Synthesis of Plasmalogen via 2,3-Bis-*O*-(4′-methoxybenzyl)-*sn*-glycerol

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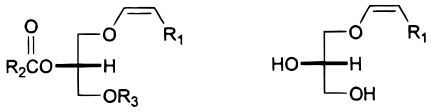
Abstract: The synthesis of the *O*-vinyl ether phospholipid plasmalogen **1** from 2,3-bis-*O*-[*p*-methoxybenzyl (PMB)]-*sn*-glycerol (**13**) is described. Treatment of **13** with potassium hydride, trichloroethylene, and *n*-butyllithium gave a 1-*O*-alkynyl glycerol derivative, which was alkylated with 1-iodohexadecane to afford the long-chain *O*-alkynyl ether **14**. The latter was quantitatively converted to *cis*-enol ether **15** (*Z*/*E* ratio between 35:1 and 100:1) with Lindlar catalyst in hexane/EtOAc 1:1 containing quinoline. The PMB groups of **15** were removed by Birch reduction (Na, NH_3), giving 1-*O*-[1′-(*Z*)-octadecenyl]-*sn*-glycerol (**2**) in 95% yield. Regioselective silylation of **2** followed by palmitoylation provided 1-*O*-[1′-(*Z*)-octadecenyl]-2-*O*-palmitoyl-3-(*tert*-butyldiphenylsilyl)-*sn*-glycerol (**17**). Desilylation with Bu_4NF/imidazole at −23 °C followed by phosphocholine insertion (using 2-chloro-2-oxo-1,3,2-dioxaphospholane with 2 equiv of pyridine in benzene at 4 °C and then trimethylamine in benzene/MeCN 1:3 at 70 °C) completes the synthesis of plasmalogen (**1**).

Introduction

Plasmalogens (**1**) are phospholipids that contain a *cis*-*O*-vinyl ether group at the *sn*-1 position of the glycerol backbone, an *O*-acyl group at the *sn*-2 position, and a phosphocholine or phosphoethanolamine group at the *sn*-3 position. They are widely distributed in mammalian cell membranes[1] and are the predominant phospholipids in membranes of the heart[2] and brain.[3] Although their specific physiological roles in cellular functions have not yet been fully established, it is well known that several properties of plasmalogens differ from those of other phospholipids. Plasmalogen phosphoethanolamines that contain an arachidonoyl group at the *sn*-2 position are prone (a) to form an inverted hexagonal phase, which promotes fusion of membrane bilayers,[4] and (b) to undergo rapid production of arachidonic acid and other lipid second messengers (eicosanoids, platelet-activating factor, and lysophosphatidic acid) upon activation of a plasmalogen-selective phospholipase A_2, especially under pathological conditions.[5] In several disease states,



1 **2**

$R_1 = C_{16}H_{33}$; $R_2 = C_{15}H_{31}$; $R_3 = P(O)(O^-)-O(CH_2)_2N^+Me_3$

the normal level of plasmalogen phosphoethanolamines is decreased, e.g., in the brain in Niemann−Pick-type C disease[6] and Alzheimer's disease,[7] and may be associated with membrane destabilization[7] and impaired secretion of amyloid precursor protein.[8] On the other hand, since the enol ether linkage is susceptible to oxidation, plasmalogens have a different pathway of oxidative degradation compared with other phospholipids. Thus, they may protect endothelial cells and plasma lipoproteins by scavenging peroxyl radicals and other reactive oxygen species,[9] thereby inhibiting initiation of atherosclerosis. Plasmalogen has also been proposed to have an important function in the processes of membrane fusion (such as exocytosis and endocytosis)[4] and high-density lipoprotein (HDL) mediated efflux of cholesterol from cells.[10]

Previous efforts[11] to achieve a chemical synthesis of plasmalogens focused on preparation of 1-*O*-[1′-(*Z*)-alkenylglycerol]

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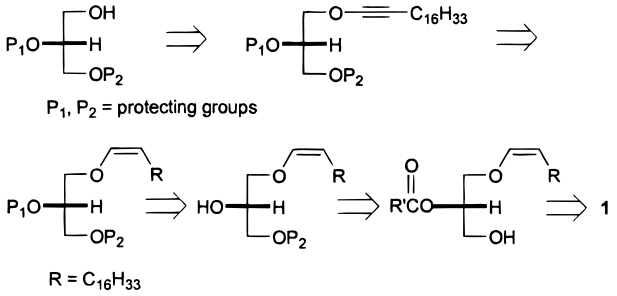
Scheme 1. Outline of the Synthetic Plan



2. The principal challenges in the preparation of **2** arise from its lability, since it is unstable to Lewis acids and oxidative reagents, and from the difficulty in generating the (*Z*)-*O*-alkenyl functionality stereoselectively. Thus many protecting groups commonly used in lipid chemistry to carry out acylation and phosphorylation cannot be manipulated without disturbing the *cis*-enol ether linkage. Obviously, basic conditions are required to accomplish the synthetic steps remaining after installation of the vinyl ether moiety; however, strongly basic conditions cannot be employed when the phosphocholine polar headgroup is present during the preparation of **1**, since phosphocholine is a good leaving group.

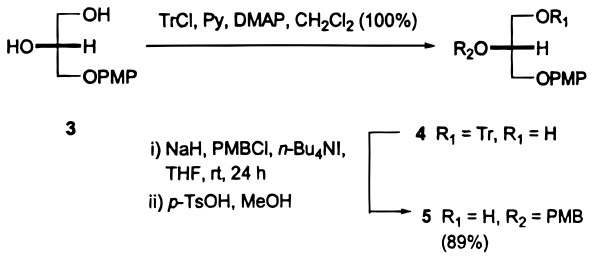
Synthesis of a *cis*-vinyl ether linkage has presented considerable difficulty. Base-mediated dehydrohalogenation of various halo ethers gave mixtures of (*E*) and (*Z*) derivatives of **2** together with 2′-alkenyl byproducts.[12] Alkylidenation of an ester has been reported to provide *Z*-alkenyl ethers[13] but was not successful when long-chain 1,1-dibromides were used.[14] Enolization of an ester, followed by Birch reduction of the α-alkoxy enol phosphate or triethylaluminum/tetrakis(triphenylphosphine)palladium-mediated hydrogenolysis,[15a] gave alkenyl diol **2** in 37% overall yield;[14,15b] the latter was subsequently converted into **1**.[15b]

We present herein an efficient total synthesis of plasmalogen (**1**) that utilizes commercially available 1,2-isopropylidene-*sn*-glycerol as the starting material and proceeds via diol **2,** with excellent stereoselectivity, in 6 steps and 60% overall yield. A key precursor to **2** is 2,3-bis-*O*-PMB-*sn*-glycerol (**13**), which to our knowledge has not been used previously as a synthon in lipid chemistry. After introduction of the *cis*-*O*-vinyl ether linkage at the *sn*-1 position, the PMB groups were removed to give diol **2**, which was converted to plasmalogen (**1**).

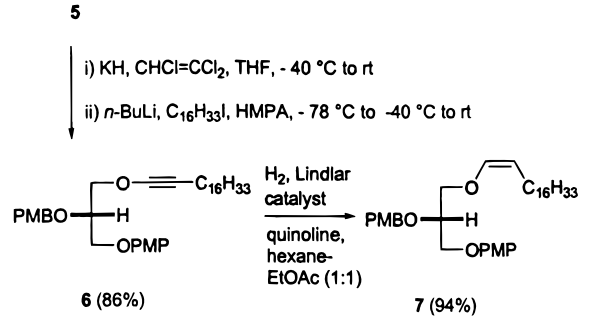
Results and Discussion

Synthetic Plan. Our approach to **1**, outlined in Scheme 1, entails cis *O*-alkenation of a 2,3-di-*O*-protected *sn*-glycerol followed by deprotection and selective introduction of the requisite 2-*O*-acyl and 3-*O*-phosphocholine moieties. Our initial route to **1** (Scheme 2) was to generate 2-*O*-[(*p*-methoxybenzyl (PMB)]-3-*O*-[(*p*-methoxyphenyl (PMP)]-*sn*-glycerol (**5**), install the *cis*-vinyl ether moiety, and then selectively remove the PMB and PMP protecting groups stepwise with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and ceric ammonium nitrate (CAN), respectively. As discussed below (Schemes 2−4), the configuration of the enol ether could not be maintained when CAN was used to remove the PMP group. The synthesis was completed, therefore, using *cis*-*O*-alkenyl diol **2**, which was generated from the bis-*O*-PMB-protected glycerol **13** (Schemes 5 and 6).

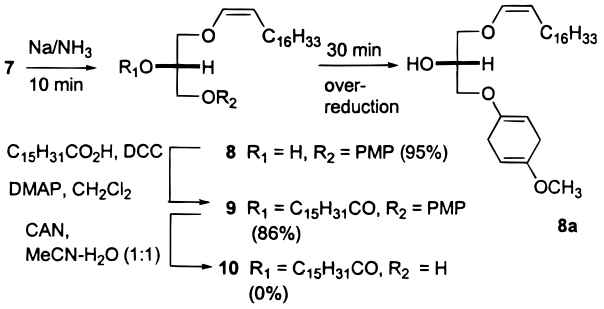
Scheme 2. Synthesis of 2-*O*-PMB-3-*O*-PMP-*sn*-Glycerol (5) from 3-*O*-PMP-*sn*-Glycerol (**3**)



Scheme 3. Synthesis of Enol Ether **7** by Partial Hydrogenation of Acetylenic Ether **6**



Scheme 4. Deprotection of the PMB Group of **7** by Birch Reduction and Decomposition of Enol *O*-PMP **9** by CAN



The protection strategy leading to glycerol **5** started with highly enantioenriched 3-*O*-PMP-*sn*-glycerol **3**[16] and was accomplished by the sequence of reactions shown in Scheme 2: (1) selective protection of the primary alcohol with a trityl group, (2) introduction of the PMB group at the *sn*-2 position, and (3) detritylation. Tritylation of glycerol **3** with trityl chloride and pyridine in methylene chloride in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) gave 1-*O*-trityl ether **4** in quantitative yield. Treatment of **4** with NaH, *p*-methoxybenzyl chloride (PMBCl), and *n*-Bu_4NI in THF followed by detritylation furnished protected glycerol **5** in 89% yield. An alternative route to **5** involved blocking of the primary hydroxy group of **3** as a *tert*-butyldiphenylsilyl ether. This route was abandoned, however, when substantial silyl group migration

(12) For dehydrohalogenation of 1′- or 2′-halo-1-alkoxy glyceryl ethers and dehalogenation of 1′,2′-dichloroalkoxy glyceryl ethers (principally glycerol 1,2-cyclic carbonates), see: (a) Chebyshev, A. V.; Serebrennikova, G. A.; Evstigneeva, R. P. *Zh. Org. Khim.* **1977**, *13*, 703−709; *Chem. Abstr.* **1977**, *87*, 38790s. (b) Chebyshev, A. V.; Serebrennikova, G. A.; Evstigneeva, R. P. *Bioorg. Khim.* **1977**, *3*, 1362−1369; *Chem. Abstr.* **1977**, *88*, 37184f. (c) Titov, V. I.; Serebrennikov, G. A.; Preobrazhenskii, N. A. *Zh. Org. Khim.* **1970**, *6*, 1154−1159; *Chem. Abstr.* **1970**, *73*, 65983z. (d) Pfaendler, H. R.; Müller, F. X. *Synthesis* **1992**, 350−352.

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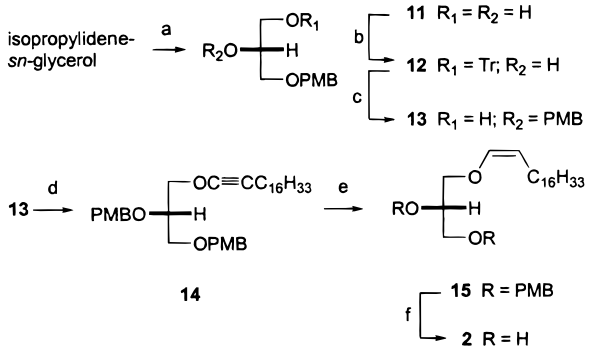
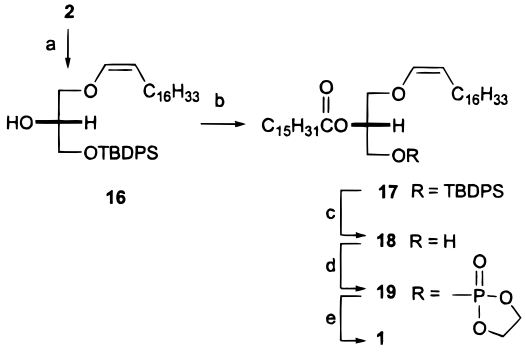
Scheme 5. Synthesis of 1-*O*-[1′-(*Z*)-Octadecenyl]-*sn*-Glycerol (**2**) via 2,3-Bis-*O*-PMB-glycerol **13**[a]



[a] Reagents: (a) i. KH, PMBCl, Bu_4NI, THF, rt, 2 h; ii. *p*-TsOH, MeOH, rt (98% overall); (b) TrCl, py, DMAP, CH_2Cl_2, rt (100%); (c) i. NaH, PMBCl, Bu_4NI, THF, rt; ii. *p*-TsOH, MeOH (97% overall); (d) i. KH, $CHCl{=}CCl_2$, THF, −42 °C to room temperature; ii. *n*-BuLi, $C_{16}H_{33}I$, HMPA, −78 to −42 °C to room temperature (67%); (e) H_2/Lindlar catalyst, quinoline, hexane/EtOAc 1:1, 2 h (100%); (f) Na/NH_3, THF, −78 °C to room temperature (95%).

Scheme 6. Synthesis of Plasmalogen (**1**) from Diol **2**[a]



[a] Reagents: (a) TBDPSCl (1.2 equiv), Im (2 equiv), DMF, 0 °C to room temperature (90%); (b) $(C_{15}H_{31}CO)_2O$, DMAP, $CHCl_3$, rt (98%); (c) Im (3.5 equiv), TBAF (3 equiv), THF, −23 °C, 1 h; (d) 2-chloro-2-oxo-1,3,2-dioxaphospholane, py (2 equiv), benzene, 4 °C; (e) NMe_3, MeCN/C_6H_6 (3:1), 70 °C, 24 h (74% in 3 steps).

was detected during the base-mediated PMB protection of the 2-hydroxy group (using NaH and PMBCl in benzene).

Synthesis of Enol Ether 7 by Partial Hydrogenation of Alkynyl Ether 6. An early report that a 1-*O*-alkynyl linkage could be introduced by reaction of an alkoxide ion with a 1-bromoalkyne[17] was found to be in error: an allenic ether was formed instead.[18] The method of Greene et al. for preparation of short-chain acetylenic ethers[19] was successful. Thus successive treatment of glycerol **5** with KH, trichloroethylene, *n*-BuLi, and $C_{16}H_{33}I$ provided 1-*O*-alkynyl ether **6** in 86% yield (Scheme 3).

Partial reduction of alkynyl ether **6** with Red-Al and $NaAlH_4$ failed; in fact, no hydrogenation was observed. Although partial hydrogenation of *O*-alkynyl ethers using Lindlar catalyst was reported to be unsuccessful,[20] we found that alkyne **6** was quantitatively converted to *cis*-enol ether **7** with Lindlar catalyst (Scheme 3). As shown in Table 1, the *Z*/*E* ratio was enhanced when the solvent was changed from MeOH (*Z*/*E* ratio, 10:1) to hexane/EtOAc 1:1 (*Z*/*E* ratio, 25:1). On addition of quinoline,[21] not only did the hydrogenation reaction proceed more slowly but also the stereoselectivity was improved, since the *Z*/*E* ratio increased to 86:1 in hexanes/EtOAc 1:1.

Table 1. Effects of Solvent and Quinoline on the Partial Hydrogenation of Alkynyl Ether **6** with Lindlar Catalyst[a]

solvent	quinoline (μL)	reaction time (h)	*Z*/*E* ratio of **7**	yield of **7** (%)
MeOH		0	10:1	95
EtOAc/hexane 1:1	0	3	25:1	95
EtOAc/hexane 1:1	20	6	35:1	94
EtOAc/hexane 1:1	50	24	86:1	94

[a] Reaction conditions: solvent volume, 10 mL; *O*-alkynyl ether **6**, 100 mg (0.18 mmol); Lindlar catalyst, 20 mg.

Deprotection of PMB and PMP Groups from Alkenyl Ether 7. Oxidative deprotection of the PMB group from alkenyl ether **7** was attempted with DDQ.[22] However, not only was the PMB group oxidized but some of the enol ether was also destroyed, even when the reaction was carried out at −78 °C in wet methylene chloride. On the other hand, Birch reduction successfully removed the PMB group from **7**, particularly when sodium metal was employed (Scheme 4). The reaction could be finished within 10 min to give alcohol **8** without cleavage of the enol ether and without affecting the PMP group. However, when a longer reaction time was applied, the PMP group was also reduced to give 4-methoxycyclohexa-1,4-dienyl derivative **8a**. Careful timing of the reaction avoids the over-reduction. When lithium was used as the metal in the Birch reduction, it was almost impossible to control the reaction time in order to avoid reduction of the PMP group. Furthermore, isomerization of the enol was observed; the *Z*/*E* ratio was reduced from 30:1 to 4:1.

Alcohol **8** was converted into ester **9** in 86% yield by reaction with palmitic acid in the presence of DCC and catalytic DMAP[23] in methylene chloride. On the basis of the precedent that acyl group migration from a secondary to a primary position was not observed during deprotection of the PMP group by CAN,[24] reaction of ester **9** with CAN in MeCN/H_2O 4:1 at 0 °C was tried. However, enol ether **9** was totally destroyed in the course of PMP deprotection, and the desired alcohol **10** was not formed. Therefore, the key intermediate **2** was assembled by the sequence of steps outlined in Scheme 5.

Synthesis of 1-*O*-(*Z*)-Octadecenyl-*sn*-glycerol 2. Since the PMP group could not be removed without cleaving the enol ether, a PMB group was used to protect the hydroxyl group at the *sn*-3 position as well. Diol **2** was prepared with excellent stereoselectivity in 6 steps and 60% overall yield starting from 1,2-isopropylidene-*sn*-glycerol (Scheme 5). A key precursor for **2** is 2,3-bis-*O*-PMB-*sn*-glycerol **13**, which to our knowledge has not been used previously as a synthon in lipid chemistry. Treatment of 1,2-*O*-isopropylidene-*sn*-glycerol with KH and PMBCl in THF followed by deacetonation with *p*-toluenesulfonic acid (*p*-TsOH) in MeOH gave 3-*O*-PMB-*sn*-glycerol (**11**) in 98% yield. *O*-Alkenyl ether bis-*O*-PMB-glycerol **15** was

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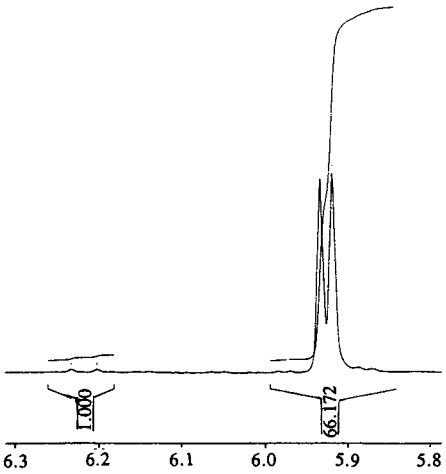

Figure 1. The *E*/*Z* ratio was determined by integration of the ^{1}H NMR spectrum of **15** on an expanded scale.

prepared by the same steps used in the synthesis of enol ether **7**. Reaction of alcohol **13** with KH, trichloroethylene, *n*-BuLi, and $C_{16}H_{33}I$ provided *O*-alkynyl ether **14** in 67% yield. Enol ether **15** was obtained in quantitative yield and with high stereoselectivity by partial hydrogenation with Lindlar catalyst. As with the reduction of **6** to **7**, the *Z*/*E* ratio was affected by the solvent used (*Z*/*E* ratio: in MeOH, 9:1; in hexane/EtOAc 1:1, 20:1). Addition of quinoline in hexane/EtOAc 1:1 raised the *Z*/*E* ratio to 66:1 (Figure 1).[25] The individual stereotopic *O*-vinylic protons in the cis and trans isomers of **15** show baseline separation. The higher field doublet (δ 5.9, $J = 6.2$ Hz) is assigned to the cis *O*-vinylic proton, and the lower field doublet (δ 6.2, $J = 12.6$ Hz) corresponds to the trans *O*-vinylic proton.

When oxidative cleavage of the PMB groups of alkenyl glycerol **15** (using DDQ or CAN) again produced mixtures, we applied Birch reduction to unmask the *sn*-2 and *sn*-3 hydroxy groups. Again, with lithium, isomerization of the enol double bond was observed (reduction in *Z*/*E* ratio from ~100:1 to 50:1). However, when sodium was used, there was no isomerization, even under extended reaction time (20 h), and 1-*O*-[1′-(*Z*)-octadecenyl)]-*sn*-glycerol (**2**) was obtained in 95% yield.

Synthesis of Plasmalogen (1). In the final stage of the synthesis of **1**, an acyl chain (palmitoyl) and a phosphocholine headgroup were introduced at the *sn*-2 and *sn*-3 positions, respectively.[26] As outlined in Scheme 6, protection of the primary hydroxy group of **2** as a *tert*-butyldiphenylsilyl ether gave silyl ether **16** in 90% yield. Isomerization of **16** to a ~1:1 mixture of **16a**/**16b** during contact with unneutralized $CDCl_3$ for several hours at room temperature was noted by ^{1}H NMR (Figure 2). Isomerization was avoided by pretreating $CDCl_3$ with potassium carbonate. Esterification of **16** with palmitic anhydride and DMAP in alcohol-free $CHCl_3$ at room temperature[23] gave ester **17** quantitatively.[27] Desilylation of **17** with Bu_4NF (TBAF) in the presence of the mild base imidazole (Im) at −23 °C gave

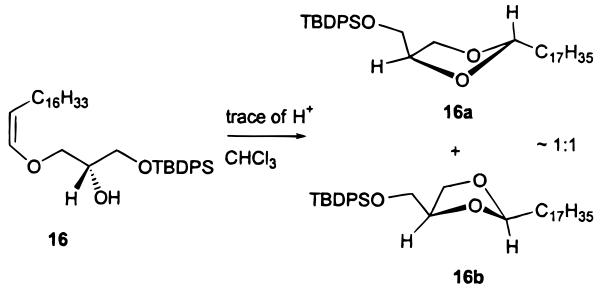

Figure 2. Isomerization of **16** by a trace of acid in chloroform.

1-*O*-(1′-(*Z*)-octadecenyl)-2-*O*-palmitoyl-*sn*-glycerol (**18**). Without addition of imidazole, substantial migration of the palmitoyl group from the *sn*-2 to the *sn*-3 position took place on desilylation. Prompt reaction of alcohol **18** with 2-chloro-2-oxo-1,3,2-dioxaphospholane[28] at 4 °C in benzene in the presence of pyridine afforded phospholane **19** and avoided acyl migration, as judged by the ^{1}H NMR signal of the *sn*-2 proton, δ 5.1 (m), and by the absence of a signal at δ 4.5 (m), which corresponds to the *sn*-2 proton in the migration product. Opening of the phospholane ring of **19** with anhydrous trimethylamine in benzene/MeCN 1:3 at 70 °C gave plasmalogen (**1**) in 74% overall yield from enol ether **16**.[29]

Conclusions

A 1-*O*-alkynyl moiety was introduced at the *sn*-1 position of 2,3-protected glycerol derivatives. Partial hydrogenation of *O*-alkynyl ether **14** with Lindlar catalyst in EtOAc/hexane 1:1 in the presence of quinoline provided cis *O*-alkenyl ether **15** almost exclusively. The PMB group of protected glycerol **7** was removed selectively by Birch reduction without affecting the PMP group. During dissolving metal reduction the configuration of the enol ether in glycerol derivatives **7** and **15** was not affected when sodium in ammonia was used, whereas with lithium in ammonia the *Z*/*E* ratio of the enol was decreased. Ring opening of phospholane **19** by NMe_3 in MeCN/benzene 3:1 gave **1** in moderate yield. This synthesis makes it possible to prepare chiral plasmalogen derivatives with different chain lengths and degrees of unsaturation.

Experimental Section

General Procedures. All reactions were carried out under dry argon atmosphere. Flash chromatography was carried out with Merck silica gel 60 (230−400 ASTM mesh). TLC was carried out using Merck $60F_{254}$ (0.25-mm thick) sheets. THF was distilled from Na and benzophenone before use. Benzene, CH_2Cl_2, and DMF were distilled from CaH_2. MeCN and $CHCl_3$ were distilled from P_2O_5. Pyridine was dried over NaOH pellets. 2-Chloro-2-oxo-1,3,2-dioxaphospholane was purchased from Fluka. NMR spectra were recorded on a Bruker spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Low- and high-resolution FAB mass spectra were recorded at the Michigan State University Mass Spectrometry Facility.

1-*O*-(Triphenylmethyl)-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (4). To a solution of 3.00 g (15.1 mmol) of PMP-*sn*-glycerol (**3**), 2.0 mL (24.7 mmol) of pyridine, and 0.18 g (1.50 mmol) of DMAP in 50 mL of CH_2Cl_2 was added 5.49 g (19.7 mmol) of Ph_3CCl at room temperature. After the mixture was stirred overnight, it was diluted

(25) The *Z*/*E* ratio is highly sensitive to the concentrations of substrate and catalyst. This ratio was obtained by using 1.0 g (1.72 mmol) of **14**, 100 mg of Lindlar catalyst, and 50 μL of quinoline in 30 mL of hexane/EtOAc 1:1; reaction time, 2 h. It should be noted that *Z*/*E* ratios higher than 66:1 were obtained when shorter reaction times were used. Under these conditions, however, unreacted alkyne was sometimes present, and when the reaction mixture was subjected to another cycle of Lindlar reduction, the *Z*/*E* ratio of **15** was reduced.

(26) Direct introduction of a phosphocholine group at the *sn*-3 position of diol **2** could not be achieved without obtaining a substantial amount of byproduct from reaction at the *sn*-2 hydroxy group. However, for selective phosphitylation of other glycerol diol derivatives, see: (a) Erukulla, R. K.; Byun, H.-S.; Bittman, R. *Tetrahedron Lett.* **1994**, *35*, 5783−5784. (b) Byun, H.-S.; Erukulla, R. K.; Bittman, R. *J. Org. Chem.* **1994**, *59*, 6495−6498.

(27) The yield of palmitoylation using palmitoyl chloride and pyridine was lower (85%), probably because the pyridinium chloride formed during the reaction caused some decomposition of enol ether **16**.

(28) For reviews about the use of this cyclic phosphochloridate for phosphorylation of glycerol derivatives, see: (a) Reference 23b. (b) Bittman, R. In *Lipid Synthesis and Manufacture*; Gunstone, F. D., Ed.; Sheffield Academic Press: Sheffield, U. K.; CRC Press: Boca Raton, FL, 1998; pp 185−207.

(29) When MeCN was the sole solvent, the yield was 53%.[15b]

with EtOAc and washed with aqueous 10% $NaHSO_4$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The product was purified by column chromatography, eluting with hexanes/EtOAc 5:1 to give 6.61 g (100%) of 1-*O*-trityl glycerol **4** as a sticky liquid: $[\alpha]^{25}_D$ −2.96° (*c* 5.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.42−7.44 (m, 6H), 7.18−7.31 (m, 9H), 6.82 (s, 4H), 4.09−4.15 (m, 1H), 3.95−4.05 (m, 2H), 3.77 (s, 3H), 3.32−3.34 (m, 2H), 2.45 (d, J = 5.12 Hz, 1H); ^{13}C NMR δ 154.02, 152.65, 143.71, 128.63, 127.88, 127.12, 115.52, 114.60, 86.79, 69.73, 69.55, 64.23, 55.72.

2-*O*-(4′-Methoxybenzyl)-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (5). To a suspension of 0.55 g (19.5 mmol, 80% in white oil, washed twice with dry hexane) of NaH in 100 mL of THF was added 5.42 g (12.3 mmol) of *O*-trityl glycerol **4** at 0 °C. After the evolution of hydrogen had stopped, 2.2 mL (16.2 mmol) of PMBCl and 0.37 g (1.0 mmol) of *n*-Bu_4NI were added, and the reaction mixture was stirred for 24 h at room temperature. After the excess amount of NaH was destroyed by addition of 1 mL of MeOH, the reaction mixture was poured into 100 mL of water, acidified with 3 N HCl, and stirred for 1 h. The product was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to give a residue that was purified by column chromatography, eluting with hexanes/EtOAc 4:1 to give 3.52 g (89%) of PMB-glycerol **5** as a yellow oil: $[\alpha]^{25}_D$ +22.2° (*c* 4.67, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 8.52 Hz, 2H), 6.89 (d, J = 8.52 Hz, 2H), 6.83 (s, 4H), 4.66 (ABq, J = 11.36 Hz, $\Delta\nu$ = 39.62 Hz, 2H), 4.05−3.99 (m, 2H), 3.63−3.88 (m, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 1.98 (br s, 1H); ^{13}C NMR δ 159.41, 154.02, 152.72, 130.12, 129.59, 115.46, 114.64, 113.94, 72.14, 68.25, 62.54, 55.74, 55.30.

1-*O*-(1′-Octadecynyl)-2-*O*-(4′-methoxybenzyl)-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (6). To a suspension of 2.10 g (17.6 mmol, 35 wt % dispersion in mineral oil, washed with dry hexane twice) of KH in 50 mL of THF was added 2.80 g (8.8 mmol) of **5** at 0 °C. After the evolution of hydrogen stopped, the reaction mixture was cooled to −40 °C, treated with 790 μL (8.8 mmol) of trichloroethylene, and allowed to warm to room temperature. After 1 h the brown reaction mixture was treated dropwise with 7.1 mL (17.8 mmol, 2.5 M in hexane) of *n*-butyllithium at −78 °C. After 0.5 h the mixture was warmed to −40 °C, and 4.05 g (11.5 mmol) of 1-iodohexadecane and 50 mL of HMPA were added. After the mixture was stirred for 24 h at room temperature, the reaction was quenched by addition of 1 mL of MeOH. The mixture was poured into saturated aqueous NH_4Cl solution. The product was extracted with Et_2O and purified by column chromatography, eluting with hexanes/EtOAc 50:1 containing 2.5% of Et_3N by volume, to give 4.29 g (86%) of *O*-alkynyl ether **6** as a colorless oil: $[\alpha]^{25}_D$ +3.88° (*c* 5.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30 (d, J = 8.48 Hz, 2H), 6.88 (d, J = 8.48 Hz, 2H), 6.81 (s, 4H), 4.67 (ABq, J = 11.40 Hz, $\Delta\nu$ = 17.80 Hz, 2H), 4.19 (ABq, J = 4.22 Hz, $\Delta\nu$ = 9.70 Hz, 2H), 4.02−4.07 (m, 1H), 3.98−4.00 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 2.08 (t, J = 6.9 Hz, 2H), 1.39−1.46 (m, 2H), 1.25 (s, 26H), 0.88 (t, J = 6.70 Hz, 3H); ^{13}C NMR δ 159.36, 154.06, 152.61, 129.95, 129.62, 115.51, 114.60, 113.82, 89.53, 77.55, 72.37, 67.66, 55.70, 55.27, 37.48, 31.94, 29.71, 29.63, 29.50, 29.38, 29.24, 28.90, 22.70, 17.14, 14.14.

1-*O*-[1′-(*Z*)-(Octadecenyl)]-2-*O*-(4′-methoxybenzyl)-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (7). To a solution of 300 mg (0.53 mmol) of **6** in 9 mL of hexane/EtOAc 1:1 were added 60 mg of Lindlar catalyst and 50 μL (0.45 mmol) of quinoline. The resulting suspension was degassed by H_2, and then a H_2 balloon was applied. The reaction mixture was stirred for 24 h. The solution was concentrated to give a light yellow residue that was purified by flash chromatography (elution with hexane/EtOAc 20:1 containing 2.5% of Et_3N by volume) to provide 284 mg (94%) of **7** as a colorless oil: $[\alpha]^{25}_D$ +5.79° (*c* 2.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 8.56 Hz, 2H), 6.87 (d, J = 8.68 Hz, 2H), 6.82 (s, 4H), 5.96 (d, J = 6.20 Hz, 1H), 4.66 (ABq, J = 11.62 Hz, $\Delta\nu$ = 5.85 Hz, 2H), 4.34−4.39 (m, 1H), 3.85−4.06 (m, 5H), 3.80 (s, 3H), 3.76 (s, 1H), 2.07 (m, 2H), 1.25 (s, 28H), 0.88 (t, J = 6.78 Hz, 3H); ^{13}C NMR δ 159.28, 153.96, 152.82, 145.02, 130.33, 129.48, 115.50, 114.79, 113.78, 107.43, 75.87, 72.29, 71.97, 68.28, 55.69, 55.25, 31.94, 29.72, 29.68, 29.53, 29.50, 29.38, 29.09, 24.01, 22.70, 14.14; FAB HRMS (M^+) calcd for $C_{36}H_{56}O_5$ 568.4128, found 568.4133.

1-*O*-(1′-(*Z*)-Octadecenyl)-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (8). To a solution of NH_3 (10 mL) and dry Et_2O (3 mL) was added 15 mg (0.654 mmol) of sodium at −78 °C. The solution was stirred until a blue color persisted. A solution of 62 mg (0.11 mmol) of **7** in 4 mL of dry Et_2O was added. After the mixture was stirred for 15 min, the reaction was quenched by addition of wet MeOH. The solution was poured into a separatory funnel and washed with H_2O (3 × 20 mL) without shaking. The ether layer was dried over Na_2SO_4. Evaporation of the solvent gave a white solid that was purified by preparative TLC to give 50 mg (95%) of **8** as a white solid: mp 41.5−42.0 °C; $[\alpha]^{25}_D$ −3.2° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.76−6.87 (m, 4H), 5.98 and 5.96 (dt, J = 6.12 Hz, J = 1.34 Hz, 1H), 4.40 (m, 1H), 4.41 and 4.39 (dt, J = 6.36 Hz, J = 7.24 Hz, 1H), 4.16−4.19 (m, 1H), 4.39−4.04 (m, 2H), 3.86−3.96 (m, 2H), 3.77 (s, 3H), 2.49 (d, J = 13.08 Hz, 1H), 2.00−2.06 (m, 2H), 1.25 (s, 28H), 0.88 (t, J = 6.52 Hz, 3H); ^{13}C NMR δ 154.18, 152.63, 144.68, 115.58, 114.70, 108.24, 72.61, 69.38, 69.22, 55.73, 31.96, 29.74, 29.71, 29.58, 29.40, 29.35, 24.84, 23.98, 22.73, 14.17.

1-*O*-[1′-(*Z*)-Octadecenyl)]-2-*O*-palmitoyl-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (9). A mixture of 42 mg (0.0938 mmol) of **8**, 58 mg (0.28 mmol) of DCC, 48 mg (0.19 mmol) of palmitic acid, and 5.7 mg (0.047 mmol) of DMAP in 4 mL of dry CH_2Cl_2 was stirred for 3 h at room temperature. The mixture was filtered through a pad of Celite. After the filtrate was concentrated, the residue was purified by preparative TLC (developed with hexane/EtOAc 20:1) to give 55 mg (86%) of **9** as a white solid: mp 54.0−54.6 °C; $[\alpha]^{25}_D$ +4.48° (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.80−6.86 (m, 4H), 5.92 and 5.94 (dt, J = 6.12 Hz, J = 1.58 Hz, 1H), 5.27−5.34 (m, 1H), 4.35−4.40 (m, 1H), 4.11 (ABq, J = 4.82 Hz, $\Delta\nu$ = 9.22 Hz, 1H), 4.07 (ABq, J = 5.21 Hz, $\Delta\nu$ = 8.89 Hz, 1H), 3.93−4.00 (m, 2H), 3.76 (s, 3H), 2.34 (t, J = 7.50 Hz, 2H), 2.04−2.09 (m, 2H), 1.59−1.66 (m, 2H), 1.25 (s, 52H), 0.88 (t, J = 6.52 Hz, 6H); ^{13}C NMR δ 173.23, 154.17, 152.64, 144.72, 115.69, 114.62, 108.12, 70.74, 70.00, 66.88, 55.68, 34.36, 31.95, 29.74, 29.69, 29.65, 29.59, 29.50, 29.39, 29.35, 29.31, 29.11, 24.95, 23.92, 22.71, 14.14.

3-*O*-(4′-Methoxybenzyl)-*sn*-glycerol (11). To a solution of (*S*)-isopropylideneglycerol (10.0 g, 75.66 mmol) in 300 mL of THF was added KH (3.64 g, 90.8 mmol) in portions over a 10-min period. The solution was stirred until the evolution of H_2 gas stopped. After 13.0 g (9.24 mmol) of PMBCl and 1.0 g (2.7 mmol) of *n*-Bu_4NI were added, the solution was stirred for 4 h. Methanol was added to destroy excess KH, and the solution was washed with saturated aqueous NH_4Cl solution and water. Evaporation of the solvent gave a residue that was redissolved in MeOH. The solution was treated with *p*-TsOH for 2 h at room temperature. After the solution was neutralized with NH_4OH, the solvent was evaporated and the residue was purified by flash chromatography (elution with hexane/EtOAc 2:1) to give 15.7 g (98%) of PMB diol **11** as a white solid: mp 42.5−43.5 °C [lit.[30] mp 43.5−45.5 °C; lit.[31] mp 40−41 °C]; $[\alpha]^{25}_D$ −2.21° (*c* 1.00, $CHCl_3$) [lit.[30] $[\alpha]_D$ −1.54° (*c* 3.7, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 8.57 Hz, 2H), 6.89 (d, J = 8.58 Hz, 2H), 4.48 (s, 2H), 3.84−3.90 (m, 1H), 3.81 (s, 3H), 3.70 (ABq, J = 5.59 Hz, $\Delta\nu$ = 10.74 Hz, 1H), 3.62 (ABq, J = 5.64 Hz, $\Delta\nu$ = 9.78 Hz, 1H), 3.56 (ABq, J = 3.96 Hz, $\Delta\nu$ = 8.77 Hz, 1H), 3.51 (ABq, J = 6.28 Hz, $\Delta\nu$ = 7.30 Hz, 1H), 2.70 (br s, 1H), 2.17 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 159.39, 129.72, 129.48, 113.90, 73.26, 71.52, 70.56, 64.11, 55.29; EI HRMS calcd for $C_{11}H_{16}O_4$ (M^+) *m*/*z* 212.1049, found 212.1052.

1-*O*-(Triphenylmethyl)-3-*O*-(4′-methoxybenzyl)-*sn*-glycerol (12). To a solution of 3.00 g (15.1 mmol) of 3-*O*-PMB-*sn*-glycerol (**11**) and 2.0 mL (24.7 mmol) of pyridine in 50 mL of CH_2Cl_2 were added 5.49 g (19.7 mmol) of Ph_3CCl and 367 mg (2.0 mmol) of DMAP at room temperature. The mixture was stirred overnight at room temperature, diluted with EtOAc, and washed with 10% aqueous $NaHSO_4$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The product was purified by flash chromatography (elution with hexanes/EtOAc 5:1) to give 6.60 g (100%) of 1-*O*-trityl-2-*O*-PMB-glycerol (**12**) as a colorless liquid: $[\alpha]^{25}_D$ −0.65° (*c* 2.50, $CHCl_3$); $[\alpha]^{25}_D$ −0.68° (*c* 4.40, $CHCl_3$/MeOH 1:1); ^{1}H NMR ($CDCl_3$)

(30) DeMedeiros, E. F.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2725−2730.

(31) Hébert, N.; Beck, A.; Lennox, R. B.; Just, G. *J. Org. Chem.* **1992**, *57*, 1777−1783.

δ 7.43 (s, 3H), 7.41 (s, 3H), 7.25−7.29 (m, 6H), 7.18−7.23 (m, 5H), 6.84 (d, J = 8.45 Hz, 2H), 4.44 (s, 2H), 3.93−4.00 (m, 1H), 3.76 (s, 3H), 3.56 (ABq, J = 4.21 Hz, $\Delta\nu$ = 8.57 Hz, 1H), 3.51 (ABq, J = 6.20 Hz, $\Delta\nu$ = 7.27 Hz, 1H), 3.22 (ABq, J = 5.95 Hz, $\Delta\nu$ = 7.24 Hz, 1H), 3.18 (ABq, J = 5.29 Hz, $\Delta\nu$ = 7.79 Hz, 1H), 2.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 159.19, 143.82, 130.03, 129.32, 128.64, 128.30, 127.80, 127.02, 113.74, 86.59, 72.97, 71.22, 69.87, 64.56, 55.21; FAB HRMS calcd for $C_{30}H_{29}O_4$ $(M - H)^+$ m/z 453.2066, found 453.2050.

2,3-Bis-*O*-(4′-methoxybenzyl)-*sn*-glycerol (13). To a solution of 12.0 g (26.43 mmol) of 1-*O*-trityl-3-*O*-PMB-glycerol (**12**) in 300 mL of THF was added 761 mg (31.7 mmol) of NaH. After the evolution of hydrogen ceased, PMBCl (4.97 g, 31.7 mmol) and *n*-Bu_4NI (975 mg, 2.64 mmol) were added. The solution was stirred at room temperature for 2 h, and MeOH was added to destroy the excess hydride. The solution was diluted with 200 mL of Et_2O and washed with saturated aqueous NH_4Cl solution and water. Evaporation of the solvents under vacuum gave a residue that was dissolved in 50 mL of MeOH. The resulting solution was treated overnight with *p*-TsOH (200 mg, 1.04 mmol) at room temperature. The solution was neutralized with concentrated aqueous NH_4OH solution, and the solvent was evaporated to give a residue that was purified by flash chromatography (elution with hexane/EtOAc 9:1) to give 8.5 g (97%) of 2,3-bis-*O*-PMB-glycerol (**13**) as a colorless oil: $[\alpha]^{25}_D$ +17.31° (*c* 1.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.24−7.27 (m, 4H), 6.86−6.87 (m, 4H), 4.58 (ABq, J = 11.38 Hz, $\Delta\nu$ = 38.89 Hz, 2H), 4.47 (ABq, J = 11.78 Hz, $\Delta\nu$ = 6.78 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.52−3.76 (m, 5H), 2.01 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 159.31, 159.26, 130.34, 130.03, 129.46, 129.32, 113.87, 113.82, 77.60, 73.18, 71.80, 69.90, 62.95, 55.28; FAB HRMS calcd for $C_{19}H_{23}O_5$ $(M - H)^+$ m/z 331.1545, found 331.1550.

1-*O*-(1′-Octadecynyl)-2,3-bis-*O*-(4′-methoxybenzyl)-*sn*-glycerol (14). A solution of 2,3-bis-*O*-PMB-glycerol (**13**) (1.10 g, 3.33 mmol) in 20 mL of THF was treated with KH (268 mg, 6.69 mmol) for 1 h. The reaction mixture was cooled to −42 °C, and trichloroethylene (302 μL, 3.34 mmol) was added. The solution was warmed slowly to room temperature and stirred for 2 h. The resulting dark brown solution was cooled to −78 °C and treated with 3.0 mL (7.0 mmol) of *n*-BuLi (a 2.5 M solution in hexane). The reaction mixture was stirred for 1 h, warmed to −42 °C, and stirred for 1 h. Hexadecyl iodide (1.29 g, 3.65 mmol) and HMPA (5 mL) were added, and the solution was warmed to room temperature and stirred for 4 h. After MeOH was added to destroy excess KH, the mixture was diluted with 100 mL of Et_2O, washed with water (3 × 50 mL), and dried over Na_2SO_4. Evaporation of the solvents under vacuum gave a brown residue that was purified by flash chromatography (elution with hexane/EtOAc 15:1 in the presence of 1% Et_3N by volume) to give 1.30 g (67%) of alkyne **14** as a light yellow oil: $[\alpha]^{25}_D$ +4.80° (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.22−7.28 (m, 4H), 6.84−6.89 (m, 4H), 4.60 (ABq, J = 11.45 Hz, $\Delta\nu$ = 15.74 Hz, 2H), 4.45 (s, 2H), 4.10 (ABq, J = 4.41 Hz, $\Delta\nu$ = 9.85 Hz, 1H), 4.05 (ABq, J = 6.04 Hz, 8.80 Hz, 1H), 3.84−3.90 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.52 (s, 1H), 3.51 (s, 1H), 2.09 (t, J = 7.04 Hz, 2H), 1.40−1.47 (m, 2H), 1.25 (s, 26H), 0.88 (t, J = 6.48 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.25, 130.24, 130.05, 129.48, 129.29, 113.77, 113.75, 89.65, 78.03, 75.25, 73.10, 72.16, 68.90, 55.23, 37.26, 31.94, 29.72, 29.64, 29.38, 29.25, 28.92, 22.71, 17.19, 14.14; FAB HRMS calcd for $C_{37}H_{55}O_5$ $(M - H)^+$ m/z 579.4050, found 579.4052.

1-*O*-(1′-(*Z*)-Octadecenyl)-2,3-bis-*O*-(4′-methoxybenzyl)-*sn*-glycerol (15). A mixture of alkyne **14** (1.00 g, 1.72 mmol), Lindlar catalyst (100 mg), and quinoline (50 μL, 0.42 mmol) in 30 mL of hexane/EtOAc 1:1 was stirred under H_2 at 1 atm for 2 h. The solid was filtered through a silica gel pad, which was washed with hexane/EtOAc 1:1. The filtrate was concentrated to give 1.00 g (100%) of *O*-alkenyl ether **15** as a light yellow oil: $[\alpha]^{25}_D$ +6.70° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.22−7.28 (m, 4H), 6.83−6.87 (m, 4H), 5.92 (d, J = 6.16 Hz, 1H), 4.60 (s, 2H), 4.45 (s, 2H), 4.31−4.36 (m, 1H), 3.86 (ABq, J = 4.42 Hz, $\Delta\nu$ = 9.63 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73−3.82 (m, 2H), 3.49−3.56 (m, 2H), 2.03−2.08 (m, 2H), 1.25 (s, 28H), 0.88 (t, J = 6.44 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.11, 159.09, 145.10, 130.52, 130.17, 129.32, 129.16, 113.65, 113.62, 106.97, 76.58, 72.97, 72.24, 71.96, 69.35, 55.11, 31.87, 29.79, 29.66, 29.61, 29.53, 29.31, 23.93, 23.64, 14.07; FAB HRMS calcd for $C_{37}H_{57}O_5$ $(M - H)^+$ m/z 581.4206, found 581.4208.

1-*O*-(1′-(*Z*)-Octadecenyl)-*sn*-glycerol (2). Twenty milliliters of liquid NH_3 was collected in a three-neck round-bottom flask by using a Dewar trap at −78 °C. Sodium (100 mg, 4.35 mmol) was added, and the solution was stirred for 1 h until it had a stable blue color. A solution of alkenyl ether **15** (1.0 g, 1.72 mmol) in 20 mL of THF was added dropwise over a 3-min period. The reaction mixture was stirred for 2 h and warmed slowly to room temperature. After MeOH was added to destroy the excess Na, the solution was diluted with 100 mL of Et_2O, and water was added slowly to remove NH_3 by separation. The organic layer was dried over Na_2SO_4, and the solvents were removed under vacuum. The residue was purified by flash chromatography (elution with hexane/EtOAc 3:1 with 1% Et_3N by volume) to give 560 mg (95%) of diol **2** as a white solid after lyophilization from benzene: mp 56.0−57.0 °C; $[\alpha]^{25}_D$ −1.65° (*c* 4.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ ∼6.2 (trace of *E* isomer, with an integral of 1/62 of that of the *Z O*-vinyl proton), 5.94 (dt, J = 6.28 Hz, J = 0.97 Hz, 1H), 4.34 (m, 1H), 3.90−3.95 (m, 1H), 3.78−3.81 (m, 2H), 3.75 (ABq, J = 3.68 Hz, $\Delta\nu$ = 10.84 Hz, 1H), 3.65 (ABq, J = 5.56 Hz, $\Delta\nu$ = 10.07 Hz, 1H), 2.51 (br s, 2H), 2.03−2.08 (m, 2H), 1.26 (s, 28H), 0.88 (t, J = 6.51 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.47, 108.30, 73.13, 70.63, 63.58, 31.91, 29.69, 29.65, 29.51, 29.35, 29.29, 23.94, 22.67, 14.10; EI HRMS calcd for $C_{21}H_{42}O_3$ (M^+) m/z 342.3134, found 342.3138.

1-*O*-(1′-(*Z*)-Octadecenyl)-3-*O*-(*tert*-butyldiphenylsilyl)-*sn*-glycerol (16). A solution of imidazole (60 mg, 0.88 mmol) and *tert*-butyldiphenylsilyl chloride (144 mg, 0.53 mmol) in 3 mL of dry DMF was stirred at room temperature for 30 min until a white precipitate formed. The suspension was cooled to 0 °C, and 150 mg (0.44 mmol) of 1-*O*-alkenyl-*sn*-glycerol **2** was added. The reaction mixture was allowed to warm to room temperature with stirring for 1 h and then diluted with 150 mL of Et_2O, washed with water, and dried (Na_2SO_4). Purification by column chromatography (elution with hexane/EtOAc 9:1) gave 230 mg (90%) of silyl ether **16** as a colorless oil: $[\alpha]^{25}_D$ +1.88° (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.65−7.67 (m, 4H), 7.37−7.46 (m, 6H), 5.94 (d, J = 6.20 Hz, 1H), 4.33−4.38 (m, 1H), 3.87−3.94 (m, 1H), 3.83 (ABq, J = 5.17 Hz, $\Delta\nu$ = 9.09 Hz, 1H), 3.78 (ABq, J = 5.86 Hz, $\Delta\nu$ = 8.67 Hz, 1H), 3.73 (d, 1H), 3.72 (s, 1H), 2.40 (d, J = 5.52 Hz, 1H), 1.98−2.03 (m, 2H), 1.25 (s, 28H), 1.06 (s, 9H), 0.88 (t, J = 6.60 Hz, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 145.75, 136.18, 133.94, 130.36, 128.32, 107.78, 73.25, 71.40, 65.11, 32.56, 30.43, 30.30, 30.16, 29.98, 29.92, 27.16, 27.12, 24.50, 23.27, 19.27, 14.33; FAB HRMS calcd for $C_{37}H_{59}O_3Si$ $(M - H)^+$ m/z 579.4233, found 579.4245.

1-*O*-(1′-(*Z*)-Octadecenyl)-2-*O*-palmitoyl-3-*O*-(*tert*-butyldiphenylsilyl)-*sn*-glycerol (17). A solution of alcohol **16** (400 mg, 0.68 mmol), palmitic anhydride (374 mg, 0.755 mmol), and DMAP (100 mg, 0.823 mmol) in 4 mL of alcohol-free $CHCl_3$ was stirred for 16 h at room temperature. The solvent was evaporated under vacuum, giving a residue that was purified by column chromatography (elution with hexane/EtOAc 9:1) to give 540 mg (98%) of product **17** as a colorless oil: $[\alpha]^{25}_D$ +4.26° (*c* 5.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.65−7.67 (m, 4H), 7.35−7.43 (m, 6H), 5.91 (d, J = 6.20 Hz, 1H), 5.09−5.14 (m, 1H), 4.32−4.37 (m, 1H), 3.95 (ABq, J = 4.87 Hz, $\Delta\nu$ = 10.10 Hz, 1H), 3.90 (ABq, J = 5.56 Hz, $\Delta\nu$ = 9.67 Hz, 1H), 3.80 (d, J = 4.91 Hz, 2H), 2.22−2.34 (m, 2H), 1.98−2.03 (m, 1H), 1.60 (quintet, J = 7.14 Hz, 2H), 1.25 (s, 52H), 1.05 (s, 9H), 0.88 (t, J = 6.73 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 173.07, 144.90, 135.58, 135.53, 133.21, 133.16, 129.75, 127.73, 127.71, 107.71, 72.58, 69.96, 62.21, 34.41, 31.96, 29.79, 29.75, 29.70, 29.67, 29.61, 29.50, 29.40, 29.37, 29.34, 29.18, 26.75, 25.01, 24.95, 23.93, 22.72, 19.26, 14.14; FAB HRMS calcd for $C_{53}H_{89}O_4Si$ $(M - H)^+$ m/z 817.6530, found 817.6533.

1-*O*-(1′-(*Z*)-Octadecenyl)-2-*O*-palmitoyl-*sn*-glycero-3-phosphocholine (1). A solution of silyl ether **17** (200 mg, 0.244 mmol) and imidazole (60 mg, 0.854 mmol) in 3 mL of THF was treated with 0.73 mL (0.73 mmol) of tetra-*n*-butylammonium fluoride (a 1.0 M solution in THF) at −23 °C for 1 h. The reaction mixture was passed through a silica gel pad, which was cooled to −78 °C and washed with cold hexane/Et_2O 1:1. The solvents were evaporated under vacuum, and the residue was lyophilized with benzene. To a solution of the resulting white solid (compound **18**) in 4 mL of benzene were added 2-chloro-2-oxo-1,3,2-dioxaphospholane (52 mg, 0.366 mmol) and pyridine (59 μL, 0.732 mmol). The reaction mixture was stirred overnight at 4 °C.

The solution was then frozen at −20 °C, and benzene was evaporated under vacuum. The resulting white solid (compound **19**) was transferred to a pressure tube with 2 mL of benzene and diluted with 6 mL of MeCN. The solution was cooled to −10 °C, and ∼4 mL (∼44 mmol) of NMe_3 was collected. The reaction mixture was stirred in the sealed pressure tube at 70 °C for 24 h, then cooled to 0 °C, and applied to a chromatography column (elution with a gradient of $CHCl_3$/MeOH/H_2O, 100:0:0, 80:20:0, 65:25:4) to give, after two filtrations through a Cameo cartridge (Fisher Scientific) to remove suspended silica, 135 mg (74%) of plasmalogen **1** as a white solid after lyophilization from benzene: $[\alpha]^{25}_D$ −2.33° (*c* 0.90, $CHCl_3$); $[\alpha]^{25}_D$ +1.50° (*c* 1.00, $CHCl_3$/MeOH 1:1); ^{1}H NMR ($CDCl_3$) δ 5.90 (d, J = 6.13 Hz, 1H), 5.10−5.18 (m, 1H), 4.28−4.35 (m, 3H), 3.76−3.98 (m, 6H), 3.36 (s, 9H), 2.30 (t, J = 7.27 Hz, 2H), 1.96−2.02 (m, 2H), 1.55−1.60 (m, 2H), 1.25 (s, 52H), 0.88 (t, J = 6.43 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 173.29, 144.82, 107.67, 71.69 (d, J_{CP} = 5.84 Hz), 70.50, 66.36 (d, J_{CP} = 3.82 Hz), 63.37 (d, J_{CP} = 3.82 Hz), 59.36, 54.43, 34.41, 31.92, 29.80, 29.74, 29.73, 29.67, 29.56, 29.42, 29.38, 29.37, 29.19, 24.97, 23.96, 22.68, 14.11; FAB HRMS calcd for $C_{42}H_{85}O_7PN$ $(M + H)^+$ m/z 746.6064, found 746.6082.

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