Stereocontrolled Synthesis of Plasmalogen-Type Lipids from Glyceryl Ester Precursors

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Two pathways for the synthesis of naturally occurring *Z* vinyl ether linkages in plasmalogen lipids (1-*O*-((*Z*)-1′-alkenyl)-2-acyl-*sn*-glycerophosphocholines and ethanolamines) have been investigated: (i) reduction of α-alkoxy enol phosphates and (ii) alkylidenation of diprotected glyceryl 1-formate esters utilizing 1,1-dibromoalkanes, zinc, $TiCl_4$, and TMEDA. While both methods reported good chemical yields and high *Z* selectivity for model substrates, the titanium-mediated coupling sequence failed when the dibromoalkyl chain length exceeded C_3. Treatment of 1-decyl-2-*O*-benzyl-3-*O*-(*tert*-butyldiphenylsilyl)-*rac*-glycerol with LDA and diethyl chlorophosphate at −78 °C followed by reduction of the vinyl phosphate intermediate using $Pd(PPh_3)_4$ and Et_3Al in DCE at 0 °C, however, gave 1-*O*-(1′-decenyl)-2-*O*-benzyl-3-*O*-(*tert*-butyldiphenylsilyl)-*rac*-glycerol in 62–65% yield and 2:1 Z:E stereoselectivity; reduction in hexane at 0 °C with slow addition of triethylaluminum improved the selectivity to >95% Z. Extension of this method to the preparation of a plasmalogen precursor (1-*O*-((*Z*)-1′-hexadecenyl)-2-hexadecanoyl-*rac*-glycerol) and the first synthesis of a choline derivative of diplasmalogen (1,2-di(*O*-(*Z*)-1′-hexadecenyl)-*rac*-glycerophosphocholine), a major component of rabbit epididymal spermatozoa phospholipid, in moderate chemical yields and excellent *Z* selectivity is reported.

Introduction

Plasmalogen lipids (1-*O*-((*Z*)-1′-Z-alkenyl)-2-acyl-*sn*-glycerophosphocholines and ethanolamines) are widely distributed components of mammalian cell membranes. In many electrically active tissues[1-3] this phospholipid subspecies comprises more than 65% of the total membrane phospholipid. A diplasmalogen fraction of rabbit sperm phosphatidylethanolamine, containing two *O*-(1′-alkenyl) linkages to the glycerol backbone of the phospholipid, has also been reported.[4] Despite this prominence and the involvement of plasmalogens in myocardial ischemia,[5] peroxisomal disorders,[6] CNS demyelination processes,[7] and cellular photooxidation,[8,9] relatively little is known about their role in nonpathological membrane biochemistry. Our interest in these labile phospholipids stems from their utility as essential constituents of a phototriggered liposomal release system.[10-12] The limited diversity of biologically-derived plasmalogens[13,14] available for our liposomal studies prompted us to investigate the synthesis of these unique and important phospholipids.

The lability of the plasmalogen vinyl ether functionality in low pH or oxidative environments and its naturally occurring Z configuration represent the primary challenges to their synthesis. Although methods for the synthesis of plasmalogens[15-17] and other glycerol vinyl ether lipids[18,19] have been reported previously, these approaches are characterized by moderate-to-low chemical yields and poor olefin stereospecificity. This report describes our efforts to develop a facile preparative methodology for plasmalogen-type lipids. Two routes have been investigated using model compounds: (i) the alkylidenation of diprotected glyceryl 1-formate esters with high *Z* selectivity[20] utilizing an alkyl 1,1-dibromide, zinc, titanium tetrachloride, and TMEDA coupling sequence (Figure 1a) and (ii) the reduction of α-alkoxy enol phosphates[21] (Figure 1b).

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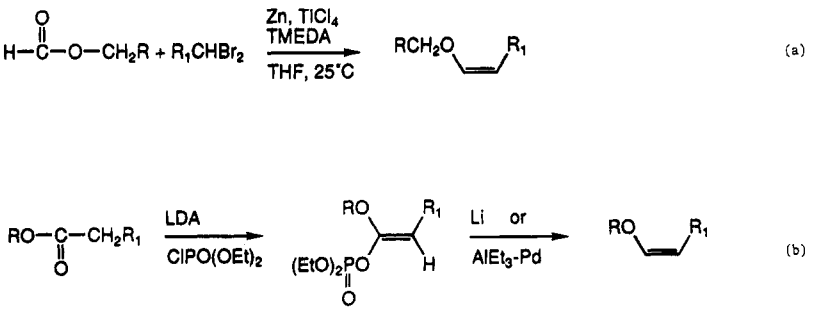

Figure 1. Synthesis of vinyl ethers via (a) formate ester coupling and (b) α-alkoxy enol phosphate reduction pathways.

Table 1

substrate	condns[a]	% yield	*Z*:*E*
ethyl palmitate	I	32	34:66
1	II	21[b]	67:33
1	III	67	>95:5
2	III	65	>95:5

[a] I: (1) LDA/(Et_2O)POCl/THF/HMPA; (2) Li/NH_3/*t*-BuOH. II: (1) LDA/$(EtO)_2$POCl/THF/HMPA; (2) $Pd(PPh_3)_4/Et_3Al$/DCE. III: (1) LDA/$(EtO)_2$POCl/THF/HMPA; (2) $Pd(PPh_3)_4/Et_3Al$/hexane. [b] See Experimental Section.

Results and Discussion

Two model substrates, ethyl palmitate and 1,1-dibromoethane, were used to screen the vinyl ether pathways shown in Figure 1. Moderate yields were obtained using both the vinyl phosphate/lithium reduction and the alkyl formate alkylidenation methods with their respective substrates; however, the desired *Z* isomer was the minor component in both cases. Since titanium-mediated alkylidenation with 1,1-dibromohexadecane gave predominantly alkyl bromide reduction products with correspondingly low yields of vinyl ether coupling,[22] this approach was abandoned and the vinyl phosphate method developed further.

The presence of both an acid-sensitive vinyl ether and a base-sensitive ester necessitated the use of protecting groups that could be selectively removed under mild conditions. Protection of glycerol as the 2-benzyl-3-(*tert*-butyldiphenylsilyl) ether, followed by acylation of the 1-position with decanoyl chloride, provided a model plasmalogen substrate for probing the vinyl phosphate reduction pathway.

Treatment of 1-decyl-2-*O*-benzyl-3-*O*-(*tert*-butyldiphenylsilyl)-*rac*-glycerol with LDA at −78 °C, followed by diethyl chlorophosphate ($(EtO)_2POCl$) trapping of the incipient carbanion, gave **1** in 90% yield. Birch reduction of **1** resulted in formation of the vinyl ether linkage with >95% *Z* selectivity; however, the yield was quite low (<5%). Reduction with $Pd(PPh_3)_4/Bu_3SnH$ was also ineffective, yielding <5% vinyl ether product. An alternative route was then investigated for reduction of **1** using $Pd(PPh_3)_4$ and Et_3Al. When the reaction was run under the conditions described by Greene and co-workers, the stereoselectivity of the doubly-protected vinyl ether product was ~2:1 *Z*:*E*. Subsequent experimentation with hexane as solvent and slower rates of triethylaluminum addition to maintain the reaction temperature at 0 °C led to conditions (Table 1) that provided the vinyl ether product in 62−65% yield and retained the >95% *Z* selectivity of the enolization−phosphorylation sequence (Figure 2).

This method was extended to the synthesis of 1,2-di-(*O*-(*Z*)-1′-hexadecenyl)-*rac*-glycerophosphocholine from 1,2-dihexadecanoyl-*rac*-glycerol (Figure 3). Silyl ether protection with *tert*-butyldiphenylsilyl chloride to give **2**, followed by conversion to the bis-vinyl phosphate using 2 equiv of LDA and $(EtO)_2POCl$, palladium-catalyzed reduction, and basic hydrolysis of the silyl ether gave 1,2-di(*O*-(Z)-1′-hexadecenyl)-*rac*-glycerol in 42% overall yield. Treatment of this intermediate with 2-chloro-1,3,2-dioxaphospholane 2-oxide prior to amination with trimethylamine[23] gave the phosphocholine derivative of diplasmalogen phospholipid in 52% yield.

Attempts to produce 1-monovinyl ether (plasmalogen) precursors from **2** by treatment with 1 equiv of LDA, followed by $Pd(PPh_3)_4/Et_3Al$ reduction, resulted in 4:1 ratios of 1′-H:1′-ethyl 1-*O*-((*Z*)-1′-hexadecenyl)-2-hexadecyl-3-(*tert*-butyldiphenylsilyl)-*rac*-glycerol that could not be resolved by column chromatography. We then adopted the strategy of protecting 1-hexadecanoyl-*rac*-glycerol as the 2-(*tert*-butyldimethylsilyl)-3-(*tert*-butyldiphenylsilyl) ether (**3**) prior to the vinyl ether transformation step. This approach reduced the ethyl coupling product to <5% (detected by GC/MS), presumably due to steric constraints at the neighboring *sn*-2 site. Its effectiveness is limited, however, since significant amounts of side products were produced at the expense of the desired vinyl ether product when the 2,3-bis(*tert*-butyldiphenylsilyl) ether of 1-hexadecanoyl-*rac*-glycerol was used as starting material. Two different methods for selective deprotection of **3** also failed; NaH in HMPA[24] removed both protecting groups and pyridinium *p*-toluenesulfonate in EtOH[25] gave no reaction. The doubly-deprotected material from the NaH reaction was then reprotected as the 3-(*tert*-butyldiphenylsilyl) ether, acylated with hexadecanoyl chloride, and deprotected with TASF in THF[26] to give a 6:1 mixture of 3-hexadecanoyl:2-hexadecanoyl products. Extensive acyl migration may be due to intramolecular attack of the solvent-separated RO^-TAS^+ ion pair at the 2-acyl group. Attempts to reduce the extent of acyl migration by using hexane as solvent failed to remove the protecting group, presumably due to poor dissociation of fluoride ion from the TASF ion pair. The search for deprotection conditions that will minimize acyl migration are currently under investigation.

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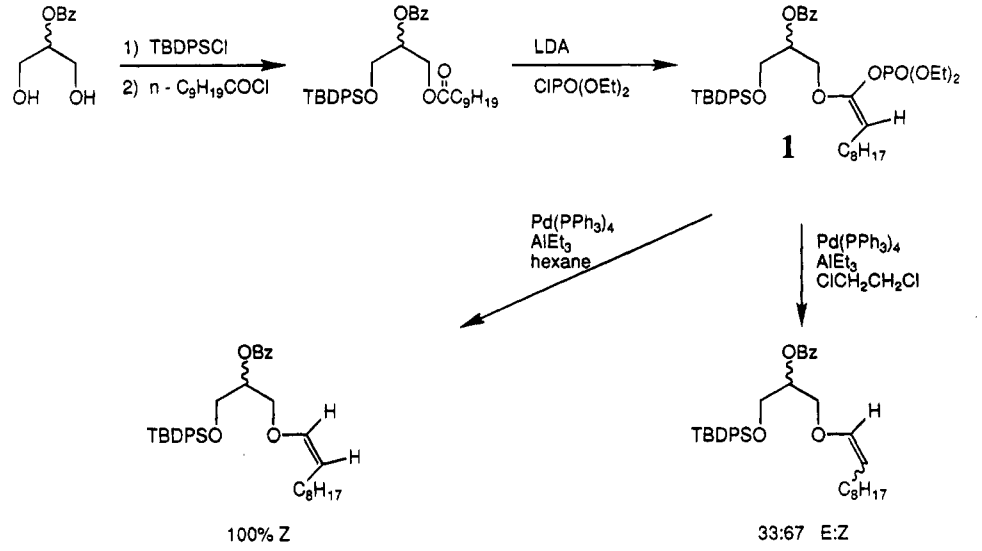

Figure 2. Synthetic pathway for 1-*O*-(*Z*)-1′-decenyl-2-*O*-benzyl-3-*O*-(*tert*-butyldiphenylsilyl)-*rac*-glycerol.

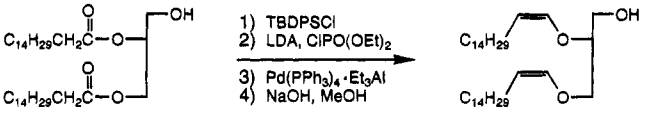

Figure 3. Synthetic pathway for 1,2-di(*O*-(*Z*)-1′-hexadecenyl)-*rac*-glycerol.

Conclusions

A direct method for synthesizing *O*-(*Z*)-1′-alkenyl)-*rac*-glycerol ether lipids in moderate chemical yields and excellent *Z* stereospecificity has been developed. The stereochemical purity of the vinyl ether product from vinyl phosphate reduction shows a strong dependence on solvent and temperature. Application of this methodology to the synthesis of isotopically labeled plasmalogens and novel vinyl ether lipids derived from chiral epoxy alcohol intermediates[27] is currently in progress.

Experimental Methods

All solvents and reagents were obtained from Aldrich Chemical Co. and used as received unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded using dry, acid-free $CDCl_3$ as solvent.

Ethyl 1-*O*-Propenyl Ether. A solution of $TiCl_4$ (1.0 M, 8.0 mmol) in CH_2Cl_2 was added at 0 °C to 20 mL of THF under Ar. TMEDA (2.4 mL, 16 mmol) was added and the mixture stirred at room temperature for 10 min. Zinc dust (1.18 g, 18.0 mmol) was then added; after the mixture was stirred for 30 min at room temperature, a solution of ethyl formate (0.148 g, 2.0 mmol) and 1,1-dibromoethane (0.827 g, 4.4 mmol) in THF (4 mL) was added. The reaction was quenched after 2 h by addition of saturated K_2CO_3 solution (2.6 mL) at 0 °C, diluted with 50 mL of Et_2O, and then chromatographed on basic Al_2O_3 using ether as eluent. The sole reaction product was identified as ethyl 1-*O*-propenyl ether by GC–MS: 86 (M^+, 21), 72 (100), 71 (92), 58 (10), 57 (17).

This method failed using the longer chain dibromides 1,1-dibromodecane and 1,1-dibromohexadecane; these substrates were reduced to the corresponding monobromoalkanes and parent hydrocarbons under these same reaction conditions.

Ethyl 1-*O*-(1′-Hexadecenyl) Ether. Ethyl palmitate (1.0 g, 3.52 mmol) in 3 mL of THF was added over a 10 min period to a THF solution of LDA (3.93 mmol in 0.6 mL THF) at −78 °C and stirred for 20 min. The lithium enolate was then treated with $(EtO)_2POCl$ (0.897 g, 5.20 mmol) in 6 mL of HMPA and stirred for another 1.5 h at room temperature. The reaction was quenched with water, extracted with Et_2O, dried over K_2CO_3, and filtered through a 1-in. plug of silica gel prior to concentration. The residue was then purified further by silica gel chromatography using pentane:Et_2O (1:1) as eluent to give ethyl 1-*O*-1′-(*E*/*Z*)-1-(diethylphosphonyl)-1-hexadecenyl) ether (1.07 g, 73% yield).

Dry, distilled ammonia (20 mL) was added to a solution of the α-alkoxy enol phosphate (0.42 g, 1 mmol) in 2.0 mL of *tert*-butyl alcohol and 1 mL of THF. Lithium metal (0.090 g, 13 mmol) was then added and the mixture allowed to reflux for ~1.5 h; the reaction was then quenched with 3 mL of ethanol and extracted with pentane. Purification by silica gel chromatography using pentane as eluent gave 0.17 g (32% yield) of vinyl ether (*Z*:*E* = 34:66); the isomers were isolated by preparative TLC (pentane). ^{1}H NMR (*E* isomer): 4.8 (dt, J_d = 15.9 Hz, 1H), 6.2 (d, J = 15.9Hz, 1H); (*Z* isomer): 4.3 (dt, J_d = 7.1 Hz, 1H), 5.95 (dt, J_d = 7.1 Hz, 1H).

2-Benzyl-3-(*tert*-butyldiphenylsilyl)-1-(1′-(diethylphosphonyl)decanoyl)-*rac*-glycerol, (1). Decanoyl chloride (0.45 g, 24 mmol) was added slowly at room temperature to a solution of 2-benzyl-3-(*tert*-butyldiphenylsilyl)-*rac*-glycerol (0.82 g, 20 mmol)[28] (prepared from 2-benzyl glycerol ether[29] via 2-benzyl-1,3-benzylideneglycerol acetal)[30] and pyridine (0.30 g, 40 mmol) in 6 mL of THF. The mixture was stirred for 30 min before purification by silica gel chromatography using hexane:Et_2O (1:1) as eluent to give 1.16 g (100% yield) of pure decyl ester. ^{1}H NMR: 0.9 (t, 3H), 1.05 (s, 9H), 1.3 (s, 12H), 2.15 (m, 2H), 2.3 (t, 2H), 3.75 (m, 3H), 4.2 (m, 1H), 4.4 (m, 1H), 4.65 (s, 2H), 7.27–7.8 (m, 15H).

2-Benzyl-3-(*tert*-butyldiphenylsilyl)-1-*O*-1′-(diethylphosphonyl)-1′-decenyl)-*rac*-glycerol. LDA (3.0 mmol in 0.8 mL THF) was added to the solution of **1** (1.16 g, 2 mmol) in 2 mL of THF at −78 °C over 10 min. After an additional 20 min, a solution of $(EtO)_2POCl$ (0.70 g, 4.0 mmol) in 4 mL of HMPA was added in aliquots, stirred vigorously for 20 min, and then allowed to warm to room temperature over 1 h. Ethyl ether (15 mL) was then added to the reaction mixture prior to filtration through a 1-in. plug of silica gel and elution with additional Et_2O. Evaporation of the solvent and chromatography of the residue using hexane:Et_2O (1:1) as eluent gave 1.28 g (90% yield) of pure vinyl phosphate product. ^{1}H NMR: 0.9 (t, 3H), 1.05 (s, 9H), 1.2–1.5 (m, 18H), 2.1 (m, 2H), 2.3 (t, 2H), 4.25 (m, 3H), 3.75 (m, 3H), 4.05–4.45 (m,6H), 4.65 (s, 2H), 7.27–7.8 (m, 15H).

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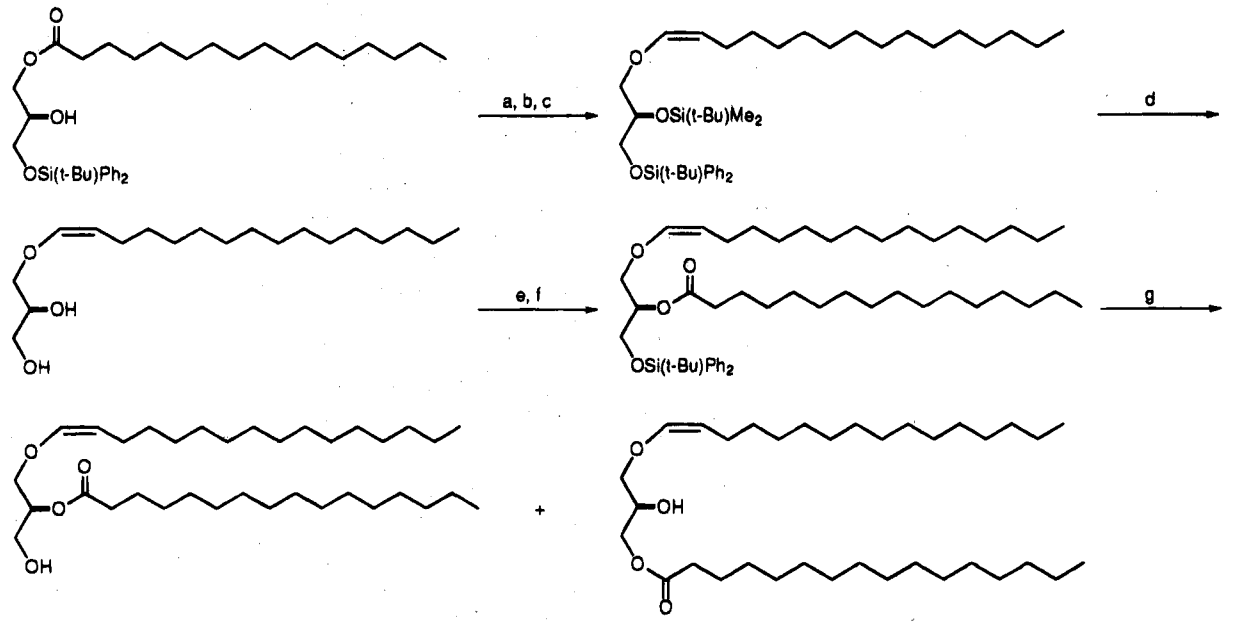

Figure 4. Synthetic pathway for 1-*O*-(1′-hexadecenyl)-2-hexadecanoyl-*rac*-glycerol. Key: (a) t-BuMe$_2$SiCl, imidazole, DMF, 25 °C; (b) LDA, (EtO)$_2$POCl, HMPA, −78 °C; (c) Et$_3$Al, Pd(PPh$_3$)$_4$, hexane, 0 °C; (d) NaH, HMPA, 0 °C; (e) t-BuPh$_2$SiCl, imidazole, DMF, 25 °C; (f) palmitoyl chloride, pyridine, THF, 25 °C; (g) TASF, THF, 25 °C.

2-Benzyl-3-(*tert*-butyldiphenylsilyl)-1-*O*-(1′-decenyl)-*rac*-glycerol. Method 1. Et$_3$Al (1.6 mL, 1.6 mmol, 1.0 M in hexane) was added dropwise at 0 °C to a solution of **2** (0.36 g, 0.5 mmol) and 0.025 g of Pd(PPh$_3$)$_4$ in 1.3 mL of dry 1,2-dichloroethane (DCE), stirred for 30 min at room temperature, and worked up as described in method 2. The solvent was evaporated and the residue separated by silica gel chromatography (1:1 hexane:Et$_2$O eluent). The desired vinyl ether product (0.068 g, *Z*:*E* ratio = 67:33 by GC and NMR, 21% yield) and 3-(*tert*-butyldiphenylsilyl)-1,2-decanylidene glycerol acetal (0.031 g, *E* and *Z* isomers), resulting from palladium-catalyzed nucleophilic addition to the 1-vinyl ether bond, were obtained in poor yields. Lower product recoveries were observed than would be suggested by TLC of the reaction mixture; this may be due to the exothermic quenching reaction of residual Et$_3$Al which may lead to thermal decomposition of the vinyl ether linkage.

Method 2. Et$_3$Al (3.3 mL, 3.3 mmol, 1.0M in hexane) was added dropwise to a 0 °C solution of **2** (1.28 g, 1.8 mmol) and Pd(PPh$_3$)$_4$ (0.063 g, 0.06 mmol) in 2.2 mL of dry hexane and the mixture was stirred for 30 min at room temperature. Ethyl ether (10 mL) was then added to the reaction mixture prior to rapid filtration through a 1-in. plug of silica gel, using additional Et$_2$O to fully elute the product. After evaporation, the residue was purified by silica gel chromatography using hexane:Et$_2$O (1:1) as eluent to give 0.664 g (75% yield) of 2-benzyl-3-(*tert*-butyldiphenylsilyl)-1-*O*-(*Z*)-1′-decenyl)-*rac*-glycerol. ^{1}H NMR: 4.35 (dt, J_d = 6.3 Hz, 1H), 5.98 (dt, J_d = 6.3 Hz, 1H).

Vinyl Phosphate Preparation from 1,2-Dihexadecanoyl-3-(*tert*-butyldiphenylsilyl)-*rac*-glycerol (2). A DMF solution (3.5 mL) of 1,2-dihexadecanoyl-*rac*-glycerol (0.95 g, 1.67 mmol), *tert*-butyldiphenylsilyl chloride (0.46 g, 1.67 mmol), and imidazole (0.228 g, 3.34 mmol) was stirred at room temperature for 24 h. The reaction mixture was then diluted with Et$_2$O, washed with H$_2$O three times, dried over Na$_2$SO$_4$, and evaporated; the residue was separated by column chromatography using hexane:Et$_2$O (1:1) as eluent to give 0.27 g of starting material and 0.80 g of product (83% yield based on converted starting material).

A solution of LDA (11 mmol in 6.8 mL THF/hexane) was added to a solution of the silyl-protected diacylglycerol (2.62 g, 3.2 mmol) in 10 mL THF at −78 °C over a 10 min period. After the solution was stirred for 30 min, a solution of (EtO)$_2$POCl (2.40 g, 13.9 mmol) in 18 mL of HMPA was added in aliquots with vigorous stirring for 20 min followed by warming to room temperature over ~1.5 h. The reaction mixture was then added to 50 mL of Et$_2$O and washed through a short silica gel column with Et$_2$O. After solvent removal, the residue was separated by silica gel chromatography (Et$_2$O eluant) to give 3.14 g of bis-vinyl phosphate (89.6% yield).

1,2-Di-*O*-((*Z*)-1′-hexadecenyl)-3-(*tert*-butyldiphenylsilyl)-*rac*-glycerol. Et$_3$Al (1.5 mmol in hexane) was added to a 0 °C solution of bis-vinyl phosphate (0.50 g, 0.46 mmol, see above) and 0.025 g of Pd(PPh$_3$)$_4$ in 3 mL of dry hexane and the mixture stirred for 1.5 h at room temperature. The reaction mixture was then added to 10 mL of Et$_2$O and washed through a short silica gel column. Column chromatography of the residue using hexane:Et$_2$O gave 0.261 g of bis-(*Z*)-vinyl ether product (73% yield). ^{1}H NMR: 4.35 (m, 2H), 5.94 (dt, 1H), 5.98 (dt, 1H).

1,2-Di-*O*-((*Z*)-1′-hexadecenyl)-*rac*-glycerol. 1,2-Di-*O*-((*Z*)-1′-hexadecenyl)-3-(*tert*-butyldiphenylsilyl)-*rac*-glycerol (0.50 g, 0.6 mmol) was dissolved in 1.0 N NaOH in EtOH (20 mL) and stirred at 60 °C for 28 h. The reaction mixture was cooled and filtered through a 1-in. bed of silica gel, prior to column chromatography using hexane:Et$_2$O (9:1) as eluent, to give 0.28 g of bis-vinyl ether glycerol product in 81% yield. ^{1}H NMR: 4.37 (dt, 1H), 4.42 (dt, 1H), 5.90 (dt, 1H), 6.02 (dt, 1H). ^{13}C NMR: 14.3, 22.8, 24.0, 24.1, 26.7, 29−30 (m), 32, 62.6, 71, 80.5, 108.2, 109, 140, 145.

1,2-Di-*O*-((*Z*)-1′-hexadecenyl)-*rac*-glycero-3-phosphocholine. A benzene solution (1.5 mL) of 2-chloro-1,3,2-dioxaphospholane 2-oxide (0.200 g, 140 mmol) was added dropwise to a solution of 1,2-di-*O*-((*Z*)-1′-hexadecenyl)-*rac*-glycerol (0.190 g, 0.354 mmol) and triethylamine (Et$_3$N) (1 mL) in 2.5 mL of benzene at 0 °C. After the solution was stirred for 30 min, MeOH (0.5 mL) was added slowly and the reaction mixture stirred another 50 min before filtering through Celite (the filter bed was subsequently washed with 5 mL of THF) and evaporation. The residue was placed in a 15 mL pressure bottle and dissolved in CH$_3$CN (2.5 mL), Me$_3$N added (1.5 mL), and the tube sealed prior to heating for 24 h at 70 °C; a white precipitate formed after ~8 h. The reaction mixture was then evaporated and chromatographed on silica gel (gradient elution of CHCl$_3$:MeOH beginning at 100:0 and finishing at 50:50) to give 0.130 g (52% yield) of bis-vinyl ether glycerophosphocholine product. ^{1}H NMR: 4.29−4.37 (m, 4H), 5.91 (d, 1H), 6.04 (d, 1H). ^{13}C NMR: 14.1, 22.7, 24.0, 24.1, 29.4−29.9 (m), 31.9, 54.4, 64.4, 66.4, 71.5, 79.8, 79.9, 107.4, 107.9, 144.2, 145.0.

1-Hexadecanoyl-2,3-bis(*tert*-butyldiphenylsilyl)-*rac*-glycerol (3). *tert*-Butyldimethylsilyl chloride (0.234 g, 1.6 mmol) was added at room temperature to a mixture of 3-(*tert*-butyldiphenylsilyl)-1-hexadecanoyl-*rac*-glycerol (0.73 g, 1.3

mmol) and imidazole (0.18 g, 2.6 mmol) in 2 mL of DMF and stirred for 2.5 h. Addition of 20 mL of Et_2O was followed by washing with water, drying with sodium sulfate, and solvent evaporation. The residue was separated by silica gel chromatography using 1:1 hexane:Et_2O as eluent to give 0.76 g of **3** (86% yield). ^1H NMR: 0–0.2 (2s, 6H), 0.85 (s, 9H), 0.9 (t, 3H), 1.05 (s, 9H), 1.3 (m, 24H), 1.6 (m, 2H), 2.3 (t, 2H), 3.5–4.5 (m, 5H), 7.3–7.8 (m, 10H).

1-*O*-(1′-Hexadecenyl)-2-(*tert*-butyldimethylsilyl)-3-(*tert*-butyldiphenylsilyl)-*rac*-glycerol. The differentially-protected intermediate **3** (0.46 g, 0.67 mmol) was treated as for **2** above using 1.2 mmol of LDA in THF/hexane and 0.24 g of $(EtO)_2POCl$ (1.4 mmol) in 2 mL of HMPA at −78 °C to give 0.35 g of vinyl phosphate (63% yield). The vinyl phosphate intermediate was reduced as above using Et_3Al (0.9 mL, 1.0M in hexane) and $Pd(PPh_3)_4$ (25 mg) in 2.5 mL of hexane to give 0.21 g (74% yield, 95% pure by GC/MS) of the doubly-protected plasmalogen precursor. ^1H NMR: 4.30 (dt, J_d = 6.2 Hz, 1H), 5.95 (dt, J_d = 6.2 Hz, 1H).

1-*O*-(1′-Hexadecenyl)-*rac*-glycerol. Sodium hydride (50 mg of a 60% dispersion in mineral oil) was washed with dry THF four times and dried with a stream of N_2. A HMPA solution (2.5 mL) of 2-(*tert*-butyldimethylsilyl)-3-(*tert*-butyldiphenylsilyl)-1-O-(1′-hexadecenyl)-*rac*-glycerol (0.19 g, 0.29 mmol) was added at ambient temperature and the resulting solution stirred for 48 h. TLC analysis during the progress of the reaction revealed that the silyl protecting groups were removed in a random fashion, indicating that the TBDMS and TBDPS residues were equally susceptible to attack by hydride. The reaction mixture was chromatographed on silica gel using a step gradient elution with 1:1 hexane:Et_2O followed by 100% Et_2O. The product was recovered in 72% yield (58.1 mg) along with 22 mg of starting material. ^1H NMR: 5.94 (dt, J_d = 6.2 Hz, 1H), 4.31 (dt, J_d = 6.2 Hz, 1H), 2.45 (d, J_d = 5.4 Hz, 1H), 1.95 (t, J_t = 6.0 Hz, 1H).

1-*O*-(1′-Hexadecenyl)-2-hexadecanoyl-3-(*tert*-butyldiphenylsilyl)-*rac*-glycerol. The doubly-deprotected product above, 1-*O*-(1′-hexadecenyl)-*rac*-glycerol, was protected as described for **2** using 58.1 mg (0.185 mmol) of the glycerol intermediate, 25.2 mg of imidazole (0.37 mmol), and 50.7 mg of *tert*-butyldiphenylsilyl chloride (0.185 mmol) in 1.3 mL of DMF to give 74 mg of silyl-protected product (75% yield). ^1H NMR: 2.42 (d, J_d = 5.4 Hz, 1H), 4.36 (dt, J_d = 6.2 Hz, 1H), 5.95 (dt, J_d = 6.2 Hz, 1H).

This intermediate (74 mg, 0.134 mmol) was acylated with hexadecanoyl chloride (73 mg, 0.265 mmol) in the presence of pyridine (80 mg in 1.5 mL THF) at room temperature for 40 min. The solid was then removed by filtration and the filtrate concentrated by evaporation. The residue was separated by silica gel chromatography using 1:1 hexane:Et_2O as eluent to give 94 mg (89% yield) of the silyl-protected plasmalogen precursor. ^1H NMR: 4.34 (dt, J_d = 6.3 Hz, 1H), 5.91 (dt, J_d = 6.3 Hz, 1H).

1-*O*-(1′-Hexadecenyl)-2-hexadecanoyl-*rac*-glycerol. TASF (17 mg) was added to a THF solution (1.5 mL) of the silyl-protected plasmalogen precursor (47 mg, 0.059 mmol) and the reaction mixture stirred at room temperature for 2.5 h. The reaction mixture was then filtered through a silica gel plug, evaporated, and separated by silica gel chromatography using 7:3 hexane:Et_2O to give 24 mg of the rearranged product, 3-hexadecanoyl-1-*O*-(1′-hexadecenyl)glycerol, and 4 mg of the desired 1-*O*-(1′-hexadecenyl)-2-hexadecanoyl-*rac*-glycerol. ^1H NMR of 3-hexadecanoyl product: 2.39 (d, J_d = 5.1 Hz, 1H), 4.42 (dt, J_d = 6.3 Hz, 1H), 5.94 (dt, J_d = 6.3 Hz, 1H). ^1H NMR of 2-hexadecanoyl product: 1.88 (t, J_t = 6.0 Hz, 1H), 4.39 (dt, J_d = 6.2 Hz, 1H), 5.92 (dt, J_d = 6.2 Hz, 1H).

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Supplementary Material Available: ^1H- and ^{13}C-NMR spectra and mass spectra (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.