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Efficient Stereoselective Synthesis of Plasmenylcholines

Yuanjin Rui and David H. Thompson*

Abstract: The first practical total chemical synthesis of a plasmenylcholine (1-*O*-1′-(*Z*)-hexadecenyl-2-hexadecanoyl-*sn*-glycero-3-phosphocholine) with pure (*Z*) olefin stereochemistry is reported. Monopalmitin was doubly protected as the 3-TBDPS-2-TBDMS ethers (*tert*-butyldiphenylsilyl-, *tert*-butyldimethylsilyl-) and converted to the corresponding 1-*O*-1′-(*Z*)-hexadecenyl-2-TBDMS-3-TBDPS-glyceryl ether (by the method of ref. [43]). Clean deprotection with tetrabutylammonium fluoride in the presence of imidazole gave 1-*O*-1′-(*Z*)-hexadecenylglycerol in >90% yield. Resilylation with TBDPSCl followed by acylation of the *sn*-2 alcohol with palmitoyl chloride and deprotection of the resulting 3-TBDPS-2-hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenylglycerol at −20 °C with Bu_4NF gave 2-hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenylglycerol in 86% yield. The 3-phosphocholine group was attached by phosphorylating the free hydroxyl with 2-chloro-2-oxo-1,3,2-dioxaphospholane in the presence of pyridine, instead of Et_3N, as base to avoid acyl migration; the dioxaphospholane triester intermediate was subsequently cleaved with Me_3N to give 1-*O*-1′-(*Z*)-hexadecenyl-2-hexadecanoyl-*sn*-glycero-3-phosphocholine in 18% overall yield from monopalmitin. The efficiency and flexibility of this route makes it well-suited to the preparation of a wide variety of 1-, 2-, and 3-substituted as well as isotopically labeled plasmenylcholines for biophysical and biochemical studies.

Keywords
enol ethers · phosphatidylcholine · plasmenyl phospholipids · total syntheses

Introduction

Plasmenyl phospholipids (plasmalogens) are a class of ether lipids derived from 1-*O*-1′-(*Z*)-alkenyl-2-acyl-*sn*-glycerol. Plasmenylcholines and ethanolamines, the most abundant ether-linked glycerophospholipids in the animal kingdom,[1–6] are found predominantly in electrically active mammalian tissues such as brain and heart, as well as numerous bacterial sources; however, no plant sources of plasmenyl derivatives are currently known.[7] Despite their high *sn*-2 arachidonyl content,[8] rapid turnover during ischemic episodes,[9–11] involvement in membrane fusion,[12–14] peroxidation,[15–18] and signal transduction processes (by polar headgroup and acyl chain remodeling),[8, 19–29] there is comparatively little known about the physical properties of this class of phospholipids. This is, in part, a result of the difficulties involved in purifying plasmenyl phospholipids as discrete chemical species from cell extracts. This limitation prompted us to investigate their total chemical synthesis to facilitate biophysical and biochemical studies.

The difficulties inherent in constructing plasmalogens are i) the stereospecific introduction of a (*Z*)-vinyl ether bond between the *sn*-1 aliphatic chain and the phosphoglycerol backbone, ii) the coexistence of both an acid-labile vinyl ether bond at the *sn*-1 position and a base-labile ester bond at the *sn*-2 site,[1] and iii) the installation of a phosphocholine headgroup under conditions sufficiently mild to obviate chain cleavage and/or acyl migration side reactions.

Earlier studies describing the construction of the plasmenyl vinyl ether bond[30–37] have been characterized by poor olefin stereoselectivities and low yields. Elimination procedures, such as debromination of cyclic glycerol-(1′-bromoalkyl)-acetals[35–37] or thermolysis of 1-(1′-ethoxyhexadecyloxy)-2,3-dipalmitoylglycerol,[31] are known to generate (*Z*)/(*E*) mixtures that favor the formation of the more thermodynamically stable (*E*) isomer. The isomeric mixtures of $>C_{12}$ derivatives, however, are difficult to separate on a preparative scale.[35, 38] Pfaendler has reported the preparation of 1-*O*-1′-(*Z*)-dodecenylglycerol by dechlorination of 1-(1′,2′-dichlorododecylglycerol)-2,3-carbonate with sodium naphthalenide to generate a ≈1:1 (*E*)/(*Z*) mixture of 1-*O*-1′-dodecenylglycerol-2,3-carbonate; chromatographic separation of the two isomers followed by deprotection of the (*Z*)-isomer gave 1-*O*-1′-(*Z*)-dodecenylglycerol in 25% overall yield.[39] Preparation of longer chain 1-*O*-1′-(*Z*)-alkenylglycerols (e.g., C_{14}–C_{18} derivatives) by this method and the subsequent acylation/phosphorylation steps required to complete the plasmenyl phospholipid synthesis were not reported, however. An unnatural (*E*)-plasmenyl derivative has also been prepared from 1-*O*-1′-(*E*)-hexadecenyl-2,3-dioleylglycerol in 11.5% yield by an enzymatic process.[32] Serebrennikova and coworkers, using a number of tedious elimination reactions that require extensive separations of the (*Z*) isomer from the resulting (*Z*)/(*E*) mixtures,[40, 41] have synthesized a plasmenylcholine, albeit in very low yield.[42]

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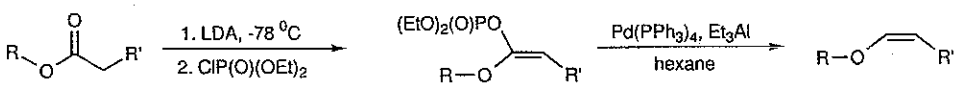
This laboratory has recently reported an efficient and stereocontrolled preparation of (*Z*)-vinyl ether bonds from acylglycerol precursors.[43] This route involves the transformation of the silyl-protected acylglycerol to a vinyl phosphate intermediate upon treatment with lithium diisopropylamide (LDA) and chlorodiethylphosphate ($ClPO(OEt)_2$), respectively, followed by reduction with triethylaluminum and tetrakis(triphenylphosphine)palladium(0) ($Et_3Al/[Pd(PPh_3)_4]$) in hexane to give the corresponding (*Z*)-vinyl ether product (Scheme 1). This route



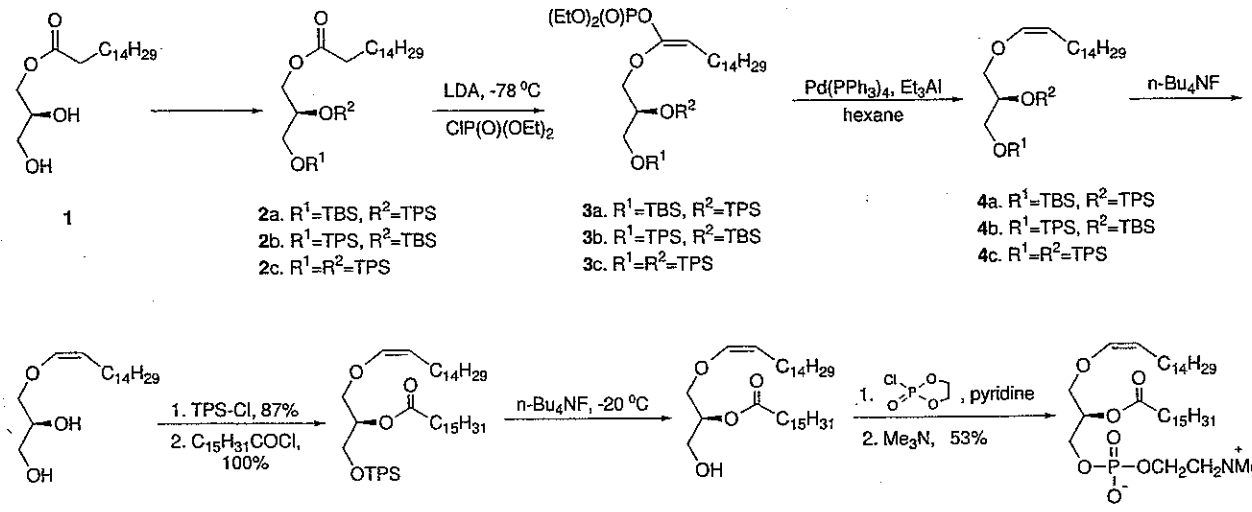
Scheme 1.

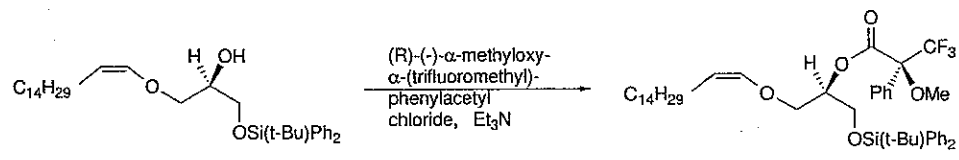
was applied to the preparation of 1-*O*-1′-(*Z*)-hexadecenyl-*rac*-glycerol, 1,2-di-*O*-1′-(*Z*)-hexadecenyl-*rac*-glycerol, and 1,2-di-*O*-(*Z*)-1′-hexadecenyl-*rac*-glycero-3-phosphocholine (diplasmalogen). The occurrence of extensive acyl-migration side-reactions during silyl deprotection of alkenylacylglycerol intermediates, however, prevented the application of this chemistry to the total synthesis of plasmenylcholines at that time.

This paper describes the total chemical synthesis of stereochemically pure plasmenylcholines (Scheme 2) by the successful application of Bu_4NF deprotection in the presence of imidazole under conditions that inhibit acyl migration and prevent attack of the vinyl ether linkage, as part of our ongoing investigation into the unique drug-delivery properties of liposomes derived from these phospholipids.[44–49] A more efficient preparation of 1-*O*-1′-(*Z*)-hexadecenylglycerol is also reported below.

Results and Discussion

Monopalmitin was doubly protected as the bissilyl ethers (**2a–c**) and converted to the corresponding vinyl phosphates (**3a–c**) by treatment at −78 °C with LDA and $ClPO(OEt)_2$; reduction of **3a–c** with $Et_3Al/[Pd(PPh_3)_4]$ in hexane provided (*Z*)-vinyl ethers **4a–c**. Several attempts were made to selectively remove the *sn*-3 *tert*-butyldiphenylsilyl group after construction of the (*Z*)-vinyl ether bond. Desilylation with SiF_4 led to rapid decomposition of the vinyl bond,[50] whereas $[Pd(OAc)_2]$ gave no reaction.[51] Pyridinium toluenesulfonate hydrolyzed the vinyl ether bond when used directly and gave no reaction when used with Et_3N.[52] Deprotection with NaOH/EtOH,[53] which worked well in the case of 3-*tert*-butyldiphenylsilyl-1,2-di-*O*-1′-(*Z*)-hexadecenylglycerol,[43] also destroyed the vinyl ether linkage in this case. When used directly, the most common desilylation reagent, Bu_4NF,[54] also caused decomposition of the vinyl ether bond. Subsequent investigations with imidazole as base to buffer the solution gave rapid, smooth conversion to the deprotected alcohol in >90% yield; however, no selectivity was observed for the cleavage of the *sn*-3 silyl group, even with careful control of the stoichiometry. Thus, the doubly desilylated intermediate 1-*O*-1′-(*Z*)-hexadecenyl-*sn*-glycerol (**5**) was selectively reprotected at the *sn*-3 position with *tert*-butyldiphenylsilyl chloride and acylated at the *sn*-2 site with palmitoyl chloride to give 3-*tert*-butyldiphenylsilyl-2-hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenyl-*sn*-glycerol (**6**). (^1H NMR analysis of **10**, the Mosher ester of the TBDPS ether **9**, revealed that





Scheme 2.

the *sn*-2 stereochemistry was retained during formation of the vinyl ether linkage.) When TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate)[55] was used to deprotect **6** in dry THF, the predominant product was the acyl-migrated 3-hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenylglycerol;[43] however, when Bu_4NF/imidazole was used, the migration reaction became temperature-dependent. At −20 °C, the migration process was suppressed and gave the neutral plasmenyl derivative (**7**) in 86% yield.

The phosphocholine headgroup was prepared by phosphorylating **7** with 2-chloro-2-oxo-1,3,2-dioxaphospholane in the presence of Et_3N in a modified procedure,[56] followed by direct amination with Me_3N without additional purification. The plasmenylcholine product recovered was a mixture of the 2-acyl and 3-acyl isomers. Isomerization of **7** presumably occurred during the phosphorylation reaction since the basicity of Et_3N ($pK_a = 10.75$) is sufficiently high to promote acyl migration on a timescale that competes with the phosphorylation reaction. This hypothesis was confirmed by conducting the phosphorylation reaction in the presence of the weaker base pyridine ($pK_a = 5.17$) where clean conversion to the 2-acyl product was observed to give the pure plasmenylcholine **8** in 53% yield.

The efficiency and flexibility of this route makes it well-suited to the preparation of a wide variety of 1-substituted (e.g., 1-*O*-1′-(*Z*)-octadecenyl, 1-*O*-1′-(*Z*),9′-(*Z*)-octadecadienyl), 2-substituted (e.g., octadecanoyl, oleyl, arachidonyl, etc), 3-substituted (e.g., phosphocholine and phosphoethanolamine), as well as isotopically labeled plasmenylcholines for biophysical and biochemical studies. Physical characterization of bilayer membranes formed from these synthetic plasmenylcholine derivatives is currently under investigation.

Experimental Procedure

3-*tert*-Butyldimethylsilyl-1-hexadecanoylglycerol: To a solution of monopalmitin (1.65 g, 5.0 mmol) and imidazole (0.68 g, 10 mmol) in dry DMF (10 mL), *tert*-butyldimethylsilyl chloride (0.75 g, 5.0 mmol) was added. After stirring at room temperature for 3 h, ether (40 mL) was added and the reaction mixture washed with water. The ether layer was dried with Na_2SO_4, evaporated under reduced pressure, and the residue purified by silica gel column chromatography with Et_2O/hexane (1:1) as eluent. The product (1.90 g) was obtained in 86% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.08$ (s, 6H), 0.80–1.0 (m, 12H), 1.1–1.4 (m, 24H), 1.5–1.75 (m, 2H), 2.3–2.4 (t, 2H), 2.50–2.55 (d, 1H), 3.55–4.25 (m, 5H). The corresponding *tert*-butyldiphenylsilyl ether was prepared in 92% yield (3.15 g 3-TPS-1-hexadecanoylglycerol from 2.0 g monopalmitin) by the same procedure. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.9$ (t, 3H), 1.1 (s, 9H), 1.3 (m, 24H), 1.6 (m, 2H), 2.3 (t, 2H), 2.55 (br, 1H), 3.7 (m, 2H), 3.9 (m, 1H), 4.2 (m, 2H), 7.3–7.7 (m, 10H).

3-*tert*-Butyldiphenylsilyl-2-*tert*-butyldimethylsilyl-1-hexadecanoyl glycerol (2a): To solution of 3-TPS-1-hexadecanoylglycerol (2.95 g, 5.18 mmol) and imidazole (0.92 g, 13.6 mmol) in dry DMF (10 mL), *tert*-butyldimethylsilyl chloride (0.844 g, 5.6 mmol) was added and stirred at room temperature for 3 h. By means of the same procedure as above, 3.45 g of **2a** was obtained in 97% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = -0.04$ (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 0.9 (t, 3H), 1.1 (s, 9H), 1.3 (m, 24H), 1.6 (m, 2H), 2.3 (t, 2H), 3.6 (d, 2H), 3.90 (m, 1H), 4.05 (dd, 1H), 4.3 (dd, 1H), 7.3–7.8 (m, 10H).

Protected compound 2b: 3-TBS-1-hexadecanoylglycerol (0.90 g, 4.27 mmol), imidazole (0.76 g, 11.2 mmol), and TBDPSCl (1.53 g, 5.6 mmol) were mixed in dry DMF (8 mL) to give 2.79 g **2b** (96% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = -0.10$ (s, 3H), −0.07 (s, 3H), 0.81 (s, 9H), 0.88 (t, 3H), 1.05 (s, 9H), 1.26 (m, 24H), 1.50–1.60 (m, 2H), 2.10–2.25 (m, 2H), 3.40–4.30 (m, 5H), 7.3–7.8 (m, 10H).

Protected compound 2c: This was prepared by treatment of 2.04 g monopalmitin with 2.4 equiv of TBDPSCl to give 4.92 g (99% yield) of **2c**. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.9$ (t, 3H), 1.1 (d, 18H), 1.3 (s, 24H), 1.5 (m, 2H), 2.1 (m, 2H), 3.6 (d, 2H), 4.0 (m, 1H), 4.15 (dd, 1H), 4.25 (dd, 1H), 7.3–7.8 (m, 20H).

Vinyl phosphate intermediate (3a): *n*-BuLi solution (2.8 mL of 2.5 M in hexane, 7.0 mmol) was added at −78 °C to a solution of diisopropylamine (0.90 g in 1.5 mL THF). After stirring for 20 min, **2a** (2.8 g, 4.0 mmol) in THF (4 mL) was added dropwise and stirred for another 40 min. Diethyl chlorophosphate (1.42 g, 8.2 mmol) in hexamethylphosphoramide (HMPA, 10 mL) was then added and stirred for 30 min before warming to room temperature over 1.5 h. The reaction mixture was separated by silica gel chromatography to give 1.84 g of product along with 0.53 g of recovered **2a** in 68% isolated yield (based on converted starting material).

Protected compound 3b (3.07 g) was prepared in 74% yield from 3.45 g of **2b**; **3c** (3.70 g) was produced in 65% yield from 4.92 g of **2c**. The isolated vinyl phosphates were then immediately used in the reduction reactions.

3-*tert*-Butyldiphenylsilyl-2-*tert*-butyldimethylsilyl-1-*O*-1′-(*Z*)-hexadecenylglycerol (4a): $[Pd(PPh_3)_4]$ (100 mg) was added at 0 °C to a solution of **3a** (1.84 g, 2.25 mmol) in dry hexane (3 mL); Et_3Al solution (4.5 mL, 1.0 M in hexane) was then added dropwise. After stirring at 0 °C for 1 h and at room temperature for another hour, the reaction mixture was filtered through silica gel and evaporated. The residue was purified by silica gel column chromatography to give 1.286 g of product in 86% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = -0.03$ (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 0.9 (t, 3H), 1.1 (s, 9H), 1.3 (s, 24H), 2.0 (m, 2H), 3.6 (m, 2H), 3.7 (m, 1H), 3.9 (m, 2H), 4.3 (q, 1H), 5.9 (d, 1H, $J_d = 6.2$ Hz), 7.3–7.8 (m, 10H).

Protected compound 4b: This was prepared in 75.1% yield (2.14 g) from 3.05 g of **3b**. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = -0.09$ (s, 3H), −0.06 (s, 3H), 0.83 (s, 9H), 0.88 (t, 3H), 1.06 (s, 9H), 1.26 (m, 24H), 2.01 (m, 2H), 3.40–4.00 (m, 5H), 4.25 (m, 1H), 5.80 (d, 1H), 7.30–7.80 (m, 10H).

Protected compound 4c: The bis(TPS) ether derivative **4c** (2.60 g) was prepared from 3.70 g of **3c** in 83% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): 0.88 (t, 3H), 1.1 (d, 18H), 1.3 (s, 24H), 2.0 (m, 2H), 3.5–4.0 (m, 5H), 4.25 (q, 1H), 5.8 (d, 1H, $J_d = 6.2$ Hz), 7.30–7.80 (m, 20H).

1-*O*-1′-(*Z*)-Hexadecenylglycerol (5): To a solution of **4a** (100 mg, 0.15 mmol) and imidazole (40 mg) in THF (1 mL), Bu_4NF (0.2 mL) was added. After stirring at room temperature for 3 h, the reaction mixture was purified by silica gel column chromatography with ether as eluant to give 43.3 mg of **5** in 92% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, 3H), 1.30 (s, 24H), 1.9–2.2 (m, 3H), 2.45 (d, 1H), 3.6–4.0 (m, 5H), 4.49 (m, 1H), 5.94 (dt, 1H).

3-*tert*-Butyldiphenylsilyl-1-*O*-1′-(*Z*)-hexadecenylglycerol (9): To a solution of **5** (120 mg, 0.38 mmol) and imidazole (52 mg) in dry DMF (2.5 mL), *tert*-butyldiphenylsilyl chloride (130 mg, 0.47 mmol) was added. After 2 h, the reaction mixture was purified by silica gel column chromatography with ether/hexane (1:3) as eluent to give 184 mg of **9** in 87% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, 3H), 1.1 (s, 9H), 1.3 (s, 24H), 2.0 (m, 2H), 2.42 (d, $J_d = 5.4$ Hz, 1H), 3.7–4.0 (m, 5H), 4.36 (dt, $J_d = 6.2$ Hz, 1H), 5.95 (dt, $J_d = 6.2$, 1H), 7.3–7.8 (m, 10H). The α-vinyl ether protons from the two enantiomers can be resolved at $\delta = 5.78$ and 5.88 after formation of the Mosher ester [57]. This was used to determine the enantiomeric purity of the glycerol vinyl ether product. Pyridine (7.9 mg) and **9** (19.3 mg) were dissolved in dry THF (0.5 mL), and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (10 mg in 0.5 mL dry THF) was added by syringe. After 1 h, the precipitate was filtered and the residue concentrated; purification of **10** by preparative TLC revealed the presence of a single diastereomer. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, 3H), 1.1 (s, 9H), 1.25 (s, 24H), 2.00 (m, 2H), 3.56 (s, 3H), 3.76 (d, 2H), 3.97 (m, 2H), 4.37 (q, 1H), 5.36 (m, 1H), 5.88 (d, 1H, $J_d = 6.2$ Hz), 7.2–7.7 (m, 15H).

Racemic 10 was prepared in the same manner from racemic **9** (derived from racemic monopalmitin starting material). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, 3H), 1.1 (s, 9H), 1.25 (s, 24H), 2.00 (m, 2H), 3.54 (s, 1.5H), 3.57 (s, 1.5H), 3.76 (d, 1H), 3.87 (t, 2H), 3.97 (m, 1H), 4.30 (q, 0.5H), 4.37 (q, 0.5H), 5.36 (m, 1H), 5.78 (d, 0.5H, $J_d = 6.2$ Hz), 5.88 (d, 0.5H, $J_d = 6.2$ Hz), 7.2–7.7 (m, 15 Hz).

3-*tert*-Butyldiphenylsilyl-2-hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenyl glycerol (6): To a solution of 3-*tert*-butyldiphenylsilyl-1-*O*-1′-(*Z*)-hexadecenylglycerol (**9**, 180 mg, 0.33 mmol) and pyridine (200 mg) in THF (3 mL), palmitoyl chloride (184 mg, 0.67 mmol) was added. After stirring at room temperature for 1.5 h, the reaction mixture was filtered through a silica gel plug and the retained solids washed thoroughly with Et_2O. After evaporation of the solvent, the residue was purified by silica gel column chromatography with hexane/ether (5:1) as eluant to give 270 mg of **6** in 100% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, 6H), 1.05 (s, 9H), 1.3 (s, 48H), 1.65 (m, 2H), 2.0 (m, 2H), 2.3 (m, 2H), 3.8 (d, 2H), 3.95 (m, 2H), 4.34 (dt, $J_d = 6.3$ Hz, 1H), 5.1 (m, 1H), 5.91 (dt, $J_d = 6.3$Hz, 1H), 7.3–7.8 (m, 10H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ =14.3, 19.4, 22.8, 24.1, 25.1, 26.9, 29.0–30.1, 34.5, 60.2, 62.3, 70.1, 72.7, 76.7, 107.8, 127.8, 129.9, 133.3, 135.7, 145.0, 173.2.

2-Hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenyl glycerol (7): Bu_4NF (0.5 mL of 1.0 M THF solution) was added at −20 °C to a solution of **6** (135 mg, 0.17 mmol) and imidazole (40 mg) in 2 mL THF. After 2 h, the cold reaction mixture was quickly filtered through a silica gel plug (prewashed with −20 °C ether) and the plug washed with cold ether/hexane (1:1). After the solvent was evaporated, the residue was separated by silica gel column chromatography with ether/hexane (1:2) as eluant to give 81.4 mg of **7** in 86% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, 6H), 1.26 (m, 48H), 1.63 (m, 2H), 1.87 (t, 1H), 2.04 (m, 2H), 2.35 (t, 2H), 3.83 (m, 2H), 3.89 (d, 2H), 4.39 (m, 1H), 5.04 (m, 1H), 5.91 (dt, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): 14.2, 22.8, 25.1, 29.0–30.0, 32.0, 34.5, 62.2, 70.3, 73.1, 108.4, 144.6, 173.7.

2-Hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenyl-*sn*-glycero-3-phosphocholine (8): A precooled solution of pyridine (22 mg, 0.28 mmol) and 2-chloro-2-oxo-1,3,2-dioxaphospholane (34 mg, 0.24 mmol) in 2 mL benzene was added to a solution of 7 (110 mg, 0.20 mmol) in 2 mL dry benzene that had been cooled to 5 °C. After stirring at 5 °C for 24 h, the reaction mixture was filtered through Celite to remove the precipitate generated and the solvent removed by evaporation. The residue was further dried by evaporation under a 1 micron vacuum for 1 h prior to being transferred to a pressure bottle that was then charged with dry acetonitrile (5 mL) and dry trimethylamine (2 mL). The reaction mixture was then stirred at 70 °C for 48 h. The product was isolated by freezing the reaction mixture at −20 °C and filtering the resulting precipitate prior to purification on a silica gel column with a $CHCl_3$/MeOH gradient elution to give 75.4 mg of plasmenylcholine **8** in 53% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.86 (t, 6H), 1.23 (m, 48H), 1.57 (m, 2H), 1.97 (m, 2H), 2.26 (t, 2H), 3.33 (t, 9H), 3.60–4.40 (m, 10H), 5.14 (m, 1H), 5.88 (d, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.2, 22.8, 24.1, 25.1, 29.3–30.2, 32.0, 34.5, 54.5, 59.3, 63.4, 66.7, 70.6, 71.9, 107.7, 144.9, 173.4; MS (CI): 718 [*M* + 1].

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