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Facile Synthesis of Plasmalogens via Barbier-Type Reactions of Vinyl Dioxanes and Vinyl Dioxolanes with Alkyl Halides in LiDBB Solution

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Received February 21, 2002

Plasmalogens (i.e. plasmenylcholines or plasmenylethanolamines) are a biologically important class of glycerophospholipids that have been difficult to synthesize due to the presence of an acid and oxidatively labile (*Z*)-vinyl ether substituent at the *sn*-1 position and a base-labile *sn*-2 acyl substituent that easily migrates during silica gel purification. We report two facile synthetic methods for the preparation of racemic plasmenylcholines via a tandem reductive vinyl dioxane/dioxolane ring opening and alkyliodide coupling process that proceeds in a single pot reaction. The key step in the formation of (*Z*)-vinyl ether precursors for the production of plasmenylcholines is accomplished using LiDBB under Barbier-type conditions to give the corresponding TBDMS-protected 1-*O*-*Z*′-vinylglycerol intermediate in moderate yields. This pathway is the most direct synthetic route for the formation of plasmenylcholines to date, requiring a total of six transformations from acrolein and glycerol or solketal as inexpensive starting materials, to generate glycerophosphocholine-type plasmalogens in 4% overall yield.

Introduction

Plasmalogens[1] (i.e. plasmenylcholines or plasmenylethanolamines) are phospholipids containing *sn*-1-*Z*-1′-*O*-vinyl chains of varying lengths and degrees of unsaturation. They are predominantly found in the electrically active tissues of mammals such as brain, myelin, and heart,[2] and are believed to be involved in important biological functions such as cell signaling,[2−4] membrane fusion,[5,6] and lipid peroxidation.[7] Plasmenylcholines have also been successfully utilized for the delivery of low molecular weight drugs, proteins, and genes by using triggering mechanisms that are activated by acidic or oxidative environments.[5,8−15] Naturally occurring plasmalogen mixtures are generally isolated from phosphocholine extracts derived from a number of animal sources; however, they are difficult to obtain as discrete molecular species. Commercially available plasmalogens contain mixtures of alkyl chain lengths at the *sn*-1 and *sn*-2 positions, greatly limiting their utility in biological and biophysical studies due to the lack of pure compounds. Rui and Thompson developed the first synthetic pathway to pure plasmenylcholines with (*Z*)-stereospecificity via transformation of acylglycerols to the corresponding vinyl phosphates, followed by reductive cleavage.[16] Bittman and co-workers have also reported a multistep synthesis of plasmenylcholine using Lindlar catalyst reduction of alkynyl ethers as the key step in vinyl ether formation.[17] Due to the difficulties surrounding the previous synthetic pathways and the biological importance of these compounds, we sought to develop a more expedient synthetic method.

The synthetic challenges of plasmalogens include (1) stereoselective formation of the naturally occurring (*Z*)-vinyl ether bond at the *sn*-1 position to avoid tedious purification of geometric isomers, (2) instability of this linkage toward acidic or oxidative conditions, which limits the choice of reagents and isolation conditions,[18]

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10.1021/jo025640u CCC: $22.00
Published on Web 08/13/2002

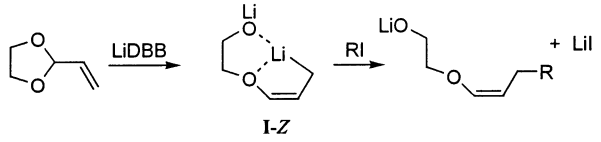
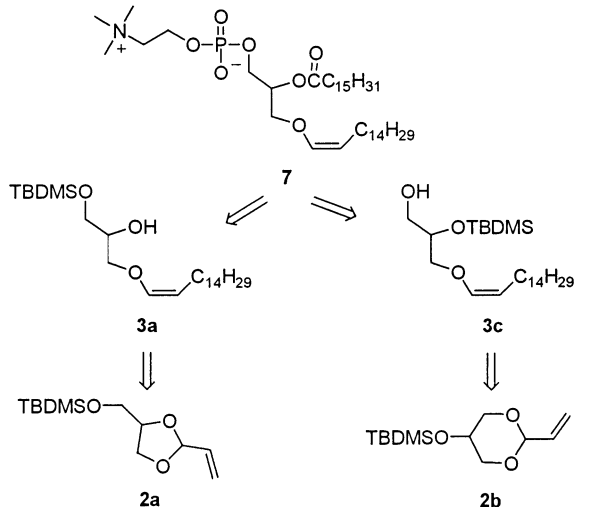


FIGURE 1. Putative mechanism of the LiDBB-mediated Barbier reaction with vinyl acetal and iodoalkanes. The internally chelated, η_1-alkoxyallyllithium form of the allyloxy carbanion is shown by analogy to ref 27.

SCHEME 1



and (3) an *sn*-2 acyl group that is prone to rapid migration to the primary *sn*-1/*sn*-3 sites under basic or mildly acidic conditions (including silica gel chromatography with aprotic solvents). The cytotoxic properties of plasmenylcholine-type analogues of ET-18-OMe have been reported.[19−21] These antitumor ether lipid derivatives have been synthesized via Barbier-type reactions[22] of vinyl acetals and 1-iodoalkanes in lithium 4,4-di-*tert*-butylbiphenyl (LiDBB) solution (Figure 1).[20] This route produces (*Z*)-vinyl ether lipid derivatives in moderate yields and excellent stereoselectivity (*Z*:*E* > 95:5). On the basis of this methodology, two important precursors for a new plasmenylcholine synthesis, monosilyl-protected *sn*-1 (*Z*)-vinyl ether glycerols (3-*tert*-butyldimethylsilyl-1-*O*-1′-(*Z*)-hexadecenyl glycerol, **3a** and 2-*tert*-butyldimethylsilyl-1-*O*-1′-(*Z*)-hexadecenyl glycerol, **3c**), can be prepared in a one-step Barbier-type reaction of TBDMS-protected vinyl acetals and 1-iodoalkanes (Scheme 1). Rui and Thompson first synthesized TBDPS-protected **3a** using a multistep protection/deprotection strategy.[16] A key step in that sequence is the successful removal of the *sn*-3 TBDPS group with TBAF in the presence of imidazole at low temperature to minimize the *sn*-2 → *sn*-3 acyl migration problem. The success of this pathway, therefore, is critically dependent on the attention given to the details of reaction and column separation conditions. Bittman and co-workers[17] also employed a multistep strategy, using PMB and TBDPS protection to prepare a TBDPS derivative of **3a** in their plasmenylcholine synthesis. We now report the use of Barbier-type reactions to generate **3a** and **3c** as key intermediates in the total synthesis of plasmenylcholine-type plasmalogens. The route employing **3c**, a precursor of lysoplasmenylcholine, benefits from greater efficiency since it avoids the acyl migration problem by introducing the acyl substituent in the last step. Formation of plasmenylcholines with stereocontrol at the *sn*-2 site, however, requires the use of a different pathway involving chiral intermediate **3a**. Effective plasmenylcholine syntheses, using either **3a** or **3c** as intermediates, are described below.

Results and Discussion

Structural Effects on the LiDBB-Mediated Synthesis of (*Z*)-Vinyl Ethers under Barbier-Type Conditions. Previous studies[20,23] revealed that Barbier-type reactions of vinyl acetals in LiDBB could potentially be applied to the synthesis of plasmenylcholines via reductive acetal ring opening followed by reaction of the resulting allyllithium species with 1-iodoalkanes (Figure 1). The ring cleavage reaction proceeds most favorably when catalytic amounts of DBB are used in the presence of excess lithium.[24] This modification is preferred since it is fast (<1 h) and self-monitoring (reappearance of the blue LiDBB radical anion species indicates the completion of the reaction). Further experimentation revealed that Barbier conditions were critical for achieving the highest reaction efficiencies, since the unstable allylic anion generated by vinyl acetal reduction undergoes rapid decomposition instead of alkylation if the iodoalkane is added after lithiation.[25] Only the γ-coupled vinyl ether product was obtained in high *Z*:*E* ratios (>20:1) under these conditions.[20] We excluded the possible involvement of a Michael-type process, since stepwise addition of preformed $C_{13}H_{27}Li$ to 2-vinyl-1,3-dioxolane gave low yields of vinyl ether product and poor stereoselectivity (*Z*:*E* 40:60).[20] The high (*Z*)-stereoselectivity observed is attributed, instead, to the formation of cyclic lithioalkoxyallyl intermediates (e.g. **I**-*Z* in Scheme 2) after reductive ring opening.[23,26,27] The simplicity and stereoselectivity of this transformation motivated us to pursue LiDBB-mediated vinyl acetal reductions for the synthesis of plasmenylcholine derivatives.

Several interesting trends were observed in Barbier couplings of vinyl dioxanes and alkyl halides (Table 1). The reactions of 5-*O*-TBDMS-protected vinyl dioxane and

(18) Vinyl ethers are also intermediates in the *t*-BuOK-mediated allylic deprotection process. See: Guibe, F. *Tetrahedron* **1997**, 53, 13509−13556.

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SCHEME 2

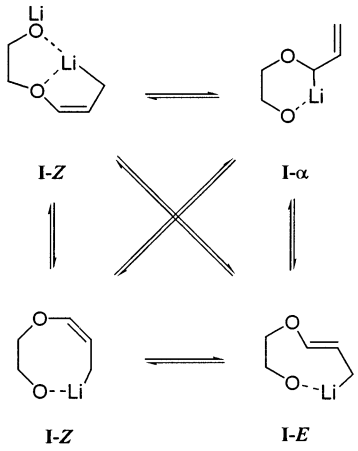
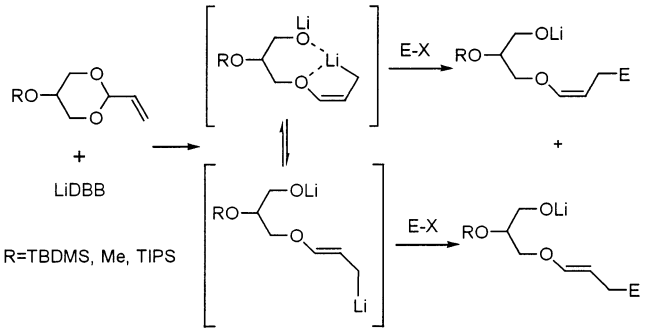


TABLE 1. Barbier-Type Reactions of 2-Vinyl-1,3-dioxanes with Alkyl Halides in LiDBB Solution



R	E−X	*Z*:*E*	% yield
TBDMS	*n*-$C_{13}H_{27}Cl$	30:70	57
TBDMS	*n*-$C_{13}H_{27}Br$	67:33	32
TBDMS	*n*-$C_{13}H_{27}I$	98:2	47
Me	*n*-$C_{13}H_{27}Cl$	88:12	49
Me	*n*-$C_{13}H_{27}I$	95:5	53
TIPS	*n*-$C_{13}H_{27}Cl$	>98% *E*	14
TIPS	*n*-$C_{13}H_{27}I$	>98% *Z*	33

1-chlorotridecane gave high yields of *E*-coupled product (*Z*:*E* 30:70), whereas *Z*-products dominated the conversions of 1-bromotridecane (*Z*:*E* 67:33) and iodotridecane (almost exclusively (*Z*)-coupled product, *Z*:*E* 98:2). We attribute this effect to the disruption of allyllithium anion chelation by the bulky TBDMS group, since the effects of halogen are minor (1-chlorotridecane, *Z*:*E* 88:12; 1-iodotridecane, *Z*:*E* 95:5) when substrates containing smaller protecting groups (i.e. methyl) are present at the *sn*-2 position. This interpretation is further supported by the dramatic influences observed with the bulkier TIPS protecting group (i.e. 1-chlorotridecane, >98% *E*; 1-iodotridecane, >98% *Z*). These results are also consistent with kinetic differences expected for the reactivity of alkyl halides with allyllithium anion intermediates (i.e. alkyl iodide coupling reactions should compete better than alkyl chlorides with cis−trans allyl isomerization, leading to greater *Z*:*E* ratios when iodoalkane substrates are used). Alternatively, the reaction may proceed via an SET mechanism involving the coupling of an alkyl halide and a lithioalkoxyallyl radical intermediate;[25] however, it is unclear how this would lead to the stereoselective formation of *Z*-vinyl ether products.

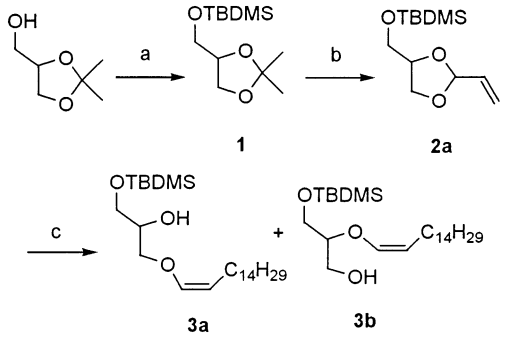


FIGURE 2. Synthesis of plasmalogen precursor **3a** from solketal. Reagents: (a) TBDMSCl, imidazole, THF, 23 °C (96.9%); (b) acrolein, *n*-$BuSnCl_3$, 23 °C (54.5%); (c) Li, DBB, $C_{13}H_{27}I$, THF, 0 °C, 0.5 h (18.4% **3a** and 32.1% **3b**).

Synthesis of 3a Starting from Solketal (Figure 2). Racemic solketal was protected with TBDMSCl to give **1** in 96.9% yield.[28] Transformation of the isopropylidene acetal to a vinyl acetal in the presence of the TBDMS protecting group is achieved in a single step by using *n*-$BuSnCl_3$ to give the vinyl dioxolane **2a** in 54.5% yield.[29] This transformation was conducted with neat acrolein, with removal of the acetone byproduct under vacuum during the reaction, to give vinyl dioxolane **2a** as a ca. 1:1 mixture of cis/trans isomers. This mixture proved difficult to separate, so it was used without further purification. Barbier-type coupling conditions were then initiated under Ar with use of a glass-coated stir bar, Li powder (7 equiv), and catalytic amounts of DBB (0.1 equiv) in THF at 0 °C to generate the dark blue LiDBB radical anion solution. A mixture of **2a** (1 equiv) and 1-iodotridecane (2 equiv, prepared in 96.3% yield by I_2/PPh_3/imidazole treatment of 1-tridecanol) in THF was added rapidly and all at once (fast addition of the mixture usually gave a higher yield than sequential additions). The reaction mixture was stirred until the blue $LiDBB^{-\bullet}$ color was regenerated (ca. 0.5−1 h). Product analysis showed that the desired product, **3a**, was isolated as the minor component in 18.4% yield, with **3b** recovered as the major product in 32.1% yield. Attempts to generate the penultimate plasmenylcholine species in a single pot reaction via addition of palmitoyl chloride to the LiDBB reaction mixture were abandoned since the regioisomeric products formed were difficult to separate.

Synthesis of Plasmenylcholine from 3a (Figure 3). A synthesis of palmitoyl plasmenylcholine, utilizing intermediate **3a** in a nine-step sequence beginning with monopalmitin, has already been described.[16] We modified this published method slightly by acylating compound **3a** with palmitoyl chloride to give compound **5** in 92.8% yield, followed by deprotection of TBDMS with TBAF/imidazole (10 equiv each) to give alcohol **6** in 55% yield. It should be noted that the reaction temperature (−23 °C), time, and chromatographic separation (fast elution from silica gel with cold solvent) require careful attention to prevent acyl migration to the *sn*-3 position upon TBDMS deprotection. The phosphocholine headgroup was introduced as described previously by treatment with 2-oxo-2-chloro-1,3,2-dioxaphospholane, followed by excess trimethylamine, to give a racemic 2-hexadecanoyl-1-*O*-1′(*Z*)-hexadecenyl-*rac*-glycero-3-phosphocholine (**7**, palmitoyl plasmenylcholine) in 67.6% yield.[16]

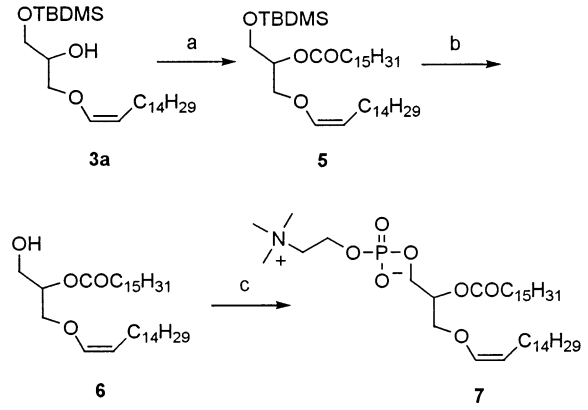


FIGURE 3. Synthesis of 2-hexadecanoyl-1-*O*-1′(*Z*)-hexadecenyl-*rac*-glycero-3-phosphocholine (**7**, palmitoyl plasmenylcholine) from **3a**. Reagents: (a) palmitoyl chloride, pyridine, THF, 23 °C (92.8%); (b) TBAF, imidazole, −23 °C (55%); (c) (i) 2-oxo-2-chloro-1,3,2-dioxaphospholane, Et_3N, C_6H_6, 8 °C; (ii) Me_3N, MeCN/C_6H_6, 70 °C (67.6% for steps i and ii, combined).

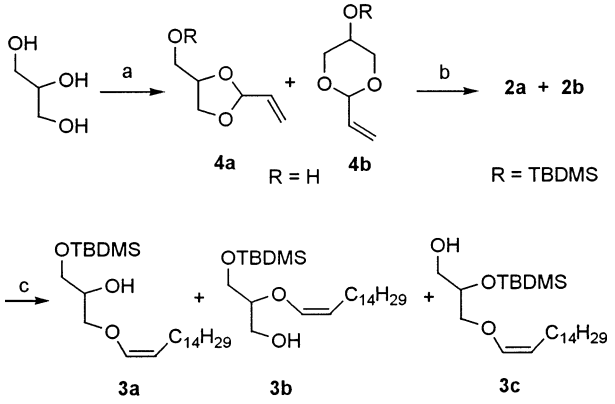


FIGURE 4. Synthesis of **3a** from glycerol. Reagents: (a) acrolein, *n*-$BuSnCl_3$, THF, 23 °C (68.1%); (b) TBDMSCl, imidazole, 23 °C (28.0% **2a**, 19.9% trans **2b**, 33.7% cis **2b**); (c) Li, DBB, $C_{13}H_{27}I$, THF, 0 °C, 1 h (37.1% **3a**, 7.28% **3b**, 3.12% **3c**).

Synthesis of 3a from Glycerol (Figure 4). A modified synthesis of racemic plasmenylcholine, starting from glycerol and acrolein, was attempted since the reaction of vinyl dioxolane **2a** in LiDBB solution under Barbier conditions gave **3a** in low yield. Condensation of glycerol and acrolein in the presence of *n*-$BuSnCl_3$ produced a mixture of *cis*/*trans*-dioxolane **4a** and *cis*/*trans*-dioxane **4b** in 68% yield. Subsequent TBDMSCl protection of alcohols **4a** and **4b** gave a mixture of silyl ethers that can be separated by silica gel column purification into three components, *cis*-**2b**, *trans*-**2b**, and a mixture of *cis*/*trans*-**2a**. We used this mixture, without separation, in the Barbier-type coupling reaction since TBDMS group migration under the basic workup conditions[30] gives **3a** (37.1% yield), **3b** (7.3% yield), and **3c** (3.1% yield) after column purification.

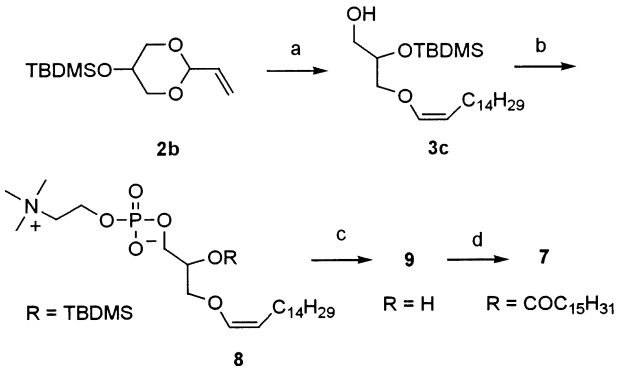


FIGURE 5. Synthesis of **7** from **3c**. Reagents: (a) Li, DBB, $C_{13}H_{27}I$, THF, 0 °C, 1 h (47%); (b) (i) 2-oxo-2-chloro-1,3,2-dioxaphospholane, Et_3N, C_6H_6, 8 °C; (ii) Me_3N, MeCN/C_6H_6, 70 °C (53.6% for steps i and ii, combined); (c) TBAF, imidazole, 23 °C (98%); (d) palmitic anhydride, DMAP, CH_2Cl_2, 23 °C (53%).

Plasmenylcholine Synthesis from 2b and 3c (Figure 5). Since acyl migration during the TBDMS deprotection step was a problematic side reaction, a new synthetic route to plasmenylcholine was developed with **3c** as the key intermediate. This strategy employs the phosphocholine headgroup as a blocking group to prevent migration followed by TBDMS deprotection and acylation. Reaction of vinyl dioxane **2b** with 1-iodotridecane under Barbier conditions gave the *sn*-2 TBDMS-protected alcohol **3c** in 47% yield. This reaction must be quenched as soon as the LiDBB blue color reappears, however, to prevent TBDMS migration to **3a**. Introduction of the phosphocholine headgroup as previously described gives the *sn*-2 TBDMS-protected lysoplasmenylcholine **8** in 53.6% yield. Deprotection of **8** with TBAF/imidazole gives lysoplasmenylcholine **9** in 98% yield. This intermediate was subsequently acylated with palmitic anhydride in the presence of DMAP to give palmitoyl plasmenylcholine **7** in 53% yield. This is the most efficient route known for plasmenylcholines since it avoids regioselectivity and acyl migration problems and circumvents the need for inefficient protection/deprotection steps. The main limitation of this approach, however, is that it is only applicable for the synthesis of racemic plasmenylcholines since reductive ring opening of **2b** occurs with equal probability at each acetal C−O bond.

Conclusions

Facile syntheses of racemic plasmenylcholines have been developed. The most efficient method that is also adaptable for the synthesis of chiral plasmenylcholines, requires only six steps beginning from the inexpensive starting materials solketal or glycerol and acrolein. The key step in this transformation, formation of (*Z*)-vinyl ether intermediates via LiDBB-mediated coupling with iodoalkanes, is accomplished under Barbier-type conditions. Even though the reaction gives modest yields, its simplicity, versatility, and applicability will be useful for the synthesis of other plasmalogen-type compounds with (*Z*)-vinyl ether configuration.

(28) The TBDPS-protected compound also was prepared; however, this intermediate produced lower yields in the subsequent Barbier-type reaction (only 7% of the desired coupling product was obtained in this case).

(29) The selective removal of an isopropylidene acetal in the presence of TBDMS is known to be difficult since the TBDMS group is usually cleaved under the same conditions required for isopropylidene acetal cleavage. An attempt with $FeCl_3/SiO_2$ [Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404−407] failed to convert any starting material over a 24-h period.

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Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz. Chemical shifts are reported in ppm relative to the residual solvent peaks as the internal standard. MS (EI/CI/ESI) was performed by the Purdue University MCMP Mass Spectrometry Service. Liquid chromatography was typically performed on 230−400 mesh silica gel, using high-grade solvents for compound purification. THF was distilled from Na. Benzene, triethylamine, MeCN, DMF, and pyridine were distilled from CaH_2. All other chemical were used without further purification unless otherwise stated.

Syntheses: 1-Iodotridecane. Triphenylphosphine (43.4 g, 162 mmol) and imidazole (11.0 g, 162 mmol) were added to 1-tridecanol (25.0 g, 125 mmol) in dichloromethane (200 mL) at 0 °C. Iodine (41,1 g, 162 mmol) was slowly added at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and at 23 °C for 3 h. Hexane (200 mL) was added and the resulting precipitate removed by filtration. The organic liquid was condensed and the resulting residue was purified by silica gel chromatography (hexane) to give a liquid (37.3 g, 120 mmol, 96.3%). ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, J = 6 Hz), 1.24 (s, 20H), 1.80 (quintet, 2H, J = 6 Hz), 3.16 (t, 2H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 7.3, 14.1, 22.7, 28.5, 29.3, 29.4, 29.5, 29.6, 30.5, 31.9, 33.6.

***tert*-Butyldimethyl(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)silane (1).** Imidazole (4.64 g, 68.1 mmol) was added to a flask containing solketal (6.00 g, 45.4 mmol) in THF (30 mL). TBDMSCl (8.55 g, 56.6 mmol) in THF (30 mL) was added slowly at 0 °C and the resulting mixture stirred at 23 °C overnight. The precipitate generated during the reaction was removed by filtration. The filtrate was then diluted in hexane (200 mL) and washed with water (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure to give product **1** as an oil (10.857 g, 44.1 mmol, 96.9%). ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6H), 0.86 (s, 9H), 1.33 (s, 3H), 1.38 (s, 3H) 3.50−4.14 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.4, 18.2, 25.4, 25.8, 26.7, 63.9, 66.8, 76.1, 109.1.

***tert*-Butyldimethyl(2-vinyl-1,3-dioxolan-4-ylmethoxy)silane (2a).** *n*-$BuSnCl_3$[31] (0.408 mL, 2.45 mmol) was added to a flask containing **1** (12.08 g, 49.02 mmol). Acrolein (3.28 mL, 49.02 mmol) was slowly added and the resulting mixture stirred at 23 °C for 30 min. The reaction mixture was placed under vacuum to remove the acetone byproduct. This sequence of operations was repeated 5 times. The resulting mixture was purified by silica gel chromatography (hexane:Et_2O, 20:1) to give a trans/cis mixture of **2a** (6.548 g, 26.79 mmol, 54.5%). ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.86 (s, 9H), 3.48−4.20 (m, 5H), 5.18−5.50 (m, 3H), 5.71−5.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −5.4, 18.3, 25.8, 63.5, 63.8, 67.2, 67.5, 76.0, 76.4, 104.0, 104.3, 119.8, 120.4, 134.5, 134.6.

2-Vinyl-1,3-dioxolan-4-ylmethanol (4a) and 2-Vinyl-1,3-dioxane-5-ol (4b). *n*-$BuSnCl_3$ (0.450 mL, 2.70 mmol) was added to a flask containing glycerol (10.0 g, 108 mmol) and the vessel was cooled in an ice bath. Acrolein (3.60 mL, 54.3 mmol) was slowly added at 0 °C, the ice bath removed, and the resulting mixture stirred at 23 °C for 45 min. The reaction mixture was directly loaded onto a silica gel column and eluted with 25:1 $CHCl_3$:MeOH to give a mixture of *trans*/*cis*-**4a** and *trans*/*cis*-**4b** (4.81 g, 37.0 mmol, 68.1%). ^{1}H NMR ($CDCl_3$) δ 3.3−4.3 (m, 6H), 4.8. 5.5 (m, 3H), 5.7−5.9 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 61.2, 63.0, 63.5, 64.3, 66.8, 67.0, 71.8, 72.2, 76.7, 77.2, 100.6, 101.3, 104.2, 104.9, 119.5, 120.5, 121.5, 134.2, 134.5.

***tert*-Butyldimethyl(2-vinyl-1,3-dioxolan-4-ylmethoxy)silane (2a) and *tert*-Butyldimethyl(2-vinyl-1,3-dioxan-5-yloxy)silane (2b).** Imidazole (4.216 g, 61.93 mmol) was added to a flask containing a mixture of *trans*/*cis*-**4a** and *trans*/*cis*-**4b** (4.03 g, 30.96 mmol) in DMF (100 mL) and TBDMSCl (7.00 g, 46.4 mmol) was added at 0 °C. The mixture was stirred at 23 °C overnight and was then diluted in Et_2O (500 mL) prior to washing with H_2O (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure. The residue was purified by silica gel chromatography (hexane:acetone, 20:1) to give *trans*-**2b** (1.506 g, 6.16 mmol, 19.9%), *cis*-**2b** (2.550 g, 10.43 mmol, 33.7%), and a mixture of *trans*/*cis*-**2a** (2.118 g, 8.67 mmol, 28.0%). *trans*-**2b**: ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0,85 (s, 9 H), 3.40 (t, 2H, J = 11 Hz), 3.80 (tt, 1H, J = 5, 11 Hz), 4.07 (dd, 2H, J = 5, 11 Hz), 4.81 (d, 1H, J = 4 Hz), 5.28 (d, 1H, J = 11 Hz), 5.44 (d, 1H, J = 17 Hz), 5.81 (ddd, 1H, J = 4,11,17 Hz); ^{13}C NMR ($CDCl_3$) δ −5.0, 18.0, 25.7, 61.9, 72.0, 100.0, 118.9, 134.0. *cis*-**2b**, ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9 H), 3.61 (s, 1H), 3.92 (s, 4H), 4.98 (d, 1H, J = 5 Hz), 5.27 (d, 1H, J = 10 Hz), 5.43 (d, 1H, J = 17 Hz), 5.88 (ddd, 1H, J = 5,10,17 Hz); ^{13}C NMR ($CDCl_3$) δ −5.0, 18.4, 26.0, 64.6, 71.4, 100.3, 119.0, 134.8.

3-*tert*-Butyldimethylsilyl-1-*O*-1′-(*Z*)-hexadecenyl Glycerol (3a) and 1-*tert*-Butyldimethylsilyl-2-*O*-1′-(*Z*)-hexadecenyl Glycerol (3b). Li (224 mg, 30 wt % in mineral oil, 9.66 mmol) was quickly added under Ar to an airtight flask containing a glass-covered magnetic stirring bar. Hexane (30 mL) was added with stirring for 20 min, and then removed to wash out the mineral oil. This procedure was repeated one more time before addition of DBB (36 mg, 0.138 mmol) and THF (30 mL) at 23 °C under Ar. The dark blue color of the radical anion appeared within 10 s. The reaction mixture was cooled to 0 °C, a mixture of 1-iodotridecane (856 mg, 2.76 mmol) and vinyl dioxolane **2a** (336 mg, 1.38 mmol) in THF (3 mL) was added all at once at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. Hexane (10 mL) was then added and the resulting mixture quenched slowly with H_2O (5 mL) at 0 °C. The organic layer was washed with water (2 × 10 mL), separated, dried over anhydrous Na_2CO_3, and filtered. The solvent was removed by evaporation under reduced pressure and the residue purified by silica gel chromatography (hexane:Et_2O, 8:1) to give the desired product **3a** (109 mg, 0.254 mmol, 18.4%) and a byproduct **3b** (190 mg, 0.443 mmol, 32.1%). **3a**: ^{1}H NMR (C_6D_6) δ 0.00 (s, 6H), 0.89 (s, 12H), 1.20−1.50 (s, 24H), 2.16 (d, 1H, J = 5 Hz), 2.27 (m, 2H), 3.57 (d, 2H, J = 5 Hz), 3.63 (d, 2H, J = 5 Hz), 3.77 (quintet, 1H, J = 5 Hz), 4.40 (q, 1H, J = 6 Hz), 5.87 (d, 1H, J = 6 Hz); ^{13}C NMR (C_6D_6) δ −5.4, 14.3, 18.2, 23.0, 24.5, 26.0, 29.8, 30.0, 30.1, 30.2, 30.3, 32.3, 64.1, 70.8, 72.8, 107.3, 145.6; CI calcd $(M + H)^+$ 429, found 429. **3b**: ^{1}H NMR (C_6D_6) δ 0.02 (s, 6H), 0.93 (s, 12H), 1.20−1.50 (s, 24H), 1.65 (s, 1H), 2.27 (m, 2H), 3.50−3.67 (m, 5H), 4.40 (q, 1H, J = 6 Hz), 5.94 (d, 1H, J = 6 Hz); ^{13}C NMR (C_6D_6) δ −5.4, 14.3, 18.4, 23.1, 24.5, 26.0, 29.8, 30.0, 30.2, 30.3, 32.3, 62.7, 63.2, 82.8, 107.3, 145.0.

2-*tert*-Butyldimethylsilyl-1-*O*-1′-(*Z*)-hexadecenyl Glycerol (3c). The Barbier-type reaction of compound **2b** and 1-iodotridecane was accomplished as described for compound **3a**/**3b**. **3c** was isolated in 47% yield after silica gel purification. ^{1}H NMR (C_6D_6) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.92 (s, 12H), 1.20−1.50 (m, 25H), 2.30 (m, 2H), 3.42 (m, 2H), 3.55 (d, 2H, J = 6 Hz), 3.73 (m, 1H), 4.40 (1H, J = 6 Hz), 5.83 (d, 1H, J = 6 Hz); ^{13}C NMR (C_6D_6) δ −5.2, 5.0, 13.8, 17.7, 22.6, 24.1, 25.5, 29.3, 29.6, 29.7, 29.8, 31.8, 63.7, 71.8, 73.5, 106.4, 145.2; CI calcd $(M + H)^+$ 429, found 429.

3-*tert*-Butyldimethylsilyl-1-*O*-1′-(*Z*)-hexadecenyl Glycerol (3a), 1-*tert*-Butyldimethylsilyl-2-*O*-1′-(*Z*)-hexadecenyl Glycerol (3b), and 2-*tert*-Butyldimethylsilyl-1-*O*-1′-(*Z*)-hexadecenyl Glycerol (3c). The Barbier-type reaction of dioxolane/dioxane **2a/2b** and 1-iodotridecane was accomplished as described for compound **3a**/**3b**. **3a** (3.260 g, 37.1%), **3b** (639 mg, 7.3%), and **3c** (274 mg, 3.1%) were isolated after silica gel purification.

3-*tert*-Butyldimethylsilyl-2-hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenyl Glycerol (5). Pyridine (3.50 mL) and palmitoyl chloride (2.72 mL, 8.97 mmol) were added to a flask containing alcohol **3a** (2.565 g, 5.982 mmol) in THF (50 mL) and the

(31) Marton, D.; Tagliavini, G. *Main Group Metal Chem.* **1990**, *13*, 363−374.

mixture stirred at 23 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue purified by silica gel chromatography (hexane:CH_2Cl_2, 1:1) to give **5** (3.705 g, 5.553 mmol, 92.8%). ^{1}H NMR (C_6D_6) δ 0.03 (s, 6H), 0.93 (m, 15H), 1.31 (m, 48H), 1.62 (m, 2H), 2.22 (t, 2H, J = 7 Hz), 2.29 (m, 2H), 3.72 (d, 1H, J = 5 Hz), 3.73 (d, 1H, J = 5 Hz), 3.80 (d, 2H, J = 5 Hz), 4.43 (q, 1H, J = 6 Hz), 5.21 (quintet, 1H, J = 5 Hz), 5.88 (d, 1H, J = 6 Hz); ^{13}C NMR (C_6D_6) δ −5.4, 14.4, 18.4, 23.1, 24.5, 25.3, 26.0, 29.4, 29.7, 29.8, 29.9, 30.1, 30.2, 30.3, 32.3, 34.5, 61.7, 70.3, 73.0, 107.4, 145.6, 172.5; CI calcd $(M + H)^+$ 667, found 667.

2-Hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenyl Glycerol (6). Imidazole (101 mg, 1.49 mmol) was added to a flask containing **5** (100 mg, 0.149 mmol) in THF (1.5 mL) and the vessel cooled to −23 °C before addition of TBAF (1.49 mL, 1.49 mmol). After the mixture was stirred at −23 °C for 1 h, the solution was loaded onto silica gel and eluted quickly with 2:1 hexane:Et_2O solution that had been cooled to −40 °C to give alcohol **6** (45 mg, 0.814 mmol, 55%). ^{1}H NMR (C_6D_6) δ 0.91 (t, 6H, J = 6 Hz), 1.20−1.50 (m, 49H), 1.57 (m, 2H), 2.16 (t, 2H, J = 7 Hz), 2.27 (m, 2H), 3.51 (d, 2H, J = 5 Hz), 3.64 (d, 2H, J = 5 Hz), 4.43 (q, 1H, J = 6 Hz), 5.05 (quintet, 1H, J = 5 Hz), 5.82 (d, 1H, J = 6 Hz); ^{13}C NMR (C_6D_6) δ 14.3, 23.1, 24.4, 25.3, 29.4, 29.7, 29.8, 29.9, 30.0, 30.1, 30.2, 30.3, 32.3, 34.4, 61.8, 70.6, 73.4, 107.7, 145.4, 172.9.

2-Hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenyl-glycero-3-phosphocholine (7). A solution of alcohol **6** (131 mg, 0.237 mmol) in benzene (25 mL) was added to a flask under Ar. Pyridine (57 μL, 0.71 mmol) and 2-oxo-2-chloro-1,3,2-dioxaphospholane (33 μL, 0.36 mmol) were then added to a flask that had been cooled to 5 °C. After the mixture was stirred at 8 °C overnight under Ar, the solvent was removed under vacuum. The residue was transferred to a pressure bottle with benzene (2 mL) and acetonitrile (5 mL). Trimethylamine (∼3 mL, 33 mmol) was then distilled into the reaction vessel, the vessel sealed, and the mixture stirred at 70 °C for 24 h. After slow release of reactor pressure at 0 °C, the resulting solution was purified with use of a silica gel column (gradient elution with CH_2Cl_2:MeOH:H_2O, 100:0:0, 80:20:0, 65:35:6). Suspended silica gel from the chromatographic fractions was removed with PTFE syringe filters (0.45 μm) to give a white solid (115 mg, 0.160 mmol, 67.6%) after lyophilization from benzene. ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 6H, J = J Hz), 1.20 (s, 48H), 1.51 (m, 2H), 1.94 (m, 2H), 2.24 (t, 2H, J = 7 Hz), 3.33 (s, 9H), 3.70−4.35 (m, 9H), 5.09 (m, 1H), 5.84 (d, 1H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 23.9, 24.9, 29.1, 29.3, 29.5, 29.6, 29.7, 29.9, 31.9, 34.4, 54.3, 59.2, 63.1, 66.2, 70.5, 71.7, 107.6, 144.7, 173.2; ESI calcd $(M + H)^+$ 718, found 718.

2-*tert*-Butyldimethylsilyl-1-*O*-1′-(*Z*)-hexadecenyl-glycero-3-phosphocholine (8). The phosphocholine headgroup was installed with use of compound **3c** as described for compound **7** in 53.6% yield. ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.83 (m, 12H), 1.21 (s, 24H), 1.98 (m, 2H), 3.35 (s, 9H), 3.60−4.30 (m, 10H), 5.88 (d, 1H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ −4.8, 14.0, 18.0, 22.6, 24.1, 25.7, 26.5, 29.3, 29.4, 29.5, 29.6, 29.8, 31.8, 54.1, 59.1, 66.1, 71.0, 71.2, 74.3, 106.2, 145.3; ESI calcd $(M + H)^+$ 594, found 594.

1-*O*-1′-(*Z*)-hexadecenyl-glycero-3-phosphocholine (9). Imidazole (50 mg, 0.732 mmol) was added to a flask containing **8** (124 mg, 0.209 mmol) in THF (3 mL). TBAF (0.626 mL, 0.626 mmol) was added and the mixture stirred at 23 °C for 5 h. The solution was directly loaded onto a silica gel column and purified by step gradient elution (CH_2Cl_2:MeOH:H_2O, 80:20:0, 65:35:6). Suspended silica gel from the chromatographic fractions was removed by using PTFE syringe filters (0.45 μm) to give the desired product (98 mg, 0.204 mmol, 98%) after lyophilization from benzene. ^{1}H NMR (CD_3OD) δ 0.89 (t, 3H, J = 6 Hz), 1.28 (s, 9H), 2.04 (m, 2H), 3.22 (s, 9H), 3.6−3.96 (m, 7H), 4.22−4.38 (m, 3H), 4.90 (s, 1H), 6.00 (d, 1H, J = 6 Hz); ^{13}C NMR (CD_3OD) δ 14.5, 23.7, 25.0, 30.5, 30.6, 30.7, 30.8, 31.0, 33.1,54.7, 60.4, 67.5, 68.0, 70.8, 73.9, 107.9, 146.3; ESI calcd $(M + H)^+$ 480, found 480.

2-Hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenyl-glycero-3-phosphocholine (7). DMAP (46 mg, 0.37 mmol) was added to a flask containing alcohol **9** (90 mg, 0.19 mmol) in CH_2Cl_2 (10 mL). Palmitic anhydride (167 mg, 0.338 mmol) was added and the mixture stirred at 23 °C for 20 h. The solution was directly loaded onto a silica gel column and purified by step gradient elution (CH_2Cl_2:MeOH:H_2O, 80:20:0, 65:35:6). Suspended silica gel from the chromatographic fractions was removed with use of PTFE syringe filters (0.45 μm) to give the desired product (71 mg, 0.099 mmol, 53%) after lyophilization from benzene.

Acknowledgment. The authors gratefully acknowledge the very helpful comments of the reviewers and also the assistance of Mr. Jason Robarge. This work was supported by the NIH (R01 GM55266 and F31 GM18546) and a generous gift of Avanti Polar Lipids.

Supporting Information Available: ^{1}H and ^{13}C NMR spectral data for compounds **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025640U