.93, 33.88, 33.4, 28.9, 28.8, 28.7, 28.5, 28.3, 26.6, 24.6 (fatty *C*H$_2$), 18.2 (*C*H$_2$C≡CH); mass spectrum (FAB) *m*/*z* 522.2978 ($C_{32}H_{42}O_6$ requires 522.2981).



15

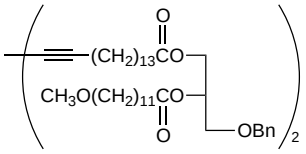
1,1′-(15,17-Dotriacontadiyne-1,32-dioyl)bis[2-(8-methoxyoctanoyl)-3-benzyl-*sn*-glycerol] (16). Bubble O_2 into a suspension of CuCl (70 mg, 0.70 mmol) and TMEDA (110 μL, 0.73 mmol) in xylenes (3 mL) at 140 °C for 15 min. Add a solution of **14** (0.31 g, 0.54 mmol) in xylenes (2 mL). Stir at 140−150 °C for 15 min. Cool to rt. Dilute with EtOAc (9 mL) and wash with water (2 × 5 mL). Dry over Na_2SO_4, filter, and rotoevaporate. Purify by flash chromatography eluting with hexanes/EtOAc (2:1) to afford 0.277 g (89%) of **16** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.36 (comp, 10 H, Ar-*H*), 5.23 (m, 2 H, C^2*H*), 4.55 (d, 2 H, *J* = 12.1 Hz, C*H*Ph), 4.50 (d, 2 H, *J* = 12.1 Hz, C*H*Ph), 4.33 (dd, 2 H, *J* = 11.8, 3.7 Hz, C^1*H*), 4.17 (dd, 2 H, *J* = 11.8, 6.5 Hz, C^1*H*), 3.58 (d, 4 H, *J* = 5.1 Hz, C^3*H*$_2$), 3.34 (t, 4 H, *J* = 6.6 Hz, CH$_3$OC*H*$_2$), 3.31 (s, 6 H, OC*H*$_3$), 2.20−2.33 (comp, 12 H, C*H*$_2$CO$_2$ and C*H*$_2$C≡C), 1.45−1.61 (comp, 16 H, fatty C*H*$_2$), 1.24−1.40 (comp, 48 H, fatty C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 172.9 (*C*═O), 137.6, 128.3, 127.7, 127.5 (Ar*C*), 73.2 (*C*H$_2$Ph), 72.7 (*C*H$_2$OCH$_3$), 70.0 (*C*^{2}), 68.2 (*C*^{3}), 65.2 (*C*≡C), 62.5 (*C*^{1}), 58.5 (*C*H$_3$O), 34.2, 34.0, 29.5, 29.4, 29.2, 29.0, 28.9, 28.8, 28.3, 25.9, 24.8 (fatty *C*H$_2$), 19.1 (*C*H$_2$C≡CH); mass spectrum (LSIMS) *m*/*z* 1143.8078 ($C_{70}H_{110}O_{12}$ + H requires 1143.8076).



16

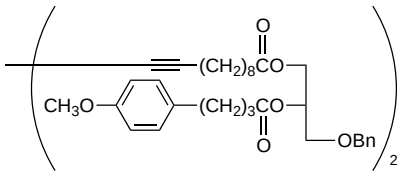
1,1′-(15,17-Dotriacontadiyne-1,32-dioyl)bis[2-(12-methoxydodecanoyl)-3-benzyl-*sn*-glycerol] (17). Bubble O_2 into a suspension of CuCl (104 mg, 1.05 mmol) and TMEDA (160 μL, 1.06 mmol) in xylenes (6 mL) at 140 °C for 15 min. Add a solution of **14** (0.42 g, 0.66 mmol) in xylenes (3 mL). Stir at 140−150 °C for 30 min. Cool to rt. Dilute with EtOAc (60 mL) and wash with brine (50 mL). Dry over Na_2SO_4, filter, and rotoevaporate. Purify by flash chromatography eluting with hexanes/EtOAc (2:1) to afford 0.40 g (95%) of **17** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19−7.26 (comp, 10 H, Ar-*H*), 5.18 (m, 2 H, C^2*H*), 4.49 (d, 2 H, *J* = 12.1 Hz, C*H*Ph), 4.44 (d, 2 H, *J* = 12.1 Hz, C*H*Ph), 4.29 (dd, 2 H, *J* = 11.9, 3.7 Hz, C^1*H*), 4.12 (dd, 2 H, *J* = 11.9, 6.3 Hz, C^1*H*), 3.52 (d, 4 H, *J* = 5.1 Hz, C^3*H*$_2$), 3.28 (t, 4 H, *J* = 6.5 Hz, CH$_3$OC*H*$_2$), 3.24 (s, 6 H, OC*H*$_3$), 2.13−2.27 (comp, 12 H, C*H*$_2$CO$_2$ and C*H*$_2$C≡C), 1.39−1.55 (comp, 16 H, fatty C*H*$_2$), 1.20 (s, 64 H, fatty C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.5 (*C*═O), 137.5, 128.1, 127.4, 127.2 (Ar*C*), 72.9 (*C*H$_2$Ph), 72.6 (*C*H$_2$OCH$_3$), 69.7 (*C*^{2}), 68.0 (*C*^{3}), 65.2 (*C*≡*C*), 62.3 (*C*^{1}), 58.1 (*C*H$_3$O), 34.0, 33.7, 29.4, 29.32, 29.26, 29.21, 29.17, 29.0, 28.82, 28.77, 28.6, 28.1, 25.9, 24.65, 24.58 (fatty *C*H$_2$), 18.9 (*C*H$_2$C≡C); mass spectrum (LSIMS) *m*/*z* 1255.9319 ($C_{78}H_{126}O_{12}$ + H requires 1255.9328), 1257 (M + H).

1,1′-(10,12-Docosadiyne-1,22-dioyl)bis[2-(4-(4′-methoxyphenyl)butyroyl)-3-benzyl-*sn*-glycerol] (18). Bubble O_2 into a suspension of CuCl (37 mg, 0.374 mmol) and TMEDA (60 μL, 0.397 mmol) in xylenes (5 mL) at 140 °C for 15 min. Add a solution of **15** (127 mg, 0.243 mmol) in xylenes (2 mL). Stir at 140−150 °C for 30 min. Cool to rt. Dilute with EtOAc



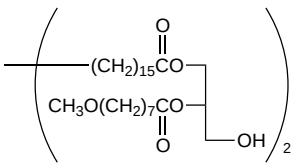
17

(25 mL) and wash with brine (25 mL). Dry over Na_2SO_4, filter, and rotoevaporate. Purify by flash chromatography eluting with hexanes/EtOAc (2:1) to afford 107 mg (84%) of **18** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.36 (comp, 10 H, OCH$_2$Ar-*H*), 7.09 (d, 4 H, *J* = 8.4 Hz, CH$_3$O-Ar-*H*), 6.83 (d, 4 H, *J* = 8.4 Hz, CH$_3$O-Ar-*H*), 5.27 (m, 2 H, C^2*H*), 4.57 (d, 2 H, *J* = 12.1 Hz, OC*H*Ph), 4.52 (d, 2 H, *J* = 12.1 Hz, OC*H*Ph), 4.37 (dd, 2 H, *J* = 11.9, 3.7 Hz, C^1*H*), 4.20 (dd, 2 H, *J* = 11.9, 6.4 Hz, C^1*H*), 3.78 (s, 6 H, OC*H*$_3$), 3.60 (d, 4 H, *J* = 5.1 Hz, C^3*H*$_2$), 2.60 (t, 4 H, *J* = 7.4 Hz, CH$_2$C*H*$_2$Ar), 2.35 (t, 4 H, *J* = 7.4 Hz, C*H*$_2$CO$_2$), 2.21−2.30 (comp, 8 H, C*H*$_2$CO$_2$ and C*H*$_2$C≡C), 1.92 (p, 4 H, C*H*$_2$CH$_2$Ar), 1.46−1.61 (comp, 8 H, fatty C*H*$_2$), 1.28−1.45 (comp, 16 H, fatty C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.6 (*C*═O), 157.7, 137.5, 133.2, 129.2, 128.2, 127.6, 127.5, 113.6 (Ar*C*), 73.1 (*C*H$_2$Ph), 70.0 (*C*^{2}), 68.1 (*C*^{3}), 65.2 (*C*≡*C*), 62.5 (*C*^{1}), 55.0 (*C*H$_3$OAr), 33.94, 33.89, 33.4, 28.91, 28.86, 28.7, 28.6, 28.1, 26.6, 24.6 (fatty *C*H$_2$), 19.0 (*C*H$_2$C═C); mass spectrum (FAB) *m*/*z* 1042.5817 ($C_{64}H_{82}O_{12}$ requires 1042.5806).



18

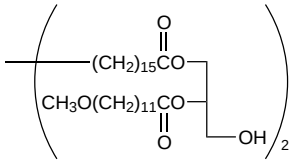
1,1′-(Dotriacontane-1,32-dioyl)bis[2-(8-methoxyoctanoyl)-*sn*-glycerol] (19). Stir a solution of **16** (0.25 g, 0.22 mmol) in absolute EtOH (4 mL) and glacial AcOH (1.5 mL) under H_2 in the presence of 10% Pd/C (26 mg) at rt overnight. Dilute with $CHCl_3$ (5 mL) and filter through Celite (the product is not soluble in EtOH/AcOH). Wash the catalyst with $CHCl_3$. Rotoevaporate the filtrate to give 0.20 g (92%) of **19** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (m, 2 H, C^2*H*), 4.24 (dd, 2 H, *J* = 11.9, 3.8 Hz, C^1*H*), 4.10 (dd, 2 H, *J* = 11.9, 6.2 Hz, C^1*H*), 3.60 (d, 4 H, *J* = 5.5 Hz, C^3*H*$_2$), 3.26 (t, 4 H, *J* = 6.6 Hz, CH$_3$OC*H*$_2$), 3.22 (s, 6 H, OC*H*$_3$), 3.08 (t, 2 H, *J* = 5.5 Hz, C^{3}H$_2$O*H*), 2.24 (t, 4 H, *J* = 7.4 Hz, C*H*$_2$CO$_2$), 2.19 (t, 4 H, *J* = 7.4 Hz, C*H*$_2$CO$_2$), 1.44−1.60 (comp, 12 H, fatty C*H*$_2$), 1.12−1.29 (comp, 64 H, fatty C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 173.1 (*C*═O), 72.6 (*C*H$_2$OCH$_3$), 71.8 (*C*^{2}), 62.1 (*C*^{1}), 60.9 (*C*^{3}), 58.2 (*C*H$_3$O), 34.0, 33.8, 29.5, 29.2, 29.0, 28.9, 28.8, 28.7, 25.7, 24.63, 24.57 (fatty *C*H$_2$).



19

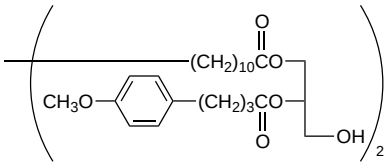
1,1′-(Dotriacontane-1,32-dioyl)bis[2-(12-methoxydodecanoyl)-*sn*-glycerol] (20). Stir a solution of **17** (103 mg, 0.082 mmol) in absolute EtOH (4 mL) and glacial AcOH (2 mL) under H_2 in the presence of 10% Pd/C (11 mg) at rt overnight. Dilute with $CHCl_3$ (5 mL) and filter through Celite (the product is not soluble in EtOH/AcOH). Wash the catalyst with $CHCl_3$. Rotoevaporate the filtrate to give 85 mg (95%) of **20** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (m, 2 H, C^2*H*), 4.29 (dd, 2 H, *J* = 11.9, 4.3 Hz, C^1*H*), 4.18 (dd, 2 H, *J* = 11.9, 5.9 Hz, C^1*H*), 3.68 (d, 4 H, *J* = 5.0 Hz, C^3*H*$_2$), 3.32 (t, 4 H, *J* = 6.7 Hz, CH$_3$OC*H*$_2$), 3.29 (s, 6 H, OC*H*$_3$), 2.30 (t, 4 H, *J* = 7.2 Hz, C*H*$_2$CO$_2$), 2.28 (t, 4 H, *J* = 7.2 Hz, C*H*$_2$CO$_2$), 1.44−1.65 (comp, 12 H, fatty C*H*$_2$), 1.08−1.35 (comp, 80 H, fatty C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 173.3 (*C*═O), 72.9

(CH_2OCH_3), 72.0 (C^2), 62.1 (C^1), 61.2 (C^3), 58.4 (CH_3O), 34.2, 34.0, 29.6, 29.54, 29.51, 29.45, 29.38, 29.3, 29.2, 29.1, 29.03, 28.97, 26.0, 24.82, 24.79 (fatty CH_2); mass spectrum (FAB) *m*/*z* 1083.9034 ($C_{64}H_{122}O_{12}$ + H requires 1083.9015), 1090 (M + Li^+).



20

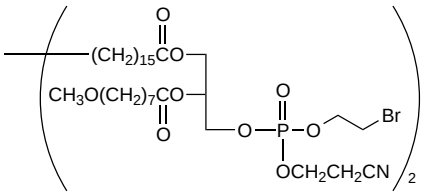
1,1′-(Docosane-1,22-dioyl)bis[2-(4-(4′-methoxyphenyl)-butyroyl)-3-benzyl-*sn*-glycerol] (21). Add absolute EtOH (4 mL) and glacial AcOH (2 mL) to **18** (107 mg, 0.102 mmol). Add EtOAc (1.5 mL) until **18** was dissolved. Stir the reaction mixture under H_2 in the presence of 10% Pd/C (17 mg) at 20 °C overnight. Dilute with $CHCl_3$ (5 mL) and filter through Celite (the product is not soluble in EtOH/AcOH). Wash the catalyst with $CHCl_3$. Rotoevaporate the filtrate to give 87 mg (98%) of **21** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 4 H, J = 8.5 Hz, CH_3O-Ar-*H*), 6.81 (d, 4 H, J = 8.5 Hz, CH_3O-Ar-*H*), 5.08 (m, 2 H, C^2H), 4.32 (dd, 2 H, J = 12.0, 4.2 Hz, C^1H), 4.20 (dd, 2 H, J = 12.0, 5.8 Hz, C^1H), 3.77 (s, 6 H, OCH_3), 3.70 (d, 4 H, J = 5.1 Hz, C^3H_2), 3.04 (s, br, 2 H, O*H*), 2.58 (t, 4 H, J = 7.5 Hz, CH_2CH_2Ar), 2.27−2.37 (comp, 8 H, CH_2CO_2), 1.91 (p, 4 H, J = 7.5 Hz, CH_2CH_2Ar), 1.56−1.61 (comp, 4 H, fatty CH_2), 1.24 (comp, 32 H, fatty CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 173.1 (*C*=O), 157.8, 133.2, 129.3, 113.6 (Ar*C*), 72.1 (C^2), 62.0 (C^1), 61.3 (C^3), 55.1 (CH_3OAr), 34.0, 33.4, 29.6, 29.5, 29.4, 29.2, 29.0, 26.6, 24.8 (fatty CH_2); mass spectrum (FAB) *m*/*z* 871.5593 ($C_{50}H_{78}O_{12}$ + H requires 871.5571).



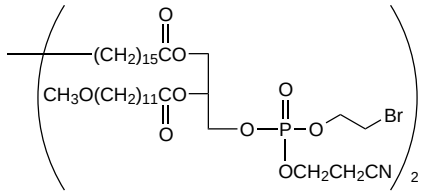
21

1,1′-(Dotriacontane-1,32-dioyl)bis[1-(8-methoxyoctanoyl)-*sn*-glycero-3-(2-bromoethyl 2-cyanoethyl phosphate)] (22). Add a solution of 2-bromoethanol (51 μL, 0.72 mmol) in dry THF (0.5 mL) dropwise to a solution of *N*,*N*-diisopropylamino chlorophosphite (0.17 mL, 0.76 mmol) and Et_3N (106 μL, 0.76 mmol) in THF (1.5 mL) at rt under Ar. Stir for 1 h. Filter through a small cotton wool plug in a 6 in. pipet. Add 1*H*-tetrazole (52 mg, 0.74 mmol) and then diol **19** (107 mg, 0.11 mmol) to the filtrate. Stir at rt for another 30 min. Add 30% aqueous H_2O_2 (0.2 mL). Stir for 15 min. Rotoevaporate. Dissolve the residue in $CHCl_3$ (15 mL). Wash with 0.5 N HCl (15 mL) and then brine (15 mL). Dry over Na_2SO_4, filter, and rotoevaporate to give a colorless oil. Purify three times by column chromatography eluting with $CHCl_3$/CH_3OH (10:1) (1.5 in. diameter × 6.5 in. height flash silica gel column) to give 118 mg (74%) of **22** as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (m, 2 H, C^2H), 4.09−4.37 (comp, 16 H, C^1H_2 and C^3H_2 and $POCH_2CH_2$Br and $POCH_2CH_2$CN), 3.52 (t, 4 H, J = 5.6 Hz, CH_2Br), 3.31 (t, 4 H, J = 6.6 Hz, CH_3OCH_2), 3.28 (s, 6 H, OCH_3), 2.71 (t, 4 H, J = 6.1 Hz, CH_2CN), 2.30 (t, 4 H, J = 7.9 Hz, CH_2CO_2), 2.28 (t, 4 H, J = 8.1 Hz, CH_2CO_2), 1.49−1.61 (comp, 12 H, fatty CH_2), 1.15−1.34 (comp, 64 H, fatty CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.6 (*C*=O), 116.1 (*C*≡N), 72.7 (CH_2OCH_3), 69.1 (d, J = 7.6 Hz, C^2), 67.2 (d, J = 5.0 Hz), 66.0 (d, J = 5.5 Hz), 62.2 (d, J = 5.9 Hz) (C^3, $POCH_2CH_2$Br, $POCH_2CH_2$CN), 61.3 (C^1), 58.4 (CH_3O), 34.0, 33.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.8, 25.8, 24.7, 24.6 (CH_2Br and fatty CH_2), 19.5 (d, J = 7.3 Hz, CH_2CN); mass spectrum (LSIMS) *m*/*z* 1449.6471 ($C_{66}H_{120}Br_2N_2O_{18}P_2$ + H requires 1449.6456), 1452 (M + H).

1,1′-(Dotriacontane-1,32-dioyl)bis[1-(12-methoxydodecanoyl)-*sn*-glycero-3-(2-bromoethyl 2-cyanoethyl phosphate)] (23). Add a solution of 2-bromoethanol (165 mg, 1.32 mmol) in dry THF (0.5 mL) dropwise to a solution of *N*,*N*-diisopropylamino chlorophosphite (0.31 mL, 1.41 mmol) and Et_3N (202 μL, 1.45 mmol) in THF (3 mL) at rt under Ar. Stir for 1 h. Filter through a small cotton wool plug in a 6 in. pipet. Add 1*H*-tetrazole (70 mg, 1.00 mmol) and then diol **20** (85 mg, 0.078 mmol) to the filtrate. Stir at rt for another 30 min. Add 30% aqueous H_2O_2 (0.2 mL). Stir for 15 min. Rotoevaporate. Dissolve the residue in $CHCl_3$ (15 mL). Wash with 0.5 N HCl (15 mL) and then brine (15 mL). Dry over Na_2SO_4, filter, and rotoevaporate to give a white solid. Purify by flash chromatography eluting with EtOAc/hexanes (3:1) (200 mL) and then EtOAc/hexanes (8:1) to give a white solid. Wash the solid with pentane. Purify again by column chromatography eluting with $CHCl_3$/CH_3OH (10:1) (1 in. diameter × 7 in. height flash silica gel column) to give 60 mg (49%) of **23** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (m, 2 H, C^2H), 4.11−4.38 (comp, 16 H, C^1H_2 and C^3H_2 and $POCH_2CH_2$Br and $POCH_2CH_2$CN), 3.53 (t, 4 H, J = 5.8 Hz, CH_2Br), 3.33 (t, 4 H, J = 6.6 Hz, CH_3OCH_2), 3.29 (s, 6 H, OCH_3), 2.76 (t, 4 H, J = 6.2 Hz, CH_2CN), 2.31 (t, 4 H, J = 7.7 Hz, CH_2CO_2), 2.29 (t, 4 H, J = 7.8 Hz, CH_2CO_2), 1.50−1.65 (comp, 12 H, fatty CH_2), 1.15−1.35 (comp, 80 H, fatty CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.7 (*C*=O), 116.1 (*C*≡N), 72.8 (CH_2OCH_3), 69.1 (d, J = 7.8 Hz, C^2), 67.3 (d, J = 5.7 Hz), 66.0 (d, J = 5.5 Hz), 62.2 (d, J = 5.0 Hz) (C^3, $POCH_2CH_2$Br, $POCH_2CH_2$CN), 6.13 (C^1), 58.4 (CH_3O), 34.0, 33.9, 29.6, 29.55, 29.46, 29.43, 29.39, 29.34, 29.27, 29.24, 29.17, 29.02, 28.97, 26.0, 24.7 (CH_2Br and fatty CH_2), 19.5 (d, J = 7.2 Hz, CH_2CN); mass spectrum (FAB) *m*/*z* 1561.7726 ($C_{74}H_{136}Br_2N_2O_{18}P_2$ + H requires 1561.7708).



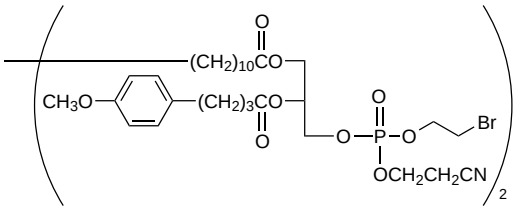
22



23

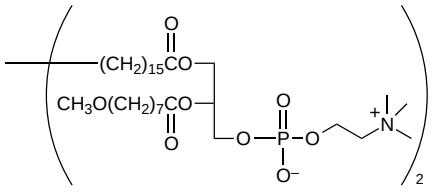
1,1′-(Docosane-1,22-dioyl)bis[2-(4-(4′-methoxyphenyl)-butyroyl)-*sn*-glycero-3-(2-bromoethyl 2-cyanoethyl phosphate)] (24). Add a solution of 2-bromoethanol (53 mg, 0.43 mmol) in dry THF (0.5 mL) dropwise to a solution of *N*,*N*-diisopropylamino chlorophosphite (0.11 mL, 0.76 mmol) and Et_3N (68 μL, 0.49 mmol) in THF (1 mL) at rt under Ar. Stir for 1 h. Filter through a small cotton wool plug in a 6 in. pipet. Add 1*H*-tetrazole (71 mg, 1.01 mmol) and then diol **21** (60 mg, 0.069 mmol) to the filtrate. Stir at rt for another 30 min. Add 30% aqueous H_2O_2 (0.2 mL). Stir for 15 min. Rotoevaporate. Dissolve the residue in $CHCl_3$ (15 mL). Dry over Na_2SO_4, filter, and rotoevaporate to give a colorless oil. Purify by flash chromatography eluting with EtOAc to give a white solid. Wash the solid with pentane (3 × 5 mL). Purify again by column chromatography eluting with $CHCl_3$/CH_3OH (10:1) (1 in. diameter × 7 in. height flash silica gel column; elution rate 2.5 mL/min) to give 67 mg (49%) of **24** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, 4 H, J = 8.4 Hz, CH_3O-Ar-*H*), 6.81 (d, 4 H, J = 8.4 Hz, CH_3O-Ar-*H*), 5.25 (m, 2 H, C^2H), 4.12−4.37 (comp, 16 H, C^1H_2 and C^3H_2 and $POCH_2CH_2$Br and $POCH_2CH_2$CN), 3.76 (s, 6 H, OCH_3), 3.51 (t, 4 H, J = 5.6 Hz, CH_2Br), 2.73 (t, 4 H, J = 6.1 Hz, CH_2CN), 2.58 (t, 4 H, J = 7.5 Hz, CH_2CH_2Ar), 2.29 (t, 4 H, J = 7.5 Hz, CH_2CO_2), 2.34 (t, 4 H, J = 7.5 Hz, CH_2CO_2), 1.90 (p, 4 H, J = 7.5 Hz, CH_2CH_2Ar), 1.53−1.60 (comp, 4 H, fatty CH_2), 1.23 (s, 32 H, fatty CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.4 (*C*=O), 157.8, 133.1, 129.3, 113.7 (Ar-*C*), 116.1 (*C*≡N), 69.2 (d, J = 7.6 Hz, C^2), 67.3

(d, J = 5.3 Hz), 66.0 (d, J = 5.6 Hz), 62.2 (d, J = 5.7 Hz) (C^3, $POCH_2CH_2Br$, $POCH_2CH_2CN$), 61.3 (C^1), 55.1 (CH_3O), 33.95, 33.87, 29.6, 29.5, 29.4, 29.31, 29.28, 29.15, 29.0, 26.5, 24.7 (CH_2-Br & fatty CH_2), 19.5 (d, J = 7.1 Hz, CH_2CN).



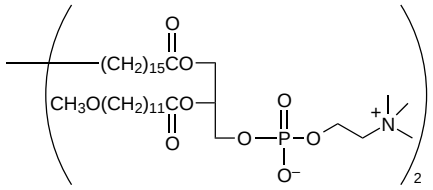
24

1,1′-(Dotriacontane-1,32-dioyl)bis[1-(8-methoxyoctanoyl)-*sn*-glycero-3-phosphocholine] (2a). Condense anhydrous trimethylamine gas (*ca*. 3 mL of liquid trimethylamine at −78 °C) in a solution of **22** (67 mg, 0.046 mmol) in anhydrous acetonitrile (3.5 mL) at −78 °C in a heavy-walled vessel. Seal the vessel tightly and warm slowly to rt. Stir at 50−60 °C for 2 days. Cool the reaction mixture to <−20 °C before opening. Evaporate excess trimethylamine slowly under a stream of N_2 in a hood. Dilute the residue with $CHCl_3$/CH_3OH (1:1) (5 mL) and transfer to a round-bottomed flask. Rotoevaporate. Purify twice by column chromatography (0.5 in. diameter × 2 in. height flash silica gel column; elution rate *ca*. 4 mL/min) eluting first with $CHCl_3$/CH_3OH/H_2O (65:35:4) to get rid of the higher R_f side product and then with $CHCl_3$/CH_3OH/acetone/H_2O (3:3:2:1) to elute off the desired bolaform phospholipid **2a** (44 mg, 73%). Lyophilize to give a white solid: ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD (1:1)) δ 5.18 (m, 2 H, C^2H), 4.38 (dd, 2 H, J = 12.0, 3.2 Hz, C^1H), 4.21 (m, 4 H, $POCH_2CH_2N$), 4.11 (dd, 2 H, J = 12.0, 6.8 Hz, C^1H), 3.95 (t, 4 H, J = 6.1 Hz, C^3H_2), 3.57 (t, 4 H, J = 4.6 Hz, CH_2N), 3.35 (t, 4 H, J = 6.6 Hz, CH_2OCH_3), 3.29 (s, 6 H, OCH_3), 3.18 (s, 18 H, $N(CH_3)_3$), 2.29 (t, 4 H, J = 7.3 Hz, CH_2CO_2), 2.27 (t, 4 H, J = 7.3 Hz, CH_2CO_2), 1.50−1.57 (comp, 12 H, fatty CH_2), 1.19−1.34 (comp, 64 H, fatty CH_2); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD (1:1)) δ 173.8, 173.3 (C=O), 72.7 (CH_2OCH_3), 70.3 (d, J = 7.8 Hz, C^2), 66.2 (CH_2N), 63.5 (d, J = 5.4 Hz, C^3), 62.4 (C^1), 58.9 (d, J = 5.0 Hz, $POCH_2CH_2N$), 57.9 (CH_3OCH_2), 53.7 ($N(CH_3)_3$), 33.93, 33.98, 33.84, 29.5, 29.3, 29.2, 29.1, 28.9, 28.8, 25.7, 24.7, 24.6 (fatty CH_2); mass spectrum (FAB) m/z 1031.8850 ($C_{66}H_{130}N_2O_{18}P_2$ + H requires 1301.8872).



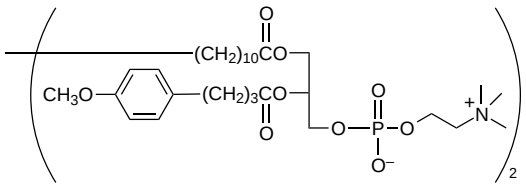
2a

1,1′-(Dotriacontane-1,32-dioyl)bis[1-(12-methoxydodecanoyl)-*sn*-glycero-3-phosphocholine] (2b). Condense anhydrous trimethylamine gas (*ca*. 3 mL of liquid trimethylamine at −78 °C) in a solution of **23** (60 mg, 0.038 mmol) in toluene (3 mL) and anhydrous acetonitrile (0.5 mL) at −78 °C in a heavy-walled vessel. Seal the vessel tightly and warm slowly to rt. Stir at 50−60 °C for 2 days. Cool the reaction mixture to <−20 °C before opening. Evaporate excess trimethylamine slowly under a stream of N_2 in a hood. Dilute the residue with $CHCl_3$/CH_3OH (1:1) (5 mL) and transfer to a round-bottomed flask. Rotoevaporate. Purify twice by column chromatography (0.5 in. diameter × 2 in. height flash silica gel column; elution rate *ca*. 4 mL/min) eluting first with $CHCl_3$/CH_3OH/H_2O (65:35:4) to get rid of the higher R_f side product and then with $CHCl_3$/CH_3OH/acetone/H_2O (3:3:2:1) to elute off the desired bolaform phospholipid **2b** (41 mg, 76%). Lyophilize to give a white solid: ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD (1:1)) δ 5.17 (m, 2 H, C^2H), 4.33−4.38 (m, 2 H, C^1H), 4.18 (m, 4 H, $POCH_2CH_2N$), 4.09 (dd, 2 H, J = 12.0, 7.0 Hz, C^1H), 3.93 (t, 4 H, J = 6.2 Hz, C^3H_2), 3.55 (t, 4 H, J = 4.5 Hz, CH_2N), 3.33 (t, 4 H, J = 6.7 Hz, CH_2OCH_3), 3.28 (s, 6 H, J = 6.6 Hz, OCH_3), 3.16 (s, 18 H, $N(CH_3)_3$), 2.22−2.29 (comp, 8 H, CH_2CO_2), 1.49−1.53 (comp, 12 H, fatty CH_2), 1.05−1.34 (comp, 80 H, fatty CH_2); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD (1:1)) δ 173.9, 173.5 (C=O), 72.9 (CH_2OCH_3), 70.3 (d, J = 8.3 Hz, C^2), 66.3 (d, J = 2.8 Hz, CH_2N), 63.5 (d, J = 5.5 Hz, C^3), 62.6 (C^1), 58.9 (d, J = 5.2 Hz, $POCH_2CH_2N$), 58.1 (CH_3OCH_2), 53.9 ($N(CH_3)_3$), 34.1, 33.9, 29.70, 29.67, 29.57, 29.4, 29.3, 29.2, 29.0, 25.9, 24.8, 24.7 (fatty CH_2); mass spectrum (FAB) m/z 1414.0106 ($C_{74}H_{146}N_2O_{18}P_2$ + H requires 1414.0124).



2b

1,1′-(Docosane-1,22-dioyl)bis[2-(4-(4′-methoxyphenyl)-butyroyl)-*sn*-glycero-3-phosphocholine] (3). Condense anhydrous trimethylamine gas (*ca*. 2 mL of liquid trimethylamine at −78 °C) in a solution of **24** (67 mg, 0.050 mmol) in toluene (3 mL) at −78 °C in a heavy-walled vessel. Seal the vessel tightly and warm slowly to rt. Stir at 60−65 °C for 2 days. Cool the reaction mixture to <−20 °C before opening. Evaporate excess trimethylamine slowly under a stream of N_2 in a hood. Dilute the residue with $CHCl_3$/CH_3OH (1:1) (5 mL) and transfer to a round-bottomed flask. Rotoevaporate. Purify twice by column chromatography (0.5 in. diameter × 2 in. height flash silica gel column; elution rate *ca*. 4 mL/min) eluting first with $CHCl_3$/CH_3OH/H_2O (65:35:4) to get rid of the higher R_f side product and then with $CHCl_3$/CH_3OH/acetone/H_2O (3:3:2:1) to elute off the desired bolaform phospholipid **3** (45 mg, 76%). Lyophilize to give a white solid: ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD (1:1)) δ 7.04 (d, 4 H, J = 8.6 Hz, CH_3O-Ar-*H*), 6.78 (d, 4 H, J = 8.4 Hz, CH_3O-Ar-*H*), 5.19 (m, 2 H, C^2H), 4.37 (dd, 2 H, J = 12.0, 3.2 Hz, C^1H), 4.18 (m, 4 H, $POCH_2CH_2N$), 4.12 (dd, 2 H, J = 12.0, 6.9 Hz, C^1H), 3.95 (t, 4 H, J = 6.1 Hz, C^3H_2), 3.73 (s, 6 H, OCH_3), 3.53 (t, 4 H, J = 4.3 Hz, CH_2N), 3.15 (s, 18 H, $N(CH_3)_3$), 2.54 (t, 4 H, J = 7.5 Hz, CH_2CH_2Ar), 2.22−2.32 (comp, 8 H, CH_2CO_2), 1.85 (p, 4 H, J = 7.5 Hz, CH_2CH_2Ar), 1.50−1.55 (comp, 4 H, fatty CH_2), 1.20 (s, 32 H, fatty CH_2); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD (1:1)) δ 175.9, 175.2 (C=O), 159.9, 135.4, 131.3, 115.8 (Ar-*C*), 72.5 (d, J = 8.1 Hz, C^2), 68.4 (CH_2N), 65.6 (d, J = 5.2 Hz, C^3), 64.6 (C^1), 61.0 (d, J = 4.9 Hz, $POCH_2CH_2N$), 57.0 (CH_3O), 55.9 ($N(CH_3)_3$), 35.9, 35.4, 31.6, 31.4, 31.2, 31.0, 28.7, 26.8 (fatty CH_2); mass spectrum (FAB) m/z 1201.6707 ($C_{60}H_{102}N_2O_{18}P_2$ + H requires 1201.6681).



3

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