thiourea under the usual conditions gave only 1-(trifluoroacetoxy)diisophor-2(7)-en-3-one (ca. 50%), indentical with authentic material (see below).

1-(Trifluoroacetoxy)diisophor-2(7)-en-3-one (26). A solution of **12** (0.89 g, 3 mmol) in CF_3CO_2H (10 mL) was refluxed for 6 h and then added to ice–water. The resinous precipitate solidified on being stirred with H_2O and gave **26**: mp 107–108 °C (from light petroleum; yield, 65%); IR 2950 s–2870 ms, 1455 m mult (CH_3, CH_2), 1765 vs (CO of $COCF_3$), 1660 vs (CO, ring), 1630 ms (C=C conjugated), 1395 vs sh, 1385 vs (CMe_2), 1220, 1210 vs (CF_3), 1175, 1160 vs (C–O ester). Anal. Calcd for $C_{20}H_{27}F_3O_3$: C, 64.5; H, 7.3; F, 15.3. Found: C, 64.75; H, 7.5; F, 15.15.

Use of Thioamides. 3,21-Dehydro-1-*S*-isothioacetamidodiisophora-2,7-dien-3-ol (24) and Phenyl Analogue 25. A solution of **12** (1.47 g, 5 mmol) and thioacetamide (0.41 g, 5.5 mmol) in CF_3CO_2H (10 mL) was refluxed for 6 h, the crimson liquid stirred into H_2O, and the precipitated resin treated in EtOH with picric acid (1.15 g, 5 mmol). The **24** picrate had mp 169–172 °C dec (from EtOH; yield, 72%). Anal. Calcd for $C_{20}H_{29}NS \cdot C_6H_3N_3O_7$: C, 57.3; H, 5.9; N, 10.3; S, 5.9. Found: C, 57.5; H, 6.8; N, 10.1; S, 5.9.

The use of thiobenzamide (0.75 g, 5.5 mmol) similarly gave orange **25** picrate: mp 157–159 °C (from EtOH; yield, 85%). Anal. Calcd for $C_{25}H_{31}NS \cdot C_6H_3N_3O_7$: C, 61.4; H, 5.6; N, 9.2; S, 5.3. Found: C, 61.4; H, 5.7; N, 9.2; S, 5.5.

Acknowledgment. We thank Mrs. J. E. Hawkes and Mrs. F. B. Gallwey, of the University of London NMR Spectroscopy Service at King's College, London, for the production of the ^{13}C NMR spectra.

A New, Asymmetric Synthesis of Lipids and Phospholipids

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Titanium-assisted nucleophilic opening of (*S*)-glycidol (**2**) with stearic acid gives (*S*)-(+)-1-stearoyl-*sn*-glycerol (**3**). Silylation of **3** with *tert*-butyldimethylchlorosilane can be done to selectively form (*R*)-(+)-1-stearoyl-3-(*tert*-butyldimethylsilyl)-*sn*-glycerol (**4**). Esterification of **4** with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride gives a "Mosher ester" (**5**) whose high-field NMR spectrum is suitable for determination of enantiomeric excess. Esterification of **4** with stearoyl chloride followed by removal of the silyl protecting group gives the diacylglyceride, (*S*)-(−)-1,2-distearoyl-*sn*-glycerol (**7**). The silyl group may be removed without acyl migration by the use of *N*-bromosuccinimide/DMSO/THF/H_2O for the hydrolysis. Literature methods may be used to complete the assembly of the phosphorylcholine head group. This short synthetic route offers a new entry to the synthesis of optically active phospholipids and mono-, di-, and triacylglycerides.

Introduction

At the crux of phospholipid chemistry is the need to generate and maintain the optical activity of a derivatized glycerol molecule. The first synthetic solution to this problem was devised by Baer and co-workers.[1] Beginning in 1937 with the preparation of (*S*)-2,3-*O*-isopropylideneglycerol from D-mannitol[2] and culminating in 1950 with the synthesis of 1,2-distearoyl-*sn*-glycero-3-phosphorylcholine,[3] Baer developed a convenient synthetic route to optically active phospholipids. The route from D-mannitol to phospholipids in which the two acyl groups are identical requires nine synthetic steps, while synthesis of phospholipids in which the two acyl groups are different requires fourteen steps. Although improvements have been made in individual steps and other chiral precursors, such as serine,[4] have been used, the synthetic scheme devised by Baer remains the basis for much of the phospholipid chemistry performed today.[5]

A second synthetic approach to phospholipids is, in reality, only semisynthetic in nature. This method uses phospholipids isolated from natural sources as substrates for enzymic cleavage, i.e., with PLA_1, PLA_2, etc., of a single substituent followed by chemical resynthesis of an analogous phospholipid.[6] This approach finds greater application in cases where small quantities of phospholipid analogs are needed.

Several recent advances in asymmetric epoxidation chemistry seemed to us to offer the possibility of a new synthetic route to optically active lipids and phospholipids. The asymmetric epoxidation of allylic alcohols, introduced by Katsuki and Sharpless in 1980,[7] is a powerful method for the introduction of chirality into organic molecules. When the simplest allylic alcohol, allyl alcohol, is used in this reaction, the product is optically active glycidol.[8] Glycidol[9] may be envisioned as a derivative of glycerol and occasionally has been used as an intermediate in lipid chemistry. Optically active glycidol has been used to prepare optically active triglycerides,[4] while racemic glycidol has been used for the synthesis of a dithio ester analogue of a phosphatidylcholine[10] and the synthesis of monoacylglycerols.[11]

Until recently, the preparation of optically active glycidol by asymmetric epoxidation of allyl alcohol was somewhat impractical because of the difficulty with which the product was isolated. Both the solubility of the product in the reaction quench and the reactivity of glycidol con-

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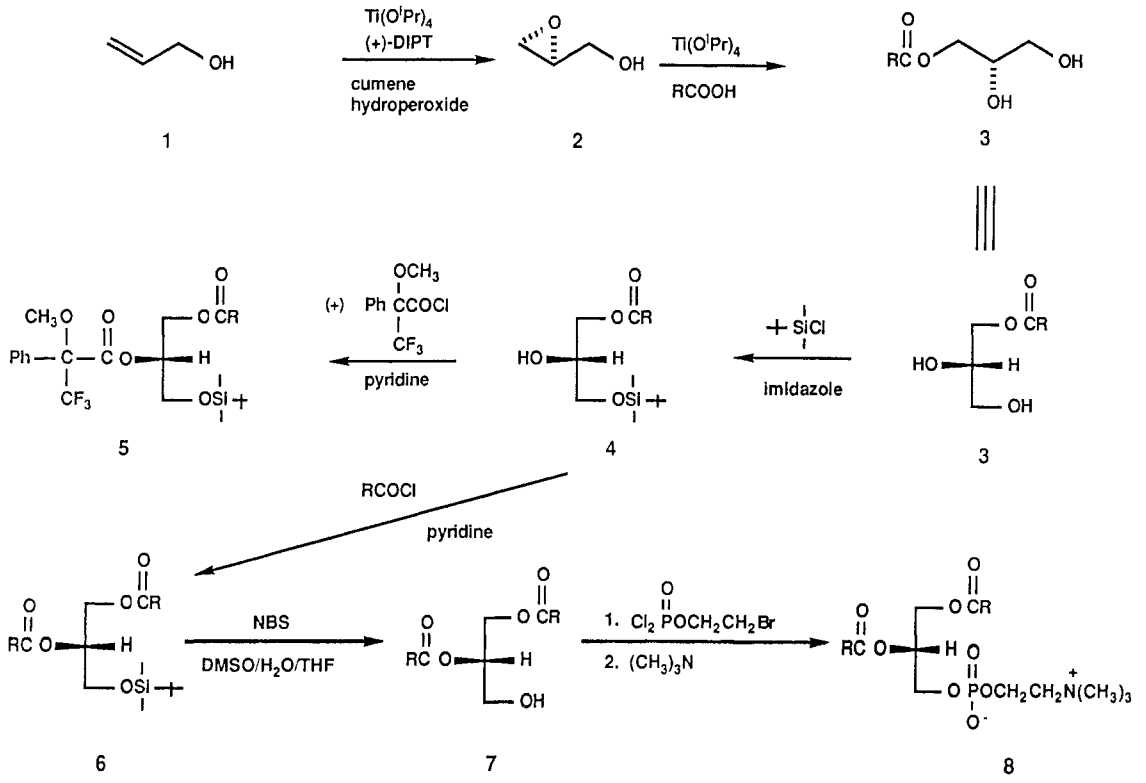
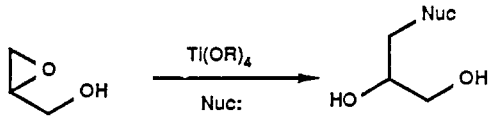
Scheme I



tributed to a reduced yield of product from this reaction. However, the recent modification of this reaction to use molecular sieves allows asymmetric epoxidation of all substrates to be done with catalytic quantities of reagents and greatly simplifies the reaction workup.[12] This modification makes the preparation of optically active glycidol considerably more attractive.[8]

A second recent development related to asymmetric epoxidation is the titanium-assisted nucleophilic opening of epoxy alcohols described by Caron and Sharpless.[13] In this reaction, summarized in eq 1, epoxy alcohols are regioselectively opened by a variety of nucleophiles including the carboxylate anions acetate, benzoate, and trimethylacetate (pivalate).



(1)

We reasoned that if we could extend the titanium-assisted nucleophilic epoxide opening reaction to a combination of optically active glycidol and a long chain carboxylate anion, we would have an efficient two-step synthesis of optically active monoglycerides. These monoglycerides would in turn serve as intermediates for the further elaboration of di- and triglycerides as well as of phospholipids. As a goal to test this plan, we chose to attempt the synthesis of (*R*)-1,2-distearoyl-*sn*-glycero-3-phosphorylcholine (**8**) via the intermediate monoglyceride, (*S*)-1-stearoyl-*sn*-glycerol (**3**). This report describes the results of our efforts to develop an asymmetric synthesis of lipids and phospholipids that allows for variation of each structural component of the final phospholipid.

Table I. Preparations of (*S*)-Glycidol

entry	yield, %	$[\alpha]_D$ (neat), deg	entry	yield, %	$[\alpha]_D$ (neat), deg
1	47	−12.90	3	50	−13.02
2	51	−12.63	4	35	−11.83

Discussion

In practice, each step of the synthesis described herein (shown in Scheme I) was first worked out with racemic compounds, but the discussion is presented with results taken primarily from the optically active series and experimental details for only the optically active series are included in the Experimental Section.

The natural phospholipids have the *R*-configuration at the asymmetric carbon; therefore, the enantiomer of glycidol required to start the synthesis is *S*. To obtain (*S*)-glycidol (**2**), the asymmetric epoxidation of allyl alcohol (**1**) was carried out with titanium(IV) isopropoxide (5 mol %), L-(+)-diisopropyl tartrate (5.8 mol %), and cumene hydroperoxide over 3-Å molecular sieves.[8] The reaction workup included the addition of triethanolamine in the quench.[14] The crude product was subjected first to a simple distillation followed by a second distillation through a short column, both at reduced pressure. (*S*)-Glycidol (**2**) was obtained in 51% yield and from the NMR spectrum appeared pure except for a trace of aromatic protons which may be attributed to cumene or cumyl alcohol. The optical rotation of the (*S*)-glycidol obtained this way varied from $[\alpha]_D$ −11.83° to −13.02° (see Table I) which, when compared to the literature value of 15°,[15] indicates a minimum enantiomeric excess (ee) of 86%. Measurements of ee on subsequent transformation products (see below) indicate

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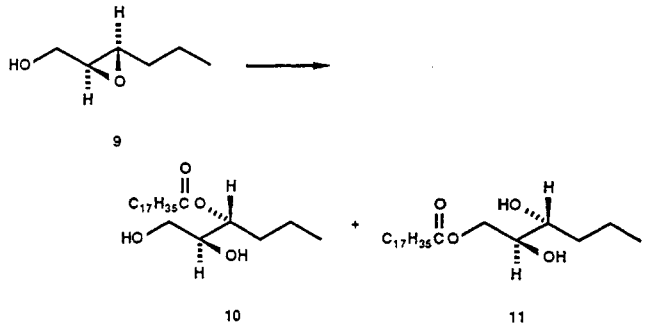
that the ee of this glycidol is slightly higher than 86%.

The titanium-assisted opening of glycidol with stearic acid required considerable practice before an acceptable yield and the preservation of ee were attained. With racemic glycidol, many variations in reaction and workup conditions were tried before modest yields (35–50%) were obtained consistently by the procedure given in the Experimental Section. One factor that may be reducing the yield of 1-stearoyl-*rac*-glycerol in this reaction is the reactivity of glycidol toward other nucleophiles. In related experiments, we have seen evidence for the formation of 1-isopropoxypropane-2,3-diol as a byproduct of the titanium-assisted opening reaction.[16] In an attempt to reduce this side reaction, we have used titanium(IV) *tert*-butoxide in place of $Ti(O\text{-}i\text{-}Pr)_4$ for the opening reaction and increased the yield of **3** to 50–65%, but, unfortunately, some loss of ee also was observed.

In the opening reaction with optically active (*S*)-glycidol (**2**), the optical rotation of the product, (*S*)-stearoyl-*sn*-glycerol (**3**), was lower than expected (+2.40°, entry 1, Table II; the reported rotation for this compound is 3.58°[17]). We were concerned about the stereochemical stability of **3** because titanium alkoxides are known to catalyze acyl migration[7] and, in the case of **3**, migration of the stearoyl group from one end of the glycerol to the other has the effect of racemizing the molecule. To make the study of this question easier, we examined the titanium-assisted opening of (2*S*,3*S*)-3-propyloxiranemethanol (**9**)[18] instead of (*S*)-glycidol. Acyl migration in the product from **9** leads to a regioisomeric ester rather than a racemized product and is a reaction that can be followed by thin-layer chromatography (TLC).

The titanium-assisted opening of **9** with stearic acid at room temperature clearly gave two products. When these were separated, the NMR spectra of the two compounds were consistent with the isomeric structures **10** and **11**.



9

10 **11**

The ratio of the two compounds was estimated to be 9 to 1 in favor of **10**. Fortunately, when the same reaction was done at 0 °C, only (2*S*,3*S*)-3-stearoylhexane-1,2,3-triol (**10**) was isolated from the reaction.

The titanium-assisted opening of (*S*)-glycidol with stearic acid therefore was carried out at 0 °C under conditions used for the preceding reaction. The (*S*)-1-stearoyl-*sn*-glycerol (**3**) obtained from this reaction had $[\alpha]_D$ +3.33° (entry 2, Table II). The results from repetition of this experiment a number of times are summarized in Table II. A single recrystallization of crude **3** from methylene chloride gives a significant improvement in the ee of the compound. Using entry 7 as an example, the quality of the crude product, $[\alpha]_D$ +3.14° (ee 88%) was improved to $[\alpha]_D$ +3.45° and ee 96% by one crystallization. The recovery of **3** from the crystallization was 70%.

Table II. Preparations of (*S*)-1-Stearoyl-*sn*-glycerol

				after recrystallization	
entry	yield, %	mp, °C	$[\alpha]_D$, deg	mp, °C	$[\alpha]_D$, deg
1	47		+2.40		
2	9		+3.33		
3	25	70–71	+3.16	72–73	+3.29
4	14		+3.00		
5	40	67–68.5	+2.94	72.5–73	+3.56
6	44	69–71	+3.21	73–73.5	+3.27
7	34	67.5–69.5	+3.14	72–73	+3.45
8	45	59–60	+2.86	73.5–74	+3.50
9	25	65–69	+2.80	72.5–73	+3.55

Table III. Preparations of (*R*)-3-(*tert*-Butyldimethylsilyl)-1-stearoyl-*sn*-glycerol

entry	yield, %	$[\alpha]_D$, deg	entry	yield, %	$[\alpha]_D$, deg
1	97		3	77	−0.96
2	53	−1.70	4	97	−1.42

The next step in the synthetic sequence is a reaction selective for the primary hydroxyl over the secondary hydroxyl group in **3**. The trityl group has frequently been used as a selective protecting group in phospholipid synthesis,[19] but as an alternative method we have examined a silylation–desilylation sequence. Silylation of **3** with *tert*-butyldimethylchlorosilane is very selective, giving the monosilyl ether **4** in nearly quantitative yield (Table III). The crude product is sufficiently pure for use in most subsequent reactions but can be chromatographed if desired.

The "Mosher ester" **5** was prepared by esterification of **4** with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[20] The NMR spectrum of the ester **5** is ideally suited for ee determination.[21] The geminal protons at both C_1 and C_3 of the glycerol chain have cleanly separated signals in the high-field NMR spectra of the diastereomeric esters. When the crude product **3** ($[\alpha]_D$ +3.33°, ee +93%) of entry 2, Table II, was carried through the silylation and Mosher ester formation steps, the ee of the ester as determined by NMR was 92%. These results indicate that the starting (*S*)-glycidol had an ee of 92% and show that there was no significant loss of optical activity during the epoxide-opening reaction.

Acylation of **4** with stearoyl chloride in pyridine gives (*R*)-(+)-3-(*tert*-butyldimethylsilyl)-1,2-distearoyl-*sn*-glycerol **6**, $[\alpha]_D$ +7.18° in 77% yield after chromatography. This experiment has been repeated several times and the results are summarized in Table IV. Clearly, the use of different acid chlorides or other acylating agents at this step would lead to diacylglycerides and/or phospholipids containing two different acyl substituents.

The *tert*-butyldimethylsilyl group has been considered unsuitable as a protecting group for diacyl glycerols because the standard methods for removal are accompanied by extensive acyl migration.[22] However, we have found that *N*-bromosuccinimide in THF/DMSO/H_2O[23] may be

(16) In reactions where the titanium-assisted opening of glycidol with butyric acid or *n*-butyl alcohol was attempted, the NMR spectra of the crude products suggested the presence of 1-isopropoxypropane-2,3-diol as a byproduct. The failure to observe this byproduct during opening with stearic acid may be due to the fact that workup of the stearic acid reaction used larger quantities of water which may have washed out the relatively polar diol byproduct.

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Table IV. Preparations of (*R*)-3-(*tert*-Butyldimethylsilyl)-1,2-distearoyl-*sn*-glycerol

entry	yield, %	$[\alpha]_D$ ($CHCl_3$), deg	entry	yield, %	$[\alpha]_D$ ($CHCl_3$), deg
1	77	+7.18	3	65	+7.28
2	59	+7.05	4	73	

used for this deprotection reaction. Using these conditions with **6**, we were able to obtain (*S*)-1,2-distearoyl-*sn*-glycerol (**7**) with only a trace of acyl migration. Care must be taken in the purification of **7** because many chromatographic methods (silica gel, flash silica gel, Florisil, alumina, deactivated alumina) are accompanied by acyl migration. A rapid chromatography over silica gel using a preparative apparatus has proven successful. The crude product also may be purified by recrystallization. The Mosher ester of **7** gives an NMR spectrum useful for determination of ee and shows that there is no loss of optical purity between **3** and **7**.

At this point, a variety of methods are available for elaboration of the phosphate head group and completion of the phospholipid synthesis.[24] For example, the reaction of **7** with (2-bromoethoxy)phosphonic dichloride followed by displacement of the bromide with trimethylamine[25] may be used to produce (*R*)-1,2-distearoyl-*sn*-glycero-3-phosphorylcholine (**8**). In this case the synthetic route from allyl alcohol to phospholipid described here consists of seven steps, two shorter than the existing route from mannitol to the same phospholipid. The same route may be used to prepare phospholipids having two different acyl groups as well as mono-, di-, and triacylglycerols enroute. The route is versatile in that as each structural component is assembled, i.e., the allylic alcohol, the carboxylic acid, the acid chloride, and the phosphate head group, the possibility for variation exists. We are continuing our exploration of these variations as well as examining ways in which the sequence might be simplified such as in situ epoxide opening and elimination of the silylation–desilylation steps.

Experimental Section

General Procedures and Reagents. All reactions were carried out under standard conditions: one-neck, round-bottom flasks equipped with magnetic stirring bars and under a nitrogen atmosphere. Reactions were monitored by TLC using plates purchased from Analtech, Inc. (silica gel GF, 250 μm in thickness, 1 in. × 4 in.) with solvent systems made up of mixtures of ethyl acetate and hexane. The compounds were visualized on the plates by spraying with a solution of 5% HNO_3 in 50% H_2SO_4 in H_2O followed by charring of the plate on a hot plate. Purifications were performed by using flash column chromatograph techniques. ^1H NMR spectra were obtained with a Varian EM-390 spectrometer. High-field NMR (used for determination of enantiomer excesses of Mosher esters) were obtained on either a Varian XL 200 or a Bruker AM 500 spectrometer. All spectra were obtained by using $CDCl_3$ as solvent and tetramethylsilane as the reference. Specific rotations were measured by using a Perkin-Elmer 241 polarimeter wth a 1-dm, 1-mL cell thermostated to 25 °C. Infrared spectra were obtained with a Digilab FTS15E spectrophotometer. High-resolution mass spectra were obtained with a Finnigan MAT CH7 spectrometer.

Most reagents were purchased from the Aldrich Chemical Co. and used as received with the following exceptions. Glycidol (racemic) was distilled at reduced pressure through a 3-in. Vigreux column [bp 50–51 °C (10 mm)] and was stored in the freezer. Cumene hydroperoxide was dried overnight over 3-Å molecular sieves. Solvents were from Burdick and Jackson and were used as supplied.

(*S*)-Glycidol (2). An oven-dried 500-mL round-bottom flask fitted with septum and stir bar was charged with powdered 3-Å molecular sieves (3.54 g) and methylene chloride (190 mL). Under a nitrogen atmosphere, (*R,R*)-(+)-diisopropyl tartrate (1.22 mL, 0.005 80 mol) was added at once followed by allyl alcohol (6.8 mL, 0.1 mol). The solution was stirred and cooled to −10 °C, and titanium tetraisopropoxide (1.48 mL, 0.0050 mol) was added. The reaction mixture was stirred at −10 ± 2 °C for 20 min, and then cumene hydroperoxide (25 mL of 80% technical grade, dried over 3-Å molecular sieves, about 0.17 mol) was added slowly (30 min) via a dropping funnel. The mixture was stirred under N_2 at −10 °C for 5 h. Triethanolamine (10 mL of a 1 M solution in CH_2Cl_2) was added, and the mixture was stirred for 30 min while still being cooled. The cooling bath was removed, and after 15 min the mixture was filtered through a pad of Celite over a layer (0.5 cm) of flash silica gel. The pad was rinsed with ether (500 mL). After the solvent was removed on the rotary evaporator, the crude product was distilled quickly through a Bantamware simple distillation apparatus, collecting all material with a bp of about 50 °C at 7–8 mmHg of pressure. This distillate was redistilled through a Bantamware 10-cm Vigreux column, and the product (3.77 g, 0.051 mol, 51%) was collected at bp 49–50 °C (7.7 mmHg): $[\alpha]_D$ −13.02° (neat) [lit.[15] $[\alpha]_D$ +15° (neat) for L-(+)-glycidol]; the NMR ($CDCl_3$) spectrum is identical with that of racemic glycidol, and the NMR spectrum also shows the presence of a small amount of cumyl alcohol or cumene.

The Mosher ester of **2** was prepared by reaction of **2** (45 μL, 0.6 mmol) with (*S*)-(+)-α-(trifluoromethyl)-α-methoxyphenylacetyl chloride (0.21 g, 0.8 mmol) in a cooled (ice bath) solution in triethylamine. The mixture was stirred at ice bath temperature for 1 h and then at room temperature for 1 h. Ether was added, and the mixture was filtered to remove a white solid. The ether layer was washed with aqueous saturated $NaHCO_3$, the layers were separated, and the aqueous layer was washed twice with ether. The ether extracts were combined, dried (Na_2SO_4), filtered, and concentrated to give 0.183 g (97%) of the desired ester: NMR ($CDCl_3$, 200 MHz) δ 7.56–7.37 (m, 5 H, Ar), 4.61 (dd, 1 H, J = 2.7 Hz, J = 12.3 Hz, CH_2OCO), 4.18 (dd, 1 H, J = 5.9 Hz, J = 12.3 Hz, CH_2OCO), 3.56 (q, 3 H, J = 1.3 Hz, OCH_3), 3.21 (m, 1 H, $CHCH_2$), 2.80 (dd, 1 H, J = 4.1, 5.1 Hz, CH_2CH), 2.61 (dd, 1 H, J = 2.5 Hz, J = 5.2 Hz, CH_2CH), (500 MHz) 4.65 (dd, J = 3 Hz, J = 12.5 Hz, CH_2OCO), 4.59 (dd, J = 3 Hz, J = 12 Hz, CH_2OCO) [ratio of integrals at 4.65 and 4.59 is 2:41.5].

(*S*)-(+)-1-Stearoyl-*sn*-glycerol (3). A mixture of stearic acid (18.946 g, 0.0666 mol) in ether (111 mL) was prepared at room temperature. Titanium(IV) isopropoxide (14.199 g, 0.050 mol) was added in one lot via syringe. Undissolved stearic acid now went into solution. The solution was cooled with the aid of an ice bath. (*S*)-(−)-glycidol (2.467 g, 0.0333 mol) was added dropwise to the cool solution. The reaction solution was stirred at the ice bath temperature for 45 min. TLC (1:1 ethyl acetate/hexane + 0.5% acetic acid) reveals the formation of a new, more polar compound. Triethanolamine (50 mL of a 1 M solution in CH_2Cl_2) was added, the solution was stirred for 20 min and then stored overnight at −34 °C. After the mixture reached room temperature, ether (300 mL), water (250 mL), and aqueous 10% sodium carbonate (100 mL) were added to the yellow reaction solution. The mixture was stirred briefly (excessive stirring leads to finer emulsions) and then left standing at room temperature for 2 h (hydrolysis of the titanium complex occurs during this time; times of hydrolysis shorter than 2 h result in lower yields of **3**, whereas the effect of longer times of hydrolysis on optical purity are not known). The mixture was filtered through a 1-in. pad of Celite, and the pad was washed with additional portions of ether. The filtrate was transferred to a separatory funnel where the aqueous layer was removed, and the organic layer was washed with aqueous 10% Na_2CO_3 until the excess stearic acid was removed (monitored by TLC). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give a white solid (3.00 g, 0.008 38 mol, 25%), mp 65–69 °C; $[\alpha]_D$ +2.80° (*c* 6.71, pyridine). Part of the crude product (2.713 g) was recrystallized from methylene chloride to give white crystals (1.725 g): mp 72.5–73 °C; $[\alpha]_D$ +3.55° (*c* 5.24, pyridine); ^1H NMR ($CDCl_3$) δ 4.23 (d, 2 H, C_1 proton), 3.95 (m, 1 H, C_2

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proton), 3.68 (m, 2 H, C_3 proton), 2.40 (m, 2 H, $OCOCH_2$), 1.65 (m, 2 H), 1.28 (m, 28 H, CH_2), 0.88 (t, 3 H, CH_3).

(*R*)-(+)-1-Stearoyl-3-(*tert*-butyldimethylsilyl)-*sn*-glycerol (4). A solution of (*S*)-(+)-1-stearoyl-*sn*-glycerol (0.841 g, 0.002 35 mol), imidazole (0.365 g, 0.005 36 mol), and *tert*-butyldimethylchlorosilane (1.507 g, 0.0100 mole) in dry tetrahydrofuran (12 mL) was stirred overnight at room temperature. TLC (25% ethyl acetate/hexane) revealed the presence of a new less polar compound and the absence of starting material. The reaction mixture was filtered, and the filter cake was washed with THF. The filtrates were evaporated in vacuo, and the crude product was dissolved in hexane/ethyl acetate (3:1, 100 mL). This solution was washed with water (2 × 100 mL), the aqueous wash was extracted with 3:1 hexane/ethyl acetate, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was flash chromatographed over silica gel (7-in. column, 20% ethyl acetate/hexane, 15-mL fractions) and a less polar impurity separated from the desired product. A second flash chromatography was necessary and gave pure **4** (0.241 g) in fractions 14–24. The specific rotation of the pure **4** was $[\alpha]_D$ +1.70° (*c* 6.00, $CHCl_3$): IR (neat) 1743, 1256, 1254, 1115, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, TMS) δ 3.86 (m, 5 H, $CH_2CH(OH)CH_2$), 2.34 (t, 2 H, $COCH_2$), 1.34 (m, 30 H, $15CH_2$), 0.94 (s, 12 H, $SiC(CH_3)_3$ and chain terminal CH_3), 0.08 (s, 6 H, $Si(CH_3)_2$); mass spectrum, calcd for $C_{27}H_{56}O_4Si$ 472.3947, found 472.3962.

The Mosher ester **5** of **4** was prepared by reaction of **4** (0.174 g, 0.368 mmol) with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (0.106 g, 0.421 mmol) in pyridine (1 mL) for 2 h at room temperature. The mixture was diluted with ether, and the ether was washed four times with water. The ether layer was dried (Na_2SO_4), filtered, and concentrated. The crude Mosher ester of **4** was examined by ^1H NMR. In the same way, the Mosher ester of *rac*-**4** was prepared and examined by ^1H NMR. The 500-MHz ^1H NMR spectrum of the latter compound in $CDCl_3$ showed the following: δ 7.57 (m, 2 H, Ar protons), 7.40 (m, 3 H, Ar), 5.35 (m, 1 H, C_2 proton), 4.49 (d of d, 0.5 H, J_{gem} = 16 Hz, $J_{H_{1A}-H_2}$ = 3.5 Hz, C_{1A} proton of (*S*)-**4**), 4.37 (d of d, 0.5 H, J_{gem} = 16 Hz, $J_{H_{1A}-H_2}$ = 3.5 Hz, C_{1A} proton of (*R*)-**4**), 4.20 (d of d, 0.5 H, J_{gem} = 20 Hz, $J_{H_{1A}-H_2}$ = 7.5 Hz, C_{1B} proton of (*S*)-**4**), 4.14 (d of d, 0.5 H, J_{gem} = 20 Hz, $J_{H_{1B}-H_2}$ = 7.5 Hz, C_{1B} proton of (*R*)-**4**), 3.85 (d of d, 0.5 H, J_{gem} = 16 Hz, $J_{H_{3A}-H_2}$ = 5.5 Hz, C_{3A} proton of (*R*)-**4**), 3.82 (d of d, 0.5 H, J_{gem} = 16 Hz, $J_{H_{3B}-H_2}$ = 5.5 Hz, C_{3B} proton of (*R*)-**4**), 3.77 (d of d, 0.5 H, J_{gem} = 16 Hz, $J_{H_{3A}-H_2}$ = 5 Hz, C_{3A} proton of (*S*)-**4**), 3.72 (d of d, 0.5 H, J_{gem} = 16 Hz, $J_{H_{3B}-H}$ = 5.5 Hz, C_{3B} proton of (*S*)-**4**), 3.58 (s, 3 H, OCH_3), 2.294 (t, 1 H, *J* = 8 Hz, OCOC*H* of (*S*)-**4**), 2.290 (t, 1 H, *J* = 8 Hz, OCOC*H* of (*S*)-**4**), 2.228 (t, 1 H, *J* = 8 Hz, OCOC*H* of (*R*)-**4**), 2.222 (t, 1 H, *J* = 8 Hz, OCOC*H* of (*R*)-**4**), 1.58 (m, 2 H, $OCOCH_2CH_2$).

(*R*)-(+)-1,2-Distearoyl-3-(*tert*-butyldimethylsilyl)-*sn*-glycerol (6). The *R*-(+)-monoester silyl ether **4** (0.539 g, 0.00114 mol) from the preceding experiment and stearoyl chloride (0.725 g, 0.00239 mol) were dissolved in pyridine (5 mL), and the resulting solution was stirred at room temperature overnight. Methanol (2 mL) was added to the solution, and stirring was continued for another hour. The reaction mixture was transferred to a separatory funnel, hexane was added, and the solution was washed with water (4×). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to an yellow oil. The crude product was chromatographed over silica gel (flash, 10% ethyl acetate/hexane, 25-mL fractions) and gave pure **4** (0.157 g) in fractions 7 and 8 and essentially pure **4** (0.498 g, total 0.655 g, 0.000 886 mol, 77%) in fractions 9–13: ^1H NMR ($CDCl_3$) δ 5.1 (m, 1 H, COOCH), 4.22 (m, 2 H, $COOCH_2$), 3.72 (d, 2 H, $SiOCH_2$), 2.30 (t, 4 H, $COCH_2$), 1.27 (s, 60 H, CH_2), 0.87 (m, 15 H, CH_3, $SiC(CH_3)_3$); mass spectrum, $C_{45}H_{90}O_5Si$ requires 738.6557, found 738.6607. The results from repetition of this experiment are summarized in Table IV.

(*S*)-(−)-1,2-Distearoyl-*sn*-glycerol (7). A solution of (*R*)-(+)-1,2-distearoyl-3-(*tert*-butyldimethylsilyl)-*sn*-glycerol (**6**; 2.426 g, 0.003 84 mol) in tetrahydrofuran at room temperature was protected from light by aluminum foil. Dimethyl sulfoxide (46 mL) and water (5 mL) were added followed by *N*-bromosuccinimide (3.203 g, 0.018 mol). The mixture was stirred overnight at room temperature, after which TLC (10% ethyl acetate/hexane) showed complete reaction of the starting material and the formation of a new more polar product. An aqueous 1% solution of $Na_2S_2O_3$ (100 mL) was added, and the mixture was stirred for 10 min and transferred to a separatory funnel. The aqueous mixture was extracted (3 × 100 mL) with hexane, the hexane extracts were combined, dried (Na_2SO_4), filtered, and concentrated to give a yellow solid (2.243 g). The solid was crystallized from 3:1 hexane/chloroform, giving a first crop (0.922 g) of white powder, mp 70–72 °C, $[\alpha]_D$ −1.96° (*c* 6.03, $CHCl_3$), and a second crop (0.147 g), mp 71.5–73 °C, $[\alpha]_D$ −2.31° (*c* 3.15, $CHCl_3$). Recrystallization of the first crop from hexane gave 0.630 g of **7**; mp 71–72.5°C, $[\alpha]_D$ −2.18° (*c* 3.39, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.08 (quintet, 1 H, OCOCH−), 4.27 (d of d, 2 H, CH_2OCO), 3.72 (d, 2 H, CH_2OH), 2.31 (2 t, 4 H, CH_2CO), 1.57 (m, 4 H), 1.26 (m, 56 H, CH_2), 0.85 (t, 6 H, CH_3).

The Mosher ester of **7** and of *rac*-**7** were prepared as described above (for the Mosher ester of **4**) and the 500-MHz ^1H NMR spectra were taken. The signal for the OCH_3 group is found at δ 3.54 for the *R*-enantiomer of **7**–Mosher ester and at δ 3.53 for the *S*-enantiomer.

Titanium-Assisted Opening of (2*S*,3*S*)-3-Propyloxiranemethanol (9) with Stearic Acid. (2*S*,3*R*)-3-Stearoylhexane-1,2,3-triol (10) and (2*S*,3*R*)-1-Stearoylhexane-1,2,3-triol (11). A. At Room Temperature. A mixture of stearic acid (2.865 g, 0.010 mol) and methylene chloride (17 mL) was prepared at room temperature. (2*S*,3*S*)-3-Propyloxiranemethanol (0.579 g, 0.0050 mol) was added followed by titanium(IV) isopropoxide (2.2 mL, 2.10 g, 0.0074 mol). The solution was stirred at room temperature and was examined by TLC (aliquot quenched in water/ether; 1:1 ethyl acetate/hexane +0.5% acetate acid) after 45 min and after 16 h. The TLC results were the same at both times. An aqueous 1 M solution of TRIS (8 mL) was added after 16 h and the resulting mixture stirred for 1 h. Addition of aqueous 10% Na_2CO_3 (50 mL) resulted in formation of a precipitate which was removed by filtration through Celite. The organic layer was washed again with 10% Na_2CO_3, the aqeuous layers were extracted once with CH_2Cl_2, and the pooled organic extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was a mixture of two components. Chromatography (flash, 8 g silica gel, 1:1 ethyl acetate/hexane) gave the less polar component (**11**, 0.063 g) in fractions 17–21, a mixture of the two components (0.496 g, predominantly the more polar component) in fractions 22–34, and the more polar component (**10**, 0.085 g) in fractions 35–38. The total yield of **10** and **11** was 0.644 g (0.001 83 mol, 36%). The structure of **11**, $[\alpha]_D$ +3.36% (*c* 0.655, $CHCl_3$), was assigned from the NMR spectrum: δ 4.27 (d, 2 H, CH_2OCO), 3.73 (m, 2 H, 2CH(OH)), 2.35 (t, 2 H, CH_2CO), 1.51 (m), 1.30 (m), 0.91 (m, 6 H, $2CH_3$). The structure of **10**, $[\alpha]_D$ +9.73°, also was assigned from the NMR spectrum: δ 4.87 (m, 1 H, CH(OC−O)), 3.60 (d and m, 3 H, C1 and C2 carbinol protons), 2.36 (t, 2 H, CH_2CO), 1.63 (m), 1.32 (m), 0.90 (m, 6 H, $2CH_3$).

At 0 °C. The reaction described above was repeated except that the reaction solution was cooled in an ice bath before addition of the (2*S*,3*S*)-3-propyloxiranemethanol (**9**). The reaction was worked up after 1 h and in the same way as described above. The crude product (**10**, 0.944 g, 0.002 68 mol, 54%) was a single component when examined by TLC and the NMR spectrum was identical with the spectrum of **10** above. Recrystallization of the product from hexane gave colorless crystals of **10**, mp 52–53 °C.

This reaction at 0 °C was repeated by using ether as solvent in place of CH_2Cl_2 and gave after recrystallization (to remove some stearic acid and an unidentified nonpolar component) 0.83 g of pure **10** having an NMR spectrum identical with that of **10** above.

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Registry No. **1**, 107-18-6; **2**, 60456-23-7; **3**, 22610-61-3; **4**, 110193-08-3; **5**, 110193-09-4; **6**, 110193-10-7; **7**, 10567-21-2; **9**, 89321-71-1; **10**, 110193-11-8; **11**, 110193-12-9; (*S*)-(+)-α-(trifluoromethyl)-α-methoxyphenylacetyl chloride, 20445-33-4; (*R*)-glycidyl (*R*)-α-(trifluoromethyl)-α-methoxyphenylacetate, 110193-07-2; stearic acid, 57-11-4; stearoyl chloride, 112-76-5.