bubbled through the suspension until the red color of Br_2 disappeared and was replaced by a pale yellow suspension of BrF. From previous work and from independent experiments with olefins, it was concluded that the yield of BrF is practically quantitative in respect to both bromine and fluorine. The amount of ethanol which was then added depended on the substrate to be brominated or dibrominated. For best results with activated aromatic rings, the ratio of EtOH:BrF should be kept around 3, while for monobromination of deactivated compounds this ratio was lowered to 2. For dibromination of the latter type of compounds, it was further lowered to 1 to 1.5 and, with the most difficult case of 1,3-dinitrobenzene, this ratio was only 0.66. In all cases, the addition of the EtOH dissolved the BrF, forming a clear reddish solution. The aromatic substrate (26–27 mmol) was dissolved in a minimum amount of precooled $CHCl_3$ and added in one portion to the reaction vessel. The reaction mixture with the activated compounds was kept at −78 °C, while with the deactivated ones at −40 °C. The reactions were monitored by GC and stopped when practically full conversion was achieved. The mixture was then poured into dilute thiosulfate solution and the organic layer was washed with water and $NaHCO_3$ until neutral, dried over $MgSO_4$, and evaporated. For products commercially available, a direct comparison with authentic samples was made. For compounds which are only described in the literature, all the physical and spectral properties were in complete agreement with the structure and the data published.

Registry No. BrF, 59680-92-1; $C_6H_5CH_3$, 108-88-3; *p*-$(CH_3)_2C_6H_4$, 106-42-3; *t*-BuC_6H_5, 98-06-6; $MeOC_6H_5$, 100-66-3; $AcOC_6H_5$, 122-79-2; AcC_6H_5, 98-86-2; BrC_6H_5, 108-86-1; NCC_6H_5, 100-47-0; $OHCC_6H_5$, 100-52-7; $EtOOCC_6H_5$, 93-89-0; $O_2NC_6H_5$, 98-95-3; *p*-$MeC_6H_4NO_2$, 99-99-0; *p*-MeC_6H_4COOMe, 99-75-2; *m*-$(NO_2)_2C_6H_4$, 99-65-0; *o*-$CH_3C_6H_4Br$, 95-46-5; *p*-$CH_3C_6H_4Br$, 106-38-7; 2,4-$Br_2C_6H_3CH_3$, 31543-75-6; 2,5-$(CH_3)_2C_6H_3Br$, 553-94-6; 1,4-$Br_2C_6H_2$-2,5-$(CH_3)_2$, 1074-24-4; *p*-*t*-BuC_6H_4Br, 3972-65-4; *o*-$MeOC_6H_4Br$, 578-57-4; *p*-$MeOC_6H_4Br$, 104-92-7; 2,4-$Br_2C_6H_3OMe$, 21702-84-1; *p*-$AcOC_6H_4Br$, 1927-95-3; *m*-AcC_6H_4Br, 2142-63-4; *p*-BrC_6H_4Br, 106-37-6; *m*-NCC_6H_4Br, 6952-59-6; *o*-NCC_6H_4Br, 2042-37-7; 2,5-$Br_2C_6H_4CN$, 57381-41-6; *m*-$OHCC_6H_4Br$, 591-20-8; 2,5-$Br_2C_6H_3CHO$, 74553-29-0; *m*-$EtOOCC_6H_4Br$, 24398-88-7; 2,5-$Br_2C_6H_3COOEt$, 76008-76-9; *m*-$O_2NC_6H_4Br$, 585-79-5; 2,5-$Br_2C_6H_3NO_2$, 3460-18-2; 2-Me-5-$O_2NC_6H_3Br$, 7745-93-9; 3-Br-4-Me-C_6H_3COOMe, 104901-43-1; 3,5-$(O_2N)_2C_6H_3Br$, 18242-39-2; Br_2, 7726-95-6; 2,5-$Br_2C_6H_3COOH$, 610-71-9; 3-Br-4-Me-C_6H_3COOH, 7697-26-9.

Facile Diacylation of Glycidyl Tosylate. Chiral Synthesis of Symmetric-Chain Glycerophospholipids

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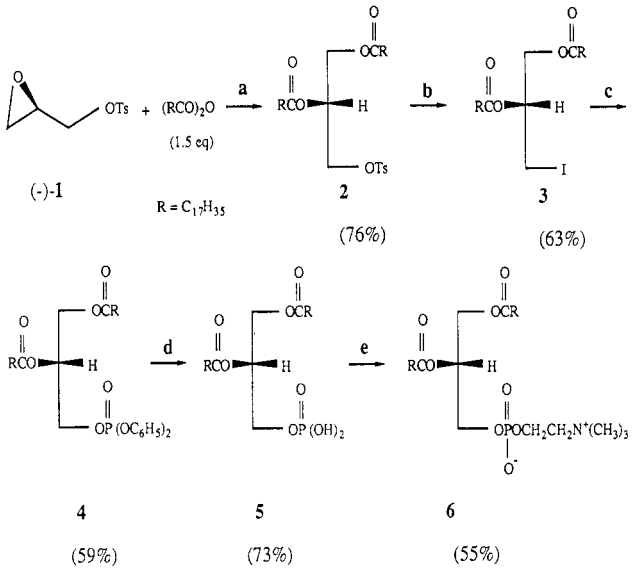
The chemical synthesis of optically active phospholipids involves the extensive use of protecting groups and requires considerable expertise in synthetic lipid chemistry. For example, the synthesis of enantiomerically pure mixed-chain glycerophospholipids from 1,2-isopropylidene-*sn*-3-glycerol or 2,3-isopropylidene-*sn*-1-glycerol entails the use of three protecting groups.[1] Since chiral epoxides have been found to be valuable intermediates in the synthesis of many optically active natural products, we have sought to prepare the natural 1,2-diacyl-*sn*-3-glycerophosphocholines by Lewis acid catalyzed ring opening of chiral epoxides. Conversion of racemic glycidol to racemic ester-linked glycerols has been reported,[2] and optically active glycidol was used as the precursor of triacylglycerols.[3] The preparation of a monoacylglycerol from optically active glycidol in the presence of titanium(IV) isopropoxide was reported during the course of our investigations; titanium-assisted nucleophilic epoxide opening with stearic acid gave glycidyl stearate in low yield.[4]

Scheme I[a]



[a] (a) BF_3·Et_2O, CH_2Cl_2, 40 °C, 2 h; (b) NaI (excess), acetone, reflux, 24 h; (c) $AgOP(O)(OPh)_2$, benzene, 80 °C, 4 h; (d) H_2/PtO_2, cyclohexane–HOAc, 1:1, 4 h; (d) $HOCH_2CH_2N^+(CH_3)_3$ OTs^-, Cl_3C-CN, Py, 50 °C, 48 h.

We report here an efficient enantiospecific synthesis of 1,2-diacyl-*sn*-3-glycerophosphocholines from (*R*)-(−)-glycidyl tosylate (1). The synthetic usefulness of the tosyl derivative of glycidol is demonstrated by (a) facile diacylation in the presence of BF_3 etherate, and (b) conversion of the 3-tosyl group into the 3-phosphocholine moiety, with retention of configuration at C-2 in both steps. Since allyl alcohol is readily converted to either (*R*)- or (*S*)-glycidyl tosylate by asymmetric epoxidation and in situ derivatization,[5] the procedures described here are also applicable to the preparation of phospholipids with the *sn*-1 configuration.

The attachment of two identical fatty acid ester linkages simultaneously to *sn*-glycero-3-phosphocholine or its $CdCl_2$ complex, to give symmetric-chain diacylphosphocholines, has been achieved by well-known methods.[6] In the absence of efficient catalysts, these methods suffer from the need to use severe reaction conditions such as high temperature and long times to obtain a homogeneous mixture

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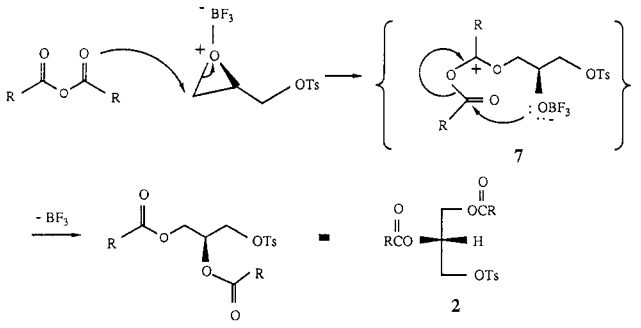
0022-3263/88/1953-5547$01.50/0

Scheme II

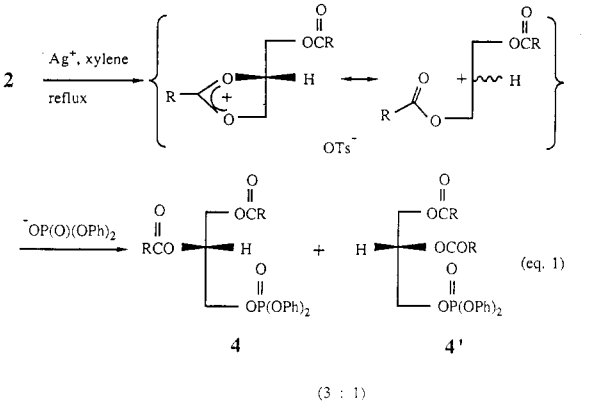


of glycerophosphocholine in the aprotic solvent used for the acylation reaction, sometimes resulting in extensive acyl and phosphoryl migration.[6h,j] In contrast, the procedure described here takes place relatively rapidly and under mild conditions, and is not limited to the stereochemistry available in a naturally occurring precursor such as glycerophosphocholine.

In our attempts to use glycidyl derivatives as C_3-synthons for the convenient preparation of glycerophospholipids, we found that exposure of *rac*-epibromohydrin to BF_3 etherate catalyst and 1.5 equiv of stearic, oleic, and capric anhydrides afforded the corresponding diacylglycerol bromohydrins in yields of 64–84%. We therefore subjected optically active (*R*)-glycidyl tosylate (−)-**1**, and its enantiomer (+)-**1**, to similar reaction conditions. Scheme I summarizes the synthesis of optically active diacylglycerophosphocholines from glycidyl tosylate. The key feature is the ring opening with 1.5 equiv of fatty acid anhydride. This is accomplished in 76% yield by stirring with a catalytic amount of BF_3 etherate in dichloromethane over 2 h. The observation that the product **6** has a specific rotation at least as high as that reported in the literature[6a,i,7] for the optically pure sample indicates that transformation of (−)-**1** into (+)-**2** occurred with complete retention of configuration at C-2. The corresponding enantiomer, (−)-**2**, was prepared analogously from (+)-**1** in 77% yield. Scheme II outlines a mechanism that may explain the stereochemistry observed. The conversion of **1** to **2** is postulated to proceed via initial attack of the anhydride carboxylic oxygen on the primary carbon of **1**, affording intermediate **7**, which undergoes acyl migration to give optically active tosylate **2**.

Direct conversion of tosylate **2** with silver diphenyl phosphate to ester **4** in 77% isolated yield was carried out in refluxing xylenes, since lower temperatures (refluxing benzene and toluene) were insufficient to effect the conversion. Unfortunately, the optical purity of the resulting phosphocholine **6** was only about 35%, suggesting that partial racemization took place at refluxing xylene temperature (eq 1). We therefore converted tosylate **2** to iodide **3**; the latter reacted with silver diphenyl phosphate in refluxing benzene, giving ester **4** in 59% yield. Phosphate ester **4** was further converted to diacylphosphocholine **6** by standard procedures.[8]

In summary, we have presented an efficient synthesis of enantiomerically pure diacylglycerophosphocholines from the derivatized epoxy alcohols (*R*)-(−)-**1** and (*S*)-(+)-**1**. The synthetic scheme does not involve the use of protecting groups in the generation of the glyceryl esters, thus making possible a substantial reduction in time compared



(3 : 1)

with published methods. The procedures are suitable for large-scale preparation of phospholipids because of the relatively low costs of the commercially available (*R*)- and (*S*)-glycidyl tosylate and the long-chain fatty acid anhydrides.

Experimental Section

General Procedures. The solvents used were dried and/or distilled as follows: THF, from sodium benzophenone ketyl; pyridine, CH_2Cl_2, benzene, toluene, and xylenes, from calcium hydride (then stored over type 4A molecular sieves); acetone, dried over $CaSO_4$. Boron trifluoride etherate was freshly distilled. Silver diphenyl phosphate was prepared as described previously.[9] Choline tosylate was prepared by the reaction of *N,N*-dimethylethanolamine and methyl tosylate in dry THF.[10] ^1H 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. Optical rotations were measured on a JASCO Model DIP-140 digital polarimeter. Elemental analyses were performed by Desert Analytics, Tucson, AZ (C, H, and N) and by Schwarzkopf Microanalytical Laboratory, Woodside, NY (P). Silica gel G TLC plates of 0.25-mm thickness from Analtech, Newark, DE, were used to monitor reactions, and E. Merck silica gel 60 (230–400 ASTM mesh) was used for flash chromatography. Phospholipids were detected on TLC plates by spraying as described previously.[8b]

1,2-Distearoyl-*sn*-glycerol 3-*p*-Toluenesulfonate ((+)-2). In a dry two-necked 100-mL flask fitted with a condenser were placed 1.5 equiv of stearic anhydride (413.2 mg, 0.75 mmol) and 114.1 mg (0.5 mmol) of (*R*)-(−)-glycidyl tosylate (**1**) in 20 mL of CH_2Cl_2. Boron trifluoride etherate (4–5 drops, about 0.4 mmol)[11] was added, and the mixture was stirred and refluxed for 2 h under nitrogen. After the reaction mixture had cooled to room temperature, 30 mL of anhydrous ether was added. The organic layer was washed with 5% aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue (580 mg) was purified by flash chromatography on silica gel, eluting with 10% ethyl acetate–hexanes, to yield 295 mg (76%) of (+)-**2**: mp 73–75 °C (lit.[12] mp 75.4 °C); $[\alpha]^{25}_D$ +5.50° (*c* 0.545, $CHCl_3$–CH_3OH, 1:1); ^1H NMR ($CDCl_3$) δ 7.8–7.37 (dd, *J* = 8.2, 8.3 Hz, 4 H, C_6H_4), 5.18–5.13 (m, 1 H, CH_2CHCH_2), 4.29–4.05 (m, 4 H, CH_2CHCH_2), 2.46 (s, 3 H, CH_3), 2.38–2.20 (t, *J* = 7.6 Hz, 4 H, $COCH_2$), 1.67–1.25 (m, 60 H, $(CH_2)_{15}$), 0.90–0.84 (t, *J* = 6.3 Hz, 6 H, ω-CH_3). Anal. Calcd for $C_{46}H_{82}O_7S$: C, 70.90; H, 10.60; S, 4.11. Found: C, 70.66; H, 10.82; S, 4.15.

2,3-Distearoyl-*sn*-glycerol 1-*p*-Toluenesulfonate ((−)-2). The above procedure was repeated with use of (*S*)-(+)-glycidyl tosylate, giving the enantiomer of **2** as a white solid in 77% yield: mp 68–70 °C; $[\alpha]^{25}_D$ −5.13° (*c* 0.545, $CHCl_3$–CH_3OH, 1:1).

(*R*)-1,2-Distearoyl-3-iodopropane ((+)-3). To a solution of 200 mg (0.26 mmol) of (+)-**2** in 10 mL of dry acetone was added

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250 mg (1.5 mmol) of sodium iodide. After the mixture was refluxed overnight under nitrogen, the solvent was removed under reduced pressure. Anhydrous ether (25 mL) was added to the residue, and the mixture was filtered through Celite to give a yellow residue on removal of the solvent. TLC analysis (elution with hexanes–ethyl acetate, 9:1) showed product **3** (R_f 0.60) and a trace of **2** (R_f 0.25). Recrystallization from methanol–petroleum ether (9:1) gave 120 mg (63%) of (+)-**3**: mp 54–55 °C; lit.[13] mp 53–54 °C; $[\alpha]^{25}_D$ +1.47° (*c* 3.185, $CHCl_3$) [lit.[13] $[\alpha]^{20}_D$ +2.5° (*c* 10, $CHCl_3$)].

Diphenyl 1,2-Distearoyl-*sn*-glycero-3-phosphate ((+)-4). The iodide **3** (90 mg, 0.12 mmol) was dried over P_2O_5 in a desiccator and dissolved in 10 mL of dry refluxing benzene in a flask protected from light with aluminum foil. Silver diphenyl phosphate (175 mg, 0.35 mmol) was added, and the reaction mixture was refluxed for 4 h, after which time TLC analysis (hexanes–ethyl acetate, 4:1) showed complete conversion of **3** into the desired diphenyl phosphate ester **4** (R_f 0.50); traces of tosylate **2** present in **3** remained unreacted. The mixture was cooled to room temperature, filtered through a sintered-glass funnel packed with Celite, and washed with chloroform (3 × 50 mL). Removal of solvent left a white solid that was dissolved in hexanes–ethyl acetate (95:5) and purified by flash chromatography on silica gel in the same solvent system, yielding 60 mg (59%) of product **4**: $[\alpha]^{25}_D$ +1.55° (*c* 1.42, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.4–7.2 (m, 10 H, C_6H_5), 5.28–5.19 (m, 1 H, CH_2CHCH_2), 4.42–4.08 (m, 4 H, CH_2CHCH_2), 2.38–2.15 (m, 4 H, $COCH_2$), 1.7–1.1 (m, 60 H, $(CH_2)_{15}$), 0.92–0.80 (t, J = 7.3 Hz, 6 H, ω-CH_3). Anal. Calcd for $C_{51}H_{85}O_8P$: C, 71.46; H, 9.99; P, 3.61. Found: C, 71.86; H, 10.19; P, 3.40.

(+)-**4** was also prepared in 77% yield directly from tosylate (+)-**2** by refluxing for 6 h in dry xylenes with 2.5 equiv of silver diphenyl phosphate. Purification by flash chromatography (elution with hexanes–ethyl acetate, 95:5) gave a white solid: mp 55–56 °C (lit.[14a] mp 58–59 °C, lit.[14b] mp 54.5–55 °C; *rac*-**4** lit.[14c,d] mp 58–59 °C); $[\alpha]^{25}_D$ +0.52° (*c* 5.07, $CHCl_3$) (34% optical purity).

1,2-Distearoyl-*sn*-glycero-3-phosphatidic Acid (5). Adams catalyst (80 mg) was suspended in 10 mL of glacial acetic acid and reduced with hydrogen for about 1 h until black granules of platinum black appeared. A solution of 60 mg (0.070 mmol) of diphenyl phosphate **4** in 10 mL of cyclohexane–glacial acetic acid (1:1) was injected into the flask through a rubber septum. The mixture was stirred vigorously at room temperature for 3 h, filtered through a sintered-glass funnel packed with Celite, and washed with $CHCl_3$ (3 × 10 mL). The filtrate was concentrated, and the product was obtained by precipitation with 10 mL of cold (−20 °C) acetonitrile. After two precipitations, phosphatidic acid **5** (R_f ~0.5 in $CHCl_3$–CH_3OH–HCO_2H, 80:15:5) was obtained as a hygroscopic white solid (36 mg, 73%), which was used in the next step without further purification.

1,2-Distearoyl-*sn*-glycero-3-phosphocholine (6). Phosphatidic acid **5** (36 mg, 0.050 mmol) was dissolved by heating (oil bath) in dry pyridine (10 mL) at 50 ± 5 °C for 30 min. Choline tosylate (140 mg, 0.50 mmol), freshly dried over P_2O_5, and trichloroacetonitrile (2 mL) were added, and the reaction mixture was stirred for 48 h at 50 ± 5 °C. The solvent was removed under reduced pressure; to ensure complete removal of pyridine, the residue was dissolved three times successively in 25 mL of $CHCl_3$–CH_3OH (1:1), and the solvents were evaporated each time under vacuum. The residue was dissolved in THF–water (9:1) and purified by column chromatography on Amberlite MB-3 (20 g; THF–water, 9:1) to give (+)-**6** as a tan solid. Chromatography on silica gel, eluting with $CHCl_3$–CH_3OH (first 9:1, then 3:2), gave 32 mg (55%) of the desired phosphocholine **6** (R_f 0.37 in $CHCl_3$–CH_3OH–H_2O, 65:25:4). The suspended silica gel was removed by filtering a chloroform solution of **6** through a 0.45-μm Metricel filter. (+)-**6**: $[\alpha]^{25}_D$ +6.95° (*c* 0.097, $CHCl_3$–CH_3OH, 1:1) [an authentic sample purchased from Sigma Chemical Co. had $[\alpha]^{25}_D$ +6.80° ($CHCl_3$–CH_3OH, 1:1); lit.[6a] $[\alpha]^{29}_D$ +6.2° ($CHCl_3$–CH_3OH, 1:1); lit.[6i] $[\alpha]^{25}_D$ +6.4° ($CHCl_3$–CH_3OH, 1:1); lit.[7a] $[\alpha]^{25}_D$ +6.1° ($CHCl_3$–CH_3OH, 1:1); lit.[7b] $[\alpha]^{20}_D$ +6.95° ($CHCl_3$–CH_3OH, 1:1)]; ^1H NMR ($CDCl_3$) δ 5.30–5.18 (m, 1 H, CH_2CHCH_2), 4.62–4.42 (m, 2 H, CH_2OP), 4.40–4.25 (m, 2 H, CH_2N), 4.18–3.98 (m, 4 H, CH_2CHCH_2), 3.4 (s, 9 H, $N(CH_3)_3$), 2.74 (br s, H_2O), 2.38–2.20 (m, 4 H, $COCH_2$), 1.65–1.50 (m, 4 H, $COCH_2CH_2$), 1.38–1.0 (m, 56 H, $(CH_2)_{14}$), 0.92–0.80 (t, J = 7.8 Hz, 6 H, ω-CH_3). Anal. Calcd for $C_{44}H_{88}O_8NP{\cdot}3H_2O$: C, 62.60; H, 11.22; N, 1.65; P, 3.67. Found: C, 62.52; H, 11.31; N, 1.44; P, 3.53.

1-Stearoyl-2-lyso-*sn*-glycero-3-phosphocholine. The optical purity of phosphocholine (+)-**6** was examined by treatment with phospholipase A_2 (*Naja naja*, Sigma) in pH 7.4 buffer for 1 h at 38 °C as described previously.[15] TLC analysis ($CHCl_3$–CH_3OH–H_2O, 65:25:4) showed complete hydrolysis of **6** (R_f 0.37) to 1-stearoyl-2-lysophosphatidylcholine (R_f 0.12) and stearic acid (R_f 0.85), confirming retention of the natural *sn*-3 configuration in 1,2-distearoylphosphatidylcholine (**6**).

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Lactone Synthesis by α,ω-Diols with Hydrogen Peroxide Catalyzed by Heteropoly Acids Combined with Cetylpyridinium Chloride

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Recently, metal-catalyzed oxidations of a wide variety of substrates with aqueous hydrogen peroxide, which have received much attention from a synthetic and industrial perspective, were accomplished by the use of heteropoly acids such as 12-molybdophosphoric acid (MPA) or 12-tungstophosphoric acid (WPA) in combination with cetylpyridinium chloride (CPE).[1-4] Furthermore, similar oxidations[5-7] with dilute hydrogen peroxide by molybdenum and tungsten catalysts have been reported by Venturello[5,7] and Modena.[5,6] These methods permit the use of commercially available aqueous hydrogen peroxide (30–35% H_2O_2), which is inexpensive, environmentally clean, and easy to handle, as the oxidant.

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