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Direct Synthesis of Plasmenylcholine from Allyl-Substituted Glycerols

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We report a new method for the facile preparation of plasmenylcholine via reaction of lithioalkoxy allyl intermediates with 1-iodoalkanes as the key step in the stereoselective formation of 1′-(*Z*)-alkenyl glyceryl ethers. The allyl anion intermediate is prepared by treating mono- or disiloxy-protected 1-allylglycerol precursors with *s*-BuLi at −65 to −80 °C. Subsequent addition of 1-iodoalkane solutions at low temperature gives moderate yields of γ-coupled, *Z*-vinyl ethers as the major product and α-coupled product as the minor component. Several different preparative strategies for the total synthesis of plasmalogens are enabled by this simple transformation.

Plasmalogens[1] are *sn*-1 (*Z*)-1′-alkenyl ether glycerophospholipids found in abundance in the electrically active tissues of mammals.[2] These unique phospholipids play important roles in biological processes such as signal transduction,[2−4] membrane fusion,[5,6] and lipid peroxidation.[7] Plasmenylcholines have also been utilized for drug and gene delivery using triggering mechanisms that are activated under acidic or photooxidative conditions.[6,8] Interest in the biochemical and biophysical properties of this unique phospholipid family has prompted several investigations into their stereocontrolled synthesis.[9−12]

Stereoselective formation of the 1′-(*Z*)-alkenyl ether moiety at the glycerol *sn*-1 position is the major challenge in plasmenylcholine synthesis. This linkage is sensitive to acidic and oxidative conditions, whereas the *sn*-2 acyl chain undergoes rapid migration under basic[13] or acidic[14,15] conditions or high temperature.[16] These considerations greatly limit the choice of reagents that can be employed after formation of the alkenyl ether bond. The most notable previous attempts to synthesize plasmenylcholines have been based on elimination reactions;[17] however, these approaches typically give poor stereoselectivity and low yields. The first synthetic pathway to plasmenylcholine with pure (*Z*)-alkenyl ether stereochemistry was accomplished via transformation of acyl glycerol precursors to vinyl phosphates, followed by Pd-catalyzed reduction.[9] The reduction of glyceryl 1′-hexadecynyl ether to glyceryl 1′-(*Z*)-hexadecenyl ether via Lindlar-catalyzed hydrogenation has also been reported;[10] however, this pathway requires multiple steps to prepare the alkynyl ether precursor.

Recently, a pathway for the facile stereoselective synthesis of (*Z*)-alkenyl ethers via reductive cleavage of vinyl acetals in the presence of 1-iodoalkanes has been used for the synthesis of racemic plasmenylcholine and plasmenylcholine analogues.[11,12] In this approach, Barbier-type reactions of vinyl acetals and 1-iodoalkanes produced (*Z*)-alkenyl ethers with high stereoselectivity

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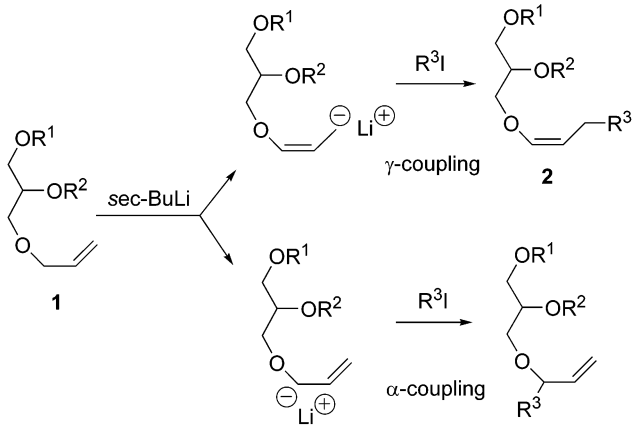
(Z/E > 95:5).[11,12] These observations were attributed to the formation of a cyclic lithioalkoxy allyl intermediate after reductive ring opening of cyclic acetal precursors.[18,19] These results naturally led us to investigate (*Z*)-alkenyl ether bond formation from the reaction of 1-iodoalkanes and lithioalkoxy allyl intermediates that could be generated by deprotonation of allyl ethers with *s*-BuLi. Allyl ethers, widely used protecting groups in carbohydrate chemistry,[20] have not been utilized for the synthesis of plasmenyl-type lipids, despite the well-documented coupling chemistry of lithioalkoxy allyl intermediates with electrophiles.[21] This paper describes a facile new synthetic pathway to chiral plasmenylcholines using lithioalkoxy allyl intermediates, generated from allyl ether with *s*-BuLi, in the key (*Z*)-alkenyl ether bond formation step. Two alternate strategies for plasmenylcholine synthesis using this simple transformation are also described.

Results and Discussion

Allyl Anion-Mediated Formation of 1-(Z)-Alkenyl Ethers. Work by Evans et al.[22] and Still and Macdonald[19] has shown that lithioalkoxy allyl intermediates react with haloalkanes to give γ- and α-coupled products in moderate to high yields. In general, reactions between allyl ether substrates bearing large alkyl substituents give high γ/α ratios (i.e., >2:1) when iodoalkane electrophiles are used. Higher γ/α ratios have also been achieved using lithium−barium transmetalation prior to electrophile addition.[23] The ease and flexibility of this transformation led us to explore the utility of this coupling reaction for the synthesis of 1-(*Z*)-alkenyl glycerol ether intermediates. Deprotonation of doubly protected allyl glycerol with *s*-BuLi, performed at −70 °C to avoid the possibility of a 1,2-Wittig rearrangement,[24] gave yellow-brown solutions upon formation of the lithium allyl intermediate. Subsequent addition of 1-iodotridecane gave moderate yields of γ-coupled (*Z*)-alkenyl ether intermediates as the major products, however, α-coupled materials were also generated as minor byproducts (Table 1). Since the desired γ-coupled products (**2**) typically displayed higher mobility on TLC than the byproducts (e.g., R_f values of **2** were usually about 0.1 units higher than the corresponding regioisomer and 0.2 higher than the starting materials when hexane-rich hexane:CH_2Cl_2 mixtures were used as developing solvent), the α- and γ-coupled regioisomers could readily be separated by silica gel column chromatography. Alkenyl ether stereocontrol was typically > 99% (*Z*), although occasionally up to 2% (*E*)-alkenyl ether product was observed by ^{1}H NMR.

Application of this transformation to the synthesis of plasmenylcholines offers several advantages over previous strategies involving stereoselective *sn*-1 (*Z*)-alkenyl ether bond formation prior to *sn*-2 acylation and phosphocholine headgroup installation in the final step.[9,10] These sequences require multiple protection and deprotection steps for controlled introduction of the alkenyl ether and acyl substituents, often requiring more than 10 steps to produce advanced plasmenylcholine intermediates. The allyl anion route considerably shortens these pathways. For example, treatment of 1-allyloxyglycerol with 2 equiv of BPSCl gives **1** in 93% yield. Deprotonation of this intermediate with *s*-BuLi at −70 °C followed by addition of 1-iodotridecane provides plasmenylcholine precursor **2d** in 48% yield.[9]

TABLE 1. Synthesis of (*Z*)-Alkenyl Glycerol Ethers from Diprotected Allyl Glycerol Triethers



1	R^1	R^2	R^3	Isolated yields **2**	Product ratio γ:α
a[a]	TBS	SEM	$C_{13}H_{27}$	44	2.3:1
b[a]	BPS	SEM	$C_{13}H_{27}$	44	2.6:1
c[b]			$C_{10}H_{21}$	32	2.5:1
d[b]	BPS	BPS	$C_{13}H_{27}$	48	3.4:1
e[a]	TBS	BPS	$C_{13}H_{27}$	47	2.0:1

[a] **1** was added to *s*-BuLi (1.3 equiv) at −70 °C and the mixture stirred for 5 min before addition of R^3I. [b] **1** was added to *s*-BuLi (1.3 equiv) at −70 °C and the mixture stirred for 2−5 min before addition of R^3I.

Dianionic Approaches to Plasmenylcholine. A more direct dianion approach[25] to the synthesis of plasmenylcholine, via double deprotonation of **3** and stepwise addition of 1-iodoalkane and acyl chloride, was then investigated as a means to further expedite the synthesis of plasmenylcholines (Table 2). Selective protection of 1-allyloxyglycerol with TBSCl or BPSCl gave **3a** in 89% yield and **3b** in 94% yield, respectively. Treatment of either **3a** or **3b** with 3 equiv of *s*-BuLi at −70 °C for 1 h, followed by stepwise addition of 1-iodotridecane and palmitoyl chloride gave **4a** in 31% yield and **4b** in 18% yield. In this reaction, **4a** and **4b** are prepared in one reaction vessel from **3a** and **3b**, respectively, enabling

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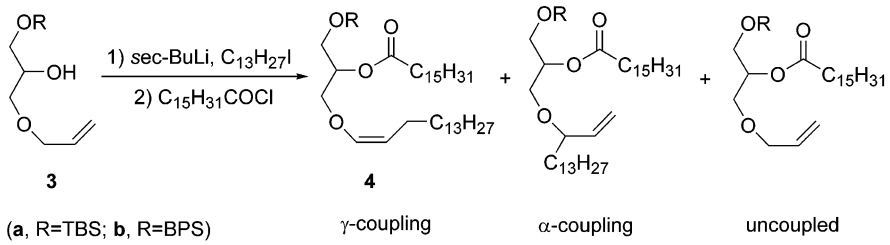
TABLE 2. Synthesis of (*Z*)-Alkenyl Glycerol Ethers from Silyl Allyl Glycerol Diethers



3 (**a**, R=TBS; **b**, R=BPS) **4** γ-coupling α-coupling uncoupled

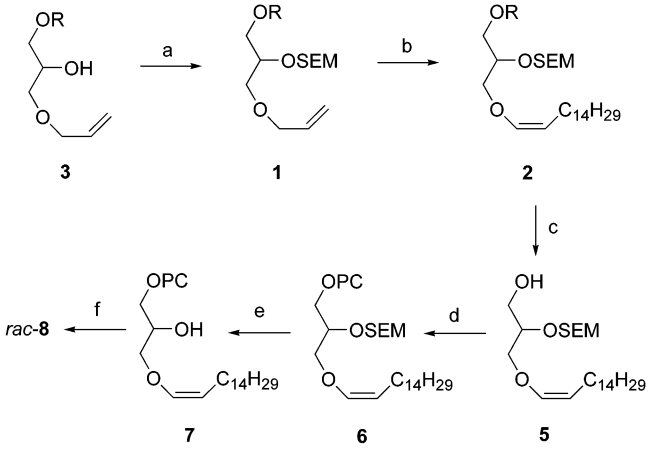
reactant	R	base	time[a] (h)	isolated yield (%) of **4**	product ratio γ/α/u[b]
3b	BPS	*s*-BuLi	1	**4b**: 18	1.5:1.3:1
3a	TBS	*s*-BuLi	1	**4a**: 31	2.6:1.8:1
3a	TBS	*s*-BuLi	2	**4a**: 12	4:n.d.:1
3a	TBS	*t*-BuLi	1	**4a**: 18	2:1:7
3a	TBS	*n*-BuLi	1	**4a**: 0	n.d.:n.d.:1

[a] Reaction time with base at ca. −70 °C before addition of 1-iodotridecane. [b] n.d. = not detected.

the total synthesis of palmitoyl plasmenylcholine with only two additional steps (i.e., silyl ether deprotection and phosphocholine installation). α-Coupled and uncoupled byproducts with acyl modification at the secondary alcohol site were typically obtained along with the desired product using this pathway. Longer reaction times (2 h) of **3a** with *s*-BuLi gave lower yields of all products, suggesting that the dianion intermediate is not stable under these reaction conditions. Lower yields of the desired product (18%) and higher yields of the uncoupled product (63%) were obtained in the reaction of **3a** with *t*-BuLi. Only uncoupled product (91% yield) was obtained in reactions with *n*-BuLi. These results suggest that different butyllithium reagents generate different dianion:monoanion ratios under these reaction conditions. The data also show that the dianionic approach is most effective when the reaction is performed using *s*-BuLi at −70 °C for 1 h. Even though **4a** is formed in modest yields using this approach, it is a one-pot transformation, making it faster and competitive with the cumulative yields of lengthier routes.

Synthetic Approaches to Plasmenylcholine Involving Selective Deprotection. The main drawback of the synthetic pathway utilizing **4** as a plasmalogen precursor is that acyl migration—which can occur during TBAF-mediated desilylation, chromatographic purification, and phosphocholine modification[9]—generates an undesired 1-(*Z*)-alkenyl-3-acylglycerol byproduct. Installation of the phosphocholine headgroup before acylation obviates this problem.[12] We, therefore, adapted this strategy for the synthesis of plasmenylcholine by differentially protecting the hydroxymethyl groups of **3a** and **3b** with TBS or BPS and the secondary glycerol hydroxyl groups with 2-(trimethylsilyl)ethoxymethyl (SEM)[26] (Scheme 1). Treatment of **3a** and **3b** with SEMCl gives the 1-allyl-3-silyl-2-SEM protected products, **1a** and **1b** in 82% and 89% yield, respectively. These intermediates were then sequentially treated with *s*-BuLi and 1-iodotridecane to give the desired (*Z*)-alkenyl ether intermediates **2a** and **2b**, both in 44% yield. TBAF deprotection of **2a** and **2b** in the presence of imidazole (to give **5** in 80% and 97% yield, respectively), installation of the phosphocholine headgroup (**6**, 77% yield), and removal of the SEM protecting group with TBAF in HMPA at 90 °C gives lysoplasmenylcholine **7** in 80% yield. Acylation[27] of **7** with palmitic anhydride in the presence of DMAP gives plasmenylcholine **8** in 53% yield.[12] ^{31}P NMR of **7** and **8** gave a single phosphorus resonance (Supporting Information), indicating that no phosphorus-containing migration byproducts were produced during the SEM deprotection and acylation steps. A major advantage of this route is that lysoplasmenylcholine (**7**) serves as the key precursor for a general plasmenylcholine synthesis, allowing many different types of biologically important plasmenylcholines with different *sn*-2 acyl chains (e.g.,

SCHEME 1. Selective Deprotection Pathway to Plasmenylcholine[a]



3 **1** **2** **5** **6** **7**

a, R = TBS **b**, R = BPS
SEM = $CH_2OCH_2CH_2Si(CH_3)_3$ PC = $PO_3(CH_2)_2NMe_3$

[a] Reagents: (a) NaH, SEMCl, THF, **1a**, 82% yield (**1b**, 89% yield); (b) *s*-BuLi, $C_{13}H_{27}I$, THF (44% yield for both **2a** and **2b**); (c) TBAF, imidazole, THF, 97% yield from **2b** (80% yield from **2a**); (d) (i) 2-oxo-2-chloro-1,3,2-dioxaphospholane, Et_3N, C_6H_6; (ii) Me_3N, $MeCN/C_6H_6$ (77% yield for steps i and ii, combined); (e) TBAF, HMPA (80% yield); (f) palmitic anhydride, DMAP, CH_2Cl_2 (53% yield).

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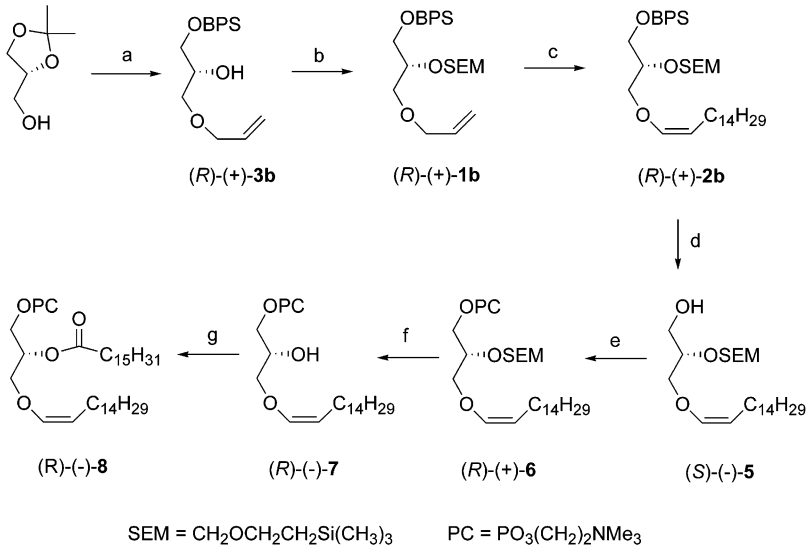
SCHEME 2. Synthesis of Chiral Plasmenylcholine via the Selective Deprotection Pathway[a]



[a] Reagents: (a) (i) NaH, allyl bromide; (ii) AG50W-X2 resin, THF/H_2O; (iii) BPSCl, imidazole, DMF (84% yield, steps i−iii, combined); (b) NaH, SEMCl, THF (74% yield); (c) *s*-BuLi, $C_{13}H_{27}I$, THF (37% yield); (d) TBAF, imidazole, THF (94% yield); (e) (i) 2-oxo-2-chloro-1,3,2-dioxaphospholane, Et_3N, C_6H_6; (ii) Me_3N, MeCN/C_6H_6 (76% yield for steps i and ii, combined); (f) TBAF, HMPA (51% yield); (g) palmitic anhydride, DMAP, CH_2Cl_2 (48% yield).

acetyl, arachidonyl) to be readily prepared via a single acylation step.

Synthesis of Chiral Plasmenylcholine from (*R*)-(−)-2,2-Dimethyl-1,3-dioxolane-4-methanol. Commercially available racemic starting materials were used to develop the previous three synthetic pathways to plasmenylcholine (Tables 1 and 2 and Scheme 1). We utilized commercially available (*R*)-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol as a starting material for the synthesis of naturally occurring chiral plasmenylcholine and (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol for the preparation of the congener with inverted stereochemistry (Scheme 2). These compounds are readily protected with allyl bromide, hydrolyzed in the presence of solid acid catalysts and protected with BPSCl to give (*R*)-(+)-**3b** and (*S*)-(−)-**3b** in 84 and 83% yield, respectively. Chiral plasmenylcholines (*R*)-(−)-**8** and (*S*)-(+)-**8** were subsequently prepared using the selective deprotection route described in Scheme 1. The reaction of (*S*)-(−)-**5**, (*R*)-(+)-**5**, and racemic **5** with (*R*)-(−)-α-methoxy-*β*-trifluoromethyl-phenylacetic acid chloride (Mosher reagent) in the presence of NEt_3 and a catalytic amount of DMAP showed that the stereochemistry at the *sn*-2 position was retained during the formation of the (*Z*)-alkenyl ether bond[9] (i.e., ^{1}H NMR spectroscopy of the Mosher ester intermediates of (*S*)-(−)-**5** and (*R*)-(+)-**5** in d^6-benzene solution clearly showed that no racemization occurred, Figure 1).

Conclusions

A facile synthetic method has been developed for the preparation of (*Z*)-alkenyl glyceryl ethers using lithioalkoxy allyl anion coupling with 1-iodoalkanes. Intermediates from this key alkenyl ether bond-forming step have been used for the total synthesis of plasmenylcholines such that each element of the plasmenylcholine structure can be varied. The most direct of these synthetic routes uses 1-allyl-3-silyl-protected glycerols as the starting material for conversion to 1-(*Z*)-alkenyl-2-acyl-3-silyl-protected glycerols. Although the yields from this step of the sequence are moderate to low, the overall efficiency benefits from the use of a one-pot reaction. An alternative route employing selective protection−deprotection schemes that eliminate acyl migration problems to prepare lysoplasmenylcholine and plasmenylcholine has also been developed. This pathway enables the synthesis of a wide variety of plasmenylcholine derivatives containing different acyl groups via lysoplasmenylcholine acylation.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm relative to the residual solvent peaks as internal standard. ^{31}P NMR spectra were recorded at 121 MHz and no internal standard material (85% H_3PO_4) was used since **7** and **8** are highly acid sensitive. MS (EI/CI/ESI) was performed by the MCMP Mass Spectrometry Service of Purdue University. Column chromatography was performed using 230−400 mesh silica gel and analytical grade solvents. THF was distilled from sodium benzophenone ketyl. Benzene, triethylamine, MeCN, DMF, and pyridine were distilled from CaH_2. All other chemical were used without further purification. The highest yields obtained for each reaction are reported. Yields were calculated without consideration of recovered starting material since, in most cases, the amount of starting material recovered was insignificant.

Synthesis. 1-Allyl-2,3-bis-*tert*-butyldiphenylsilyl-*rac*-glycerol (1d). Imidazole (3.268 g, 48.0 mmol) was added to 3-allyloxy-1,2-propanediol (1.32 g, 10.0 mmol) in DMF (25 mL) at 0 °C. BPSCl (6.00 g, 24.0 mmol) was slowly added at 0 °C and the mixture stirred overnight under Ar at 23 °C. Diethyl ether (150 mL) was added and the reaction mixture extracted with water (2 × 50 mL). The ether layer was dried over $MgSO_4$ and evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/Et_2O, 16:1) to give **1d** as an oil (5.68 g, 9.33 mmol, 93% yield): ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9H), 1.06 (s, 9H), 3.44 (dd, 1H, J = 5, 10 Hz), 3.58 (dd, 1H, J = 5, 10 Hz), 3.70 (d, 2H, J = 5 Hz), 3.75−3.84 (m, 2H), 3.94−4.01 (m, 1H), 5.07−5.20 (m, 2H), 5.72−

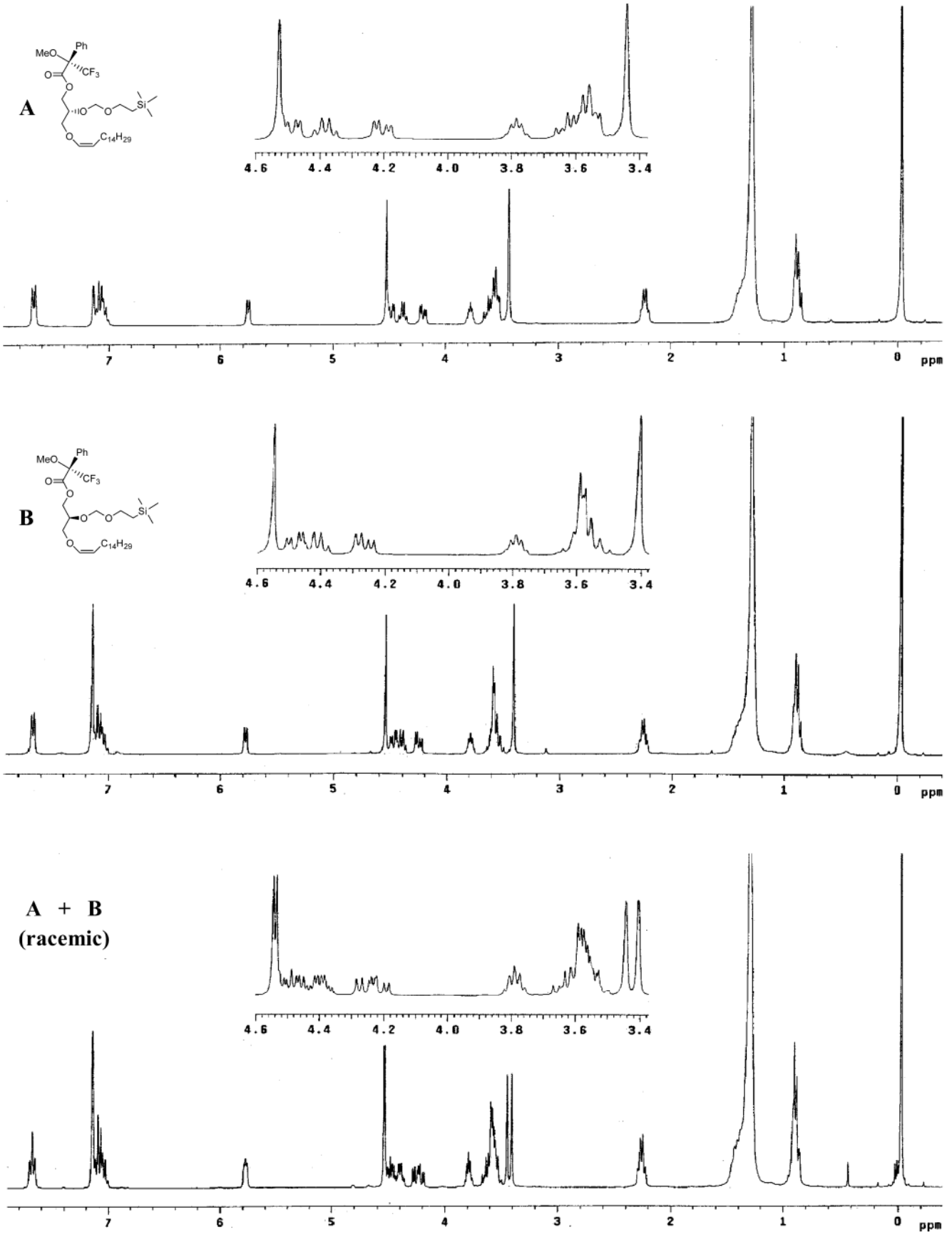


FIGURE 1. ^{1}H NMR spectra of Mosher esters of chiral and racemic **5**.

5.85 (m, 1H), 7.27−7.43 (m, 12H), 7.60−7.72 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 19.3, 19.4, 26.9, 27.0, 65.0, 71.2, 72.1, 72.9, 116.5, 127.5, 127.6, 129.6, 133.7, 134.1, 134.3, 135.0, 135.6, 135.7, 135.9; CI $(M - H)^+$ calcd 607, found 607.

2,3-Bis-*tert*-butyldiphenylsilyl-1-*O*-1′-(Z)-hexadecenyl-*rac*-glycerol (2d). *sec*-BuLi (0.61 mL, 1.3 M in cyclohexane) was added to THF (7 mL) at −70 °C. **1d** (371 mg, 0.609 mmol) in THF (1 mL) was added slowly, and the reaction mixture was stirred under Ar at −70 °C for 2 min. 1-Iodotridecane (245 mg, 0.792 mmol) in THF (4 mL) was slowly added and the mixture stirred at −70 °C for 10 min before warming to 0 °C. Hexane (30 mL) was then added and the mixture washed with H_2O (2 × 5 mL). Silica gel chromatography (hexane/CH_2Cl_2, 8:1) of the organic residue gave **2d**[9] as an oil (229 mg, 29.0 mmol, 48% yield): ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 6 Hz), 1.06 (s, 9H), 1.10 (s, 9H), 1.3 (m, 24H), 2.04 (m, 2H), 3.66−4.18 (m, 5H), 4.28 (q, 1H, J = 6 Hz), 5.82 (d, 1H, J = 6 Hz), 7.30−7.45 (m, 12H), 7.61−7.74 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.3, 19.4, 22.8, 23.4, 24.1, 26.9, 27.0, 29.5, 29.7, 29.8, 30.0, 32.0, 64.5, 72.8, 106.5, 127.6, 127.7, 129.6, 129.7, 133.6, 134.0, 135.6, 135.7, 135.9, 136.0, 145.5.

1-Allyl-3-*tert*-butyldimethylsilyl-*rac*-glycerol (3a). Imidazole (3.268 g, 48.0 mmol) was added to 3-allyloxy-1,2-propanediol (2.64 g, 20.0 mmol) in DMF (25 mL) at 0 °C. TBSCl (3.620 g, 24.0 mmol) was slowly added at 0 °C and the mixture stirred under Ar at 23 °C for 3 h. Hexane (300 mL) was added and the reaction mixture washed with water (2 × 50 mL). Silica gel chromatographic purification (hexane/Et_2O, 2:1) from the organic residue gave **3a** as an oil (4.377 g, 17.8 mmol, 89% yield). **3a**: ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.84 (s, 9H), 2.58 (m, 1H), 3.37−3.47 (m, 2H), 3.59 (d, 2H, J = 5 Hz), 3.75 (quintet, 1H, J = 5 Hz), 3.95 (d, 2H, J = 6 Hz), 5.12 (d, 1H, J = 10 Hz), 5.20 (d, 1H, J = 17 Hz), 5.84 (ddt, 1H, J = 10, 17, 6 Hz); ^{13}C NMR ($CDCl_3$) δ −5.5, 18.2, 25.7, 64.0, 70.6, 70.9, 72.2, 117.0, 134.5; CI (M + H)$^+$ calcd 247, found 247.

1-Allyl-3-*tert*-butyldiphenylsilyl-*rac*-glycerol (3b). Compound **3b** was prepared as described for **3a** using BPSCl in 94% yield. **3b**: ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 2.50 (s, 1H), 3.49−3.59 (m, 2H), 3.73 (d, 2H, J = 5 Hz), 3.92 (quintet, 1H, J = 5 Hz), 4.00 (dt, 2H, J = 6, 1 Hz), 5.18 (ddt, 1H, J = 10, 1, 1 Hz), 5.26 (ddt, 1H, J = 17, 1, 1 Hz), 5.89 (ddt, 1H, J = 10, 17, 6 Hz), 7.36−7.46 (m, 6H), 7.66−7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.3, 26.9, 64.9, 70.8, 71.0, 72.4, 117.2, 127.8, 129.9, 133.3, 134.6, 135.6.

***3-tert*-Butyldimethylsilyl-2-hexadecanoyl-1-*O*-1′-(Z)-hexadecenyl-*rac*-glycerol (4a).** *s*-BuLi (2.3 mL, 1.3 M in cyclohexane) was slowly added to **3a** (246 mg, 1.00 mmol) in THF (8 mL) at −70 °C and the reaction mixture stirred under Ar at −70 °C for 1 h. 1-Iodotridecane (680 mg, 2.09 mmol) was added and the reaction mixture stirred for an additional 10 min at −70 °C before warming to 0 °C. Palmitoyl chloride (450 μL, 1.50 mmol) was then added with stirring at 0 °C for 10 min. Hexane (30 mL) was then added and the mixture extracted with water (2 × 5 mL). Silica gel chromatographic purification (hexane/CH_2Cl_2, 2:1) of the organic residue gave **4a**[12] as an oil (206 mg, 0.309 mmol, 31% yield). During silica gel column purification, the desired γ-coupled product, **4a**, was isolated from early fractions due to its lower polarity compared to the α-coupled byproducts. **4a**: ^{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.

***3-tert*-Butyldiphenylsilyl-2-hexadecanoyl-1-*O*-1′-(Z)-hexadecenyl-*rac*-glycerol (4b).** Compound **4b**[9,10] was prepared from **3b** as described for **4a** in 18% yield. **4b**: ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 6H), 1.05 (s, 9H), 1.25 (m, 48H), 1.59 (m, 2H), 2.00 (q, 2H, J = 7 Hz), 2.27 (td, 2H, J = 7, 2 Hz), 3.79 (d, 1H, J = 5 Hz), 3.93 (m, 2H), 4.34 (q, 1H, J = 6 Hz), 5.10 (quintet, 1H, J = 5 Hz), 5.91 (d, 1H, J = 6 Hz), 7.34−7.45 (m, 6H), 7.64−7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.3, 22.7, 24.0, 25.0, 26.8, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 32.0, 34.5, 62.2, 70.0, 72.6, 107.8, 127.8, 129.8, 133.2, 135.6, 144.9, 173.1; ESI calcd (M + Na)$^+$ 813, found 813.

1-Allyl-3-*tert*-butylmethylsilyl-2-(2-trimethylsilanylethoxymethyl)-*rac*-glycerol (1a). Compound **3a** (1.48 g, 6.00 mmol) in THF (5 mL) was slowly added to a solution containing NaH (182 mg, 7.20 mmol) in THF (30 mL) and the reaction mixture stirred under Ar at 23 °C for 30 min. SEMCl (0.90 mL, 5.08 mmol) was added and the reaction mixture heated at reflux for 1 h. Hexane (200 mL) was added after cooling and the mixture extracted with water (2 × 20 mL). Silica gel chromatographic purification (hexane/Et_2O, 8:1) gave **1a** as an oil (1.569 g, 4.16 mmol, 82% yield). **1a**: ^{1}H NMR ($CDCl_3$) δ 0.00−0.07 (m, 15H), 0.88−0.95 (m, 11H), 3.35−3.68 (m, 6H), 3.78 (quintet, 1H, J = 5 Hz), 3.98 (d, 2H, J = 5 Hz), 4.76 (s, 2H), 5.14 (d, 1H, J = 10 Hz), 5.24 (d, 1H, J = 17 Hz), 5.87 (ddt, 1H, J = 10, 17, 5 Hz); ^{13}C NMR ($CDCl_3$) δ −5.4, −1.4, 18.0, 18.2, 25.9, 62.9, 65.0, 70.0, 72.3, 76.6, 94.5, 116.7, 134.8.

1-Allyl-3-*tert*-butyldiphenylsilyl-2-(2-trimethylsilanylethoxymethyl)-*rac*-glycerol (1b). Compound **1b** was prepared from **3b** as described for **1a** in 89% yield. **1b**: ^{1}H NMR ($CDCl_3$) δ −0.02 (s, 9H), 0.88 (t, 2H, J = 7 Hz), 1.05 (s, 9H), 3.51−3.69 (m, 4H), 3.75 (d, 2H, J = 6 Hz), 3.89 (quintet, 1H, J = 5 Hz), 4.00 (dt, 2H, J = 6, 1 Hz), 4.75 (s, 2H), 5.16 (ddt, 1H, J = 10, 1, 1 Hz), 5.25 (ddt, 1H, J = 17, 1, 1 Hz), 5.89 (ddt, 1H, J = 10, 17, 6 Hz), 7.33−7.44 (m, 6H), 7.66−7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −1.4, 18.1,19.3, 26.9, 63.5, 65.1, 70.1, 72.4, 76.4, 94.4,116.9, 127.7, 129.7, 133.5, 134.9, 135.6; CI (M + H)$^+$ calcd 501, found 501.

***(R)*-(+)-1b.** This was prepared as described above using (*R*)-(+)-**3b**: $[\alpha]^{25}_D$ +13.0 (*c* 1.00, $CHCl_3$).

***(S)*-(−)-1b.** This was prepared as described above using (*S*)-(−)-**3b**: $[\alpha]^{25}_D$ −11.2 (*c* 1.00, $CHCl_3$).

3-*tert*-Butyldimethylsilyl-1-*O*-1′-(*Z*)-hexadecenyl-2-(2-trimethylsilanylethoxymethyl)-*rac*-glycerol (2a) and 3-*tert*-Butyldiphenylsilyl-1-*O*-1′-(*Z*)-hexadecenyl-2-(2-trimethylsilanylethoxymethyl)-*rac*-glycerol (2b). The products **2a** (44% yield) and **2b** (44% yield) were prepared from **1a** and **1b**, respectively, as described for **2d**. **2a**: ^{1}H NMR ($CDCl_3$) δ −0.01−0.04 (m, 15H), 0.84−0.94 (m, 14H), 1.24 (m, 24H), 2.03 (q, 2H, J = 6 Hz), 3.59−3.85 (m, 7H), 4.29 (q, 1H, J = 6 Hz), 4.75 (s, 2H), 5.90 (d, 1H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ −5.4, −1.4, 14.1, 18.1, 18.3, 22.7, 24.0, 25.8, 25.9, 29.4, 29.6, 29.7, 29.9, 31.9, 62.7, 65.2, 71.9, 76.6, 94.6, 107.0, 145.2; CI (M + H)$^+$ calcd 559, found 559. **2b**: ^{1}H NMR ($CDCl_3$) δ −0.02 (s, 9H), 0.88 (m, 5H), 1.06 (s, 9H), 1.26 (m, 24H), 2.03 (q, 2H, J = 6 Hz), 3.55−3.98 (m, 7H), 4.32 (q, 1H, J = 6 Hz), 4.73 (s, 2H), 5.95 (d, 1H, J = 6 Hz), 7.35−7.44 (m, 6H), 7.67 (d, 4H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ −1.4, 14.2, 18.1, 19.3, 22.7, 24.0, 26.9, 29.4, 29.6, 29.7, 29.8, 29.9, 32.0, 63.3, 65.2, 72.1, 76.3, 94.5, 107.2, 127.7, 129.7, 133.4, 135.6, 145.2; CI (M + H)$^+$ calcd 683, found 683.

***(R)*-(+)-2b.** This was prepared as described above using (*R*)-(+)-**1b**: $[\alpha]^{25}_D$ +7.0 (*c* 1.00, $CHCl_3$).

***(S)*-(−)-2b.** This was prepared as described above using (*S*)-(−)-**1b**: $[\alpha]^{25}_D$ −6.6 (*c* 1.00, $CHCl_3$).

1-*O*-1′-(*Z*)-Hexadecenyl-2-(2-trimethylsilanylethoxymethyl)-*rac*-glycerol (5). Imidazole (276 mg, 4.06 mmol) and TBAF (3.5 mL, 1.0 M in THF) were added to **2b** (794 mg, 1.16 mmol) in THF (20 mL) and the reaction mixture stirred at 23 °C for 2 h. The reaction mixture was filtered through a silica gel plug and the plug washed with Et_2O. The organic solution was concentrated and purified by silica gel chromatography (hexane/Et_2O, 1:1) to give **5** as an oil (500 mg, 1.13 mmol, 97% yield). **5** was similarly prepared from **2a** in 80% yield: ^{1}H NMR ($CDCl_3$) δ −0.02 (s, 9H), 0.84 (t, 3H, J = 7 Hz), 0.92 (t, 2H, J = 8 Hz), 1.22 (m, 24H), 2.00 (q, 2H, J = 7 Hz), 2.88 (dd, 1H, J = 5, 8 Hz), 3.53−3.78 (m, 7H), 4.31 (q, 1H, J = 6 Hz), 4.70 (d, 1H, J = 7 Hz), 4.77 (d, 1H, J = 7 Hz), 5.87 (d, 1H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ −1.4, 14.1, 18.1, 22.7, 24.0, 29.3, 29.4, 29.6, 29.7, 29.8, 31.9, 63.0, 65.7, 71.7, 79.1, 95.2, 107.8, 144.7; CI (M + H)$^+$ calcd 445, found 445.

(*S*)-(−)-5. This was prepared as described above using (*R*)−(+)-**2b**: $[\alpha]^{25}_D$ −16.0 (*c* 1.00, $CHCl_3$).

(*R*)-(+)-5. This was prepared as described above using (*S*)-(−)-**2b**: $[\alpha]^{25}_D$ +19.0 (*c* 1.00, $CHCl_3$).

1-*O*-1′-(*Z*)-Hexadecenyl-2-(2-trimethylsilanylethoxymethyl)-*rac*-glycero-3-phosphocholine (6). Triethylamine (550 μL, 3.94 mmol) and 2-oxo-2-chloro-1,3,2-dioxaphospholane (155 μL, 1.69 mmol) were added to a flask containing **5** (500 mg, 1.13 mmol) in benzene (25 mL) that had been cooled to 5 °C. The solvent was removed under vacuum after stirring at 23 °C for 3 h under Ar. The residue was transferred to a pressure vessel with benzene (10 mL) and acetonitrile (20 mL). Trimethylamine (∼15 mL) was then condensed into the vessel with liquid nitrogen cooling and the mixture stirred at 70 °C for 24 h. After slow release of high NMe_3 pressure at 0 °C, the resulting solution was purified using a silica gel column (100:0:0, 80:20:0, and 65:35:6 CH_2Cl_2/MeOH/H_2O step gradient). Suspended silica gel from the chromatographic fractions was removed using a 0.45 μm PTFE syringe filter to give a white solid (529 mg, 0.867 mmol, 77% yield) after lyophilization from benzene: ^{1}H NMR ($CDCl_3$) δ −0.07 (s, 9H), 0.79 (m, 5H), 1.17 (m, 24H), 1.93 (q, 2H, J = 6 Hz), 3.29 (s, 9H), 3.47−3.83 (m, 9H), 4.21 (m, 3H), 4.64 (d, 1H, J = 7 Hz), 4.70 (d, 1H, J = 7 Hz), 5.85 (d, 1H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ −1.4, 14.1, 18.0, 22.6, 24.0, 29.3, 29.4, 29.6, 29.7, 29.8, 31.9, 54.3, 59.2, 64.4, 65.3, 66.3, 72.4, 75.0, 94.3, 107.0, 145.1; ESI $(M + H)^+$ calcd 610, found 610.

(*R*)-(+)-6. This was prepared as described above using (*S*)-(−)-**5**: $[\alpha]^{25}_D$ +20.8 (*c* 1.00, $CHCl_3$).

(*S*)-(−)-6. This was prepared as described above using (*R*)-(+)-**5**: $[\alpha]^{25}_D$ −16.9 (*c* 1.00, $CHCl_3$).

1-*O*-1′-(*Z*)-Hexadecenyl-*rac*-glycero-3-phosphocholine (7). TBAF (2.4 mL, 1.0 M in THF) was added to **6** (260 mg, 0.426 mmol) in HMPA (5 mL) and the mixture stirred at 90 °C for 18 h. The solution was directly loaded onto a silica gel column and purified via step gradient elution with CH_2Cl_2/MeOH/H_2O (80:20:0, then 65:35:6). Suspended silica gel from the chromatographic fractions was removed using a 0.45 μm PTFE syringe filter to give **7**[12] (164 mg, 0.342 mmol, 80% yield) 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; ^{31}P NMR ($CDCl_3$) δ 1.468; ESI calcd $(M + H)^+$ 480, found 480.

(*R*)−(−)-7. This was prepared as described above using (*R*)-(+)-**6**: $[\alpha]^{25}_D$ −8.3 (*c* 1.00, $CHCl_3$).

(*S*)-(+)-7. This was prepared as described above using (*S*)-(−)-**6**: $[\alpha]^{25}_D$ +12.0 (*c* 1.00, $CHCl_3$).

2-Hexadecanoyl-1-*O*-1′-(*Z*)-hexadecenyl-*rac*-glycero-3-phosphocholine (8), (*R*)-(−)-6, and (*S*)-(+)-8. Racemic **8**,[12] chiral (*R*)-(−)-**8**,[9,10] and (*S*)-(+)-**8** was prepared from **7**, (*R*)-(−)-**7**, and (*S*)-(+)-**7**, respectively, by the reaction of palmitic anhydride in the presence of DMAP:[12] ^{31}P NMR ($CDCl_3$) δ 0.156. **(*R*)-(−)-8**: $[\alpha]^{25}_D$ −1.7 (*c* 1.00, $CHCl_3$). **(*S*)-(+)-8**: $[\alpha]^{25}_D$ +0.5 (*c* 1.00, $CHCl_3$).

(*R*)-(+)-1-Allyl-3-*tert*-butyldiphenylsilyl-*sn*-glycerol ((*R*)-(+)-3b). (*R*)-(−)-2,2-Dimethyl-1,3-dioxolane-4-methanol (5.00 g, 37.8 mmol) was added to a solution containing NaH (1.43 g, 56.7 mmol) in THF (150 mL) at 0 °C and the mixture stirred at 23 °C until gas evolution ceased. Allyl bromide (4.9 mL, 56.7 mmol) was added slowly and the mixture stirred under Ar at 23 °C for 2 h. Hexane (200 mL) was then added and the solution extracted with H_2O (2 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated to give an oil. AG50W-X2 (1 g) and THF/H_2O (4:1, 50 mL) solution were added to the oil. The reaction mixture was heated at reflux overnight before the solid resin was removed by filtration. The solution was evaporated under reduced pressure and CH_2Cl_2 (100 mL) added. The organic layer was dried over $MgSO_4$ and concentrated to give an oil (4.80 g). The oil was further dried under high vacuum. Imidazole (5.44 g, 80 mmol) was added to the oil in DMF (80 mL). BPSCl (9.3 mL, 36.3 mmol) was slowly added at 0 °C and the mixture stirred under Ar at 23 °C for 1 h. Hexane (200 mL) was added and the reaction mixture washed with water (2 × 50 mL). Silica gel chromatographic purification (CH_2Cl_2) of the organic residue gave (*R*)-(+)-**3b** as an oil (11.75 g, 31.7 mmol, 84% yield): $[\alpha]^{25}_D$ +2.9 (*c* 1.00, $CHCl_3$).

(*S*)-(−)-1-Allyl-3-*tert*-butyldiphenylsilyl-*sn*-glycerol ((*S*)-(−)-3b). This was prepared as described above using (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol in 83% yield: $[\alpha]^{25}_D$ −3.5 (*c* 1.00, $CHCl_3$).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data for compounds **1a**,**b**,**d**, **2a**,**b**,**d**, and **3**−**8**. ^{31}P NMR spectral data for compounds **7** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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