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Guivisdalsky, Pedro N., Ph.D.

City University of New York, 1989

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CHIRAL SYNTHESIS OF ETHER-LINKED LIPIDS VIA RING OPENING OF GLYCIDYL DERIVATIVES MEDIATED BY BORON TRIFLUORIDE ETHERATE

by

PEDRO N. GUIVISDALSKY

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1989

This manuscript has been read and accepted for the graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy

9/22/89
Date

Robert Bittman
Chair of Examining Committee

10/2/89
Date

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Executive Officer

Robert Engel

William Frost Berkowitz

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Supervisory Committee

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Abstract

Chiral Synthesis of Ether-linked Lipids via Ring Opening of Glycidyl Derivatives Mediated by Boron Trifluoride Etherate

by

Pedro N. Guivisdalsky

Advisor: Professor Robert Bittman

The boron trifluoride etherate mediated regio- and stereoselective nucleophilic opening of (*R*)- and (*S*)-glycidyl derivatives, such as the tosylate, *p*-nitrobenzenesulfonate, and oxiranemethanol *tert*-butyldiphenylsilyl ether is reported in this dissertation. The stereoselectivity of the ring-opening reaction with different nucleophiles such as benzyl alcohol, thiophenol, and various long-chain alcohols (1-hexadecanol, oleyl alcohol, and petroselenyl alcohol), was determined by chiral high-pressure liquid chromatography and high-field ^{1}H-NMR spectroscopy of the (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid esters. The regioselectivity of the ring opening reaction (C_3 vs. C_1) was studied by reverse-phase high-pressure liquid chromatography. When long-chain alcohols are used as the nucleophiles, the ring-opened product is converted into ether-linked phospho- and glycolipids of biological importance. The syntheses of 1-*O*-hexadecyl-2-acetyl-*sn*-3-glycerophosphocholine (platelet activating factor) and 1-*O*-hexadecyl-2-*O*-methyl-*sn*-3-glycerophosphocholine and their enantiomers are described in detail.

Acknowledgment

I am sincerely grateful to my advisor, now a friend and colleague, Professor Robert Bittman, whom with his support and friendship this thesis became a reality. His knowledge, patience, and unrestricted confidence in me made me not only a better scientist but also a better person.

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Special thanks to Queens College of The City University of New York for providing me with the physical space that through these wonderful years has became my second home.

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I appreciate the help of Dr. Michael Blumenstein of Hunter College for recording the 400- MHz ^{1}H NMR spectra.

I am deeply greateful to my mother Nilda and father Leon for their guidance, understanding, and enormous moral support through all this years, which have made me whom I am today.

At last, very special thanks to my wife and friend, Berti, who has also been a major part of this thesis. Her love, kindness and companionship during good and bad times have given me the strengh to arrive at the most important stage of my career, the Ph. D. degree.

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Dedicated to those who made this thesis possible:

My parents, my wife, and my wonderfull daugther Alison

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Pedro N. Guivisdalsky and Robert Bittman, *Tetrahedron Lett.*, **1988,** *29,* 4393-4396.

CHAPTER 1: Introduction

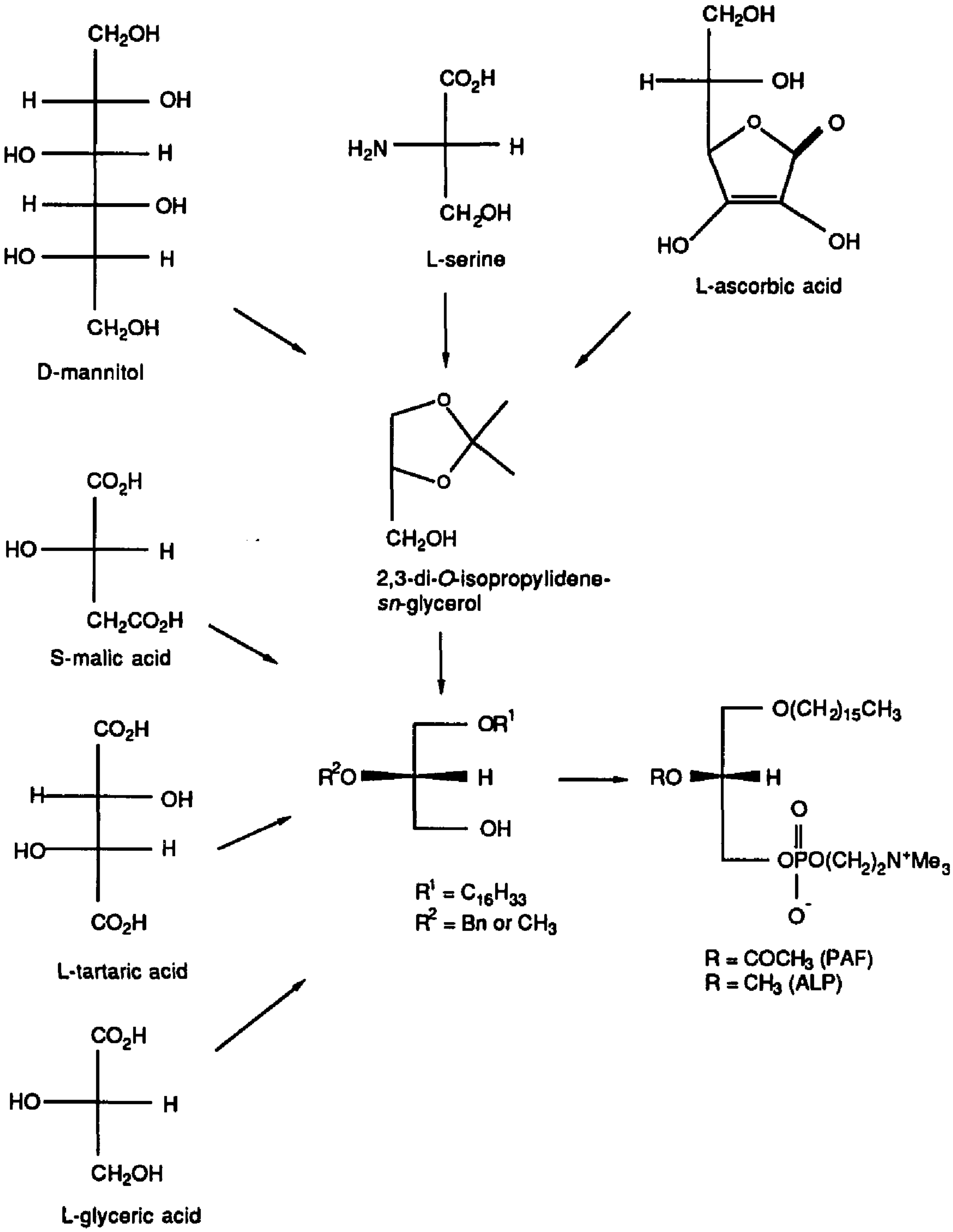
Ether-linked phospholipids are important structural constituents of membranes. Some ether-linked phospholipids are highly biologically active molecules. Scheme 1 shows the synthetic routes to these liopids that have been used in the past. All of the previous synthetic approaches use natural sources as the starting materials such as D-mannitol, [1] L-serine, [2] L- or D-tartaric acid, [3] L-ascorbic acid, [4] L-malic acid, [5] L-glyceric acid. [6] In all of these routes shown in Scheme 1 the chirality of the natural product determines the configuration at the *sn*-2 position of the glycerol backbond, making the synthesis of the unnatural enantiomer difficult because of the need to use inversion of chirality or expensive unnatural sources. Furthermore, these routes require many steps because of the extensive use of protection-deprotection steps, making the synthesis of phospholipids tedious.

Glycidyl derivatives are shown in these dissertation to serve as excellent C_3-synthons for the synthesis of various ether-linked phospholipids.

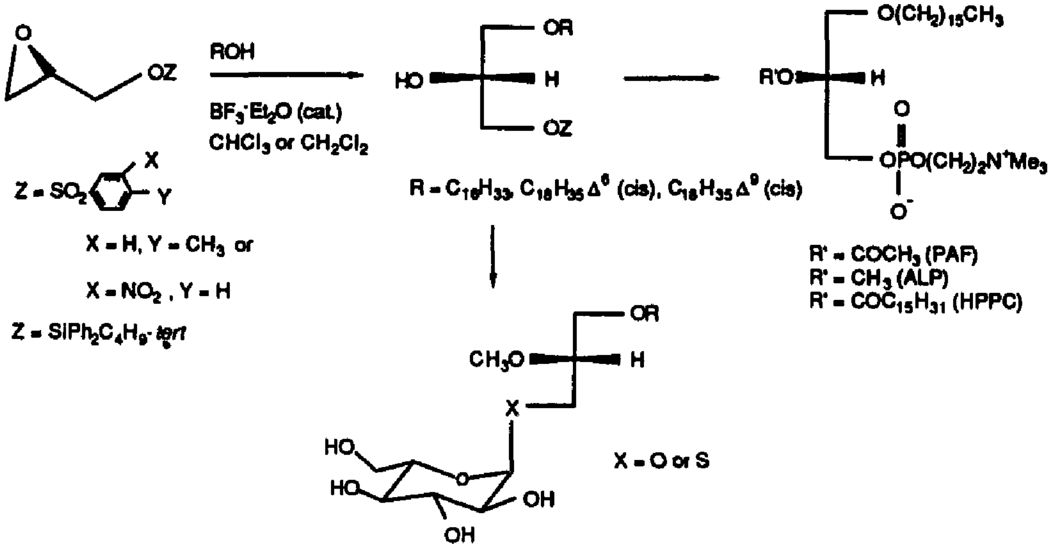
Epoxides are highly versatile and important intermediates in organic synthesis because of their reactivity.[7] Chiral epoxides are available by the titanium-catalyzed asymmetric epoxidation of prochiral allylic alcohols either by using stoichiometric[8]or catalytic[9] amounts of the titanium tartrate complex. The latter procedure is more economical, reaction conditions are milder, products are easier to isolate, and offers potential for in-situ derivatization. Under the catalytic conditions, low molecular weight water-soluble epoxy alcohols, such as glycidol, are isolable either as the parent compound or as its silyl ether, arenesulfonate, or 4-nitrobenzoate derivative via in-situ silylation, sulfonation or esterification, respectively. [10]

Nucleophilic opening of epoxides occurs under a wide spectrum of conditions, ranging from basic[11] to acidic.[12]Lewis acids have been found to be very effective mediators of regio- and stereoselective epoxide opening reactions. Ti(OPr-*i*)$_4$ is a well-known mediator of these process,[12a,13] but in our hands it failed to afford the opening of glycidyl derivatives with a variety of nucleophiles. Chapter 2 illustrates our finding that $BF_3 \cdot Et_2O$ is a very effective catalyst for the opening of glycidyl derivatives, giving monoprotected 1,2-diols in high optical purity. HPLC on a chiral stationary phase (Pirkle Type 1-A, J.T. Baker) and 400-MHz ^{1}H-NMR spectroscopy of the Mosher esters of the ring-opened product with a variety of nucleophiles were used to determined the enantiomeric excess. The regioselectivity was determined by reversed-phase HPLC (C_{18}-Carbosphere column). Since the boron trifluoride etherate mediated reaction proceeds with very high regio- and stereoselectivity, this novel methodology has been used to prepare different biologically active ether-linked phospholipids. Scheme 2 shows how the opening of a series of glycidyl derivatives, obtained by the asymmetric epoxidation of allyl alcohol using (+)DIPT followed by in-situ derivatization, leads to the synthesis of biologically active ether-linked phospholipids having a long-chain ether group at the *sn*-1 position and a long or short (acetyl) or a methyl group at the *sn-2* position of the glycero backbone. Ring- opened glycidyl derivatives were used to synthesize β-glycolipids having either a sulfur or oxygen atom at the anomeric position. Since both enantiomeric forms of the glycidyl derivatives available, (*S*)-ether-linked phospholipids are synthesized by following the same methodology (Scheme 2).

Scheme I: Previous approaches to ether-linked phospholipids



Scheme II: Route to 1-*O*-alkyl-2-*O*-methyl- and 1-*O*-alkyl-2-acyl-*sn*-glycerophospho- and glycolipids



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Chapter 2: Glycidyl Derivatives as Chiral C_3 Synthons. Ring Opening Catalyzed by BF_3 Etherate

Abstract: We report here the first examples of BF_3 etherate mediated regio- and stereoselective opening reactions of glycidyl arenesulfonates **1** and **2** and *tert*-butyldiphenylsilyl ether **3** with various oxygen- and sulfur-based nucleophiles in chlorinated solvents. Boron trifluoride etherate is shown to be a more effective catalyst than other Lewis acids used previously for opening of glycidol, giving rise to chiral monoprotected diols (including intermediates for ether lipid synthesis) in good yield and high ee. Glycidyl arenesulfonates underwent attack exclusively at C_3, whereas the silyl ether gave products resulting from C_3:C_2 attack in a ratio of 9:1. The BF_3 etherate catalyzed opening of glycidyl derivatives is a more convenient method for preparing suitably protected vic-diols than the previously described Ti-mediated opening of the parent glycidol.

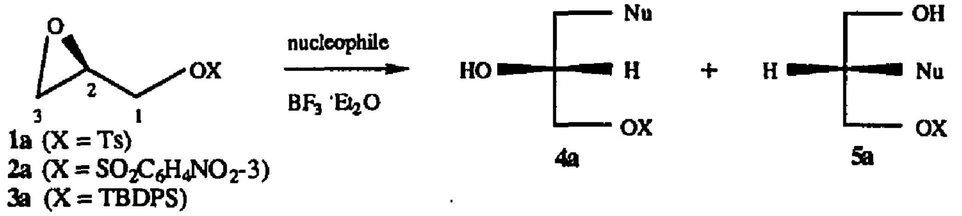
Derivatives of glycidol such as the 4-nitrobenzoate[1] and arenesulfonates[2] possess widespread synthetic utility as chiral building blocks because of their stability and convenience in preparation. Since some glycidyl derivatives can be obtained in high optical purity,[3] we have sought to prepare some monoprotected 1,2-diols via nucleophilic opening reactions. Although a variety of Lewis acids have been found to be effective mediators of regio- and stereoselective epoxide openings,[4] no reports of Lewis acid mediated opening of glycidyl derivatives have appeared.[5] The well-known $Ti(OPr\text{-}i)_4$-mediated epoxy alcohol opening process[4g,h] *failed* to afford the desired opening of glycidyl derivatives **1**-**3** when benzyl alcohol, thiophenol, and various long-chain alcohols were used as nucleophiles. Other Lewis acids such as $TiCl_4$, $AlCl_3$, and $ZnCl_2$ gave complex reaction mixtures. We report here the first use of BF_3 etherate as an efficient catalyst for the opening of glycidyl derivatives **1**-**3** with a variety of nucleophiles.[6] The high regio- and stereoselectivity of the BF_3-mediated reaction makes this new methodology attractive for the preparation of chiral monoprotected vic-diols from glycidyl derivatives.

Nucleophilic ring-opening reactions of (*R*)- and (*S*)-**1**-**3** with catalytic amounts of BF_3 etherate are outlined in eq 1 and 2, and the results are summarized in Table I. The regioselectivity (attack at C_3 vs. C_2) is very high (≥89:11). Both arenesulfonates gave exclusive formation of the C_3-opened product **4**, whereas the TDBPS ether **3** gave slightly lower regioselectivity with the nucleophiles we used. Although BF_3 etherate is a known desilylating agent when used in excess,[7] no desilylation of **3** occurred under the conditions employed. The two methods used for determination of %ee of **4** agreed with the exception of opening by hexadecanol, in which the %ee estimated by ^1H NMR was anamolously high. Figures 1 and 2 (pp. 15 and 16) show examples of the chromatograms obtained by chiral HPLC. The peaks corresponding to the R-(+)-MTPA esters of a racemic mixture of the opening product with benzyl alcohol (Fig. 1A, R_t 15.06 and 16.76 min) and oleyl alcohol (Fig. 2A, R_t 22.16 and 25.92 min) are baseline separated and are of equal areas. The areas of the peaks with retention times of 15.98 and 17.68 minutes were used to calculate the enantiomeric excess of 1-*O*-benzyl-*sn*-3-glycero-*tert*-butyldiphenylsilyl ether, and Fig. 1C shows the corresponding analysis of the R-(+)-MTPA ester of 3-*O*-benzyl-*sn*-1-*tert*-butyldiphenylsilyl ether. Figure 2 shows the results obtained from chiral HPLC analysis of the R-(+)-MTPA esters of 1-*O*-oleyl-*sn*-3-glycero-*tert*-butyldiphenylsilyl ether (Fig. 2B) and its enantiomer (Fig. 2C) .

With regard to optical purity, the %ee of the opening products in entries 13-20 are higher than the literature[3] %ee value of the starting epoxide **3**. In our hands, however, the specific rotation of **3** is higher[8] than the reported value, which may explain the unexpectedly high optical purities of the ring-opened products we obtained. On the other hand, the low apparent %ee values of the opening products shown in entries 7-12 reflect the relatively low optical purity of commercially available (-)-**2a** and (+)-**2b** compared with twice-recrystallized (+)-**2b**.[9] We also note that the ee of the crystalline product **4** from reaction of (-)-**1a** with 1-hexadecanol, as estimated by chiral HPLC, was improved by three recrystallizations from 94 to ~98% (entry 5).

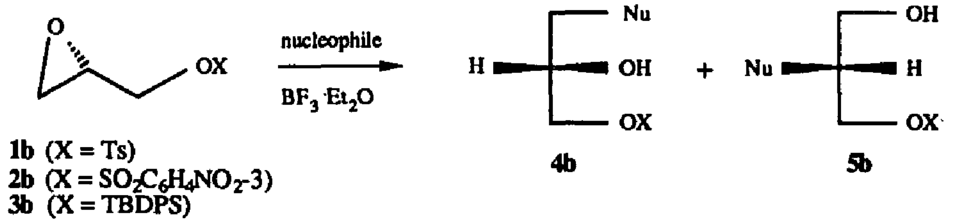
Entries 1 and 3 represent a more efficient route to 3-*O*-benzyl- and 3-phenylthio-2-hydroxy-1-tosyloxypropane than have been reported previously.[10] Both of these are important chiral synthons; for example, **4a** (Nu = OBn) is a precursor in carbohydrate, terpene, and alkaloid chemistry,[10c] and **4a** (Nu = SPh) has been used to prepare insect pheromones.[10b]

In summary, opening of (*R*)- and (*S*)-glycidyl derivatives catalyzed by BF_3 etherate is highly efficient and proceeds with excellent regio- and stereoselectivity. The results summarized in Table I with hexadecanol, oleyl alcohol, and petroselinyl alcohol as nucleophiles show that glycidyl derivatives **1-3** are precursors to optically active ether-linked lipids, an important class of biologically active compounds.[11] Many previous syntheses of ether-linked lipids involved D-mannitol or its derivatives as starting material, and were thus lengthy.[12] Optically active glycidol has been used as a lipid precursor, but gives *unprotected* monoglycerides in low yield on ring opening.[4h,13] In contrast, the route reported in this communication is a practical, short synthesis of the enantiomers of alkyl lipids and other chiral 1,2-monoprotected diols.



1a (X = Ts)
2a (X = $SO_2C_6H_4NO_2$-3)
3a (X = TBDPS)

(1)



1b (X = Ts)
2b (X = $SO_2C_6H_4NO_2$-3)
3b (X = TBDPS)

(2)

Table I. Opening of Glycidyl Derivatives with Nucleophiles Mediated by BF_3 Etherate[a]

					HPLC R_f (min)[d]		%ee by HPLC[e]		%ee by NMR[f]	
entry	epoxide	Nu	yield[b]	%4/%5[c]	4a	4b	4a	4b	4a	4b
1	**1a**	BnO	84	100/0	17.3[g]	-	96.2	-	95.0	
2	**1b**	BnO	81	100/0	-	19.3[g]	-	95.3	-	94.0
3	**1a**	PhS	81	100/0	13.4[h]	-	92.3	-		
4	**1b**	PhS	83	100/0	-	14.8[h]	-	95.3		
5	**1a**	$C_{16}H_{33}O$	80	100/0	17.2[i]	-	94.0 (97.7)[j]		~99	
6	**1b**	$C_{16}H_{33}O$	79	100/0	-	19.0[i]	-	95.7	-	~99
7	**2a**[k]	$C_{18}H_{35}O$[l]	75	100/0	21.5[m]	-	93.3	-		
8	**2b**[k]	$C_{18}H_{35}O$[l]	77	100/0	-	23.4[m]	-	88.4		
9	**2a**	$C_{16}H_{33}O$	83	100/0	21.1[m]		-	94.1	-	
10	**2b**	$C_{16}H_{33}O$	80	100/0	-	23.0[m]	-	86.9		
11	**2a**	$C_{18}H_{35}O$[n]	78	100/0	23.8[o]		-	92.1	-	
12	**2b**	$C_{18}H_{35}O$[n]	75	100/0	-	25.7[o]	-	85.6		
13	**3a**	BnO	70	89/11	15.1[p]	-	94.4	-	93.6	
14	**3b**	BnO	68	89/11	-	16.8[p]	-	95.3	-	94.5
15	**3a**	PhS	79	93/7	13.3[q]	-	93.7	-	92.5	
16	**3b**	PhS	78	93/7	-	14.6[q]	-	95.2	-	96.8
17	**3a**	$C_{16}H_{33}O$	74	90/10	20.7[r]	-	93.8	-	96.0	-
18	**3b**	$C_{16}H_{33}O$	68	90/10	-	23.4[r]	-	95.3	-	98.0
19	**3a**	$C_{18}H_{35}O$[l]	72	90/10	22.4[p]	-	92.6	-		
20	**3b**	$C_{18}H_{35}O$[l]	70	90/10	-	25.4[p]	-	94.0		

[a]Ring-opening reactions were carried out in dichloromethane (except for entries 5 and 6, in which chloroform was used) in the presence of catalytic (~5-10 mol %) BF_3 etherate for ~18 h at room temperature (entries 5-12) or 4 °C (entries 1-4 and 13-20). Reactions with the glycidyl arenesulfonates **1** and **2** used 1.1-1.4 equiv of nucleophile. Reactions with glycidyl *tert*-butyldiphenylsilyl (TBDPS) ether **3** used 0.83 equiv of nucleophile to suppress formation of byproduct NuOTBDPS. [b] The % yield refers to the major regioisomer obtained after workup and flash chromatography. [c]The ratio of regioisomers was determined by reverse-phase HPLC (4.6 x 250 mm C_{18} Carbosphere) of the crude reaction mixture. [d]Retention times were recorded on a Perkin-Elmer Model 410 HPLC equipped with a LC235 diode array detector and LCI 100 recorder. [e]The %ee was determined by chiral HPLC (Pirkle type IA column, 4.6 x 250 mm, J.T. Baker) of the crude (*R*)-(+)-MTPA esters[13] derived from **4**. In each case, baseline separation of the diastereomeric Mosher esters was achieved. [f]The %ee was determined by 400-MHz ^1H NMR analysis of the crude (*R*)-(+)-MTPA ester derived from **4**. To calculate %ee, the methoxy peaks of the two diastereomers were used for entries 1 and 2, whereas the AB quartets of the , $C\underline{H}_2OTs$, $C\underline{H}_2OBn$ and $C\underline{H}_2SC_6H_5$ were used for entries 5, 6, and 13-14, 15-16, respectively. For entries 17 and 18, the $C\underline{H}_2OMTPA$ peaks of the bis-Mosher ester (prepared from desilylated **4**) were used to calculate %ee (Guivisdalsky, P.N., and Bittman, R., unpublished results). In each case, baseline separations of the respective peaks in the two diastereomers were attained. [g]Flow 0.65 mL/min,

hexanes-*i*-PrOH 85:15. [h]Flow 0.70 mL/min, hexanes-*i*-PrOH 80:20. [i]Flow 0.40 mL/min, hexanes-*i*-PrOH 90:10. [j]The ring-opened product was recrystallized three times from ether-hexanes prior to conversion to the (*R*)-(+)-MTPA ester. [k]The %ee of the starting material can be strikingly enhanced (to 99%) by multiple recrystallizations from ethanol (ref. 8). Based on the lit.[8] $[\alpha]^{25}_D$ of (+)-**2b**, the %ee values of the lots of (-)-**2a** and (+)-**2b** we used are ca. 92 and 89, respectively. [l]Oleyl, $C_{18}H_{35}O$ (Δ^9 *cis*). [m]Flow 0.50 mL/min, hexanes-*i*-PrOH 90:10. [n]Petroselinyl, $C_{18}H_{35}O$ (Δ^6 *cis*). [o]Flow 0.45 mL/min, hexanes-*i*-PrOH 90:10. [p]Flow 0.65 mL/min, hexanes-*i*-PrOH 100:0. [q]Flow 0.75 mL/min, hexanes-*i*-PrOH 100:0. [r]Flow 0.45 mL/min, hexanes-*i*-PrOH 100:0.

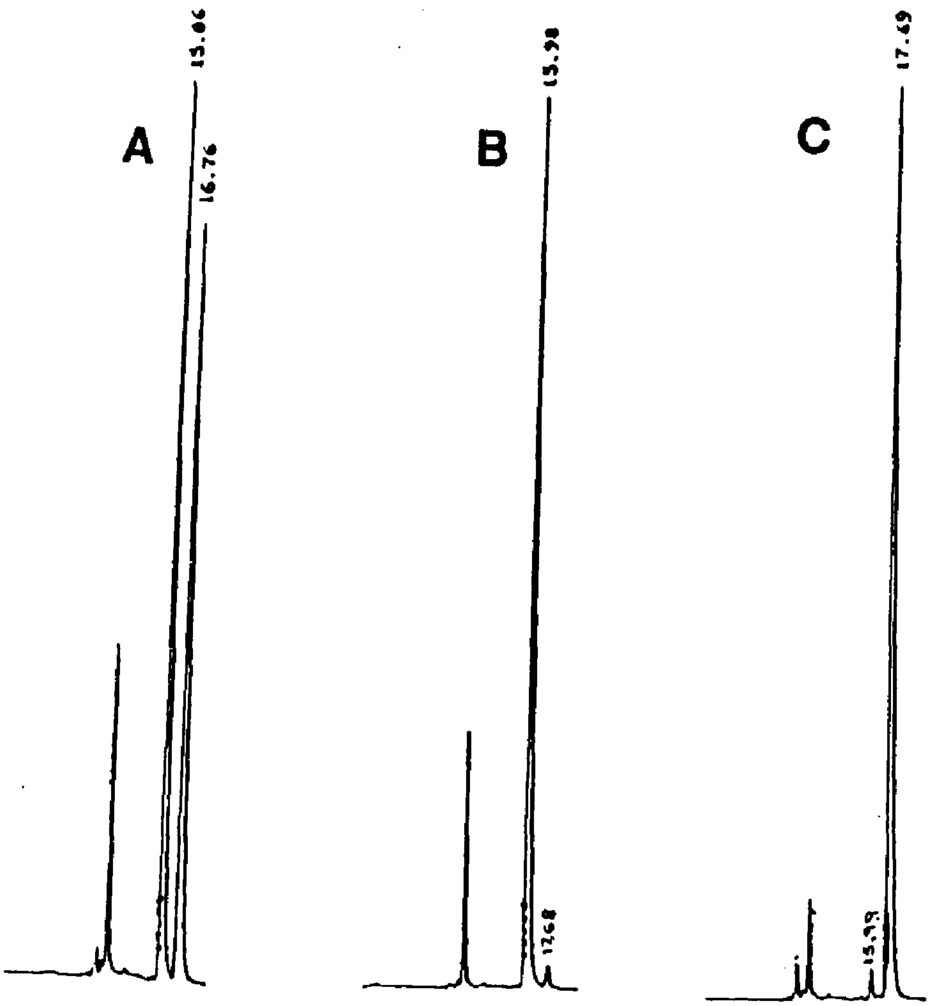


Figure 1. HPLC chromatograms of 1-*O*-benzyl-2-[*O*-(*R*)-(+)-MTPA]- 3-(*O*-TBDPS): **A,** racemic mixture of 1-*O*-benzyl-2-[*O*-(*R*)-(+)-MTPA]-3- (*O*-TBDPS) and 3-*O*-benzyl-2-[*O*-(*R*)-(+)-MTPA]-1-(*O*-TBDPS); **B,** 1-*O*-benzyl-2-[*O*-(*R*)-(+)-MTPA]-3-(*O*-TBDPS); **C,** 3-*O*-benzyl-2-[*O*-(*R*)-(+)- MTPA]-1-(*O*-TBDPS). See entries 13 and 14 of Table 1, page 10.

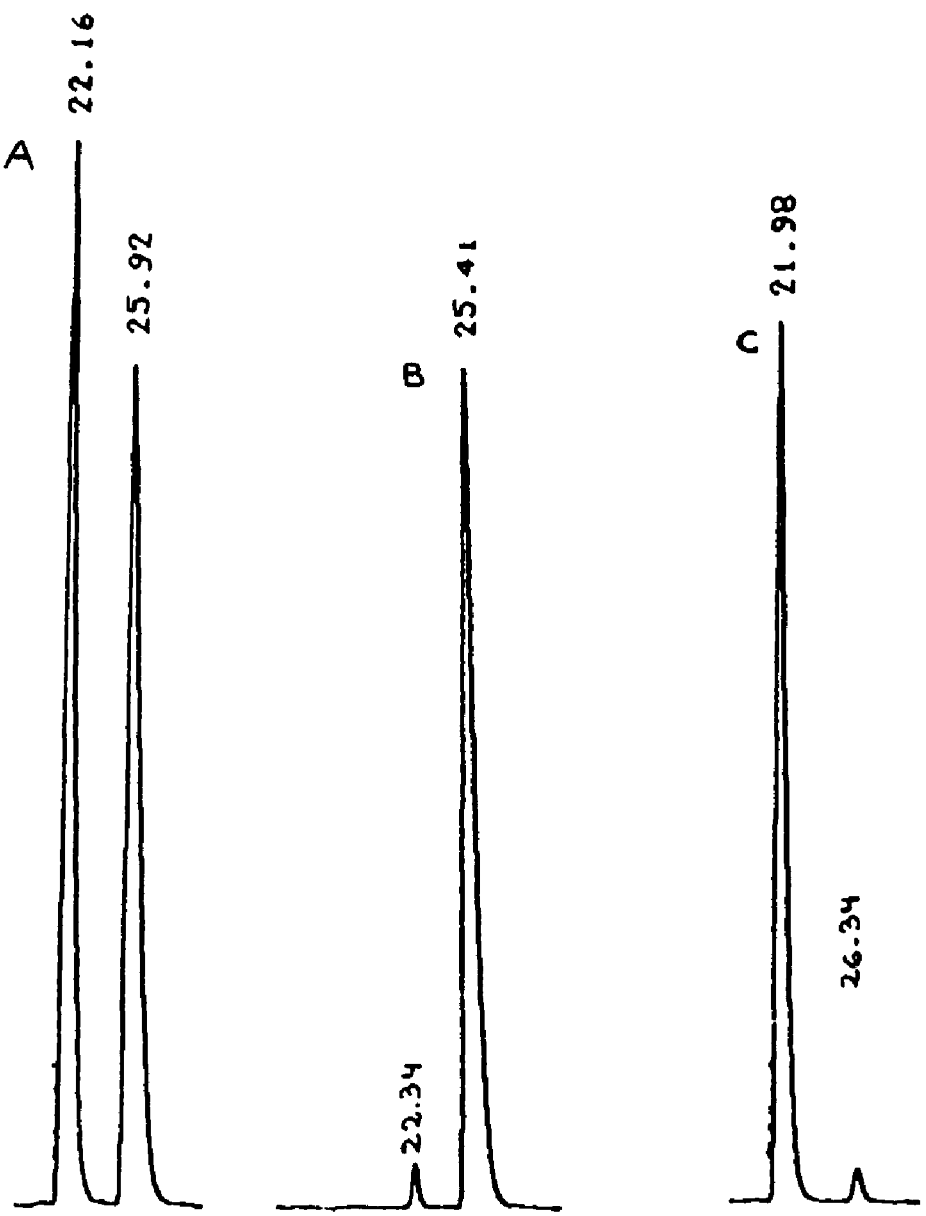


Figure 2. HPLC chromatograms of 1-*O*-oleyl-2-[*O*-(*R*)-(+)-MTPA]- 3-(*O*-TBDPS): **A,** racemic mixture of 1-*O*-oleyl-2-[*O*-(*R*)-(+)-MTPA]-3- (*O*-TBDPS) and 3-*O*-oleyl-2-[*O*-(*R*)-(+)-MTPA]-1-(*O*-TBDPS); **B,** 1-*O*-oleyl-2-[*O*-(*R*)-(+)-MTPA]-3-(*O*-TBDPS); **C,** 3-*O*-oleyl-2-[*O*-(*R*)-(+)- MTPA]-1-(*O*-TBDPS). See entries 19 and 20 of Table 1, page 10.

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Chapter 3: Novel Enantioselective Synthesis of Platelet Activating Factor and Its Enantiomer via Ring Opening of Glycidyl Tosylate with 1-Hexadecanol

Abstract: (2*R*)- and (2*S*)- glycidyl tosylate **3** and **3'** are used to synthesize platelet activating factor **1** and its enantiomer **2** in very high optical purity via the ring-opened ether-linked glycerol tosylate **4** and **4'**.

The discovery in 1979 that platelet activating factor (PAF, **1**) is an ether-linked phospholipid has led to the development of efficient chemical methods to prepare biologically active ether phospholipid analogs. The starting materials used in previous synthetic methods to prepare PAF and its analogs include D-mannitol,[1] L-ascorbic acid, [2] L-serine,[3] D-tartaric acid,[4] and *S*-malic acid.[5] Synthesis of the unnatural enantiomer of PAF (**2**) has also attracted considerable interest because **2** is useful in assessing the structural requirements of PAF for biological activity, especially in studies of the involvement of stereospecific receptors.[6] Syntheses of **2** have been achieved from L-tartaric acid, [6] and by inversion of configuration at C-2 of various precursors.[7] Recent advances in the asymmetric epoxidation of low molecular weight allyl alcohols by using catalytic amounts of the required reagents in the presence of molecular sieves, followed by *in situ* trapping of the formed epoxide[8] offer the possibility of a new route to **1** and its enantiomer **2**. We report here the preparation of chiral lipids **1** and **2** in very high optical purity wherein the key step is the stereo- and regioselective opening of epoxides **3** and **3'**.

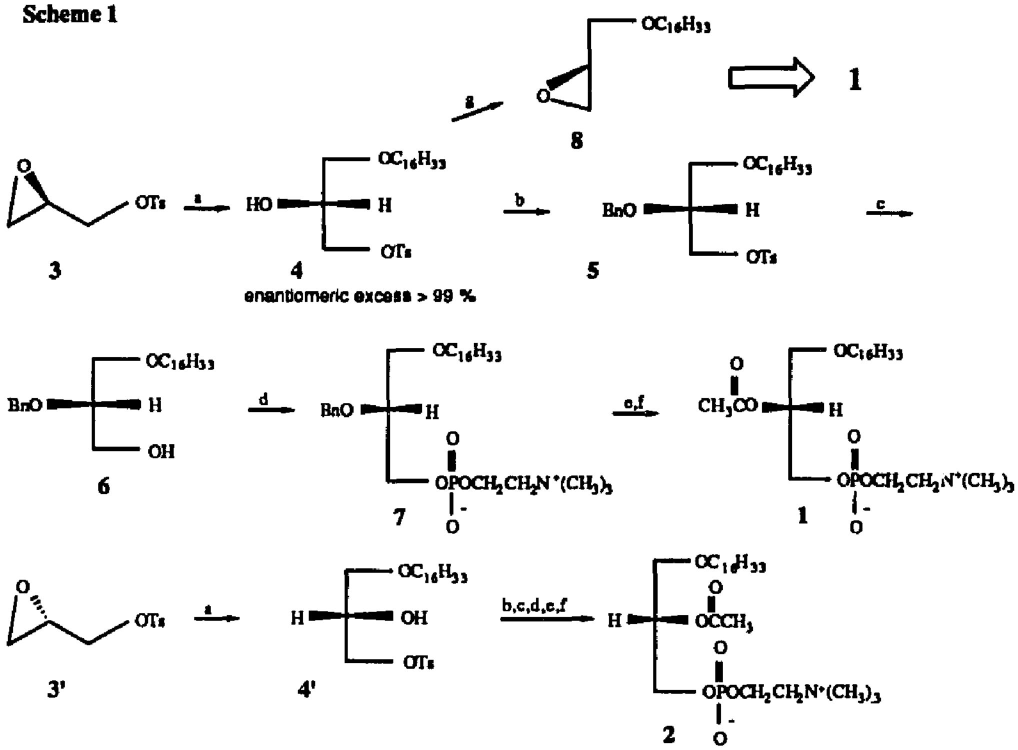
(2*R*)-(-)-Glycidyl tosylate **3** and (2*S*)-(+)-glycidyl tosylate **3'** were synthesized from allyl alcohol by asymmetric epoxidation using (+)-DIPT and (-)-DIPT, respectively, and in situ derivatization.[8] Regiospecific opening of epoxide **3** and **3'** with 1-hexadecanol was achieved using catalytic amounts of boron trifluoride etherate in alcohol-free chloroform (Scheme 1). Tosylates **4** and **4'** were isolated and purified by flash chromatography in 80% yield, mp 68-69° C; lit. mp 68-69°C;[7] **4**: $[\alpha]_D^{25} = -6.24$ (c 5.0, C_6H_6); lit. $[\alpha]_D^{25} = -5.55$ (c 5.0, C_6H_6);[7] **4'**: $[\alpha]_D^{25} = +6.37$ (c 5.0, C_6H_6); lit. $[\alpha]_D^{25} = +5.75$ (c 5.0, C_6H_6).[7] ^1H NMR analysis (400 MHz) of the Mosher ester of **4** (prepared according to ref. 9) showed > 99% e.e.; HPLC of the diastereomeric Mosher ester (C18 Carbosphere, CH_3CN-2-PrOH 9:1) indicated > 99% purity. Conversion of **4** into **5** was carried out using mild benzylation conditions[10] with preformed benzyl triflate to avoid base-induced epoxide formation of **4**, affording **5** in 96% yield; $[\alpha]_D^{25} = -7.32$ (c 5.0, $CHCl_3$). Attempted detosylation of **5** with potassium superoxide in the presence of 18-crown-6 [11] gave a complex mixture; however, the reaction sequence of displacement of tosylate **5** with cesium acetate [12] followed by lithium aluminum hydride reduction without isolation of the intermediate acetate afforded alcohol **6** in 92% overall yield; mp 29-31°C; lit. mp 28-30°C; [7] $[\alpha]_D^{25} = -9.27$ (c 5.0, C_6H_6); lit. $[\alpha]_D^{25} = -8.76$ (c 5.0, C_6H_6).[7] Phosphorylation of **6** was achieved using phosphorus oxychloride at -10°C in alcohol-free chloroform in the presence of triethylamine; addition of dry choline tosylate in pyridine at r.t., then water,[13] yielded phosphocholine **7** in 75% overall yield; $[\alpha]_D^{25} = +3.92$ (c 5.0, $CHCl_3$-CH_3OH 1:1); lit. $[\alpha]_D^{25} = +3.54$ (c 5.0, $CHCl_3$-CH_3OH 1:1).[7] Debenzylation of **7** with Pearlman's catalyst for 24 h gave 2-lysophosphocholine (100%), which was filtered, dried, and acetylated to give PAF **1** in 100% yield; mp 247°C (dec); lit. mp 247°C (dec); [6] $[\alpha]_D^{25} = -3.39$ (c 0.53, $CHCl_3$-CH_3OH 1:1); lit.

$[\alpha]_D^{25}$ = -3.30 (c 0.53, $CHCl_3$-CH_3OH 1:1).[6] Similarly, the same methodology (Scheme 1) was used to convert tosylate **4'** into the enantiomer of PAF (**2**); mp 247°C (dec); lit. mp 247°C (dec); [6] $[\alpha]_D^{25}$ = +3.20 (c 0.53, $CHCl_3$-CH_3OH 1:1); lit. $[\alpha]_D^{25}$ = +3.18 (c 0.53, $CHCl_3$-CH_3OH 1:1).[6]

Hirth and Barner used 1-*O*-hexadecyl-2,3-epoxypropane (**8**), which was prepared from D-mannitol, as the precursor for the preparation of PAF **1**. [7] We prepared epoxide **8** in quantitative yield from tosylate **4** using potassium carbonate in methanol; mp 42-43°C; lit. 41-42°C; [7] $[\alpha]_D^{25}$ = +9.74 (c 5.0, C_6H_6); lit. $[\alpha]_D^{25}$ = +9.00 (c 5.0, C_6H_6).[7]

In conclusion, this methodology offers a route for the asymmetric synthesis of other glycerophospholipids from derivatives of glycidol. Our studies of the conversion of other glycidol derivatives, such as its silyl ether, to different PAF analogs and other ether-linked lipids are currently in progress in our laboratory.

Scheme 1



(a)$C_{16}H_{33}OH$, $BF_3{\cdot}Et_2O$, $CHCl_3$. (b) BnOTf, 2,6-di-*t*-butyl-4-methyl- pyridine, CH_2Cl_2. (c) CsOAc, DMF / DMSO (4:1); then $LiAlH_4$ / Et_2O. (d) $POCl_3$, Et_3N, $CHCl_3$; then $HO(CH_2)_2N^+Me_3$ OTs^-, pyridine; then H_2O. (e) H_2, $Pd(OH)_2$ / C, MeOH / H_2O (9:1). (f) Ac_2O, DMAP, $CHCl_3$. (g) K_2CO_3, MeOH.

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Chapter 4: Regiospecific Opening of Glycidyl Derivatives Mediated by Boron Trifluoride. Asymmetric Synthesis of Ether-Linked Phospholipids

Abstract: A short, chiral synthesis of unnatural, cytotoxic ether-linked phospholipids is reported in which the key step is the very high regio- and stereospecific nucleophilic opening of the *p*-toluenesulfonate (**1a**, **1b**) or *tert*-butyldiphenylsilyl ether (**6a**, **6b**) derivatives of (*R*)- or (*S*)-glycidol with 1-hexadecanol using boron trifluoride etherate as catalyst. The enantiomeric excess (ee) of the ring-opened products was >94%, as judged by ^{1}H NMR and chiral HPLC analysis of the Mosher ester derivatives, indicating that ring opening of **1** and **6** proceeds without significant loss of optical purity. The synthetic strategy of using optically active glycidyl derivatives as the precursor of the glycerol backbone permits the desired enantiomers of 1(3)-*O*-alkyl-2-*O*-methylphosphocholines (**5a**, **5b**) to be generated in good yield and high optical purity from the ring-opened intermediates (**2**, **7**) in three steps without the use of protecting groups.

Introduction: Unnatural ether-linked phospholipids, often referred to as alkyl phospholipids (ALPs), represent an important group of biologically active molecules that act on cytoplasmic targets. The ALPs that contain a sixteen- or eighteen-carbon aliphatic chain at the *sn*-1 position[1] and an *O*-methyl group at the *sn*-2 position of glycerophosphocholine (GPC) have potent cytotoxic activity toward various tumor cells.[2] The cytotoxic ether phospholipids accumulate in membranes of tumor cells, where they may affect the structural order of membrane lipids and alter tumor cell invasion[3] or interfere with cellular phospholipid metabolism.[4] They may also activate tumor-specific cytotoxic macrophages in the host cells.[5] Since 1-*O*-alkyl-2-*O*-methyl-GPC is a structural analog of the naturally occurring platelet activating factor (PAF), the possible involvement of ALP binding to a specific PAF membrane receptor has been considered in the mechanism of action of this class of new antitumor agents, particularly at the cell surface of macrophages.[6] Interaction of ALP or its metabolites with the phospholipid-requiring enzyme protein kinase C may also contribute to the mechanism of cytotoxic action.[7] With very few exceptions,[6,8] a racemic mixture of 1-*O*-alkyl-2-*O*-methyl-GPC (available commercially)[9] was used in the biochemical, biological, and pharmacological studies cited above. The development of methods to prepare optically pure isomers of ALP analogs would accelerate efforts to advance the understanding of the antitumor activity of synthetic tumoricidal ether lipids. Enantiomers **5a** and **5b** could be used, for example, to analyze whether conversion to metabolic products and/or binding to receptors in biological systems play important roles in the selective toxicity of **5** to tumor cells.

Epoxides have served as important synthetic intermediates because of their high chemical reactivity, ease of preparation, and availability in optically active form. In previous applications of epoxides as lipid precursors, (*S*)-glycidol has been used to prepare optically active triacylglycerols,[10] and *rac*-glycidol has been used to prepare *rac*-mono- and diacylglycerols[11] and phospholipids.[12] The discovery that Ti(O-*i*-Pr)$_4$ mediates the regioselective attack of a variety of nucleophiles at C_3 of 2,3-epoxy alcohols under mild experimental conditions[13] was the basis for the Ti(O-*i*-Pr)$_4$-assisted opening of (*S*)-glycidol with stearic acid, which gave (*S*)-glycidyl stearate in low yield.[14] Recent advances in asymmetric epoxidation of low molecular weight allylic alcohols by the use of catalytic amounts of Ti(O-*i*-Pr)$_4$ and tartrate ester in the presence of molecular sieves, followed by in situ derivatization of the epoxide formed[15] offer a convenient synthetic route to optically active lipids. We demonstrate here the use of the *p*-toluenesulfonate and *tert*-butyldiphenylsilyl ether (TBDPS) derivatives of (*R*)- and (*S*)-glycidol (**1** and **6**) as precursors in a short synthesis of both enantiomeric forms of 1-*O*-alkyl-2-*O*-methyl-3-GPC (**5a**) and 3-*O*-alkyl-2-*O*-methyl-1-GPC (**5b**).[16] The key carbon-oxygen bond-forming step is the regio- and stereospecific nucleophilic opening of glycidyl derivatives **1** and **6** with a long-chain alcohol using BF$_3$ etherate as a catalyst. Although BF$_3$-mediated opening reactions of epoxides using organometallic reagents[17] and acetone[18] have been reported, to our knowledge BF$_3$-mediated nucleophilic opening of glycidyl derivatives has not yet been reported.[19] In this paper we show that BF$_3$ etherate is a much better Lewis acid than Ti(O-*i*-Pr)$_4$ for ether lipid synthesis, probably because a non-nucleophilic molecule (ether) is displaced during ring opening; on the other hand, the nucleophilic species (2-propanol) liberated when excess Ti(O-*i*-Pr)$_4$ is used to mediate the ring opening[13] would be expected to compete with the long-chain alcohol. Furthermore, our BF$_3$-mediated procedure for opening of epoxide derivatives with a long-chain alcohol provides ether-linked lipids in much higher yield and optical purity than the Ti(O-*i*-Pr)$_4$-mediated opening of glycidol with a long-chain fatty acid.[14]

Results

Epoxide Opening. Attempts to effect base-induced opening of TBDPS ether **6** with the sodium salt of 1-hexadecanol in DMF were unsuccessful. Reaction of the alkoxide ion with **6** resulted in attack on silicon, giving *n*-

hexadecyl *tert*-butyldiphenylsilyl ether as the sole product. Alkoxide ion attack on glycidyl tosylate **1** is also not suitable for the preparation of chiral products **5a** and **5b**; alkoxide attack is known to give direct displacement of the tosyl group together with ring opening followed by internal displacement of the tosyl group, forming partially racemized product.[20] It is known, however, that Ti(O-*i*-Pr)$_4$ mediates the opening of glycidol by thiophenol and *N*-isopropylbenzylamine with high regioselectivity[21] and the opening of glycidyl *p*-nitrobenzoate by a variety of nucleophiles.[22] In the present paper, BF$_3$ etherate is shown to be the Lewis acid of choice for opening of glycidyl derivatives with 1-hexadecanol. In fact, glycidyl derivatives **1** and **6** did not react with 1-hexadecanol when Ti(O-*i*-Pr)$_4$ was used in either catalytic or stoichiometric amounts. Use of TiCl$_4$, SnCl$_4$, and ZnCl$_2$ as potential catalysts resulted in attack by chloride ion with only small amounts of attack by the long-chain alcohol. However, we found that when BF$_3$ etherate was used as the catalyst, ring-opened products **2** and **7** were obtained in good yields. Excellent regioselectivites were realized in this reaction. Attack of 1-hexadecanol on tosylate **1** gave regioisomer **2** exclusively, whereas attack on TBDPS ether **6** resulted in a 9:1 ratio of the desired regioisomer **7** (C$_3$ attack) to the undesired positional isomer (C$_2$ attack). Furthermore, ring opening proceeded with very high stereoselectivity (see **Enantiomeric Purity**). We also found that the *p*-toluenesulfonate and TBDPS ether derivatives **1** and **6** were far superior as C3 synthons compared with the *p*-nitrobenzoate ester of glycidol. The latter compound gave *n*-hexadecyl *p*-nitrobenzoate as the major product when treated with 1-hexadecanol and BF$_3$ etherate.

Synthesis. Scheme I shows the conversion of (*R*)- and (*S*)-glycidyl tosylates (**1a**, **1b**) into the desired enantiomers of *O*-hexadecyl-2-*O*-methyl-GPC (**5a**,

5b). Mild conditions were required for the conversion of ring-opened product **2** into *O*-methyl compound **3** in order to avoid epoxide formation. Methylation using diazomethane in the presence of excess silica gel[23] gave **3** in only 64% yield. Better results were obtained by methylating **2** using methyl triflate in the presence of the hindered 2,6-di-*tert*-butyl-4-methylpyridine in refluxing dichloromethane, giving **3** in 90% yield. The latter method has been applied to the methylation of carbohydrates under mild conditions.[24] Conversion of tosylate **3** into alcohol **4** was first attempted by displacement with iodide followed by MCPBA oxidation,[25] affording the alcohol in 61% overall yield. We improved the yield of this step to 81% by carrying out the reaction of **3** with potassium superoxide in the presence of 18-crown-6. These conditions have been reported to accomplish the direct displacement of tosylates to form alcohols.[26] In the final step, the phosphocholine moiety was introduced by reaction of alcohol **4** with 2-chloro-2-oxo-1,3,2-dioxaphospholane, followed by reaction of the cyclic phosphate intermediate with dry trimethylamine.[27]

Scheme II shows the conversion of (*R*)-(+)- and (*S*)-(-)-oxiranemethanol *tert*-butyldiphenylsilyl ethers ((+)-**6a** and (-)-**6b**), which were prepared by trapping glycidol with *tert*-butyldiphenylsilyl chloride,[15] into alcohols (-)-**4a** and (+)-**4b**. Although the regioselectivity of the ring-opening reaction of **6** - **7** was not quite as high as that of **1** - **2**, the desired regioisomer **7** was obtained in high yield. The sodium salt of **7** was methylated using methyl iodide in benzene, giving **8** in almost quantitative yield. Desilylation using tetrabutylammonium fluoride[28] gave alcohol **4** in quantitative yield.

Evaluation of Optical Purity. To determine the enantiomeric excess of the ring-opened products **2** and **7** we prepared their (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((*R*)-(+)-MTPA) esters.[29] The diastereomeric ratio of the resulting mixture was analyzed by two methods: 400-MHz ^{1}H NMR and HPLC on a chiral stationary phase. Figure 1A shows the ^{1}H NMR spectrum (δ 4.0-4.3) of a mixture prepared from 80% of (-)-**2a** and 20% of (+)-**2b**. Integration of the two doublets of AB quartets on an expanded scale indicated a 4:1 ratio of the areas of the signals at δ 4.15-4.3 vs. those at d 4.0-4.1. The individual diastereotopic protons of C$\underline{H}_2$OTs in each enantiomer show baseline separation. The lower field doublet of doublets (δ4.28) is assigned to H_a of stereoisomer (-)-**2a** (see Figure 1B), and the other doublet of doublets (δ4.20) of (-)-**2a** is assigned to H_b. Enantiomer (+)-**2b** has a low-field doublet of doublets at δ4.09 (H_a of (+)-**2b**) and a higher field doublet of doublets at δ4.04 (H_a of (+)-**2b**; Figure 1C). The absence in Figure 1B of the signals at δ4.09 and δ4.04, and the absence in Figure 1C of the signals at δ4.28 and δ4.20 indicate that the optical purities of (-)-**2a** and (+)-**2b** are >99% (the limits of detection).

We were unable to determine the optical purities of (+)-**7a** and (-)-**7b** directly by 400-MHz ^{1}H NMR because the diastereotopic protons of the OC$\underline{H}_2$ signals of their Mosher esters overlapped. Therefore, (+)-**7a** and (-)-**7b** were desilylated, and the bis-(*R*)-MTPA esters were prepared from 1-*O*-hexadecyl- and 3-*O*-hexadecyl-*sn*-glycerol ((-)-**9a** and (+)-**9b**, respectively). Figure 2A shows that the two C$\underline{H}_2$OMTPA signals exhibited by the bis-Mosher ester of *rac*-**9** are baseline separated in the region of δ 4.3-4.8. The A proton doublet (split by the methine proton) of the AB quartet of each diastereoisomeric C$\underline{H}_2$OMTPA group is clearly visible, with baseline separation in the region of δ 4.58-4.75. The B segments are not so readily separable, and our estimation of enantiomeric purity was thus based only on the A segments. The integrated ratio of the signals centered at δ4.73 : δ4.62 in Figure 2B (on an expanded scale) indicated 96% ee for (-)-**9a**. Similarly, Figure 2C was analyzed to give 98% ee for (+)-**9b**. Thus we conclude that the optical purities of the precursors of (-)-**9a** and (+)-**9b**, i.e. (+)-**7a** and (-)-**7b**, are of the same magnitude. (Note that the specific rotations of (-)-**9a** and (+)-**9b** are higher than those reported in the literature.)

Since NMR analysis of the (*R*)-(+)-MTPA ester of **2** indicated a higher ee than that reported[15] for epoxide **1**,[30] we reevaluated the ee of the MTPA esters derived from **2** by chiral HPLC. The % ee values of the (*R*)-(+)-MTPA esters of (-)-**2a** and (+)-**2b** were 94.0 and 95.7, respectively.[31] Moreover, three recrystallizations of (-)-**2a** from ether-hexanes prior to conversion to the MTPA derivative enriched its chiral purity to 97.7% ee. Although the (*R*)-(+)-MTPA esters of (+)-**7a** and (-)-**7b** were not suitable for ee determination by NMR, chiral HPLC analysis was successful (Figure 3). The values obtained (93.8 and 95.3% ee, respectively)[32] are consistent with the higher optical purity estimated by comparing the specific rotation of (*S*)-**6b** with the literature[15] value. Thus, chiral HPLC analysis indicated that the ring opening of **1** and **6** by 1-hexadecanol proceeded without any significant loss of chiral purity.

Discussion

We have shown that BF_3 etherate serves as an excellent catalyst for the opening of glycidyl derivatives **1** and **6**, giving monoprotected diols **2** and **7** in high yield, regioselectivity, and optical purity. Our synthesis of the cytotoxic phospholipid, 1-*O*-alkyl-2-*O*-methyl-GPC (**5a**), from glycidyl synthons **1a** and **6a** is short and efficient. Enantiomer **5b**, which has not been reported previously in pure form,[33] has been prepared by the same methodology from **1b** and **6b**. The enantiomerically pure compounds **5a** and **5b** will be useful for the study of the mechanism of cytotoxic activity and tumor specificity of these antineoplastic agents.

Previous syntheses of **5a** used natural sources as starting materials, such as D-mannitol,[34] L-glyceric acid, [35] and L-tartaric acid.[36] The previous synthetic routes involve many steps and require the extensive use of protection-deprotection reactions. Since these published routes rely on a natural source, the stereochemistry of the product is limited to the chirality of the starting material. In contrast, our asymmetric synthesis proceeds from inexpensive starting materials, which are prepared by asymmetric epoxidation of allyl alcohol followed by in situ sulfonation or silylation. Our synthesis of glycerolipids is short since no protecting groups are required. This methodology is flexible and can, therefore, be applied to prepare related analogs of ALPs. For example, the Lewis acid catalyzed ring-opening reaction (**1** -- **2**, **6** -- **7**) can be carried out with various aliphatic alcohols. Oleyl and petroselinyl [(*Z*)-9- and (*Z*)-6-octadecen-1-yl, respectively] groups were introduced at the *sn*-1 position of **2**[37a] and **7**[37b] in very high regio- and stereospecificity by use of the unsaturated alcohols as nucleophiles. These ring-opened intermediates can be converted into unsaturated long-chain ALP analogs of **5** by the same procedures used for the hexadecyl derivative. A variety of alkyl groups can be introduced at the 2 position by carrying out the *O*-alkylation of **2** and **7** with long-chain alkyl triflates or short-chain alkyl iodides (unpublished results). Such analogs are useful for examining the relationship between ALP structure and antitumor activity. The ability to prepare both enantiomers of ALPs and its analogs in high enantiomeric excess is expected to facilitate the study of the molecular mechanisms of action of ALPs, especially the possible involvement of a stereospecific receptor in the cellular responses elicited by these compounds.

Experimental Section

General Procedures. Melting points are uncorrected. Silica gel G TLC plates of 0.25-mm thickness (Analtech, Newark, DE) were used to monitor reactions, with 10% sulfuric acid in ethanol and/or short-wave ultraviolet light to visualize the spots. E. Merck silica gel 60 (230-400 ASTM mesh) was used for flash chromatography. Solvents were dried as follows: chloroform, dichloromethane, dimethyl sulfoxide (Me_2SO), dimethylformamide (DMF), and acetonitrile were distilled from calcium hydride and stored over type 3A molecular sieves; benzene and hexane were distilled from and stored over sodium; tetrahydrofuran was refluxed over sodium benzophenone ketyl for several hours, then used immediately; acetone was stored over calcium sulfate for at least one week. (*R*)-Glycidyl tosylate ((*R*)-oxiranemethanol 4-methylbenzenesulfonate, (-)-**1a**) was purchased from Aldrich Chemical Co. (*S*)-Glycidyl tosylate ((+)-**1b**) was prepared in 40% yield as described by Gao et al.;[15] $[\alpha]^{25}_D$ +17.1°(*c* 2.75, $CHCl_3$). In later experiments, commercially available (+)-**1b** was used (Aldrich). 1-Hexadecanol and (*R*)-(+)-MTPA were purchased from Aldrich.

1-*O*-Hexadecyl-*sn*-glycerol 3-*O*-*p*-Toluenesulfonate ((-)-2a). To 1.0 g (4.4 mmol) of (-)-**1a** and 1.5 g (6.2 mmol) of 1-hexadecanol in 25 mL of alcohol-free chloroform was added three drops (~5 mol %) of freshly distilled BF_3 etherate. After the mixture was stirred for 24 h under nitrogen, the solvent was removed under reduced pressure to give a residue which gave 1.65 g (80%) of (-)-**2a** after flash chromatography (elution with 5:1 hexane/EtOAc, R_f 0.25); mp 68.0-69.0 °C (lit.[38] mp 68.0-69.0 °C); TLC (20% ethyl acetate-hexanes) R_f 0.30; $[\alpha]^{25}_D$ -6.24° (*c* 5.0, C_6H_6) (lit.[38] $[\alpha]^{25}_D$ -5.55° (*c* 5.0, C_6H_6)); 94.0% ee,[31] 97.7% ee after three recrystallizations from ether-hexanes; IR (KBr): 3600, 1360, 1182, 1130, 1102, 846, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 4.05 (m, 3 H, $C\underline{H}_2OTs$ and $CH_2C\underline{H}CH_2$), 3.44 (d, *J* = 5.0 Hz, 2 H, $C\underline{H}_2OC_{16}H_{33}$), 3.39 (t, *J* = 7.0 Hz, 2 H, $OC\underline{H}_2CH_2$), 2.45 (s, 3 H, $C\underline{H}_3C_6H_4$), 2.15 (s, 1 H, $O\underline{H}$), 1.29 (br s, 28 H, $CH_3(C\underline{H}_2)_{14}$), 0.91 (br t, 3 H, ω-$C\underline{H}_3$). Anal. Calcd for $C_{26}H_{45}O_5S$: C, 66.41; H, 9.89; S, 6.86. Found: C, 66.49; H, 9.66; S, 6.83.

3-*O*-Hexadecyl-*sn*-glycerol 1-*O*-*p*-Toluenesulfonate ((+)-2b). The title compound was prepared in 79% yield from (+)-**1b** by the same procedure used to prepare (-)-**2a**; mp 68.0-69.0 °C (lit.[38] mp 68.0-69.0 °C); $[\alpha]^{25}_D$ +6.37° (*c* 5.0, C_6H_6) (lit.[38] $[\alpha]^{25}_D$ +5.75° (*c* 5.0, C_6H_6)); 95.7% ee;[31] IR and ^1H NMR spectra were identical to those obtained for (-)-**2a**.

General Procedure for Preparation of Mosher Esters. To 1.5 g (6.4 mmol) of (*R*)-(+)-MTPA in 1 mL of hexane were added sequentially 1.67 mL (19.2 mmol) of oxalyl chloride and 1 drop of DMF. The mixture was stirred at room temperature for 30 min, and then was refluxed for 3 h. After the volatiles were removed under reduced pressure, the Mosher chloride was distilled under vacuum (50 °C, 0.6 mm Hg) (lit.[39] 50 °C, 0.6 mm Hg). To a solution of 0.15 mmol of the alcohol [(-)-**2a**, (+)-**2b**, (+)-**7a**, (-)-**7b**] in 1 mL of pyridine was added 30 mL of neat (*R*)-(+)-MTPA chloride. The mixture was stirred until all of the starting material had been consumed (approximately 2 h), as monitored by TLC (hexane/EtOAc, 4:1 for (-)-**2a** and (+)-**2b**, 9:1 for (+)-**7a** and (-)-**7b**). Ether (50 mL) was added, the ether layer was washed with water (4 x 30 mL), dried (Na_2SO_4), filtered, and concentrated, affording the crude Mosher ester.

Mosher Ester of (-)-2a. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* =

8.5 Hz, 2 H), 7.35-7.45 (m, 5 H), 7.31 (d, J = 8.5 Hz, 2 H), 5.38 (m, 1 H, $CH_2C\underline{H}CH_2$), 4.28 (dd, J_{AC} = 3.0 Hz, J_{AB} = 11.5 Hz, 1 H), 4.20 (dd, J_{BC} = 7.5 Hz, J_{AB} = 11.5 Hz, 1 H), 3.52 (dd, J_{AC}= 5.4 Hz, J_{AB} = 10.3 Hz, 1 H), 3.51 (s, 3 H, $C\underline{H}_3O$), 3.46 (dd, J_{BC} = 5.4 Hz, J_{AB} = 10.3 Hz, 1 H), 3.27 (t, J = 6.59 Hz, 2 H, $OC\underline{H}_2CH_2$), 2.45 (s, 3 H, $C\underline{H}_3C_6H_4$), 1.26 (br s, 28 H, $CH_3(C\underline{H}_2)_{14}$), 0.88 (br t, 3 H, ω-$C\underline{H}_3$). See Figure 4 for chiral HPLC chromatograms.

Mosher Ester of (+)-2b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2 H), 7.35-7.45 (m, 5 H), 7.31 (d, J = 8.5 Hz, 2 H), 5.41 (m, 1 H, $CH_2C\underline{H}CH_2$), 4.09 (dd, J_{AC} = 3.66 Hz, J_{AB} = 10.74 Hz, 1 H), 4.04 (dd, J_{BC} = 6.35 Hz, J_{AB} = 10.74 Hz, 1 H), 3.31-3.59 (m, 4 H, $OC\underline{H}_2(CH_2)_{14}CH_3$ and $C\underline{H}_2OC_{16}H_{33}$), 3.49 (s, 3 H, $C\underline{H}_3O$), 2.45 (s, 3 H, $C\underline{H}_3C_6H_4$), 1.26 (br s, 28 H, $CH_3(C\underline{H}_2)_{14}$), 0.88 (br t, 3 H, ω-$C\underline{H}_3$). See Figure 4 for chiral HPLC chromatograms.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-*p*-toluenesulfonyl-*sn*-glycerol ((-)-3a). This compound was prepared by using two different procedures. **Procedure A:** To a mixture of (-)-**2a** (235 mg, 0.5 mmol) in 15 mL of ether and 1.2 g (50 wt. equiv based on substrate **2a**) of silica gel (Baker, 60-200 mesh, dried overnight at 120 °C) was added a solution of diazomethane (20 mol equiv based on substrate **2a**) in ether. The mixture was stirred at room temperature for 6 h, filtered, and washed with ether. The solvents were evaporated under vacuum, leaving a residue that was purified by flash chromatography (elution with 8:1 hexane/EtOAc) to give 155 mg (64%) of (-)-**3a**. **Procedure B:** A solution of (-)-**2a** (141 mg, 0.3 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (616 mg, 3.0 mmol) in dry dichloromethane (3 mL) was treated with methyl triflate (340 mL, 3.0 mmol). After the mixture was refluxed for 16 h under nitrogen, the solvents were evaporated. To the residue EtOAc

(50 mL) and 2*N* HCl (30 mL) were added. The organic phase was isolated and washed again with 30 mL of 2*N* HCl. To recover the excess hindered pyridine, the combined aqueous phase was neutralized with 20% aqueous NaOH, and 2,6-di-*tert*-butyl-4-methylpyridine was extracted into dichloromethane. The EtOAc phase was washed with water, saturated $NaHCO_3$, and water, then dried (Na_2SO_4). Removal of the solvents gave a residue that was purified by flash chromatography (elution with 8:1 hexane/EtOAc) to yield 130 mg (90%) of (-)-**3a** as a yellow oil at room temperature. $[\alpha]^{25}_D$ -4.82° (*c* 5.0, $CHCl_3$); IR ($CHCl_3$): 1360, 1182, 1130, 846, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.3 Hz, 2 H), 4.17 (dd, J_{AC} = 4.15 Hz, J_{AB} = 10.42 Hz, 1 H, C_3-$\underline{H}_a$), 4.05 (dd, J_{BC} = 5.6 Hz, J_{AB} = 10.42 Hz, 1 H, C_3-$\underline{H}_b$), 3.36 (s, 3 H, $OC\underline{H}_3$), 3.33-3.53 (m, 5 H, $-C\underline{H}_2OC\underline{H}_2-$ and $-CH_2C\underline{H}CH_2-$), 2.45 (s, 3 H, $C\underline{H}_3C_6H_4$), 1.26 (br s, 28 H, $CH_3(C\underline{H}_2)_{14}-$), 0.88 (br t, 3 H, ω–$C\underline{H}_3$). Anal. Calcd for $C_{27}H_{48}O_5S$: C, 66.90; H, 9.98 S, 6.61. Found: C, 66.98; H, 9.82; S, 6.58.

3-*O*-Hexadecyl-2-*O*-methyl-1-*O*-*p*-toluenesulfonyl-*sn*-glycerol ((+)-3b). This compound was prepared from (+)-**2b** in 89% yield by Procedure B described above; $[\alpha]^{25}_D$ +4.80° (*c* 5.0, $CHCl_3$); IR and ^1H NMR spectra were identical with those obtained for (-)-**3a**.

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol ((-)-4a). This compound was prepared by two procedures. **Procedure A:** To a mixture of potassium superoxide (42 mg, 0.6 mmol) and 18-crown-6 (159 mg, 0.6 mmol) in 3 mL of Me_2SO/DMF/1,2-dimethoxyethane (1:1:1) at room temperature under nitrogen was added 70 mg (0.15 mmol) of (-)-**3a**. After the mixture was stirred for 6 h, 2 mL of cold brine was added slowly and cautiously. The product was extracted with ether (2 x 30 mL), the ether layer was washed with water (20 mL) and dried (Na_2SO_4). Removal of the solvents under vacuum gave a yellow residue that was purified by flash chromatography (elution with 4:1 hexane/EtOAc) to give 40 mg (81%) of (-)-**4a** as a low-melting solid, mp 29-30 °C (lit.[36] mp 30-31 °C); $[\alpha]^{25}_D$ -9.96° (*c* 1.64, $CHCl_3$); (lit.[36] $[\alpha]^{25}_D$ -9.95° (*c* 1.64, $CHCl_3$); IR (neat) 3370, 2930, 2840, 1640, 1460, 1375, 1190, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.38-3.85 (m, 10 H, $C\underline{H}_2OC\underline{H}_2$, $C\underline{H}_2OH$, $CH_2C\underline{H}CH_2$), 3.47 (s, 3 H, $OC\underline{H}_3$), 1.26 (br s, 29 H, $CH_3(C\underline{H}_2)_{14}$, $O\underline{H}$), 0.89 (br t, 3 H, ω-$C\underline{H}_3$). **Procedure B:** To a solution of (-)-**3a** (83 mg, 0.17 mmol) in 10 mL of dry acetone was added 51 mg (0.34 mmol) of sodium iodide. The mixture was refluxed for 24 h under nitrogen. The solvents were evaporated under reduced pressure, and dichloromethane was added to the residue. After the salts were removed by filtration, the filtrate was treated with 1.5 equiv of *m*-chloroperbenzoic acid (MCPBA) at 0 °C for 1 h and then was allowed to stir at room temperature for 24 h. The mixture was filtered, the filtrate was washed with 0.5 N NaOH, and the aqueous layer was extracted twice with dichloromethane. The combined organic phase was dried over Na_2SO_4 and the solvent was removed under vacuum to give a residue that was purified by flash chromatography (elution with 4:1 hexane/EtOAc), yielding 36 mg (61% overall) of (-)-**4a** as a low-melting solid with the same physical properties as described for the product obtained from Procedure A.

3-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol ((+)-4b). This compound was prepared from (+)-(**3b**) in 89% yield by Procedure A; mp 29-30 °C; $[\alpha]^{25}_D$ +9.92° (*c* 1.64, $CHCl_3$); IR and ^1H NMR spectra were identical with those obtained for (-)-**4a**.

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycero-3-phosphocholine ((-)- 5a). To a solution of 2-chloro-2-oxo-1,3,2-dioxaphospholane (51.3 mg, 0.36 mmol) in 3 mL of benzene at 0 °C was added slowly with stirring a mixture of 94 mg (0.30 mmol) of (-)-**4a** and 50 mL (0.36 mmol) of triethylamine in 3 mL of benzene. During a period of 2 h of stirring at room temperature the starting material (R_f 0.32) had completely disappeared as monitored by TLC (4:1 hexane/EtOAc). After the crystalline triethylamine hydrochloride was removed by filtration, the solvent was removed under vacuum to give 128 mg (100%) of the desired cyclic phosphate as a white solid, which was used as soon as possible in the next step. The cyclic phosphate (128 mg, 0.30 mmol) was transferred into a pressure bottle with 4 mL of dry acetonitrile. The mixture was cooled to -78 °C and excess (approximately 0.5 mL) of dry trimethylamine (Fluka) was allowed to condense into the solution. The bottle was sealed and heated at 65-70 °C for 36 h. On cooling at -20 °C for 3 h, 152 mg of crystalline product was obtained. Flash chromatography ($CHCl_3/CH_3OH/H_2O$ 65:25:4) gave 94 mg (63% overall yield) of the product (-)-**5a**; $[\alpha]^{25}_D$ -5.41° (*c* 0.95, $CHCl_3/CH_3OH$ 1:1); (lit.[36] $[\alpha]^{25}_D$ -5.38° (*c* 0.95, $CHCl_3$ /CH_3OH 1:1)); IR (Nujol) 3385, 1220, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$ 1:1) d 3.38-3.85 (m, 10 H, $C\underline{H}_2OC\underline{H}_2$, $C\underline{H}_2OH$, $CH_2C\underline{H}CH_2$), 3.46 (s, 3 H, $OC\underline{H}_3$), 3.39 (s, 9 H, $N(C\underline{H}_3)_3$), 1.26 (br s, 28 H, $CH_3(C\underline{H}_2)_{14}$), 0.89 (br t, 3 H, ω-$C\underline{H}_3$). Anal. Calcd for $C_{25}H_{54}O_6PN \cdot H_2O$: C, 58.45; H, 10.99; N, 2.73; P, 6.03. Found: C, 58.71; H, 10.86; N, 2.53; P, 5.98.

3-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycero-1-phosphocholine ((+)- 5b). This compound was prepared from (+)-**4b** in 65% overall yield; $[\alpha]^{25}_D$ +5.45° (*c* 0.95, $CHCl_3/CH_3OH$ 1:1).

***(R)*-(+)-Oxiranemethanol *tert*-Butyldiphenylsilyl Ether ((+)-6a).** Epoxide (+)-**6a** was prepared in 45% yield by asymmetric epoxidation of allyl alcohol using the procedure of Gao et al.[15] with minor modification; $[\alpha]^{25}_{D}$ +2.40° (*c* 9.07, $CHCl_3$); IR ($CHCl_3$) 2968, 2962, 2940, 1365, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67-7.71 (m, 5 H), 7.35-7.45 (m, 5 H), 3.86 (dd, *J* = 2.9, 12.5 Hz, 1 H), 3.70 (dd, *J* = 4.4, 12.5 Hz, 1 H), 3.10-3.13 (m, 1 H), 2.73 (dd, *J* = 3.3, 5.8 Hz, 1 H), 2.60 (dd, *J* = 3.3, 5.1 Hz, 1 H), 1.06 (s, 9 H).

***(S)*-(-)-Oxiranemethanol *tert*-Butyldiphenylsilyl Ether ((-)-6b).** Epoxide (-)-**6b** was prepared in 49% yield as described above using D-(-)-DIPT. GC/MS analysis of the oil obtained from vacuum distillation (138-140 °C, 0.1 mm Hg) indicated the presence of 10% impurity (allyl *tert*-butyldiphenylsilyl ether); therefore, (-)-**6b** was purified by flash chromatography (20:1 hexane/EtOAc); TLC (9:1 hexane/EtOAc) R_f 0.59; $[\alpha]^{25}_{D}$ -2.46° (*c* 9.07, $CHCl_3$); (lit.[15] $[\alpha]^{25}_{D}$ -2.28° (*c* 9.07, $CHCl_3$)).

1-*O*-Hexadecyl-3-(*O*-*tert*-butyldiphenylsilyl)-*sn*-glycerol ((+)- 7a). To a solution of 625 mg (2.0 mmol) of (+)-**6a** and 510 mg (2.1 mmol) of 1-hexadecanol in 12 mL of dry dichloromethane under nitrogen atmosphere were added catalytic amounts (2 drops, ~5 mol %) of BF_3 etherate. After the mixture was stirred for 24 h, water (30 mL) was added and the products were extracted into dichloromethane (3 x 60 mL). The organic layer was dried (Na_2SO_4) and the solvents were removed under vacuum. TLC analysis (9:1 hexane/EtOAc) of the residue indicated the presence of a small amount of less polar material; flash chromatography (96:4 hexane/EtOAc) gave 819 mg (74%) of (+)-**7a** as an oil that crystallized on storing at -20 °C and 93 mg (8%) of the regioisomer. (+)-**7a:** $[\alpha]^{25}_{D}$ +2.56° (*c* 11.05, $CHCl_3$); 93.8% ee;[32] IR ($CHCl_3$) 3600, 2985, 2930, 1130, 1105 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (m, 5 H), 7.41 (m, 5 H), 3.86 (quintet, 1 H, $CH_2C\underline{H}CH_2$), 3.69 (d, 2 H, $C\underline{H}_2OSi$), 3.40-3.55 (m, 4 H, $C\underline{H}_2OC\underline{H}_2$), 2.15 (br s, 1 H, OH), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 1.05 (s, 9 H, $(CH_3)_3Si$), 0.89 (br t, 3 H, ω-CH_3). Anal. Calcd for $C_{35}H_{58}O_3Si$: C, 74.75; H, 10.54. Found: C, 74.79; H, 10.44.

3-*O*-Hexadecyl-1-(*O*-*tert*-butyldiphenylsilyl)-*sn*-glycerol ((-)- 7b). The TBDPS ether (-)-**7b** was prepared from (-)-**6b** in 68% yield as described above; $[\alpha]^{25}_D$ -2.60° (*c* 11.05, $CHCl_3$); 95.3% ee.[32] The IR and ^1H NMR spectra were identical with those obtained for (+)-**7a**. Anal. Calcd for $C_{35}H_{58}O_3Si$: C, 74.75; H, 10.54. Found: C, 74.80; H, 10.53.

1-*O*-Hexadecyl-2-*O*-methyl-3-(*O*-*tert*-butyldiphenylsilyl)-*sn*-glycerol ((+)-8a). Sodium hydride (97%, 24 mg, 1.0 mmol) was added under a stream of dry nitrogen to a solution of 277 mg (0.5 mmol) of (+)-**7a** in dry benzene (5 mL) at room temperature. After the evolution of hydrogen had stopped, 0.4 mL (6.4 mmol) of methyl iodide was added, and the reaction mixture was stirred for 12 h at room temperature. Hexane (5 mL), ethanol (1 mL), and water (0.5 mL) were added successively, and the product was extracted with hexane (2 x 50 mL). The organic layer was dried over Na_2SO_4 and the solvents were evaporated under vacuum. The residue was purified by flash chromatography (97:3 hexane/EtOAc) to give 279 mg (98%) of (+)-**8a**; $[\alpha]^{25}_D$ +5.98° (*c* 4.09, $CHCl_3$); IR ($CHCl_3$) 2985, 2930, 1130, 1110 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (m, 5 H), 7.39 (m, 5 H), 3.69 (d, 2 H, CH_2OSi), 3.40-3.65 (m, 5 H, CH_2OCH_2, CH_2CHCH_2), 3.38 (s, 3 H, OCH_3), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 1.05 (s, 9 H, $(CH_3)_3Si$), 0.89 (br t, 3 H, ω-CH_3). Anal. Calcd for $C_{36}H_{60}O_3Si$: C, 76.00; H, 10.63. Found: C, 76.16; H, 10.84.

3-*O*-Hexadecyl-2-*O*-methyl-1-(*O*-*tert*-butyldiphenylsilyl)-*sn*-glycerol ((-)-8b). This compound was prepared from (-)-**7b** in 97% yield as described above; $[\alpha]^{25}_D$ -6.01° (*c* 4.09, $CHCl_3$). The IR and ^1H NMR spectra were identical with those obtained for (+)-**8a**. Anal. Calcd for $C_{36}H_{60}O_5Si$: C, 76.00; H, 10.63. Found: C, 75.80; H, 10.75.

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol ((-)-4a). To a solution of 256 mg (0.45 mmol) of (+)-**8a** in 5 mL of tetrahydrofuran was added 0.9 mL (0.90 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran. After the mixture was stirred for 2 h at room temperature, water was added and the product was extracted into ether (3 x 50 mL). The organic layer was dried over Na_2SO_4 and the solvents were removed under vacuum. The residue was purified by flash chromatography (4:1 hexane/EtOAc) to give 148 mg (100%) of (-)-**4a**; mp 29-30 °C (lit.[36] mp 29-30 °C); $[\alpha]^{25}_D$ -9.46° (*c* 1.64, $CHCl_3$), 97.5 % ee based on lit.[36] $[\alpha]^{25}_D$ -9.92° (*c* 1.64, $CHCl_3$) and 97% ee based on ^1H NMR analysis of its (*R*)-(+)-MTPA ester. Anal. Calcd for $C_{20}H_{42}O_3$: C, 72.67; H, 12.80. Found: C, 72.49; H, 12.79.

Mosher ester of (-)-4a. ^1H NMR (200 MHz, $CDCl_3$) δ 7.46 (m, 5 H), 4.52 (dd, J_{AC} = 3.8 Hz, J_{AB} = 11.6 Hz), 4.36 (dd, J_{BC} = 6.0 Hz, J_{AB} = 11.6 Hz, 1 H), 3.33-3.61 (m, 5 H, $CH_2C\underline{H}CH_2$, $OC\underline{H}_2(CH_2)_{14}CH_3$, and $C\underline{H}_2OC_{16}H_{33}$), 3.56 (s, 3 H, $C\underline{H}_3O$), 3.39 (s, 3 H, $C\underline{H}_3O$), 1.26 (br s, 28 H, $CH_3(C\underline{H}_2)_{14}$), 0.89 (br t, 3 H, ω-$C\underline{H}_3$).

3-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol ((+)-4b). This compound was prepared from (-)-**7b** in 100% yield by using the same procedure as described for (-)-**4a**; $[\alpha]^{25}_D$ +9.51° (*c* 1.64, $CHCl_3$). Anal. Calcd for $C_{20}H_{42}O_3$: C, 72.67; H, 12.80. Found: C, 72.65; H, 13.08.

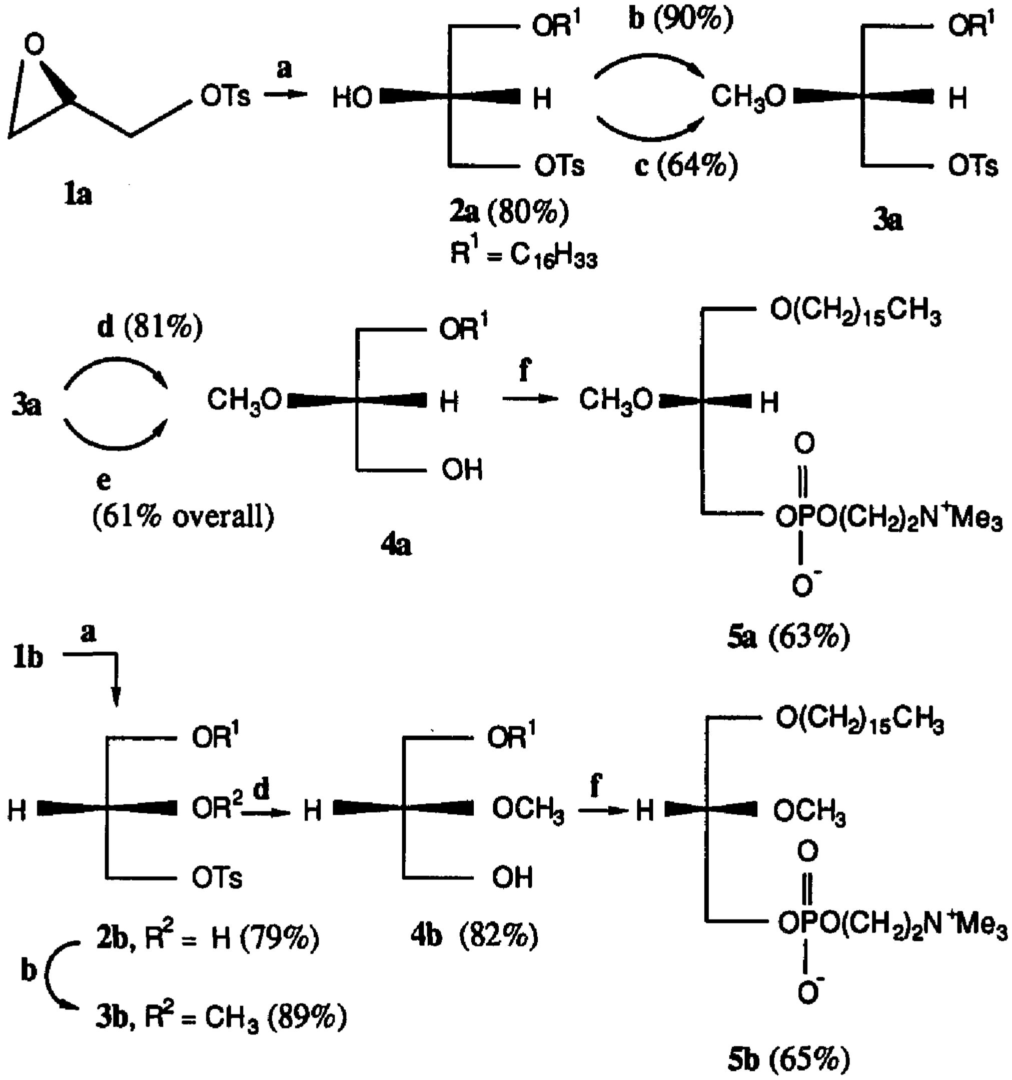
1-*O*-Hexadecyl-*sn*-glycerol ((-)-9a). A solution of 832 mg (1.50 mmol) of (+)-**7a** in 25 mL of tetrahydrofuran was treated with 3 mL (3.0 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran for 2 h at room temperature. Workup as described above for (-)-**4a** gave a white solid that was purified by flash chromatography (1:1 hexane/EtOAc), yielding 460 mg (97%) of (-)-**9a**; mp 63.0-64.0 °C (lit.[40] mp 62.5-63.5 °C); TLC (2:1 hexane/EtOAc) R_f 0.16; $[\alpha]^{25}_D$ -2.68° (*c* 3.5, THF), $[\alpha]^{25}_D$ -3.40° (*c* 1.0, $CHCl_3$); (lit.[40] $[\alpha]^{25}_D$ -3.20° (*c* 1.0, $CHCl_3$)).

3-*O*-Hexadecyl-*sn*-glycerol ((+)-9b). This compound was prepared from (-)-**7b** in 98% yield by using the same procedure as described for (-)-**9a**; mp 63.0-64.0 °C (lit.[40] mp 62.5-63.5 °C); TLC (2:1 hexane/EtOAc) R_f0.16;$[\alpha]^{25}_D$ +2.69° (*c* 3.5, THF), $[\alpha]^{25}_D$ +3.50° (*c* 1.0, $CHCl_3$); (lit.[40] $[\alpha]^{25}_D$ +2.28° (*c* 3.5, THF), lit.[38] $[\alpha]^{25}_D$ +3.1° (*c* 1.0, $CHCl_3$)).

Bis-Mosher Ester of (-)-9a, (+)-9b, and *rac*-9. The MTPA chloride was prepared as described under General Procedure for Preparation of Mosher Esters. To a solution of the diol (0.15 mmol) in 2 mL of pyridine was added 60 mL of neat (*R*)-(+)-MTPA chloride. After the mixture had stirred overnight, TLC analysis (1:1 hexane/EtOAc) indicated the complete conversion of the diols into the corresponding bis-Mosher esters. Workup was as described above. **^{1}H NMR (400 MHz, $CDCl_3$) of bis-Mosher ester of (-)-9a**: δ 7.45 (m, 10 H), 5.45 (m, 1 H, $CH_2C\underline{H}CH_2$), 4.73 (dd, 1 H, J_{AB} = 12.45 Hz, J_{AC} = 2.93 Hz, H_a of C_3 of $C\underline{H}_2OH$), 4.42 (dd, 1 H, J_{AB} = 12.45 Hz, J_{BC} = 6.34 Hz, H_b of C_3 of $C\underline{H}_2OH$), 3.31-3.59 (m, 10 H, $C\underline{H}_2OC_{16}H_{33}$, $OC\underline{H}_2(CH_2)_{14}CH_3$, and two $OC\underline{H}_3$), 1.26 (br s, 28 H, $CH_3(C\underline{H}_2)_{14}$), 0.89 (br t, 3 H, ω-$C\underline{H}_3$). **^{1}H NMR (400 MHz, $CDCl_3$) of bis-Mosher ester of (+)-9b**: δ 7.45 (m, 10 H), 5.48 (m, 1 H, -$CH_2C\underline{H}CH_2$-), 4.62 (dd, 1 H, J_{AB} = 12.45 Hz, J_{AC} = 3.40 Hz, H_a of C_1 of $C\underline{H}_2OH$), 4.36 (dd, 1 H, J_{AB} = 12.45 Hz, J_{BC} = 5.08 Hz, H_b of C_1 of $C\underline{H}_2OH$), 3.31-3.59 (m, 10 H, $C\underline{H}_2OC_{16}H_{33}$, $OC\underline{H}_2(CH_2)_{14}CH_3$, and two $OC\underline{H}_3$), 1.26 (br s, 28 H, $CH_3(C\underline{H}_2)_{14}$), 0.89 (br t, 3 H, ω-$C\underline{H}_3$). **^{1}H NMR (400 MHz, $CDCl_3$) of bis-Mosher ester of *rac*-9**:

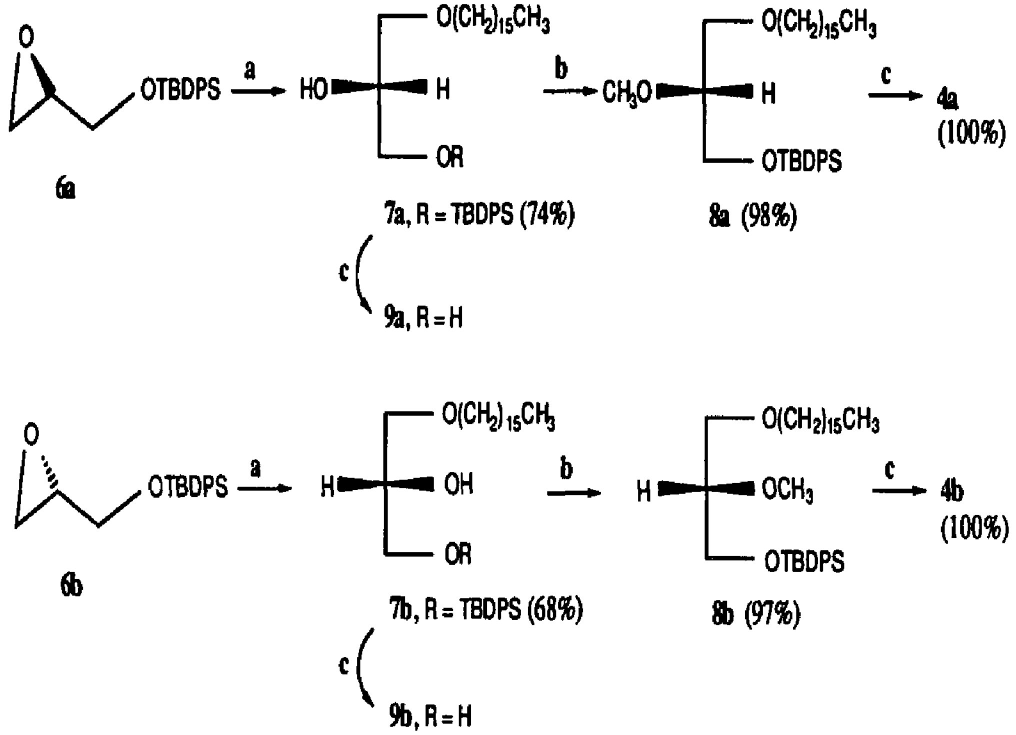
δ 7.45 (m, 10 H), 5.48 (m, 1 H, $CH_2C\underline{H}CH_2$), 4.73 (dd, 0.5 H, J_{AB} = 12.45 Hz, J_{AC} = 2.93 Hz, H_a of C_3 of $C\underline{H}_2OH$), 4.62 (dd, 0.5 H, J_{AB} = 12.45 Hz, J_{BC} = 3.40 Hz, H_b of C_1 of $C\underline{H}_2OH$), 4.42 (dd, 0.5 H, J_{AB} = 12.45 Hz, J_{AC} = 6.34 Hz, H_a of C_3 of $C\underline{H}_2OH$), 4.36 (dd, 0.5 H, J_{AB} = 12.45 Hz, J_{BC} = 5.08 Hz, H_b of C_1 of $C\underline{H}_2OH$), 3.31-3.59 (m, 10 H, $C\underline{H}_2OC_{16}H_{33}$, $OC\underline{H}_2(CH_2)_{14}CH_3$, and two $OC\underline{H}_3$), 1.26 (br s, 28 H, $CH_3(C\underline{H}_2)_{14}$), 0.89 (br t, 3 H, ω-$C\underline{H}_3$).

Scheme I[a]



Scheme I (a) $CH_3(CH_2)_{15}OH$, $BF_3{\cdot}Et_2O$, $CHCl_3$; (b) CH_3OTf, 2,6-di-*t*-C_4H_9-4-CH_3-pyr, CH_2Cl_2, reflux; (c) CH_2N_2, SiO_2, Et_2O; (d) KO_2, 18-crown-6, Me_2SO/DMF/DME, 1:1:1; (e) i. NaI, Me_2CO, reflux; ii. MCPBA, CH_2Cl_2; (f) i. 2-chloro-2-oxo-1,3,2-dioxaphospholane, Et_3N, C_6H_6, 0°C; ii. Me_3N, CH_3CN, 65-70°C.

Scheme II[a]



Scheme II (a) $CH_3(CH_2)_{15}OH$, $BF_3 \cdot Et_2O$, CH_2Cl_2; (b) CH_3I, NaH, C_6H_6; (c) $(n\text{-}C_4H_9)_4N^+F^-$, THF.

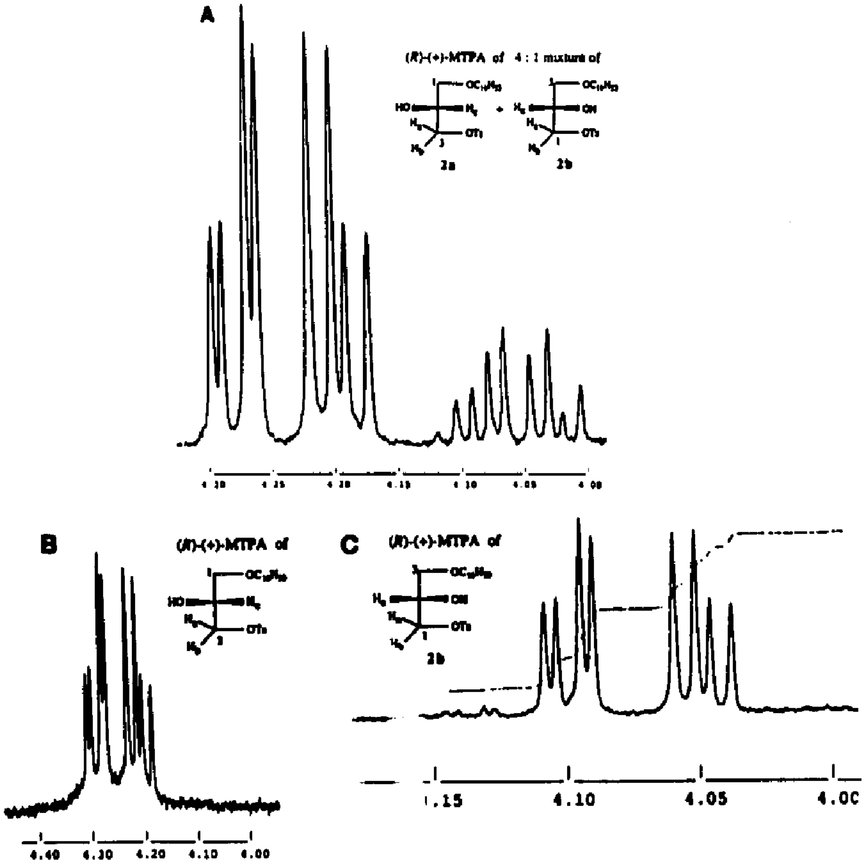


Figure 1. ^1H NMR spectra (400 MHz) of the (*R*)-(+)-MTPA esters of tosylate **2** corresponding to the $C\underline{H}_2OTs$ protons (H_a, H_b) at C_3 of (-)-**2a** and C_1 of (+)-**2b**. (A) a 4:1 mixture of (-)-**2a**/(+)-**2b**, (B) (-)-**2a**, (C) (+)-**2b**.

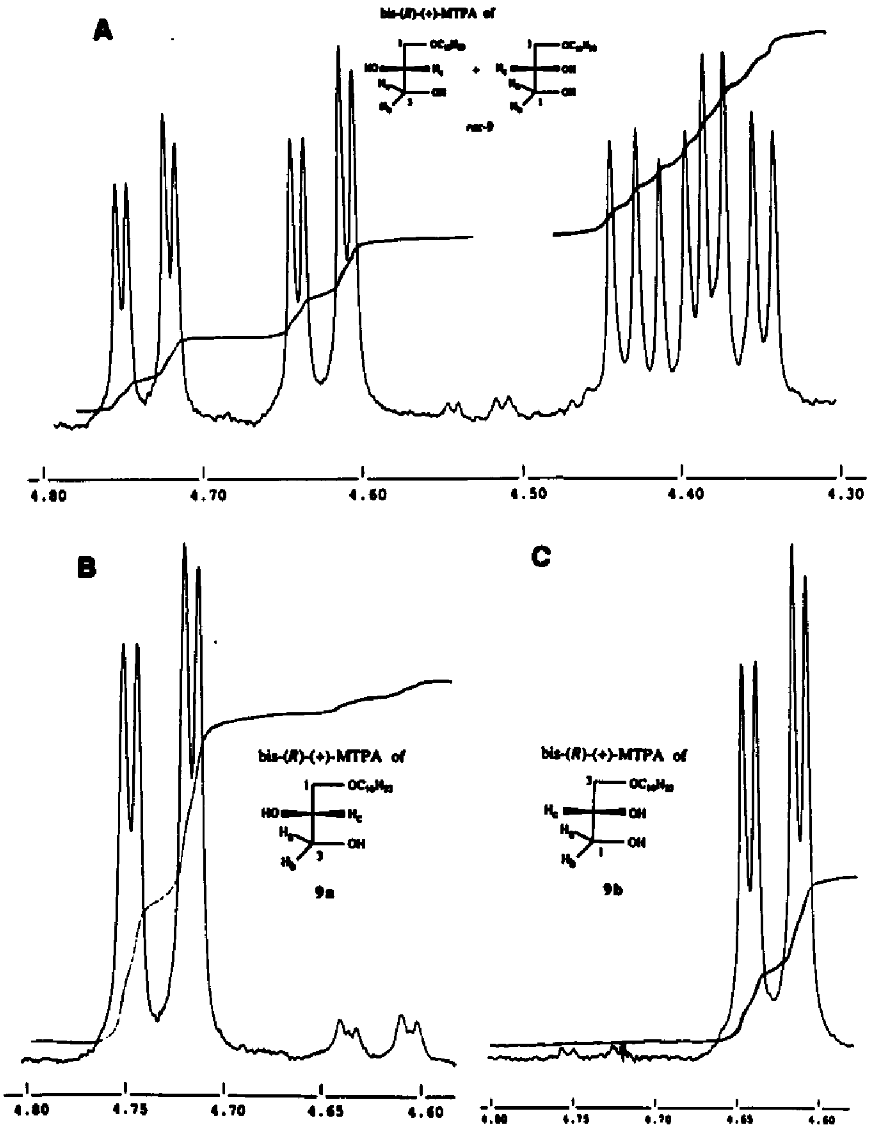


Figure 2. ^{1}H NMR spectra (400 MHz) of the bis-(*R*)-(+)-MTPA esters of *rac*- **9**, (-)-**9a**, and (+)-**9b** corresponding to the C$\underline{H}_2$OMTPA protons (H_a, H_b) at C_3 of (-)-**9a** and C_1 of (+)-**9b**. (A) *rac*-**9**, (B) (-)-**9a**, (C) (+)-**9b**.

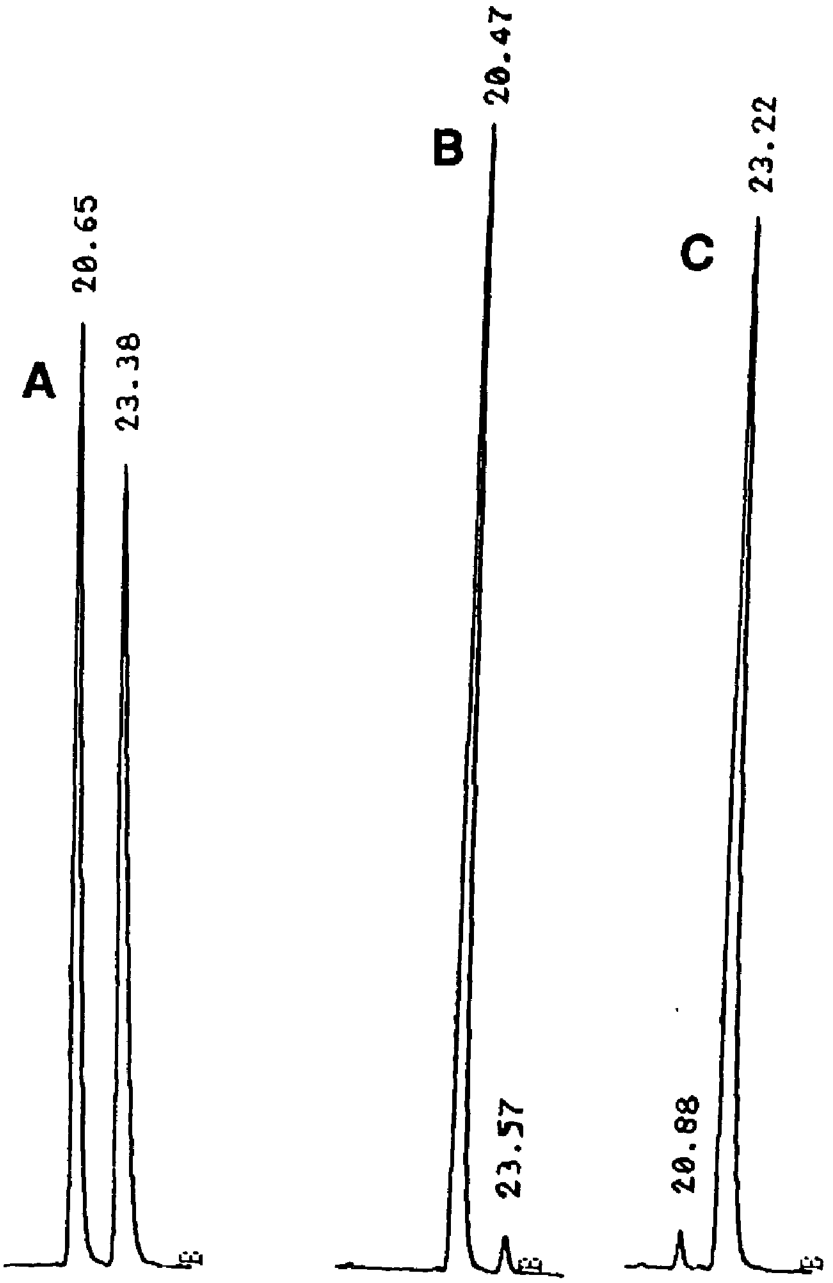


Figure 3. HPLC chromatograms of the (*R*)-(+)-MTPA ester of **7**: **A**, racemic mixture of **7**; **B**, **7a**; **C**, **7b**. See Table 1, page 10, footnote *r*, for HPLC conditions.

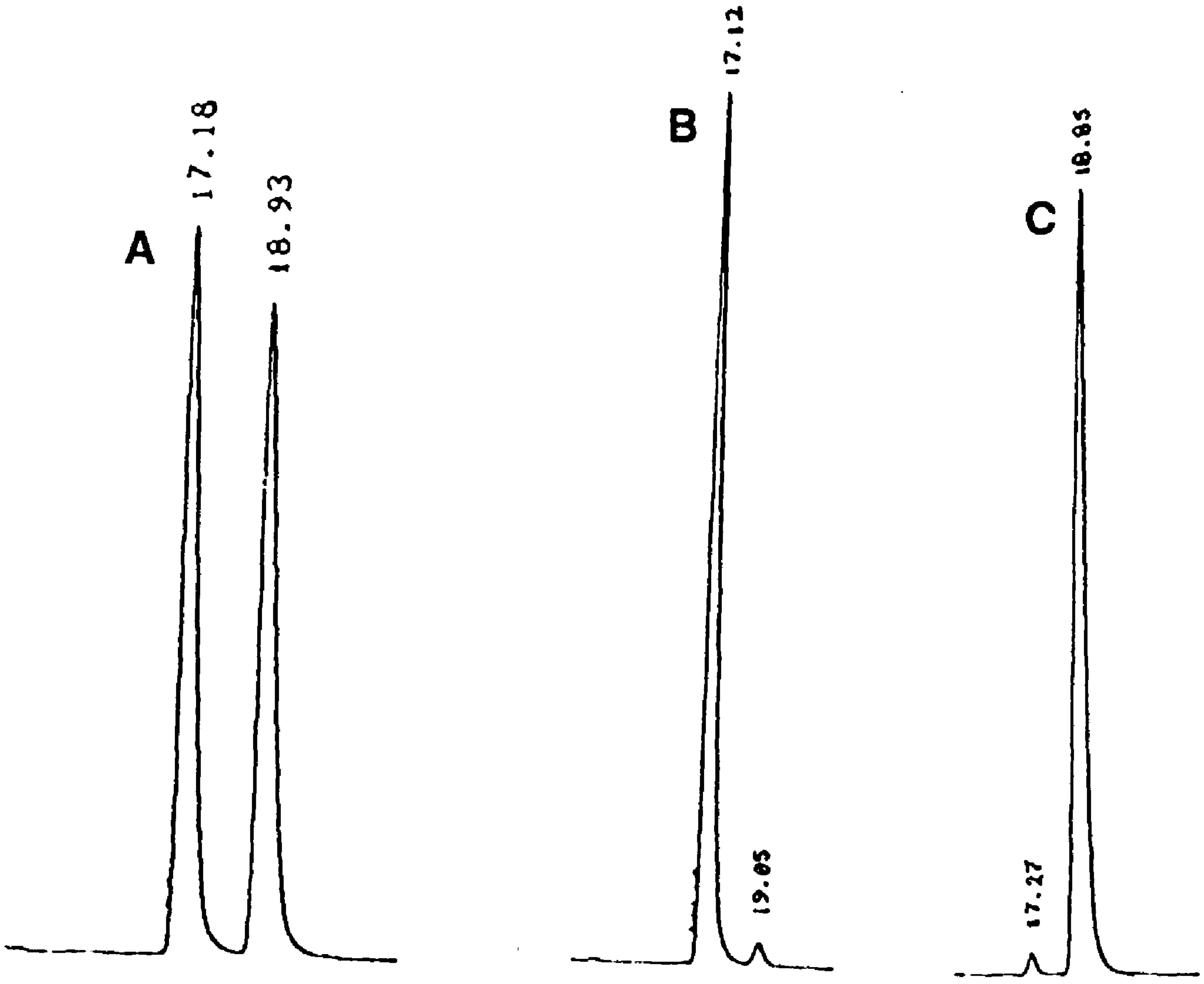


Figure 4. HPLC chromatograms of the (*R*)-(+)-MTPA ester of **2**: **A**, racemic mixture of **2**; **B, 2b**; **C, 2a**. See Table 1, page 10, footnote *i*, for HPLC conditions.

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Chapter 5: An Efficient Stereocontrolled Route to Both Enantiomers of Platelet Activating Factor and Analogs with Long-chain Esters at C_2: Saturated and Unsaturated Ether Glycerolipids by Opening of Glycidyl Arenesulfonates

Abstract: Both enantiomers of various ether/ester glycerophosphocholines (*R*)- and (*S*)-**1**, including platelet activating factor (PAF, **2**), have been synthesized from arenesulfonate derivatives of glycidol ((*R*)- and (*S*)-**3**) that are readily available in high enantiomeric purity. Regio- and stereospecific opening of (*R*)- or (*S*)-**3** with 1.0-1.4 equiv of long-chain saturated or unsaturated alcohol using boron trifluoride etherate as catalyst in CH_2Cl_2 or $CHCl_3$ solvent afforded 1(3)-*O*-alkyl-3(1)-*O*-arenesulfonyl-*sn*-glycerol (**4**) in good yields (73-83%) and with the same very high optical purity of the parent glycidyl arenesulfonate (94-99% ee). For saturated alkyl/acyl **1** and **2**, *O*-benzylation of **4** was achieved with retention of the arenesulfonate group by using benzyl trifluoromethanesulfonate in the presence of excess 2,6-di-*tert*-butyl-4-methylpyridine; the C_2 hydroxyl of unsaturated *O*-alkyl **4** was protected as the methoxymethyl ether under mild conditions in which the arenesulfonate group is retained. Displacement of the arenesulfonate group and introduction of the phosphocholine group to produce PAF analogs complete this synthetically useful route to chiral ether-ester phospholipids with various alkyl and acyl functionalities.

Ether-linked phosphoglycerides bearing a long-chain ester at C_2 ((*R*)-**1**) are important structural constituents of cellular membranes of various tissues.[1] Since they contain the *O*-alkyl linkage, alkylacyl phosphoglycerides **1** may also play important roles in cellular function by serving as precursors of bioactive ether-linked lipids. The potent ether-linked mediator of many biochemical and physiological activities, platelet activating factor (PAF, (*R*)-**2**), can be synthesized when cells are appropriately stimulated by the sequential action of a phospholipase A_2 and an acetyl-CoA transferase on alkylacylglycerophosphocholine.[2]

Many glycerol derivatives have been used as starting materials in chemical syntheses of alkylacyl glycerophospholipids (**1**). For example, *rac*-1-*O*-alkylglycerol, which is available by alkylation of the isopropylidene derivative of glycerol, can be converted into **1** by acylation and phosphorylation procedures.[3] 1-*O*-Alkyl-*sn*-glycerol was prepared from D-mannitol in eight steps, and the same route without Walden inversion gave 3-*O*-alkyl-*sn*-glycerol;[4a-d] 1,2-*O*-isopropylidene-*sn*- glycerol is a key intermediate in this synthetic scheme, and 2,3-*O*-isopropylidene-*sn*-glycerol[4e-g] and its tosylate[4f,h] also serve as a useful chiral C_3-synthon. *rac*-1-*O*-Alkyl-2-*O*-benzylglycerophosphochol- ine, which is available from 1,3-benzylideneglycerol,[5a] and *rac*-1-deoxy-1-iodo-3-*O*-alkylglycerol[5b] have also served as precursors of **1**. Naturally occurring *O*-alkylglycerols are also starting materials for the preparation of alkyl phospholipids with a limited range of alkyl chains at the 1(3) position.[4c] A mixture of 1-*O*-alkyl-2-acyl-*sn*-glycerols was obtained from the liver oil of the ratfish (*Hydrolagus colliei*), which can be converted to alkylacylglycerophosphocholine.[6] A semisynthetic synthesis of the *sn*-1 and *sn*-3 enantiomers of alkylacylglycerophosphocholine was accomplished by treatment of *rac*-alkylacylglycerophosphocholine with phospholipase A_2, followed by isolation and reacylation of 1-*O*-alkylglycerophosphocholine.[7]

Platelet activating factor ((*R*)-**2**) has been the object of many synthetic efforts that have employed natural sources as the starting material, such as D-mannitol,[8a] D-tartaric acid,[8b,c] S-malic acid,[8d] and L-glyceric acid.[8e] Since the chirality of the naturally occurring starting material determines the configuration of the product in this synthetic approach, we sought to develop a stereocontrolled route to the enantiomers of **2** that does not rely on a naturally occurring precursor.

Previous syntheses of lipids from epoxide starting materials have been limited to the preparation of *ester*-linked glycerolipids. For example, the conversions of (*S*)-glycidol to optically active acylglycerols,[9] *rac*-glycidol to *rac*-mono- and 1,2-diacylglycerols[10] and phospholipids,[10c] *rac*-glycidyl esters to *rac*-1,3-diacylglycerols,[11] and glycidyl derivatives **3a** and **3b** to diacyl glycerophospholipids[12] have been reported. As part of a program to prepare ether-linked lipid precursors by the nucleophilic opening of derivatized epoxy alcohols with alcohols,[13] we undertook a synthesis of both enantiomers of PAF (**2**) and of related phospholipids **1** bearing a long-chain ester at the 2 position via the ring opening of stable, crystalline arenesulfonates derivatives of glycidol (**3**). Epoxide opening is catalyzed by $BF_3 \cdot OEt_2$, and the attack of long-chain saturated or unsaturated alcohol occurs exclusively at C_3 of **3**. The approach to the preparation of **1** outlined in Scheme I was disappointing, however, because reaction of the arenesulfonate of alkylacylglycerol **5a** with silver diphenyl phosphate led to (*R*)-**1** in low optical purity. Moreover, this approach could not be applied successfully to the synthesis of **2** because direct acetylation of alcohol **4a** gave a low yield of the desired 3-arenesulfonate of 1-*O*-alkyl-2-acetyl-*sn*-glycerol. Therefore, the synthesis of **1** and **2** outlined in Scheme II was developed.

Results and Discussion

Opening of 3 with Long-Chain Alcohols. Epoxide opening with *n*-hexadecyl, oleyl, and petroselinyl alcohols occurred exclusively at C_3, as shown by reversed-phase HPLC (C_{18} Carbosphere column),[13a] giving **4** as the only regioisomer in good yields (73-83%). Table I shows that the $BF_3 \cdot OEt_2$-catalyzed opening of **3a** takes place stereospecifically, affording the opening product **4** in very high ee (94-99%) as determined by HPLC on a chiral stationary phase.[13a] Glycidyl 3-nitrobenzenesulfonate (**3b**), when recrystallized twice from ethanol,[14] gave **4** in higher ee than did glycidyl tosylate (**3a**). However, the ee of the hydroxy tosylates **4a** produced from **3a** can be enhanced to ≥97% by multiple recrystallization of **3a**[14] or of **4a** (Table I). Thus, both arenesulfonates derivatives are effective chiral C_3 synthons for the preparation of ether-linked lipids.

Preparation of 1 from 4. Partial racemization took place in Scheme I, apparently during the conversion of tosylate **5a** to diphenyl phosphate ester **6** in refluxing xylenes. (Low yields were obtained when refluxing benzene and toluene were used.) We have recently suggested that a resonance-stabilized dioxolane-type oxocarbonium ion is the intermediate responsible for partial racemization during the conversion of 1,2-distearoyl-*sn*-glycero-3-*p*-toluenesulfonate into its diphenyl phosphate ester in refluxing xylenes.[12] Detosylation of **4a** into 1-*O*-hexadecyl-2-palmitoyl-*sn*-glycerol was not attempted because acyl migration from the secondary to primary position is recognized as a serious problem.[12,15]

To obtain isomerically and enantiomerically pure products **1** and **2** we developed an alternative route, which is outlined in Scheme II. The key features of Scheme II are (a) *O*-benzylation of ring-opened arenesulfonate **4a** under basic conditions that proved to be so mild that epoxide formation via arenesulfonate displacement did not occur and (b) conversion of *O*-benzyl tosylate **8** into *O*-benzyl glycerol **9** by displacement using cesium acetate followed by lithium aluminum hydride reduction. It should be noted that acetate displacement proceeded much more rapidly with 3-nitrobenzenesulfonate **12** and **13** than with tosylate **8**; thus, use of **3b** as starting material offers an advantage over **3a** when displacement-reduction reactions are involved. Alcohol **9** and its enantiomer (**9'**) were converted to optically pure ether-ester phosphocholines (*R*)- and (*S*)-**1**, **2** using standard procedures. Attempts to prepare (*R*)-**2** via direct acetylation of **4a** were unsuccessful, although acylation with long-chain acid anhydrides and acyl chlorides gave **5** in satisfactory yields. The *O*-acetyl analog of **5** may undergo acetyl migration with tosylate displacement through a dioxolane-type intermediate to give a mixture of the 2- and 3-acetyl derivatives of 1-*O*-alkylglycerol. To avoid this side reaction, we used a route to **2** involving protection of the C_2 hydroxyl as the benzyl ether **8** (Scheme II) and subsequent conversion to lysophosphocholine **11** after removal of the benzyl group. To obtain unsaturated ether intermediates of **4**, the C_2 hydroxyl was protected as its methoxymethyl ether, again using mild conditions in which the arenesulfonate group is retained (see Scheme III). The methoxymethyl ether, which has not been used previously to our knowledge in lipid synthesis,[16] is shown here to be a useful protecting group of the C_2-hydroxyl group of substituted glycerol derivatives bearing unsaturated alkyl chains.

The new approach to 1-*O*-alkyl-2-acyl-*sn*-glycero-3-phosphocholine using chiral epoxides such as **3a** and **3b** as starting materials will make it possible to conveniently prepare phospholipids with systematic modifications of the alkyl and acyl functionalities at the *sn*-1 and *sn*-2 positions, respectively, and is compatible with the preparation of alkylacyl phosphoglycerides with labeled chains. Products **1** and **2** and related analogs will be of value in studies of the influence of chirality on the interaction of phospholipids with other membrane components and of the action of lipolytic enzymes on alkylacyl phosphoglycerides.[17]

Summary

In the present paper we have shown that (*R*)- and (*S*)-**3** are useful chiral building blocks for the synthesis of both enantiomers of phosphocholines **1** and **2**. The chiral purity of each stereoisomer of **4** was established by examination of the diastereomeric mixture of the (*R*)-(+)-MTPA ester by chiral HPLC. Comparison of the optical rotations of the stereoisomers of **4**, **9**, **10**, and **11** with the literature values also indicates that the ring-opening reaction with 1-hexadecanol and subsequent reactions occur with high stereospecificity. In fact, the optical rotations of these compounds are higher than those reported by Hirth and Barner,[18] who used 1,2-*O*-isopropylidene-*sn*-glycerol as the starting material. Our route is thus a facile and valuable alternative to the use of 1,2-isopropylidene-*sn*-glycerol and 2,3-isopropylidene-*sn*-glycerol. Since partial racemization can occur during storage of isopropylidene-*sn*-glycerol,[3c] and complete racemization can occur in the presence of a trace of acidic impurity,[19] the use of chiral glycidyl derivatives as starting materials offers significant advantages. Furthermore, the use of unsaturated long-chain (such as oleyl and petroselinyl)[20] alcohols as nucleophiles in the ring-opening reaction gives precursors of unsaturated analogs of PAF (**2**) and **1** in excellent chemical and optical yields.

Experimental Section

General Procedures. The solvents used were dried as follows: dichloromethane and ethanol-free chloroform were distilled from calcium hydride and stored over type 3A molecular sieves. Hexane was distilled from and stored over sodium. Xylene was distilled from calcium hydride and stored over type 4A molecular sieves. Alcohol-free chloroform was obtained from J.T. Baker (Phillipsburg, NJ). Triethylamine was dried and stored over calcium hydride. Commercially available $BF_3{\cdot}OEt_2$ from Aldrich (8.1 M) was distilled and then diluted with 9 volumes of dichloromethane. The stock solutions of $BF_3{\cdot}OEt_2$ (0.81 M) in dichloromethane were used as the catalyst in the ring-opening reactions described here within about two months. Other chemicals were obtained from the following sources: (*R*)-(-)- and (*S*)-(+)-Glycidyl tosylate (oxiranemethanol 4-methylbenzenesulfonate), (*R*)-(-)- and (*S*)-(+)-glycidyl 3-nitrobenzenesulfonate, oleyl alcohol, petroselinyl alcohol, palmitoyl chloride, palmitic anhydride, 4-(*N*,*N*-dimethylamino)pyridine, 2,6-di-*tert*-butyl-4-methylpyridine, phosphorus oxychloride, phosphorus pentoxide, trichloroacetonitrile, and trifluoromethanesulfonic anhydride were from Aldrich. Choline tosylate[21] and silver diphenyl phosphate[22] were prepared as described previously. (*R*)-(+)-a-Methoxy-a-(trifluoromethyl)phenylacetic acid (MTPA) was obtained from Aldrich and Fluka Chemical Corp.

Reactions were monitored on 0.25-mm thick silica gel GF TLC plates purchased from Analtech, Newark, DE. Detection of the compounds on TLC plates was by short-wavelength ultraviolet light or by spraying with 10% sulfuric acid in ethanol or with molybdate spray as described previously.[21] Flash chromatography was carried out with silica gel 60 (230-400 ASTM mesh) of E. Merck, purchased from Aldrich.

All ^{1}H NMR spectra were recorded at 200 MHz unless indicated otherwise. Melting points are uncorrected.

1-*O*-Hexadecyl-*sn*-glycerol 3-*O*-*p*-Toluenesulfonate ((-)-4a). This compound was prepared as described in Chapter 4; 94.0% ee, 97.7% ee after three recrystallizations from ether-hexanes.[23]

3-*O*-Hexadecyl-*sn*-glycerol 1-*O*-*p*-Toluenesulfonate ((+)-4'a). This compound was prepared by the procedure described in the Chapter 4; 95.7% ee.[23]

1-*O*-Oleyl-*sn*-glycerol 3-*O*-*m*-Nitrobenzenesulfonate ((-)-4b). To a mixture of 104 mg (0.40 mmol) of (*R*)-(-)-**3b** [$[\alpha]^{25}_D$ -23.3° (*c* 2.14, $CHCl_3$)] and 107 mg (0.40 mmol) of oleyl alcohol in 3 mL of dichloromethane was added four drops (~5 mol %) of a 10% stock solution of boron trifluoride etherate in dichloromethane. After the mixture had stirred at room temperature under nitrogen for 18 h, the solvent was removed under reduced pressure, leaving a residue that was purified by flash chromatography (elution with 20% ethyl acetate-hexanes) to give 156 mg (73%) of **4b** as a pale yellow oil; TLC (20% ethyl acetate-hexanes) R_f 0.26; $[\alpha]^{25}_D$ -7.04° (*c* 2.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.78 (t, 1 H, $J = 1.7$ Hz, C_6H_4), 8.54 (m, 1 H, C_6H_4), 8.29 (m, 1H, C_6H_4), 7.81 (t, 1 H, $J = 7.9$ Hz, C_6H_4), 5.34 (m, 2 H, vinyl), 4.23 (dd, 1 H, $J_{AC} = 4.7$ Hz, $J_{AB} = 10.2$ Hz, $CH_CCH_AH_BOSO_2Ar$), 4.19 (dd, 1 H, $J_{BC} = 5.7$ Hz, $J_{AB} = 10.4$ Hz, $CH_CCH_AH_BOSO_2Ar$), 4.01 (m, 1 H, CHOH), 3.37-3.48 (m, 4 H, $CHCH_2OC_{18}H_{35}$, $OCH_2C_{17}H_{33}$), 2.44 (s, 1 H, OH), 2.01 (m, 4 H, $CH_2CH{=}CHCH_2$), 1.27 (br s, 24 H, $(CH_2)_{12}$), 0.88 (br t, 3 H, ω-CH_3). Determination of the enantiomeric excess of the (*R*)-(+)-MTPA ester of (-)-**4b** by chiral stationary phase HPLC gave 99% ee.[24] Anal. Calcd for $C_{27}H_{45}O_7SN$:

C, 61.45; H, 8.59; N, 2.65. Found: C, 60.82; H, 8.81; N, 2.75.

3-*O*-Oleyl-*sn*-glycerol 1-*O*-*m*-Nitrobenzenesulfonate ((+)-4'b). This compound was prepared in 76% yield from **(*S*)-3b** as described above; $[\alpha]^{25}{}_{D}$ +6.88° (*c* 2.33, $CHCl_3$); 97.1% ee.[24]

1-*O*-Petroselinyl-*sn*-glycerol-3-*O*-*m*-Nitrobenzenesulfonate ((-)-4c). A mixture of 130 mg (0.5 mmol) of (*R*)-(-)-**3b** [$[\alpha]^{25}{}_{D}$ -23.3° (*c* 2.14, $CHCl_3$)], 160 mg (0.60 mmol) of petroselinyl alcohol, and three drops of 10% boron trifluoride etherate in 3 mL of dichloromethane was stirred under nitrogen for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (elution with 20% ethyl acetate in hexanes) to give 217 mg (82%) of (-)-**4c** as a colorless oil; TLC (20% ethyl acetate-hexanes) R_f 0.26; $[\alpha]^{25}{}_{D}$ -6.98° (*c* 2.33, $CHCl_3$); IR (neat) 3566-3319, 3120, 3013, 2919, 2849, 1602, 1537, 1461, 1445, 1431, 1373, 1349, 1190, 1119, 973, 932, 879, 761, 732, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.78 (t, 1 H, J = 1.7 Hz, C_6H_4), 8.54 (m, 1 H, C_6H_4), 8.29 (m, 1 H, C_6H_4), 7.80 (t, 1 H, J = 8.0 Hz, C_6H_4), 5.34 (m, 2 H, vinyl), 4.24 (dd, 1 H, J_{AC} = 4.7 Hz, J_{AB} = 10.2 Hz, $CH_CC\mathit{H}_AH_BOSO_2Ar$), 4.21 (dd, 1 H, J_{BC} = 5.8 Hz, J_{AB} = 10.2 Hz, $CH_CCH_A\mathit{H}_BOSO_2Ar$), 4.01 (m, 1 H, $C\mathit{H}OH$), 3.38-3.47 (m, 4 H, $CHC\mathit{H}_2OC_{18}H_{35}$, $OC\mathit{H}_2C_{17}H_{33}$), 2.44 (s, 1 H, OH), 2.01 (m, 4 H, $C\mathit{H}_2CH{=}CHC\mathit{H}_2$), 1.27 (br s, 24 H, $(C\mathit{H}_2)_{12}$), 0.88 (br t, 3 H, ω-CH_3). Determination of the enantiomeric excess of the (*R*)-(+)-MTPA ester of (-)-**4c** by chiral stationary phase HPLC gave >99% ee (see Figure 1).[24] Anal. Calcd for $C_{27}H_{45}O_7SN$: C, 61.45; H, 8.59; S, 6.08; N, 2.65. Found: C, 61.38; H, 8.80; S, 6.18; N, 2.67.

3-*O*-Petroselinyl-*sn*-glycerol-1-*O*-*m*-Nitrobenzenesulfonate ((+)-4'c). This compound was prepared from **(*S*)-3b** in 75% yield as described above; $[\alpha]^{25}_{D}$ +6.86° (c 2.33, $CHCl_3$); 98.1% ee (see Figure 1).[24]

1-*O*-Petroselinyl-2-*O*-methoxymethyl-3-*O*-*m*-nitrobenzenesulfonyl-*sn*-glycerol ((-)-13). To a mixture of 159 mg (0.30 mmol) of ring-opened intermediate (-)-**4c** and an excess (3 mL, 33.9 mmol) of dimethoxymethane in 3 mL of dry chloroform was added 750 mg (5.3 mmol) of phosphorus pentoxide. The mixture was stirred at room temperature under nitrogen for 24 h, then cooled to 0 °C, and treated with 10% aqueous sodium carbonate solution (about 2 mL, added dropwise) to consume the excess phosphorus pentoxide. The product was extracted into chloroform (2 x 50 mL), and the organic layer was dried (K_2CO_3) and evaporated to give 168 mg (98%) of (-)-**13**; TLC (25% ethyl acetate-hexanes) R_f 0.36; $[\alpha]^{25}_{D}$ -4.97° (c 1.88, $CHCl_3$); IR (neat) 3084, 2919, 2849, 1608, 1537, 1461, 1373, 1349, 1307, 1273, 1119, 1114, 1038, 973, 879, 808, 732, 673, 662, 585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.78 (t, 1 H, J = 1.7 Hz, C_6H_4), 8.54 (m, 1 H, C_6H_4), 8.29 (m, 1 H, C_6H_4), 7.80 (t, 1 H, J = 7.9 Hz, C_6H_4), 5.35 (m, 2 H, vinyl), 4.63 (s, 2 H, CH_3OCH_2O), 4.33 (dd, 1 H, J_{AC} = 3.8 Hz, J_{AB} = 10.4 Hz, $CH_CCH_AH_BOSO_2Ar$), 4.22 (dd, 1 H, J_{BC} = 5.7 Hz, J_{AB} = 10.4 Hz, $CH_CCH_AH_BOSO_2Ar$), 3.94 (m, 1 H, $CHOMOM$), 3.35-3.49 (m, 4 H, $CHCH_2OC_{18}H_{35}$, $OCH_2C_{17}H_{33}$), 3.33 (s, 3 H, CH_3OCH_2), 2.01 (m, 4 H, $CH_2CH{=}CHCH_2$), 1.27 (br s, 24 H, $(CH_2)_{12}$), 0.88 (br t, 3 H, w-CH_3).

1-*O*-Petroselinyl-2-*O*-methoxymethyl-*sn*-glycerol ((+)-15). A mixture of arenesulfonate (-)-**13** (114 mg, 0.2 mmol) in 4 mL of dimethylformamide-dimethyl sulfoxide 4:1 and cesium acetate (154 mg, 0.8 mmol) was stirred under nitrogen for 4 h at room temperature. The mixture was extracted with diethyl ether (2 x 75 mL), washed with water (2 x 50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to a volume of ~5 mL.

The crude acetate was cooled to 0 °C and lithium aluminum hydride (16 mg, 0.4 mmol) was added in one portion. The mixture was stirred at 0 °C for 30 min and at room temperature for 1 h, then quenched by slow addition of water. The mixture was filtered to remove aluminum salts and extracted with chloroform (40 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a residue that was purified by flash chromatography (elution with hexanes-ethyl acetate 4:1). There was isolated 69 mg (89%) of (+)-**15** as a clear, colorless oil: TLC (25% ethyl acetate-hexanes) R_f 0.34; $[\alpha]^{25}_{D}$ +19.92° (*c* 4.20, $CHCl_3$); IR (neat) 3448, 3013, 2919, 2849, 1461, 1155, 1114, 1032, 917 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.33 (m, 2 H, vinyl), 4.75 (s, 2 H, $CH_3OC\mathit{H}_2O$), 3.44-3.78 (m, 7 H, $C\mathit{H}OMOM$, $CHC\mathit{H}_2OC_{18}H_{35}$, $OC\mathit{H}_2C_{17}H_{33}$, $C\mathit{H}_2OH$), 3.42 (s, 3 H, $C\mathit{H}_3OCH_2$), 2.76 (br s, 1 H, OH), 2.01 (m, 4 H, $C\mathit{H}_2CH{=}CHC\mathit{H}_2$), 1.28 (br s, 24 H, $(C\mathit{H}_2)_{12}$), 0.87 (br t, 3 H, ω-CH_3).

1-*O*-Hexadecyl-2-palmitoyl-*sn*-glycerol-3-*p*-Toluenesulfonate ((-)-5). To a solution of 376 mg (0.80 mmol) of (-)-**4a** in 8 mL of hexane containing 97 mL (1.20 mmol) of pyridine was added dropwise 264 mg (0.96 mmol) of palmitoyl chloride in 10 mL of hexane. After the mixture was heated under reflux for 4 h, water (2 mL) was added to destroy the excess palmitoyl chloride, and refluxing was continued for 10 min. The mixture was cooled and diluted with hexane. The organic layer was washed with dilute sulfuric acid, water, saturated aqueous sodium bicarbonate solution, and water, then dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The free fatty acid was removed by dissolving the crude product in 100 mL of methanol-dichloromethane-hexane, 40:33:27, followed by extraction with 40 mL of 1 N potassium hydroxide. The upper layer containing the fatty acid salt was separated from the lower layer, which was diluted with

100 mL of hexane and washed with water three times to neutrality. The organic extracts were dried with $MgSO_4$ and concentrated by rotary evaporation to give a residue that afforded 452 mg (81%) of (-)-**5** after two recrystallizations from cold (-20 °C) acetonitrile; mp 55-56 °C; TLC (20% ethyl acetate-hexanes) R_f 0.70; $[\alpha]^{25}_D$ -7.62° (*c* 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.75 (d, 2 H, *J* = 8.5 Hz, C_6H_4), 7.32 (d, 2 H, *J* = 8.5 Hz, C_6H_4), 5.04 (m, 1 H, CH_2CHCH_2), 4.35 (dd, 2 H, *J* = 4.5 and 11.5 Hz, CH_2OTs), 3.48 (dd, 2 H, *J* = 4.5 and 11.5 Hz, $CH_2OC_{16}H_{33}$), 3.35 (t, 2 H, *J* = 7.0 Hz, $OCH_2C_{15}H_{31}$), 2.43 (s, 3 H, $OSO_2C_6H_4CH_3$-*p*), 2.22 (t, 2 H, *J* = 8.0 Hz, $O_2CCH_2C_{14}H_{29}$), 1.29 (br s, 54 H, $OCH_2(CH_2)_{14}$ and $O_2CCH_2(CH_2)_{13}CH_3$), 0.86 (br t, 6 H, ω-CH_3). Anal. Calcd for $C_{42}H_{76}O_6S$: C, 70.64; H, 10.86; S, 4.79. Found: C, 70.58; H, 10.86; S, 4.79.

3-*O*-Hexadecyl-2-palmitoyl-*sn*-glycerol-1-*p*-Toluenesulfonate ((+)-5'). This compound was prepared as described above for (-)-**5**; yield, 83%; TLC (20% ethyl acetate-hexanes) R_f 0.70; $[\alpha]^{25}_D$ +7.48° (*c* 0.32, $CHCl_3$).

Diphenyl 1-*O*-Hexadecyl-2-palmitoyl-*sn*-glycero-3-phosphate ((+)-6). A mixture of 100 mg (0.14 mmol) of (-)-**5** and 126 mg (0.35 mmol) of silver diphenyl phosphate in 7.5 mL of dry xylene was refluxed in the dark under nitrogen atmosphere for 6 h. The mixture was cooled to room temperature, filtered through a Celite pad, and washed with chloroform (3 x 30 mL). Evaporation of the solvent gave a yellow oil that was purified by flash chromatography (elution with hexanes-ethyl acetate 8:1). There was isolated 82 mg (75%) of diphenyl phosphate ester (+)-**6**, mp 44-45 °C; TLC (hexanes-ethyl acetate 8:1) R_f 0.28; $[\alpha]^{25}_D$ +2.14° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.41 (br s, 10 H, C_6H_5), 5.04 (m, 1 H, CH_2CHCH_2), 4.41 (t, 2 H, *J* = 7.6 Hz,

$CH_2OP(O)(OC_6H_5)_2$), 3.48 (d, 2 H, $J = 8.2$ Hz, $CH_2OC_{16}H_{33}$), 3.35 (t, 2 H, $J = 7.0$ Hz, $OCH_2C_{15}H_{31}$), 2.22 (t, 3 H, $J = 8.0$ Hz, $O_2CCH_2C_{14}H_{29}$), 1.29 (br s, 54 H, $OCH_2(CH_2)_{14}$ and $O_2CCH_2(CH_2)_{13}CH_3$), 0.86 (br t, 6 H, ω-CH_3).

1-*O*-Hexadecyl-2-palmitoyl-*sn*-glycero-3-phosphatidic Acid (7). A mixture of 100 mg (0.44 mmol) of platinum oxide in 10 mL of glacial acetic acid was stirred in a 50-mL two-necked flask under hydrogen atmosphere for 1 h at room temperature. A solution of 107 mg (0.14 mmol) of (+)-**6** in 20 mL of acetic acid-cyclohexane 1:1 was added rapidly via syringe, and the mixture was stirred at room temperature for 6 h. The mixture was filtered through a Celite pad, which was washed with chloroform. Evaporation of the filtrate under vacuum gave a white solid, which was dissolved in a small volume of chloroform. Precipitation twice from cold (-20 °C) acetonitrile afforded 70 mg (79%) of **7**, which was used in the next step without further purification.

1-*O*-Hexadecyl-2-palmitoyl-*sn*-glycero-3-phosphocholine ((*R*)-(-)-1); see Scheme I. To a solution of 70 mg (0.11 mmol) of phosphatidic acid **7** in 5 mL of dry pyridine were added 305 mg (1.1 mmol) of choline tosylate and 3 mL of trichloroacetonitrile. The mixture was heated under nitrogen at 50 ± 5 °C for 2 days, during which time the mixture became brown. After 10 mL of chloroform-methanol 1:1 was added, the solvents were removed under reduced pressure, leaving a brown residue. The residue was dissolved in 20 mL of tetrahydrofuran-water 9:1, and the solution was applied to a column of Amberlite MB-3 (25 g) that had been previously equilibrated with the same same solvent system. Elution with 500 mL of tetrahydrofuran-water 9:1, evaporation of the solvents under reduced pressure, and azeotropic evaporation of water in a rotary evaporator with 2-propanol (3 x 50 mL) gave a brown residue that was purified by flash chromatography (elution with chloroform-methanol-water, 65:25:4). There was isolated 27 mg (35%) of the desired phosphocholine (*R*)-(-)-**1**; TLC (chloroform-methanol-water, 65:25:4) R_f 0.33; $[\alpha]^{25}{}_D$ -1.09° (*c* 0.52, $CHCl_3$-CH_3OH, 1:1) (32% optical purity, see below). Treatment of (*R*)-**1** prepared by this procedure with phospholipase A_2 (*Naja naja*, Sigma Chemical Co.) in pH 7.4 buffer at 38 °C resulted in incomplete hydrolysis to 1-*O*-hexadecyl-2-lyso-*sn*-glycero-3-phosphocholine and palmitic acid (R_f 0.13 and 0.86, respectively, in chloroform-methanol-water, 65:25:4). Comparison of the $[\alpha]^{25}{}_D$ values of (*R*)-**1** prepared by the routes outlined in Schemes I and II also indicates that partial racemization at C_2 occurred in Scheme I, probably at the refluxing xylene temperature used in the conversion of tosylate (-)-**5** to diphenyl phosphate ester (+)-**6**; partial racemization via a dioxolane-type intermediate has been proposed previously.[12]

1-*O*-Hexadecyl-2-*O*-benzyl-*sn*-glycerol-3-*p*-Toluenesulfonate ((-)-8). Trifluoromethanesulfonic anhydride (168 mL, 1.0 mmol) was added to 5 mL of dry dichloromethane at -78 °C in an oven-dried 50-mL round-bottom flask equipped with a Claisen head and a nitrogen-filled balloon. A solution of 104 mL (1.0 mmol) of benzyl alcohol and 205 mg (1.0 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine in 2 mL of dry dichloromethane was added dropwise over a 5-min period. After the reaction was stirred at -78 °C for 15 min, a solution of 235 mg (0.5 mmol) of (-)-**4a** and 268 mg (1.3 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine in 2 mL of dry dichloromethane was added dropwise over a 5-min period. The mixture was stirred for 30 min at -78 °C, then allowed to warm to room temperature with stirring until all of (-)-**4a** had disappeared (about 4 h) as monitored by TLC (25% ethyl acetate-hexanes). The excess of benzyl trifluoromethanesulfonate was then destroyed by slowly adding 167 mL (2.07 mmol) of pyridine. The reaction mixture was diluted with 30 mL of dichloromethane and washed with water (3 x 10 mL). The organic phase was dried (Na_2SO_4), the solvents were evaporated under reduced pressure, and the residue was purified by flash chromatography (elution with hexanes-ethyl acetate 8:1) to furnish 268 mg (96%) of *O*-benzyl product (-)-**8** as a colorless oil; TLC (hexanes-ethyl acetate 8:1) R_f0.33; $[\alpha]^{25}_D$ -7.32° (*c* 5.0, $CHCl_3$); IR ($CHCl_3$) 1602, 1499, 1360, 1182, 1102, 820, 766, 756, and 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2 H, J = 8.3 Hz, aromatic), 7.29 (m, 7 H, aromatic), 4.58 (s, 2 H, $OCH_2C_6H_5$), 4.17 (dd, 1 H, J_{AC} = 4.1 Hz, J_{AB} = 10.4 Hz, $CH_CH_AH_BOTs$), 4.08 (dd, 1 H, J_{BC} = 5.8 Hz, J_{AB} = 10.4 Hz, $CH_CH_AH_BOTs$), 3.75 (m, 1 H, CH_2CHCH_2), 3.45 (collapsed AB quartet, 2 H, J = 7.86 Hz, Du = 4.66, $CH_2OC_{16}H_{33}$), 3.34 (t, 2 H, J = 6.6 Hz, $OCH_2C_{15}H_{31}$), 2.43 (s, 3 H, $OSO_2C_6H_4CH_3$), 1.26 (br s, 28 H, $OCH_2(CH_2)_{14}$), 0.89 (br t, 3 H, ω-CH_3).

3-*O*-Hexadecyl-2-*O*-benzyl-*sn*-glycerol-1-*p*-Toluenesulfonate ((+)-8'). This compound was prepared in 92% yield as described above for (-)-**8**; $[\alpha]^{25}_D$ +7.48° (*c* 5.0, $CHCl_3$).

1-*O*-Hexadecyl-2-*O*-benzyl-*sn*-glycerol ((-)-9). To a solution of 192 mg (1.0 mmol) of cesium acetate in 5 mL of dry dimethyl sulfoxide-dimethylformamide 4:1 was added 280 mg (0.5 mmol) of (-)-**8**. After the mixture was stirred at room temperature for 36 h under a drying tube, water (30 mL) was added and the product was extracted with ether (3 x 50 mL). The organic phase was dried with Na_2SO_4, and the solvents were concentrated under reduced pressure to a volume of about 10 mL. The solution was cooled to 0 °C and 40 mg (1.0 mmol) of lithium aluminum hydride was added. After the mixture was stirred for 30 min at 0 °C and for 2 h at room temperature, water was added. The aluminum salts were removed by filtration and the product was extracted with chloroform (60 mL). Evaporation of the solvents under reduced pressure gave 187 mg (92% overall yield) of (-)-**9** as a low-melting solid, mp 27-28 °C (lit.[18] mp 28-30 °C); $[\alpha]^{25}_D$ -9.27° (*c* 5.0, C_6H_6) [lit.[18] $[\alpha]^{25}_D$ -8.76° (*c* 5.0, C_6H_6)]; IR (Nujol) 3450, 1520, 1126,1072, 742,700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (s, 5 H, C_6H_5), 4.81 (d, 1 H, J = 12.0 Hz, $OCH_AH_BC_6H_5$), 4.69 (d, 1 H, J_{AB} = 12.0 Hz, $OCH_AH_BC_6H_5$), 3.25-3.98 (m, 7 H, CH_2OCH_2, CH_2OH, CH_2CHCH_2), 2.15 (s, 1 H, OH), 1.26 (br s, 28 H, $OCH_2(CH_2)_{14}$), 0.88 (br t, 3 H, ω-CH_3).

3-*O*-Hexadecyl-2-*O*-benzyl-*sn*-glycerol ((+)-9'). This compound was prepared in 93% overall yield by the procedure described above for (-)-**9**; mp 29-31 °C (lit.[18] mp 28-30 °C); $[\alpha]^{25}_D$ +9.19° (*c* 5.0, C_6H_6) [lit.[18] $[\alpha]^{25}_D$ +8.70° (*c* 5.0, C_6H_6)].

1-*O*-Hexadecyl-2-*O*-benzyl-*sn*-glycero-3-phosphocholine ((+)-10). To a solution of 134 mg (0.90 mmol) of phosphorus oxychloride and 163 mL (0.90 mmol) of triethylamine in 4 mL of alcohol-free chloroform at -10 °C under nitrogen was added a solution of 243 mg (0.72 mmol) of (-)-**9** in 4 mL of alcohol-free chloroform over a 30-min period. The mixture was allowed to warm to room temperature and was stirred for an additional 30 min. Choline tosylate (300 mg, 1.08 mmol) and pyridine (0.5 mL) were added, and the mixture was stirred under nitrogen for 16 h. Water (0.2 mL) was introduced, and stirring was continued for 30 min. After the solvents were removed under reduced pressure, 30 mL of dichloromethane-toluene 1:1 was added to the residue and the mixture was filtered. Evaporation of the filtrate left a residue that was dissolved in tetrahydrofuran-water 9:1 and passed through an Amberlite MB-3 column two times (elution with tetrahydrofuran-water 9:1). The solvents were removed under vacuum, and the residue was purified by flash chromatography (elution with chloroform-methanol-water, 65:35:4) to give 318 mg (75%) of (+)-**10** as a white solid, mp 200 °C; $[\alpha]^{25}_D$ +3.92° (*c* 5.0, $CHCl_3$-CH_3OH 1:1) [lit.[18] $[\alpha]^{25}_D$ +3.54° (*c* 5.0, $CHCl_3$-CH_3OH 1:1)]; IR (Nujol) 3413 (H_2O), 3048, 1493, 1256, 1106,1089, 1069, 1067, 705, 645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (s, 5 H, C_6H_5), 4.74 (s, 2 H, $OCH_2C_6H_5$), 3.32-4.62 (m, 11 H, CH_2OCH_2, $CHCH_2OP$, $P(O)(O^-)OCH_2$, $CH_2N^+(CH_3)_3$), CH_2CHCH_2), 3.25 (s, 9 H, $N^+(CH_3)_3$), 1.26 (br s, 28 H, $OCH_2(CH_2)_{14}$), 0.88 (br t. [illegible] H, ω-CH_3).

3-*O*-Hexadecyl-2-*O*-benzyl-*sn*-glycero-1-phosphocholine ((-)-10'). This compound was prepared in 73% yield by the procedure described above for (+)-**10**; $[\alpha]^{25}_D$ -3.95° (*c* 5.0, $CHCl_3$-CH_3OH 1:1) [lit.[18] $[\alpha]^{25}_D$ -3.53° (*c* 5.0, $CHCl_3$-CH_3OH 1:1)].

1-*O*-Hexadecyl-2-lyso-*sn*-glycero-3-phosphocholine ((-)-11). A mixture of 150 mg (0.24 mmol) of (+)-**10** and 100 mg of 20% palladium hydroxide on carbon in 9 mL of methanol and 1 mL of water was stirred under hydrogen atmosphere for 24 h. The mixture was filtered through Celite, the Celite was washed with methanol, and the filtrate was evaporated under reduced pressure. The residue was dried by azeotropic removal of water using 2-propanol, giving 128 mg (100%) of (-)-**11**, mp 250 °C (dec); $[\alpha]^{25}_D$ -6.09° (*c* 1.04, $CHCl_3$-CH_3OH 1:1) [lit.[18] $[\alpha]^{25}_D$ -6.03° (*c* 1.04, $CHCl_3$-CH_3OH 1:1)]; IR (Nujol) 3280, 1252, 1095, 1062 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48-3.51 (m, 11 H, CH_2OCH_2, $CHCH_2OP$, $P(O)(O^-)OCH_2$, $CH_2N^+(CH_3)_3$, CH_2CHCH_2), 3.28 (s, 9 H, $N^+(CH_3)_3$), 1.26 (br s, 28 H, $OCH_2(CH_2)_{14}$), 0.88 (br t, 3 H, ω-CH_3). Anal. Calcd for $C_{24}H_{52}O_6PN{\cdot}1.5H_2O$: C, 56.67; H, 10.89;

N, 2.71. Found: C, 56.66; H, 10.80; N, 2.24.

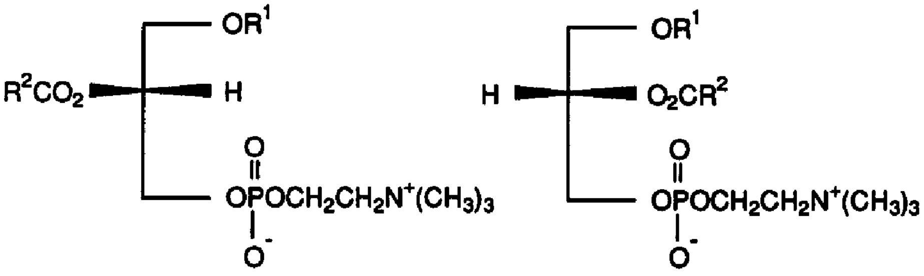
3-*O*-Hexadecyl-2-lyso-*sn*-glycero-1-phosphocholine ((+)-11'). The same procedure described above for the preparation of (-)-**11** was used to prepare **11'** in 100% yield; mp 250 °C (dec); $[\alpha]^{25}{}_{D}$ +6.11° (*c* 1.05, $CHCl_3$-CH_3OH 1:1).

1-*O*-Hexadecyl-2-palmitoyl-*sn*-glycero-3-phosphocholine ((*R*)-(-)-1); see Scheme II. A mixture of 53 mg (0.12 mmol) of (-)-**11**, 291 mg (0.60 mmol) of palmitic anhydride, and 15 mg (0.12 mmol) of 4-(dimethylamino)pyridine in 2 mL of alcohol-free chloroform was stirred under nitrogen for 24 h. The solvents were removed under reduced pressure, leaving a residue that was purified by flash chromatography (elution with 200 mL of chloroform, followed by 200 mL of chloroform-methanol 9:1, and 500 mL of chloroform-methanol 3:2). There was isolated 85 mg (98%) of (*R*)-(-)-**1**, which was lyophilized from 3 mL of benzene; $[\alpha]^{25}{}_{D}$ -3.38° (*c* 0.53, $CHCl_3$-CH_3OH 1:1); ^1H NMR ($CDCl_3$) δ 5.16 (m, 1 H, $CH_2C\mathit{H}CH_2$), 3.25-3.59 (m, 10 H, CH_2OCH_2, $CHC\mathit{H}_2OP$, $P(O)(O^-)OCH_2$, $C\mathit{H}_2N^+(CH_3)_3$), 3.22 (s, 9 H, $N^+(CH_3)_3$), 2.33 (t, 3 H, $J = 8.0$ Hz, O_2CCH_2), 1.26 (br s, 54 H, $OCH_2(C\mathit{H}_2)_{14}$ and $O_2CCH_2(C\mathit{H}_2)_{13}$), 0.88 (br t, 3 H, ω-$CH_3$). Anal. Calcd for $C_{40}H_{82}O_7PN{\cdot}3H_2O$: C, 61.06; H, 11.05; N, 1.81; P, 4.00. Found: C, 59.80; H, 11.06; N, 1.73; P, 4.00.

3-*O*-Hexadecyl-2-palmitoyl-*sn*-glycero-1-phosphocholine ((*S*)-(+)-1). This compound was prepared in 97% yield by the procedure described above for (*R*)-(-)-**1**; $[\alpha]^{25}{}_{D}$ +3.42° (*c* 0.50, $CHCl_3$-CH_3OH 1:1). Anal. Calcd for $C_{40}H_{82}O_7PN{\cdot}4H_2O$: C, 60.06; H, 11.45; N, 1.77; P, 3.91. Found: C, 60.09; H, 11.06; N, 1.72; P, 4.61.

1-*O*-Hexadecyl-2-acetyl-*sn*-glycero-3-phosphocholine ((*R*)-2). A mixture of 30 mg (0.060 mmol) of lyso-PAF (**11**), 7 mg (0.066 mmol) of 4-(dimethylamino)pyridine, and 110 mL (1.2 mmol) of acetic anhydride in 2 mL of chloroform was stirred at room temperature for 24 h. The solvents were removed under reduced pressure to leave a residue that was purified by flash chromatography (elution with $CHCl_3$-CH_3OH-H_2O, 65:25:4), yielding 30 mg (93%) of (*R*)-**2** as a white solid, mp 248 °C (dec); $[\alpha]^{25}_D$ -3.39° (*c* 0.53, $CHCl_3$-CH_3OH, 1:1); lit.[8c] $[\alpha]^{25}_D$ -3.30° (*c* 0.53, $CHCl_3$-CH_3OH, 1:1); ^1H NMR ($CDCl_3$) δ 5.11 (m, 1 H, CH_2CHCH_2), 4.20 (m, 4 H, CH_2CHCH_2), 3.40-3.52 (m, 10 H, CH_2OCH_2, CH_2OP, $P(O)(O^-)OCH_2$, $CH_2N^+(CH_3)_3$), 3.30 (s, 9 H, $N^+(CH_3)_3$), 2.08 (s, 3 H, O_2CCH_3), 1.29 (br s, 28 H, $(CH_2)_{14}$), 0.89 (t, *J* = 8.0 Hz, 3 H, w-CH_3); IR (KBr): 3428, [illegible]926 2856, [illegible]2, 1627, 1460, 1372 cm^{-1}. Anal. Calcd for $C_{26}H_{54}O_7PN{\cdot}1.5H_2O$: C, 56.7[illegible], H, 10.43; N, 2.54. Found: C, 56.66; H, 10.80; N, 2.24.

3-*O*-Hexadecyl-2-acetyl-*sn*-glycero-1-phosphocholine ((*S*)-2). The above procedure was repeated with **1** [illegible] giving (*S*)-**2** in 92% yield; $[\alpha]^{25}_D$ +3.20° (*c* 0.53, $CHCl_3$-CH_3OH, 1:1); lit.[8c] $[\alpha]^{25}_D$ +3.18° (*c* 0.53, $CHCl_3$-CH_3OH, 1:1).

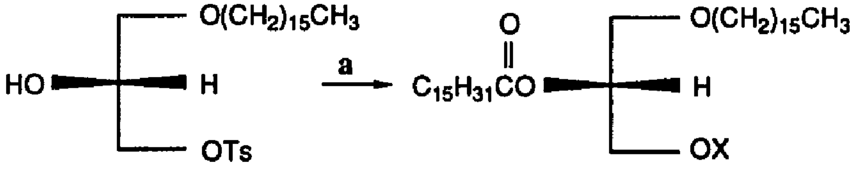


$R^1 = C_{16}H_{33}, C_{18}H_{35}\text{-}\Delta^9\text{-}cis, C_{18}H_{35}\text{-}\Delta^6\text{-}cis$

Alkylacyl-PC (*R*)-1: $R^2 = C_{15}H_{31}$ **(*S*)-1:** $R^2 = C_{15}H_{31}$

PAF (*R*)-2: $R^2 = CH_3$ **(*S*)-2:** $R^2 = CH_3$

Scheme I. Synthesis of (*R*)-1 from Glycidyl Tosylate [(*R*)-3a] without the Use of Protecting Groups [a]

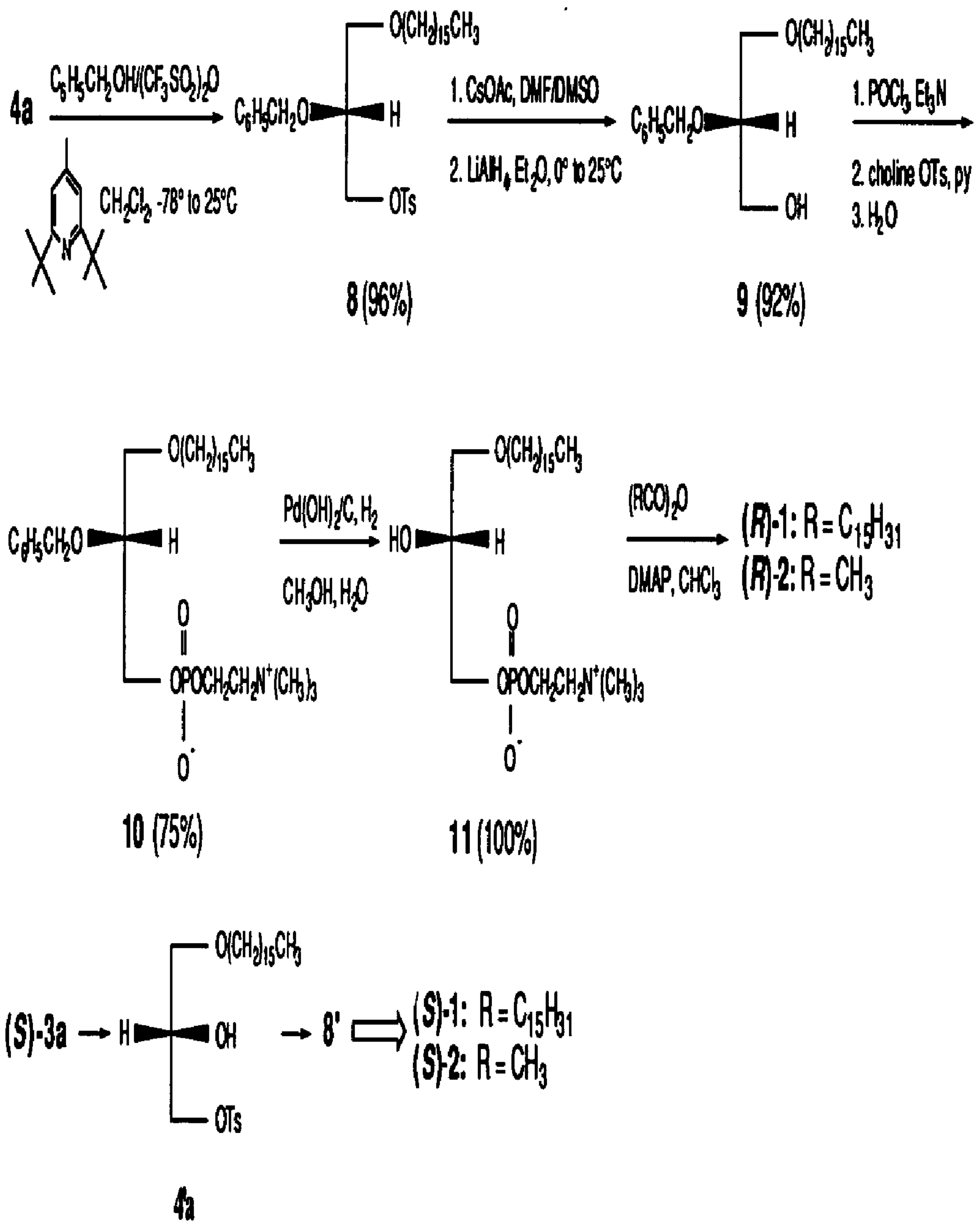


4a **5**

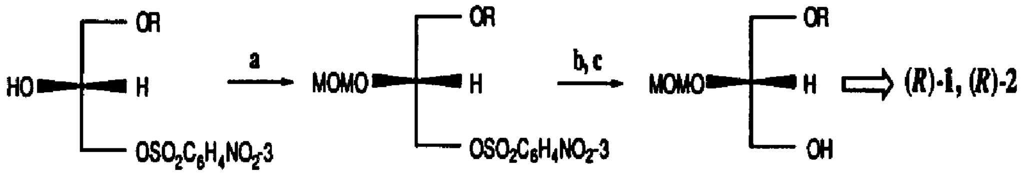
$$5\ X = Ts \xrightarrow{b} 6\ X = P(O)(OC_6H_5)_2 \xrightarrow{c} 7\ X = P(O)(OH)_2 \xrightarrow{d} (R)\text{-}1$$

[a] Reagents: (a) $C_{15}H_{31}COCl$, py, hexane; (b) $AgOP(O)(OC_6H_5)_2$, xylene, reflux; (c) PtO_2, H_2; (d) choline tosylate

Scheme II. Stereocontrolled Synthesis of (*R*)- and (*S*)-1 via 2-*O*-Protected Glycerol 8



Scheme III. Stereocontrolled Synthesis of Unsaturated Ether-Linked Analogs of 1 and 2^{a}



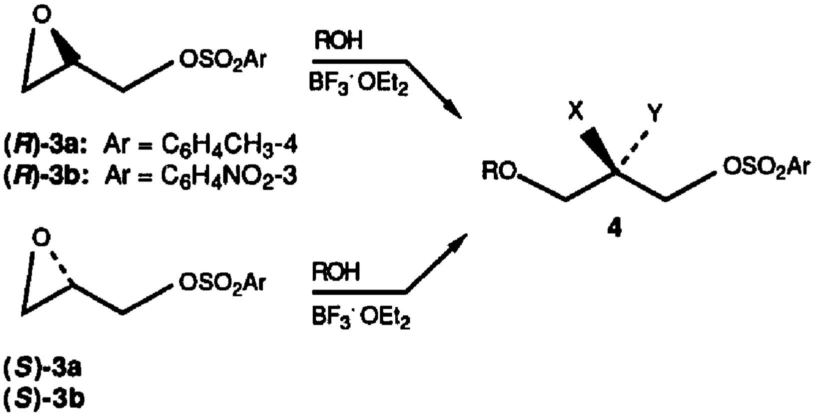
4b: R = oleyl
4c: R = petroselinyl

12: R = oleyl
13: R = petroselinyl

14: R = oleyl
15: R = petroselinyl

Scheme III: ^{a} Reagents: (a) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$; CsOAc, DMF/DMSO 4:1; (c) $LiAH_4$, Et_2O, 0 ° to 25 °C.

Table I. Preparation of Saturated and Unsaturated Ether-Linked Glycerol Arenesulfonates by Stereospecific Opening of 3 Catalyzed by $BF_3 \cdot OEt_2$[a]



	Ring-opened product						
	X	Y	R	Ar	yield, %	$[\alpha]^{25}_{D}$,deg	%ee[c]
4a	OH	H	hexadecyl	$C_6H_4CH_3$-4	80	-6.24[d]	94.0(97.7)[e]
4'a	H	OH	hexadecyl	$C_6H_4CH_3$-4	79	+6.37[d]	95.7
4b	OH	H	oleyl	$C_6H_4NO_2$-3	73	-7.04[f]	>99
4'b	H	OH	oleyl	$C_6H_4NO_2$-3	76	+6.88[f]	97.1
4c	OH	H	petroselinyl	$C_6H_4NO_2$-3	82	-6.98[f]	>99
4'c	H	OH	petroselinyl	$C_6H_4NO_2$-3	75	+6.86[f]	98.1
4d[g]	OH	H	hexadecyl	$C_6H_4NO_2$-3	83	-6.45[f](-6.93)[h]	93.3[g]
4'd[i]	H	OH	hexadecyl	$C_6H_4NO_2$-3	80	+6.12[f](+6.76)[h]	88.4[i]

[a] Substrate **3** and long-chain alcohol (1.0-1.4 equiv) were reacted in CH_2Cl_2 or ethanol-free $CHCl_3$ at room temperature for 18-24 h in the presence of ~5 mol % $BF_3 \cdot OEt_2$. The regioselectivity (exclusive attack at C_3) was determined by reversed-phase HPLC (4.6 x 250 mm C_{18} Carbosphere). Recrystallized **3b** (99% ee) was used to prepare **4b**, **4'b**, **4c**, and **4'c**. [b] Isolated yield. [c] Determined by HPLC on a chiral stationary phase (4.6 x 250 mm) column (Pirkle type IA, J. T. Baker). [d] *c* 5.0, C_6H_6. [e] **4a** was recrystallized three times from ether-hexanes prior to conversion to the (*R*)-(+)-MTPA ester. [f] *c* 2.33, $CHCl_3$. [g] The % ee of the commercially available starting material [(**s**)-**3b**], $[\alpha]^{25}_{D}$ -21.42° (*c* 2.14, $CHCl_3$), was 92.2. [h] $[\alpha]^{25}_{D}$ (*c* 2.33, $CHCl_3$) normalized to 99% ee of **3**, which is attained by two recrystallizations.[14] [i] The % ee of th commercially available starting material[(*S*)**3b**],$[\alpha]^{25}_{D}$ +20.82° (*c* 2.14, $CHCl_3$), was 89.6.

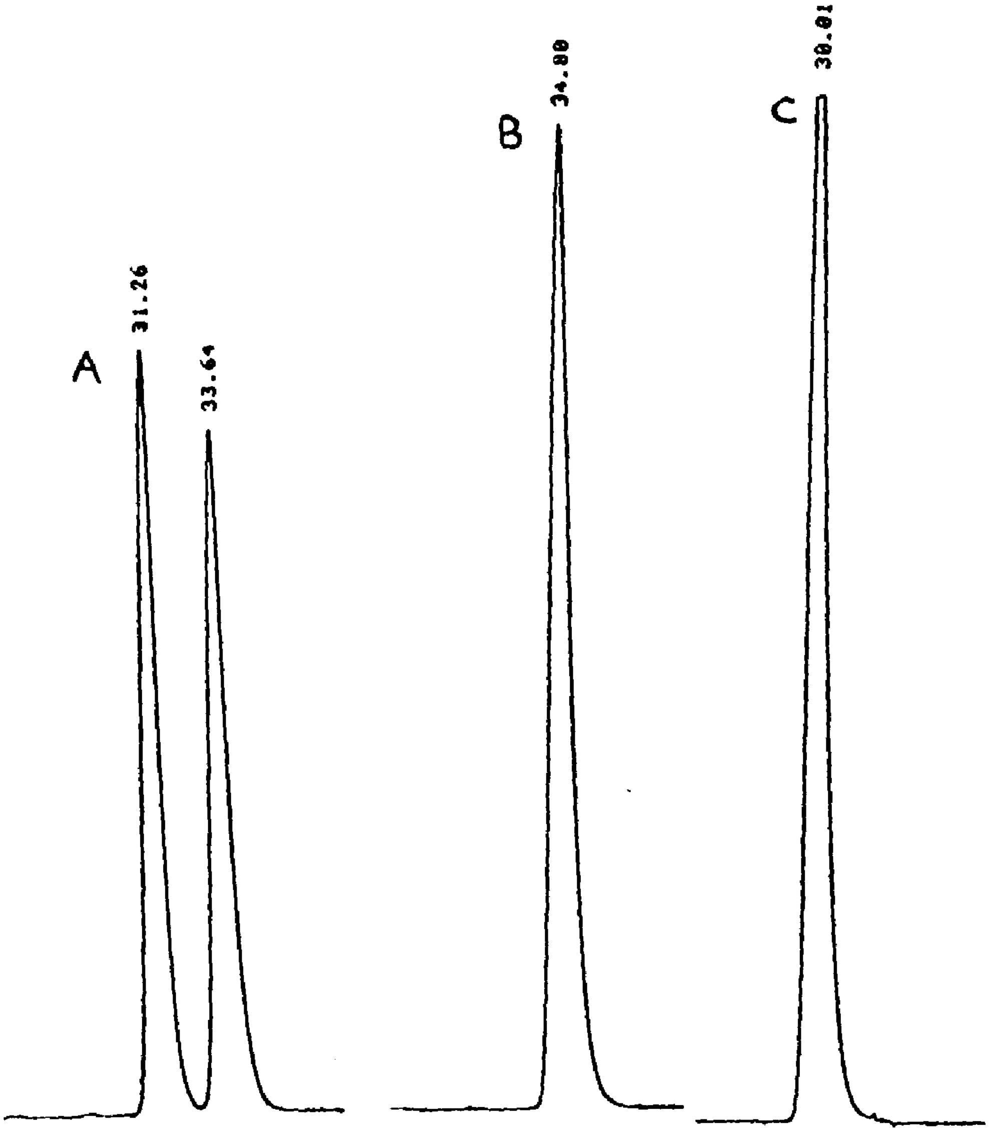


Figure 1. HPLC Chromatograms of the (*R*)- (+)-MTPA ester of **4**:**A**, *rac*-**4**; **B**, **4c**; **C**, **4'c**. See Table 1, page 10, footnote *o*, for HPLC conditions.

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Chapter 6: Preparation of 1-*O*-Hexadecyl-2-*O*-methoxy-*sn*-glycero-3-(β-D-thioglucose)

Abstract:

Synthetic glyceroglycolipids containing a long alkyl chain at the *sn*-1 position and a methoxy group at the *sn*-2 position (**1**) possess cancerostatic activities.[1] The mechanism of antitumor action of ether glycolipids **1e** has not yet been established, nor is the mode of action of ether phospholipids ("alkyl lysophospholipids") fully understood.[2] The recent finding that 1-*O*-alkyl-2-*O*-methylglycero-3-β-D-glucopyranose and 3-phosphocholine are converted into 1-*O*-alkyl-2-*O*-methylglycerol indicates that metabolism of synthetic 1-*O*-alkyl-2-*O*-methylglyceroglyco- and phospholipids is involved in the cytotoxicity of these compounds.[1a] 1-*O*-Hexadecyl-2-*O*-methylglycerol was found to inhibit protein kinase C in mouse fibrosarcoma cells;[3] this phospholipid-dependent enzyme is implicated in signal transduction pathways. 1-*O*-Alkyl-2-*O*-methylglycerol or a metabolite derived therefrom has been suggested to be the active agent in the expression of the cytotoxic effects of 1-*O*-alkyl-2-*O*-methylglyceroglycolipids and 1-*O*-alkyl-2-*O*-methylglycero- 3-phosphocholine.[4] Studies of the metabolism of antineoplastic glycosylglycerolipids would be facilitated if a radiolabeled derivative were available for radioautography of the chloroform extract of cells or if a continuous spectrophotometric assay of the b-glucosidase were available. We report here a practical, short, stereoselective synthetic route to the ether-linked glycerothioglycolipid **1c** from 1-thio–β-D-glucose tetraacetate. The latter is available from the

reaction of thiourea with tetraacetyl-α-bromoglucose[5] and thus can be prepared with ^{35}S by use of [^{35}S]thiourea. Furthermore, if the thiol group is liberated on incubation of **1c** with cells, colorimetric assay using agents that react with sulhydryl groups is possible. The biological properties of **1c** (and its anomer **1b**) in various cell lines are currently under investigation in the laboratories of Dr. Hassan Salari (University of British Columbia, Vancouver, B. C.) and Dr. Fred Snyder (Oak Ridge Associated Universities, Oak Ridge, TN).

Discussion. Scheme 1 shows the conversion of **2a** (obtained by the method described in Chapter 5, p. 58) into the glycerothioglycolipids **1c** and **1f**. The syntheses of **1e** and its *sn*-2 epimer **1'e** starting with 1-*O*-hexadecyl-2-*O*-methyl-sn-3-*tert*-butyldiphenylsilyl ether **2b** and its enantimer **2'b** are also outlined in the scheme. Treatment of **2a** with 1-thio-β-D-glucose in the presence of the base DBU [6] in THF resulted in a 3/1 mixture of **1a/1b**, indicating that epimerization at the anomeric carbon occurred. The β and α epimers are easily separated by flash chromatography (hexanes/ethyl acetate, 4/1). The individual spectral characteristics of **1a** and **1b** were determined by the *J* value of the glucosyl $H_{1'}$ (for the *β* anomer $J = 5.77$ Hz and for the α anomer $J = 10.80$ Hz); furthermore, their connectivities were determined by 2D-NMR (COSY). The peracetylated compounds **1a** and **1b** were hydrolyzed by treatment with catalytic barium oxide in dry methanol, giving **1c** and **1f** in almost quantitative yield. Conversion of **2b** and **2'b** (Z = H) into the β–glycolipids **1e** and **1'e** was achieved by well- known procedures using acetobromo-α-D-glucose in the presence of mercuric cyanide in benzene/nitromethane (1/1), followed by base hydrolysis with methanolic sodium hydroxide.

Materials and General Procedures. The solvents were dried as follows: THF, distilled from sodium benzophenone ketyl and collected over sodium; nitromethane, dried over calcium chloride and distilled prior to use; benzene, washed with concentrated sulfuric acid, then aqueous 10% sodium bicarbonate and water, then dried over calcium chloride, and distilled over sodium; methanol, dried over magnesium sulfate. 1-*O*-Hexadecyl-2-*O*-methyl- 3-*O*-(*p*-tolylsulfonyl)-*sn*-glycerol (**2a**), 1-*O*-hexadecyl-2-*O*-methyl- 3-*O*-(*tert*-butyldiphenylsilyl)-*sn*-glycerol (**2b**), and 3-*O*-hexadecyl-2-*O*-methyl-1-*O*-(*tert*-butyldiphenylsilyl)- *sn*-glycerol (**2'b**) were synthesized as described previously[7]. Acetobromo-α-D-glucose (2,3,4,6-tetraacetyl-α-bromo-D-glucose) was obtained from Sigma Chemical Co. 1-Thio–β-D-glucose tetraacetate, mercuric cyanide, barium oxide, ethyl formate, and DBU were purchased from Aldrich Chemical Co. Dowex 50W-X8 was from J. T. Baker. Reactions were monitored on 0.25-mm thick silica gel GF TLC plates (Analtech, Newark, DE). Compounds were detected by spraying with 10% sulfuric acid in ethanol. Flash chromatography was carried out with silica gel 60 (230-400 ASTM mesh) from E. Merck, purchased from Aldrich. ^{1}H NMR spectra were recorded on a GE Model QE spectrometer (300.5 MHz). Chemical shifts are given in parts per million from tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Optical rotations were measured at room temperature in a 1-dm cell on a JASCO DIP-140 digital polarimeter. Melting points are uncorrected. Elemental analyses were performed by Desert Analytics (Tucson, AZ).

Experimental Section

1-*O*-Hexadecyl-2-*O*-methoxy-*sn*-glycero-3-(D-thioglucopyranosyl 2,3,4,6-tetraacetate) (ca. 3:1 mixture of β and α anomers) (1a, 1b, X = S, R = Ac). To a mixture of 220 mg (0.46 mmol) of 1-*O*-hexadecyl-2-*O*-methoxy-*sn*-glycerol 3-*p*-toluenesulfonate and 182 mg (0.5 mmol) of 2,3,4,6-tetra-*O*-acetyl-1-mercapto-β-D-glucopyranose in 4 mL of dry tetrahydrofuran was added 75 mL (0.5 mmol) of DBU. The mixture was stirred under nitrogen at room temperature for 18 h; TLC (hexane-ethyl acetate 4:1) indicated that all of the starting tosylate had been consumed. The solvent was evaporated under reduced pressure, giving a brown residue that was purified by flash chromatography (hexane-ethyl acetate 4:1). There was obtained 312 mg (92%) of a mixture of the a and b anomers, which were separated by flash chromatography (hexane-ethyl acetate 4:1) to give 234 mg (69%) of the β tetraacetate (R_f 0.38) and 75 mg (22%) of the α tetraacetate (R_f 0.27) as pale yellow oils. IR (neat): 2919, 2849, 1749, 1461, 1367, 1224, 1113, 1090, 1037, 912 cm^{-1}. Anal. Calcd for $C_{34}H_{60}O_{11}S$: C, 60.33; H, 8.93; S, 4.74. Found: β anomer: C, 60.48; H, 8.86; S, 4.69. α anomer: C, 60.37; H, 8.91; S, 4.71. ^1H NMR (300 MHz, $CDCl_3$) β anomer: δ: 5.69 (d, J = 5.77 Hz, 1 H, glucosyl $H_{1'}$), 5.36 (dd (apparent t), J = 9.98 Hz, J = 9.53, 1 H, glucosyl $H_{3'}$), 5.03 (m, 2 H, glucosyl $H_{2'}$ and $H_{4'}$), 4.41 (m, 1 H, glucosyl $H_{5'}$), 4.29 (dd, $J_{H6'a\text{-}H5'}$ = 4.55 Hz, $J_{H6'a\text{-}H6'b}$ = 12.33 Hz, glucosyl $H_{6'a}$), 4.07 (dd, $J_{H6'b\text{-}H5'}$ = 1.85 Hz, $J_{H6'a\text{-}H6'b}$ = 12.33 Hz, glucosyl $H_{6'b}$), 3.38-3.57 (m, 8 H, with singlet at δ 3.41 (3H), $CH_2OCH_2C_{15}H_{31}$, CH_3OCH), 2.60-2.87

(distorted AB quartet, 2 H, $C\mathit{H}_2S$), 2.09 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 1.55 (br t, 2 H, $OCH_2C\mathit{H}_2C_{14}H_{29}$), 1.26 (br s, 26 H, $(CH_2)_{13}$), 0.89 (br t, 3 H, ω-CH_3). α anomer: δ: 5.21 (dd (apparent t), *J* = 9.32 Hz, *J* = 9.27, 1 H, glucosyl $H_{3'}$), 5.08 (dd (apparent t), *J* = 9.82 Hz, *J* = 9.20, 1 H, glucosyl $H_{4'}$), 5.01 (dd (apparent t), *J* = 9.61 Hz, *J* = 9.37, glucosyl $H_{2'}$), 4.63 (d, *J* = 10.08 Hz, 1 H, glucosyl $H_{1'}$), 4.25 (dd, $J_{H6'a\text{-}H5'}$ = 4.84 Hz, $J_{H6'a\text{-}H6'b}$ = 12.04 Hz, glucosyl $H_{6'a}$), 4.12 (dd, $J_{H6'b\text{-}H5'}$ = 2.06 Hz, $J_{H6'a\text{-}H6'b}$ = 12.04 Hz, glucosyl $H_{6'b}$), 3.69 (m, 1 H, glucosyl $H_{5'}$), 3.36-3.55 (m, 8 H, with singlet at δ 3.42 (3H), $C\mathit{H}_2OC\mathit{H}_2C_{15}H_{31}$, $C\mathit{H}_3OC\mathit{H}$), 2.75-2.92 (distorted AB quartet, 2 H, $C\mathit{H}_2S$), 2.09 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 1.56 (br t, 2 H, $OCH_2C\mathit{H}_2C_{14}H_{29}$), 1.26 (br s, 26 H, $(CH_2)_{13}$), 0.89 (br t, 3 H, ω-CH_3).

1-*O*-Hexadecyl-2-*O*-methoxy-*sn*-glycero-3-(β-D-thioglucose) (1c, X = S, R = H). The tetraacetate of the b anomer was hydrolyzed by adding 4.5 mg (0.03 mmol) of barium oxide to a solution of 102 mg (0.15 mmol) of the tetraacetate in 4 mL of dry methanol. After the mixture had stirred for 24 h at room temperature under nitrogen, Dowex 50W-X8 (H^+ form) was added, and stirring was continued for an additional 2 h (during which period the solution became clear). The mixture was filtered to remove the ion-exchange resin, which was washed with 20 mL of THF. The filtrate was dried over sodium bicarbonate to remove traces of acid. After filtration, the solvents were removed under reduced pressure to give 75 mg (100%) of the product as white crystals, mp ~210 °C (decomp.); R_f 0.45 (chloroform-methanol 85:15); $[\alpha]^{25}_D$ 122.4° (*c* 1.06, THF). IR (KBr): 3359, 2919, 2849, 1407, 1365, 1223, 1112, 1090, 1037, 913 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.40 (d, *J* = 5.3 Hz, 1 H, C$_{H1'}$), 3.41-3.81 (m, 14 H, with a singlet at d 3.44), 2.74 (m, 2 H), 1.26 (br s, 28 H), 0.89 (br t, 3 H). Anal. Calcd for $C_{26}H_{52}O_7S$: C, 61.38; H, 10.30; S, 6.30. Found: C, 61.17; H, 10.21; S, 5.73.

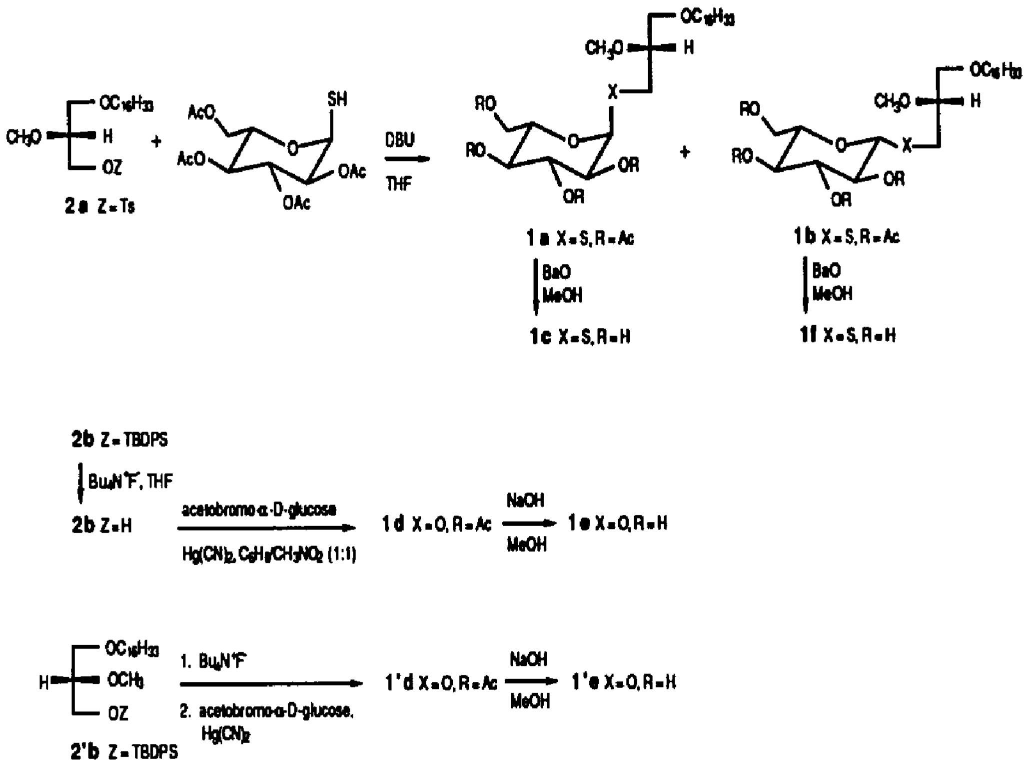
1-*O*-Hexadecyl-2-*O*-methoxy-*sn*-glycero-3-(β-D-glucopyranosyl 2,3,4,6-tetraacetate) (1d, X = O, R = Ac). A mixture of 330 mg (1.0 mmol) of 1-*O*-hexadecyl-2-*O*-methoxy-*sn*-glycerol, 495 mg (1.2 mmol) of acetobromoglucose, and 308 mg (1.2 mmol) of mercuric cyanide in 10 mL of dry benzene-nitromethane (1:1) was stirred under nitrogen at 80 °C for 8 h. Additional amounts of mercuric cyanide (156 mg, 0.6 mmol) and acetobromoglucose (248 mg, 0.6 mmol) were added, and the mixture was stirred for an additional 16 h. After cooling to room temperature, the mixture was diluted with ether (50 mL) to precipitate the mercury salts, and then filtered through a Celite pad, which was washed with 100 mL of ether. The filtrate was washed twice with 10% aqueous sodium bicarbonate solution (75 mL), brine (75 mL), and water (75 mL). The ether layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (elution with hexane-ethyl acetate 2:1) to give 560 mg (85%) of the product as white crystals, mp 61-62 °C (lit. mp 61-62 °C--CPL 41, 93-100 '86); R_f 0.41 (hexane-ethyl acetate 2:1); $[\alpha]^{25}_D$ -13.56° (*c* 1.0, chloroform-methanol 1:1). IR (CCl$_4$): 2919, 2849, 1749, 1367, 1224, 1118, 1090, 1038, 911 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.24 (dd (apparent t), *J* = 9.42 Hz, *J* = 9.39 Hz, 1 H, glucosyl-H$_{3'}$), 5.12 (dd (apparent t), *J* = 9.76 Hz, *J* = 9.43 Hz, 1 H, glucosyl-$H_{4'}$), 5.01 (dd, $J_{H2'\text{-}H3'}$ = 9.42 Hz, $J_{H1'\text{-}H2'}$ = 7.98 Hz, 1 H, glucosyl-$H_{2'}$), 4.59 (d, $J_{H1\text{-}H2}$ = 7.91 Hz, 1 H, glucosyl-$H_{1'}$), 4.31 (dd, $J_{H6'a\text{-}H6'b}$ = 12.6 Hz, $J_{H6'a\text{-}H5'}$ = 4.75 Hz, 1 H, glucosyl-$H_{6'a}$), 4.17 (dd, $J_{H6'a\text{-}H6'b}$ = 12.6 Hz, $J_{H6'b\text{-}H5'}$ = 2.30 Hz, 1 H, glucosyl-$H_{6'b}$), 3.93 (dd, $J_{H1'\text{-}H3a}$ = 3.62 Hz, $J_{H3a\text{-}H3b}$ = 9.65 Hz, 1 H, C_3-H_a), 3.74 (m, 1 H, glucosyl-$H_{5'}$), 3.68 (dd, $J_{H1'\text{-}H3b}$ = 4.41 Hz, $J_{H3a\text{-}H3b}$ = ~9.6 Hz, 1 H, C_3-H_b), 3.41-3.58 (m, 8 H, with a singlet at d 3.46, $C\mathit{H}_2OC\mathit{H}_2C_{15}H_{31}$, $C\mathit{H}_3OC\mathit{H}$), 2.09 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 1.56 (br t, 2 H, $OCH_2C\mathit{H}_2C_{14}H_{29}$), 1.26 (br s, 26 H, $(CH_2)_{13}$), 0.88 (br t, J = 7.8 Hz, 3 H).

3-*O*-Hexadecyl-2-*O*-methoxy-*sn*-glycero-1-(β-D-glucopyranosyl 2,3,4,6-tetraacetate) (1'd, X = O, R = Ac). This compound was prepared in 87% yield by the same procedure as described above; mp 56-58 °C [lit. mp of racemate at C-2: 52-54 °C][1b]; R_f 0.41 (hexane-ethyl acetate 2:1); $[\alpha]^{25}_D$ -6.33° (*c* 1.0, chloroform-methanol 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): same as its C-2 enantiomer in the region δ 4.17-5.24; different at δ 3.98 (dd, $J_{H1'\text{-}H1b}$ = 3.65 Hz, $J_{H1a\text{-}H1b}$ = 9.71 Hz, 1 H, C_1-H_a), 3.74 (m, 1 H, glucosyl-$H_{5'}$), 3.61 (dd, $J_{H1'\text{-}H1b}$ = 4.45 Hz, $J_{H1a\text{-}Hb}$ = 9.7 Hz, C_1-H_b).

1-*O*-Hexadecyl-2-*O*-methoxy-*sn*-glycero-3-(β-D-glucose) (1e, X = O, R = H). The hydrolysis procedure of Weber and Benning[1b] was used without modification; yield, 100%; mp 200 °C (decomp.); $[\alpha]^{25}_D$ -11.9° (*c* 1.0, chloroform-methanol 1:1); lit. $[\alpha]^{25}_D$ -11° (*c* 1.0, chloroform-methanol 1:1)[1b]; IR (KBr) 3359, 2919, 2849, 1112, 1090, 1037, 913 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41-4.61 (m with a singlet at δ 3.44, 17 H, assignment), 1.26 (br s, 28 H, $(CH_2)_{14}CH_3$), 0.89 (br t, 3 H ω-CH_3).

3-*O*-Hexadecyl-2-*O*-methoxy-*sn*-glycero-1-(β-D-glucose) (1'e, X = O, R = H). This compound was prepared as described above; $[\alpha]^{25}_D$ -7.30° (*c* 1.0, chloroform-methanol 1:1).

Scheme I. Conversion of ether-linked glycerols 2 into glyceroglycolipids 1 (X = O and S)



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