epimer of 5-stigmastene-3β-24-diol (**1q**): mp 161.0–162.0 °C (from hexane); $[\alpha]_D$ −34.2° (c 5 × 10^{-3}, $CHCl_3$).

Acknowledgment. We are indebted to Dr. William Fenical, Scripps Institution of Oceanography, La Jolla, for sterol samples of soft corals from Palau, to Professor N. Ikekawa, Tokyo Institute of Technology, for samples of 24-vinylcholesterol and saringosterol, to Professor G. Russo, University of Milan, for samples of the acetates of the isofucosterol 24,28-epoxides, to Dr. Sven Zea, El Instituto de Investigacions Marinas de Punta Betin, Columbia, for the identification of *X. muta*, and to Dr. Howard Jones, Merck, Sharp & Dohme, Rathway, New Jersey, for the extract of giant kelp. CANC thanks the Consejo Nacional de Investigaciones Cientificas y Tecnicas de la Republica Argentia for a postdoctoral fellowship. Financial support to C. Duque was provided by Fondo Colombiano de Investigaciones Cientificas y Proyectos Especiales 'Francisco Jose de Caldas' COLCIENCIAS (Grant 10000-1-126-80) and by El Programa Multinacional de Quimica of the OAS. The research at Stanford was supported by Grants GM-06840 and GM-28352 from the National Institutes of Health. 360-MHz ^1H NMR spectra were recorded in the Stanford Magnetic Resonance Laboratory which is supported by grants from the National Science Foundation (GP-23633) and the National Institutes of Health (RR-00711). The acquisition of a Nicolet 300-MHz NMR spectrometery by the Stanford Chemistry Department was made possible by a grant from the National Science Foundation (CHE 81-09064). High-resolution mass spectra were recorded at the Midwest Center for Mass Spectrometry, University of Nebraska—Lincoln, which is supported by grants from the National Science Foundation.

Registry No. **1a**, 474-63-5; **1a**·tosylate, 87801-42-1; **1f**, 58507-55-4; **1g**, 87859-96-9; **1h**, 83-46-5; **1i**, 83-47-6; **1p**, 71208-86-1; **1q**, 87859-97-0; **1r**, 87859-98-1; **1s**, 87859-99-2; **2j**, 51297-12-2; **2l**, 57173-62-3; **2m**, 57173-63-4; **2n**, 57173-69-0; **2o**, 57173-70-3; **3p**, 87801-43-2; **3q**, 87860-00-2; **4a**, 68844-31-5; **4b**, 68844-34-8; **4c**, 68889-65-6; **4d**, 87801-44-3; **4e**, 87860-01-3; **4f**, 87801-45-4; **4g**, 87860-02-4; **4h**, 53139-46-1; methyltriphenylphosphonium iodide, 2065-66-9.

Phospholipid Synthesis Based on New Sequential Phosphate and Carboxylate Ester Bond Formation Steps

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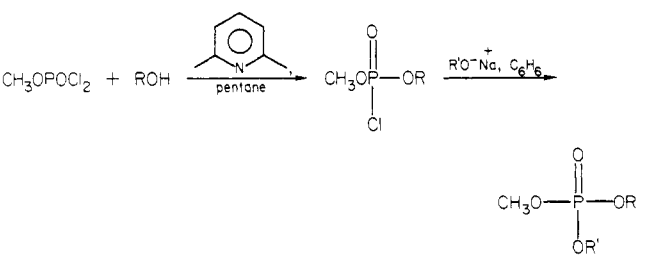
A total synthesis of racemic phosphatidylcholine is based on two novel but straightforward reaction sequences. The phosphate diester portion is constructed by successive displacement of the chlorines on methyl dichlorophosphate by allyl alcohol and dimethylethanolamine. The resulting triester isomerizes smoothly to allyl choline phosphate. The double bond is then converted to the bromohydrin to allow the sequential introduction of the two acyl ester linkages. Esterification of the hydroxyl with palmitoyl chloride produces 2-bromo-2-deoxylysophosphatidylcholine as the only isomer. The bromide is displaced in the final step upon treatment with the carboxylate form of an anion-exchange resin. The distinctive ^{31}P–^{13}C coupling patterns in the ^{13}C resonances of the glycerol backbone allow the regiochemistry of the various steps to be conveniently monitored. Also, employment of palmitic-*1*-^{13}C acid in the final step indicated a 70% rearrangement accompanied formation of the mixed acid phosphatidylcholine.

The synthesis of phospholipids has been actively and successfully pursued for over 70 years.[1] With our focus restricted to the preparation of phosphatidylcholine (PC), the available methods can be approximately divided into three approaches: (1) the formation of phosphate ester linkages to a diglyceride and choline as the last steps;[2] (2) the introduction of both fatty acid ester linkages simultaneously into glycerophosphorylcholine to provide symmetrical PC;[3] (3) the preparation of mixed carboxy ester PC by acylation of lysophosphatidylcholine (the latter is obtained by enzymatic hydrolysis of a symmetrical PC).[3c,4]

Scheme I



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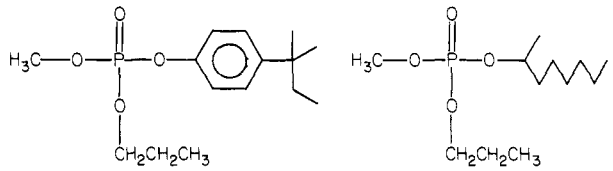
The approach described herein does not fit very well into any of these classifications. It allows the preparation of mixed carboxy ester PC from a phosphate diester of choline and the bromohydrin of allyl alcohol. The latter is prepared in a synthesis based on the methyl protecting group[5] which also serves to quaternize the choline moiety in the deprotection step.[6] The synthesis may be easily modified, however, for the preparation of other classes of phospholipids. Indeed, it is the flexibility and generality of the procedures for introduction of both the phosphate and carboxylate ester linkages that may make this approach attractive and useful.

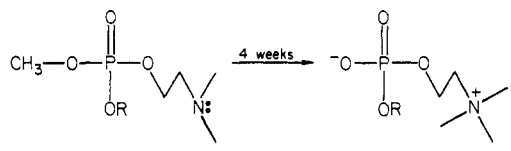
Results and Discussion

Phosphate Diesters. The methyl protecting group has been advocated for a "triester" nucleic acid synthesis.[5] We have found that methyl dichlorophosphate could be used to sequentially phosphorylate alcohols in a straightforward manner to directly provide the mixed esters (Scheme I). The choice of nonpolar solvent and hindered base halts the reaction at the monoalkoxylation stage with the first alcohol and avoids nucleophilic displacement at the methyl.[7] In model reactions, a variety of alcohols could be introduced at this point via their alkoxides; thus, **1** and **2** were prepared in 55% and 33% overall yields, respectively. The methyl groups can be quantitatively removed with a strong nucleophile to provide a simple diester synthesis.[5] It is interesting to note that the methyl group is relatively immune to the alkoxide anion, a hard base, introduced in the second step of Scheme I. It also acts as an NMR probe for the extent of alkoxylation. The distinctive doublet in the ^1H NMR spectrum travels upfield as successive chlorides are displaced (4.04 to 3.75 ppm) with a concomitant decrease in ^{31}P–^1H coupling (17 Hz to 11 Hz).



1 2

The labile methyl group can be utilized as a reagent as well as a protecting group in the preparation of choline alkyl phosphates. If dimethylethanolamine is used as the second alcohol in Scheme I (and one has sufficient patience), the isomerization in eq 1 occurs spontaneously.[6]

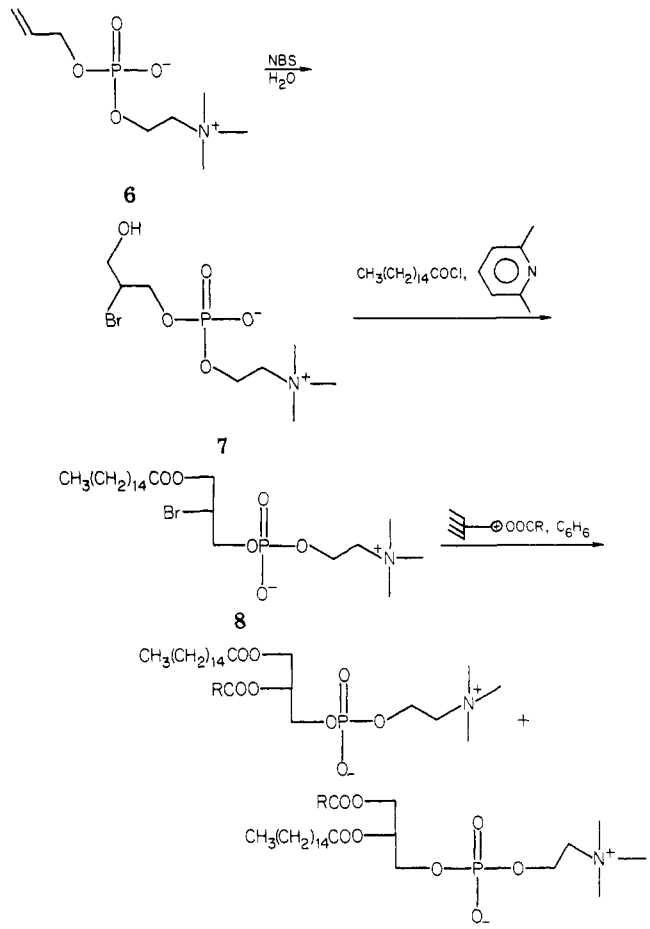


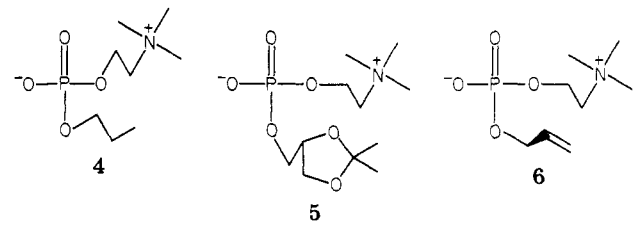
(1)

3

This reaction was studied by Manninen[8] and occurs by a bimolecular mechanism. It is thus allowed to proceed neat at room temperature to minimize any competing unimolecular process such as elimination of dimethyl aziridinium ion. Compounds **4**, **5**, and **6** were prepared in this way in overall yields of 36%, 28%, and 37%, respectively.

Scheme II





4 5 6

Diester **5** can be hydrolyzed to glycerolcholine phosphate (GCP) in 83% yield. However, it is allyl choline phosphate, **6**, which is the key intermediate for the rest of our PC synthesis.

Introduction of Acyl Chains. Scheme II summarizes the remainder of the synthesis. The key feature is the differentiation between positions 1 and 2 of the glycerol moiety to allow sequential introduction of two different fatty acids. This is accomplished via bromohydrin **7** which is obtained as the dominant regioisomer upon treatment of the $CdCl_2$ complex of **6** with aqueous *N*-bromosuccinimide. The use of $CdCl_2$ allows simple isolation of the intermediates as relatively nonhygroscopic solids which can be precipitated from alcohol. The isomeric bromohydrins are not separated but, despite a large excess of palmitoyl chloride, only the 2-bromo isomer is acylated in the next step (see below). The yield for this step is 49%; on the basis of **6**, the yield to this stage is 27%.

Several procedures for displacement of the bromide were attempted. These included employing the silver carbox-

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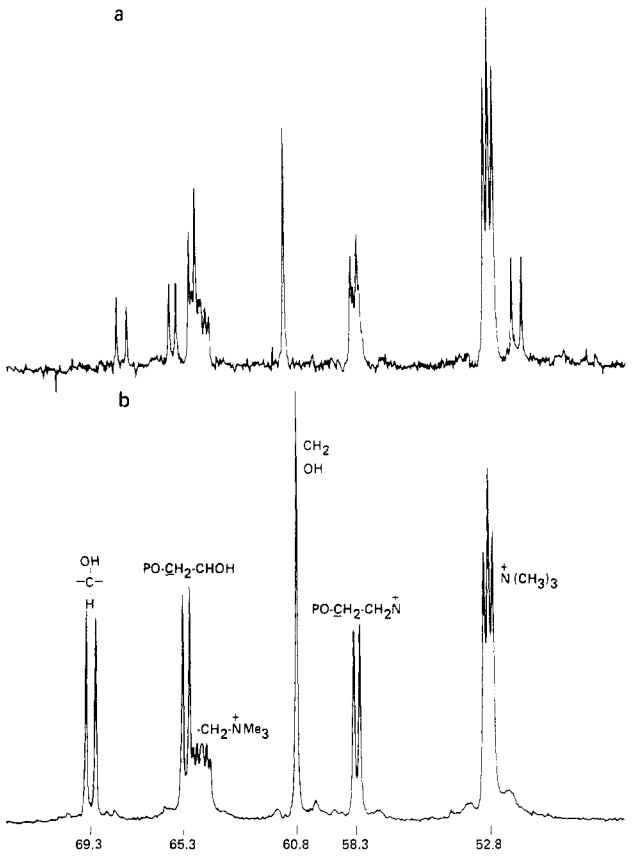


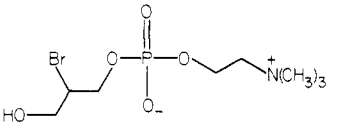
Figure 1. Proton-decoupled ^{13}C NMR spectra of the mixture of bromohydrins **7** and **9** (a) and of GCP (b) in D_2O. Chemical shifts are in ppm downfield from the methyl resonance of sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) (external standard).

ylate salt, carboxylic acid and triethylamine, and the potassium carboxylate in acetone or Me_2SO. These resulted in complex mixtures with lysophosphatidylcholine (lyso-PC) as the primary product. The application of several recent methods involving "naked" carboxylate anions gave better results. A solution of the carboxylic acid and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in benzene[9] gave significant amounts of phosphatidylcholine product according to TLC, but purification was difficult. An experiment employing a crown ether to provide a naked carboxylate from its potassium salt[10] also led to numerous side products with R_f values close to that of PC. The most satisfactory procedure was treatment of **8** with a carboxylated anion exchange resin.[11] The reaction was carried out in refluxing benzene after azeotroping off any water still associated with the carboxylated resin beads. The reaction was periodically monitored by TLC; the disappearance of starting material was accompanied by the appearance of both PC and lyso-PC as the only products. Column chromatography provided the pure mixed acid PC in 30% yield when either lauric or undecenoic acid was employed.

The lyso-PC may result from displacement of the bromide by residual hydroxide on the resin following incomplete conversion to the carboxylate form. This incomplete conversion may stem from the possibility that the acid was too large for the particular resin so that all sites could not be occupied by a carboxylate group, or that not all resin sites are "active" in general toward a carboxylic acid. The resin used (Bio Rad AG1-X8 (Cl^-)), converted to the hydroxide form and then to the carboxylate form, was more efficiently converted using the smaller acids (C_{11} and C_{12}) as compared to the larger acids such as stearic acid. Lauric acid and 10-undecenoic acid were exchanged with the hydroxide form of the resin in 69% and 78%, respectively. Reaction of the hydroxide form of the resin with stearic acid gave only a 44% conversion; therefore, preparation of stearoyl palmitoyl PC was not attempted.

In order to determine the ultimate positions occupied by the two fatty acid residues, palmitic-*1*-^{13}C acid was used to prepare a resin. The conversion was only 54%. The reaction produced only enough product to obtain a ^{13}C NMR spectrum. Use of a larger pore resin such as IRA 900[11] may allow for the use of longer chain fatty acids and probably can improve the yields in the cases of lauric and 10-undecenoic acid but at the same time reduces the amount of lyso-PC produced.

Positional Isomers of Intermediates and Products. Straightforward analysis of ^{13}C NMR data allowed rather unambiguous elucidation of the regiochemistry in each step of Scheme II. The simple Markownikov prediction for the addition of HOBr to an olefin[12] might not be expected to apply for a system as complex as an allyl phosphate. It was important, therefore, to establish which regioisomer, **7** or **9**, was the primary bromohydrin product. Indeed, the



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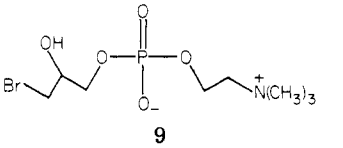

9

^{13}C NMR spectrum, a portion of which is displayed in Figure 1a, did indicate the presence of both the regioisomers. Reference to the ^{13}C NMR spectrum of glycerocholine phosphate (Figure 1b), which has been previously assigned,[13] allows straightforward analysis of the spectrum in Figure 1a.

The low-field doublet centered at 67.9 ppm with J = 8.4 Hz can be identified as the -CHOH- carbon in compound **9** The coupling has increased by 0.7 Hz and the position shifted upfield relative to the same carbon of GCP. The intense singlet at 61.2 ppm represents the terminal $-CH_2OH$ carbon of compound **7** (cf. 60.8 ppm for GCP $-CH_2OH$ carbon). Since in structure **7** the three carbon moiety is quasisymmetrical, the effect of replacing the 2-OH group of GCP with -Br would be expected to be similar on adjacent carbons. Therefore, the doublet at 65.8 ppm, J = 5.7 Hz, has been assigned to the P-O-CH_2-C-HBr- carbon, a downfield shift approximately equal in magnitude to that noted for the $-CH_2OH$ carbon of **7** compared to the same carbon of GCP. The upfield shift of the -CHOH- carbon in **9**, caused by replacing the terminal -OH group of GCP with -Br, is also noted for the P-OCH_2-glyceryl carbon of **9**; however, the influence has diminished. Therefore, the doublet centered at 65.0 ppm, J = 5.0 Hz, is assigned to the P-OCH_2-glyceryl carbon of

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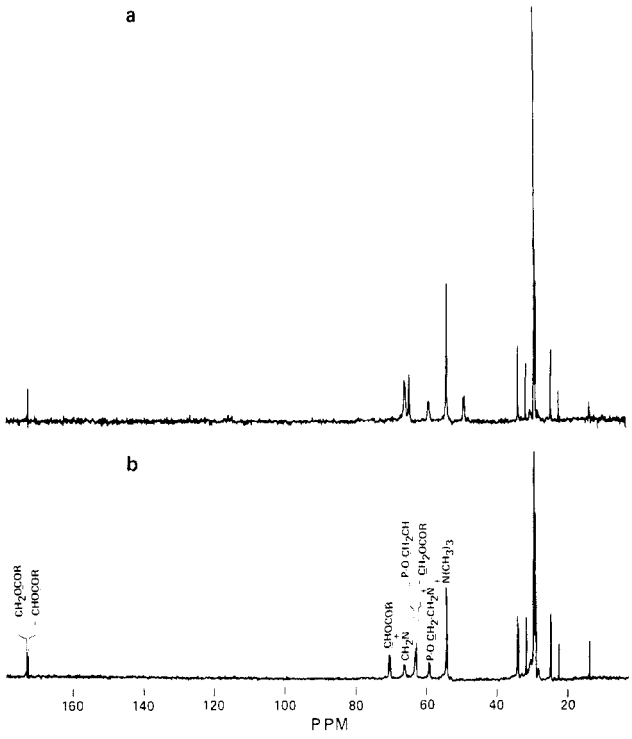

Figure 2. Proton-decoupled ^{13}C NMR spectra of 8 (a) and dipalmitoyl-PC (b) in $DCCl_3$. Chemical shifts are in ppm downfield from the methyl resonance of tetramethylsilane (Me_4Si) (external standard).

9. This signal partially overlaps the multiplet from the $-CH_2N^+Me_3$ carbon whose absorption frequency is the same for **7** and **9** and essentially identical to that of the same carbon in GCP. Next, the overlapping doublets at 58.3 ppm, J = 4.9 Hz, and 58.2 ppm, J = 4.8 Hz, are the $P-O-CH_2-CH_2N^+Me_3$ carbons of **7** and **9**, respectively, on the basis of the chemical shift trends noted above. However, the signals are very close to the signal from the same carbon in the spectrum of GCP. The very intense triplet is representative of the three methyl group carbons of the quaternary ammonium group. At 51.6 ppm is the resonance from the -CHBr- carbon of **7**, concluded simply on the basis of the large coupling constant, J = 8.4 Hz. The last peak of major importance to this discussion is the rather intense singlet at 33.0 ppm (not shown in Figure 1a). This is in the region for a primary bromide and is assigned to $-CH_2Br$ in **9**. Because the isomers **7** and **9** were not separated, the relative proportions of each cannot be precisely determined. A rough approximation of the ratio of the products might be obtained by comparison of the peak heights of the signals from the -CHOH-, -CHBr-, $-CH_2OH$ and $-CH_2Br$ carbons. An average value of **7**:**9** = 65:35 is obtained.

The mixture of the bromodeoxyglycerophosphorylcholines, **7** and **9**, was used without attempts at separation for the preparation of the monoacylbromodeoxyglycerophosphorylcholine. Should the acylation reaction produce both isomers, the products would be analogous to the monoacylchlorodeoxy derivatives prepared by Aneja et al.[14] The most direct method for acylating the hydroxyl groups of compounds **7** and **9** seemed to be by the reaction with an acid chloride and a tertiary base (Scheme II). Surprisingly, the sole product obtained was 2-bromo-2-deoxy-1-plamitoylglycerophosphorylcholine, **8**.

This is demonstrated quite convincingly, again, by examination of the ^{13}C NMR spectrum, Figure 2a. For reference, the published[13] assignments of the glycerol and choline resonances in the spectrum of dipalmitoyl PC are displayed in Figure 2b. The lone carbonyl carbon of **8** appears far downfield at 173.4 ppm while the carbons of the fatty acid chain are upfield at 34.2 (C_2), 31.9 (C_{14}), 29.5 (C_4–C_{13}), 24.9 (C_3), 22.7 (C_{15}), and 14.1 ppm (C_{16}).[15]

Focusing now on the resonances of interest, it is clear that some of the coupling patterns which were so distinct for GCP and the bromohydrins in D_2O (Figure 1) are rather poorly resolved for PC or **8** in $CDCl_3$. The peak centered at approximately 66.4 ppm and displaying splitting is the $-CH_2N^+Me_3$ carbon. The next signal at 65.1 ppm is actually two overlapping lines derived from the $-CH_2-OP$ carbon and the $-CH_2-OCOR$ carbon, both of the glycerol backbone. The $-CH_2OP$ glyceryl carbon has shifted upfield with respect to the $-CH_2N^+Me_3$ carbon in the acylated compound as compared to the respective carbon of the simple bromohydrin. (This reversal of field position is also found in Figure 2b.) The doublet at 59.5 ppm, J = 5.1 Hz, represents the choline $P-O-CH_2-$ carbon. The methyl carbons of the quaternary nitrogen appear as a singlet at 54.4 ppm. Finally, the doublet centered at 49.4 ppm, J = 7.3 Hz, clearly represents the -CHBr- carbon. The absence of a doublet at lower field, ~71 ppm, and a singlet at higher field, ~36 ppm, definitely excludes the possibility of any 1-bromo-1-deoxy-2-palmitoylglycerophosphorylcholine being present. Also, if a mixture of the two isomers was present, two carbonyl peaks would be observed (cf. Figure 2b).

Speculation as to the recovery of a single product leads to several possible suggestions. The acylation procedure may be allowing for acylation of only a terminal hydroxyl group. Yields for diacylation of $GCP/CdCl_2$ using an acid chloride are reported to be low.[3d] Also, isomerization of the fatty acid residue from the 2-position to the less hindered 1-position may be occurring if the 1-acylated product is being produced. The bridging ability of both the bromine and the carboxyl group would favor such a migration, perhaps in the reaction mixture or on the silica gel column used during isolation. Admittedly, the yield for this acylation step is low. It may be possible that the desired material is being converted to lyso-PC by the ion exchange process in the workup procedure where the hydroxide form of the resin (Rexyn 201) might cause replacement of -Br with -OH. At any rate a very interesting PC derivative is obtained in pure form.

As indicated above, PC displays two distinct ^{13}C NMR resonances for the carbonyl carbon of the 1- and 2-acyl chains. The assignment of these resonances has been achieved by a series of very elegant experiments in a variety of solvents and in lipid vesicles.[16,17] In organic solvents, including $CDCl_3$, the 1-carbonyl (i.e., substituted at the terminal carbon of the glycerol) is downfield from the 2-carbonyl resonance (Figure 2b). Thus, employment of palmitic-*1*-^{13}C acid allowed us to determine the regiochemistry of the last step in Scheme II. Surprisingly, the major isomer (~70%) has the labeled fatty acid chain in the 1-position. This is probably due to rearrangement resulting from anchimeric assistance in the displacement.

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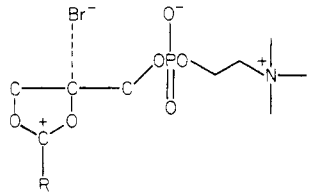

It is less likely that this isomer ratio results from scrambling of the fatty acids after product formation; this would result in, at most, a 50:50 mixture of the 1- and 2-labeled product.

After discovering this rearrangement, it was necessary to assure that the final PC product did have both fatty acids incorporated to an equal extent in order to preclude a disproportionation process in the last step. This concern was addressed via a 360 MHz ^{1}H NMR of the product of the reaction of 10-undecenoic acid with **8**. The integration of the methyl triplet at 0.88 ppm and the integration of the combined vinylic protons at 4.9–5.9 ppm are within 7% of each other. Further, these are also each within 10% of the theoretical in comparison with the integration of the choline methyl resonance at 3.35 ppm. Thus, both fatty acid chains are present in the PC product in the appropriate proportions.

To summarize, we have presented a simple procedure employing several novel features for the preparation of mixed fatty acid phosphatidylcholines. The procedure does not allow for the preparation of optically active PC nor does it provide good regioselectivity in the introduction of the two acyl chains. It should be particularly useful, however, for the synthesis of membrane probes where stereo- and regiochemistry are usually unimportant factors.

Experimental Section

Methyl dichlorophosphate, 2,6-lutidine, *N*,*N*-dimethylethanolamine, and palmitoyl chloride were obtained from Aldrich Chemical Co. and were distilled prior to use. Obtained from Eastman Chemicals were the following: glycerol, allyl alcohol, *p-tert*-amylphenol, 2-octanol, undecanoic acid, lauric acid, and 10-undecenoic acid. Palmitic-*1*-^{13}C acid was obtained from Prochem/Isotope, Inc.

Ion exchange resins Rexyn 101 (H^+) and Rexyn 201 (OH^-) used in workup procedures were obtained from Fisher Scientific while the preparative ion exchange resin AG1-X8 (Cl^-) was obtained from Bio-Rad, Inc. For lipid analysis the standard TLC solvent system used was a 65:25:4 (v/v) solution of chloroform–methanol–water. Preparative TLC was performed using plates purchased from Analtech, Inc. (Silica Gel GF, 2000 microns, 200 mm × 200 mm). For analytical TLC, compounds containing a quaternary ammonium group were visualized on TLC plates by spraying with Dragendorff reagent. Other phospholipids were visualized by spraying TLC plates with 2′,7′-dichlorofluoroscien solution. Elemental analyses were performed by Galbraith Laboratories. A Varian Associates EM-360 60-MHz NMR was used to obtain ^{1}H NMR spectra. A Varian FT80-A NMR provided the ^{13}C NMR spectra. All ^{13}C NMR spectra were proton decoupled. Low-resolution mass spectra were obtained on a Hewlett Packard Model 599S. High-resolution mass spectral analysis was performed by the Cornell U. Mass Spec. Lab.

Methyl *n*-Propyl Chlorophosphate (10). A solution of 0.09 mol each of *n*-propyl alcohol and 2,6-lutidine in 35 mL of anhydrous ether or pentane (dried over 4-Å molecular sieves) is added dropwise over a period of $\sim^1/_2$ hour to a stirred and ice bath-cooled solution of 0.11 mol (20% excess) of methyl dichlorophosphate in 50 mL of anhydrous ether under a positive nitrogen pressure. White 2,6-lutidine hydrochloride precipitates immediately. Stirring is continued overnight at room temperature to allow for total precipitation of the salt. The precipitate is filtered off by suction in a glove box and is washed with fresh solvent. Recovery of the hydrochloride salt is essentially quantitative. The solvent is removed via a rotary evaporator equipped with a drying tube, and the residual oil is distilled, 47–50 °C (0.2 torr). A yield of 10.40 g (67%) is obtained. ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.00 (t, 3 H, $-CH_3$), 1.75 (m, 2 H, $-CH_2-$), 3.92 (d, 3 H, J = 11 Hz, $-OCH_3$), 4.15 (m, 2 H, $-OCH_2-$) ppm.

Methyl Propyl *p-tert*-Amylphenyl Phosphate (1). A solution of 2.90×10^{-2} mol of *p-tert*-amylphenol in ~65 mL of dry benzene is allowed to react with excess sodium metal, which had been freed from oxide by boiling in xylene, overnight at gentle reflux. The solution, followed by one or two 25-mL washings with fresh benzene, is siphoned into an ice bath-cooled and stirred solution of 2.90×10^{-2} mol of **10** in 50 mL of benzene (or anhydrous ether). The solution is allowed to stir overnight. The sodium chloride produced is centrifuged down, the supernatant removed, and the salt pellet washed with fresh solvent. The combined solution is evaporated to yield the crude triester, a yellow oil with an R_f value of 0.39 on silica gel plates developed in ether. Aliquots of 0.5 g of crude triester in 5 mL of chloroform are applied to a preparative TLC plate for purification. The plate is developed in ether, the product extracted with chloroform, and the solvent removed on a rotary evaporator to give pure triester in 82% yield after drying under vacuum: ^{1}H NMR ($CDCl_3$/Me_4Si) δ 0.67 (t, 3 H, $-C(CH_3)_2CH_2CH_3$), 0.93 (t, 3 H, $-OCH_2CH_2CH_3$), 1.27 (s, 6 H, $-C(CH_3)_2CH_2CH_3$), 1.63 (m, 4 H, $-OCH_2CH_2CH_3$ and $-C(CH_3)_2CH_2CH_3$), 3.85 (d, 3 H, J = 11 Hz, $-OCH_3$), 4.12 (m, 2 H, $-OCH_2CH_2CH_3$), 7.25 (m, 4 H, Ar); mass spectrum, m/e (relative intensity) 300 (M+, 7.3), 272 (140), 271 (100), 229 (34), 135 (20), 107 (18). High-resolution mass spectrum, calcd for $C_{15}H_{25}O_4P$, m/e 300.1490; obsd, 300.1490.

Methyl Propyl 2-Octyl Phosphate (2). This triester is prepared from 2-octanol and **10** according to the procedure described for **1**. The crude triester has an R_f value of 0.30 on silica gel plates developed in ether. Aliquots of 0.5 g of crude **2** can be purified by preparative TLC providing a 49% yield of **2**, a yellow oil, after drying under vacuum: ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.35 (m, 21 H, $-OCH(CH_3)CH_2(CH_2)_4CH_3$ and $-OCH_2CH_2CH_3$), 3.74 (d, 3 H, J = 11 Hz, $-OCH_3$), 3.98 (m, 2 H, $-OCH_2CH_2CH_3$), 4.52 (m, 1 H, $-OCH(CH_3)CH_2(CH_2)_4CH_3$); mass spectrum, m/e (relative intensity) 181 (M+ – C_6H_{13}, 21), 155 (82), 139 (77), 113 (100), 95 (34). High-resolution mass spectrum, calcd for $C_6H_{14}O_4P$, m/e 181.0630; obsd, 181.0627.

Choline Propyl Phosphate (4). Excess sodium metal is boiled in xylene to remove the hydroxide coating and after cooling is transferred to a glove box. The sodium spheres are placed in a three-neck flask containing a stirring bar and covered with 50 mL of dry benzene. The flask is then removed from the glove box and equipped with a condenser, an addition funnel and a stopper which allows for siphoning through teflon tubing. A positive nitrogen pressure is applied. A 20-mL solution of 2.32×10^{-2} mol of dimethylethanolamine in benzene is added dropwise to them stirring mixture of sodium in benzene. After the evolution of hydrogen gas has nearly ceased the mixture is refluxed for 3 h. The warm alkoxide solution is then siphoned through teflon tubing (1.5 mm) into an ice bath-cooled and stirred solution of **10** in 50 mL of anhydrous ether. After siphoning is complete the flask containing the sodium is rinsed several times with 10–20 mL portions of fresh benzene. The washings are also siphoned into the flask containing the solution of **10**. The solution is then allowed to stir at room temperature for 1 h. The sodium chloride produced is removed by centrifugation (10 000 rpm, 45 min). The supernatant is drawn off and placed in a 250-mL round-bottom flask. The pellet of sodium chloride is washed with pentane, the washings added to the supernatant, and the pellet dried in a desiccator. The supernatant is concentrated on a rotary evaporator to a viscous gold oil which is dried under vacuum overnight. A yield of 85.8% of crude methyl propyl 2-(dimethylamino)ethyl phosphate is obtained: ^{1}H NMR ($CDCl_3$/Me_4Si) δ 0.98 (t, 3 H, $-CH_3$), 1.70 (m, 2 H, $-CH_2$), 2.25 (s, 6 H, $-N(CH_3)_2$), 2.55 (t, 2 H, $-CH_2NMe_2$), 3.73 (d, 3 H, J = 11 Hz, $-OCH_3$), 4.10 (m, 4 H, $-OCH_2CH_2NMe_2$ and $-OCH_2Et$).

The triester is allowed to stand at room temperature under vacuum for 28 days during which time the isomerization to the diester takes place. The isomerization can be followed visually by observing the formation of a solid glassy phase below the fluid triester. Addition of methylene chloride to the hardened mass converts it to a white powder upon standing for one day. The product is suction filtered in a glove box and dried in a vacuum

desiccator for one day. The product may be slowly recrystallized from 2-propanol/methylene chloride at 4 °C. The yield of **4** is 53% based on (dimethylamino)ethanol or 36% overall from 1-propanol. Anal. Calcd for $C_8H_{20}NO_4P·H_2O$: C, 39.50; H, 9.11; N, 5.75; P, 12.75. Found: C, 39.50; H, 9.25; N, 5.80; P, 12.65. ^{1}H NMR (D_2O/DSS) δ 1.10 (t, 3 H, $-CH_3$), 1.80 (m, 2 H, $-OCH_2CH_2CH_3$), 3.40 (s, 9 H, $-N^+(CH_3)_3$), 3.75 (t, 2 H, $-OCH_2CH_2N^+Me_3$), 4.00 (m, 2 H, $-OCH_2Et$), 4.35 (m, 2 H, $-OCH_2CH_2N^+Me_3$).

Choline 2,2-Dimethyl-1,3-dioxolane-4-methyl Phosphate (5). 2,2-Dimethyl-1,3-dioxolane-4-methanol (acetone glycerol) is prepared by refluxing overnight a solution of 3.85×10^{-1} mol of glycerol in 250 mL of acetone and a catalytic amount of *p*-toluenesulfonic acid. After the solution is stirred with solid K_2CO_3, the filtered acetone solution is evaporated, and the residue is distilled under vacuum.

To a stirred and ice bath-cooled solution of 2.69×10^{-2} mol (4.00 g) of methyl dichlorophosphate in 25 mL of benzene under a positive N_2 pressure is added dropwise a 20-mL solution of 2.69×10^{-2} mol each of 2,6-lutidine and acetone glycerol in benzene. After addition is complete ($\sim^1/_2$ h) the mixture is allowed to stir at ice bath temperature for an additional hour. Stirring at room temperature is continued overnight. The hydrochloride salt is filtered off by suction in a glove box. A 50-mL solution of 2.69×10^{-2} mol of alkoxide of dimethylethanolamine is siphoned into the stirred and ice bath-cooled solution of methyl 2,2-dimethyl-1,3-dioxolane-4-methyl chlorophosphate in 25 mL of benzene. After siphoning is complete ($\sim$20 min) the flask containing the sodium is rinsed with 10 mL of fresh benzene which is then siphoned into the reaction flask. The contents of the reaction flask are decanted into a separatory funnel and washed with 25 mL of half-saturated sodium chloride solution. The benzene layer is then dried over Na_2SO_4. After the solvent is removed, the residue is placed on a vacuum line overnight. A 74% yield of crude triester methyl 2-(dimethylamino)ethyl 2,2-dimethyl-1,3-dioxolane-4-methyl phosphate is obtained: ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.37 (s, $-CH_3$), 1.43 (s, $-CH_3$), 2.30 (s, $-N(CH_3)_2$), 2.60 (t, $-CH_2NMe_2$), 3.40 (s, $-N^+(CH_3)_3$), 3.77 (d, J = 11 Hz, $-OCH_3$), 4.03 (m, $-OCH_2CHCH_2$ and $-OCH_2CH_2NMe_2$). Because isomerization had already begun, only key features of the spectrum are given and no integration reported.

Upon standing for 25 days in a stoppered round-bottom flask the fluid triester isomerizes to a crystalline material. The product diester is taken up in dichloromethane and precipitated by adding tetrahydrofuran (THF). The product is collected by suction filtration performed in a glove box and dried under vacuum. A second crop of crystals is obtained by cooling the mother liquor for several days in the refrigerator. The yield is 1.83 g, 28% based on acetone glycerol, of choline 2,2-dimethyl-1,3-dioxolane-4-methyl phosphate (**5**). Anal. Calcd for $C_{11}H_{24}NO_6P·H_2O$: C, 41.90, H, 8.25, N, 4.44. Found: C, 42.24, H, 7.77, N, 4.46.

Glycerolcholine Phosphate (11). Deacetonation of **5** is effected in the following manner. A solution of 3.43×10^{-3} mol of **5** in 25 mL of distilled water is treated with 0.1 N HCl until the resulting solution is strongly acidic as tested with pH paper (pH $\leq$2). The solution is allowed to stir at room temperature for 15 h. The water is evaporated and the gummy residue dissolved in 18 mL of absolute ethanol. To 1.02 g (10% escess) of anhydrous cadmium chloride is added 12 mL of absolute ethanol and 1 mL of distilled water. The resulting cadmium chloride solution is added dropwise to the stirred solution of **11**. The white addition complex precipitates immediately. After stirring for $^1/_2$ h the mixture is placed in the refrigerator for 1 h. The complex is filtered by suction, washed with absolute ethanol and anhydrous ether, placed in a desiccator, and dried under vacuum overnight. A yield of 1.51 g, 83%, of the cadmium chloride addition complex of **11** is obtained. The ^{13}C NMR spectrum is identical to the published spectrum[13] and is provided in Figure 1b.

Allyl Choline Phosphate (6). Into a 500-mL round-bottom flask equipped with a stirring bar is placed 14.2 g (9.53×10^{-2} mol, 10% excess) of methyl dichlorophosphate and 75 mL of anhydrous ether. The flask is placed in an ice bath and the solution is stirred under a positive N_2 pressure. Dropwise addition of a 100-mL solution of 8.66×10^{-2} mol each of allyl alcohol and 2,6-lutidine in anhydrous ether is performed over $\sim$45 min. The addition funnel is rinsed with 2 × 10 mL portions of anhydrous ether and the rinsings are added to the reaction flask. The ice bath is removed, and stirring is continued overnight. The lutidine hydrochloride is filtered by suction in a glove box and washed with fresh anhydrous ether. The combined filtrate is evaporated on a rotary evaporator. The crude material is distilled under vacuum and stored in dry benzene in a glove box. The yield of allyl methyl chlorophosphate, bp 55–57 °C (0.3 torr), is 54%: ^{1}H NMR ($CDCl_3$/Me_4Si) δ 3.87 (d, 3 H, J = 13 Hz, $-OCH_3$), 4.65 (m, 2 H, $-OCH_2-$), 5.23 (m, 1 H, cis H of HC=C*H*H), 5.47 (m, 1 H, trans H of HC=CH*H*), 5.98 (m, 1 H, *H*C=CH_2).

A 2 molar equiv (6.70×10^{-2} mol) of sodium metal is boiled in xylene. Under a dry N_2 atmosphere within a glove box, the sodium spheres are transferred to a three-neck flask containing a stirring bar and covered with 150 mL of dry benzene. The flask is removed from the glove box and equipped with a reflux condenser, addition funnel, and septum stopper designed for siphoning. A 20-mL solution of 3.35×10^{-2} mol (2.99 g) of dimethylethanolamine in benzene is added dropwise to the stirred and ice bath-cooled mixture of sodium and benzene. After addition is complete the total volume of solution is brought to 200 mL by rinsing through the addition funnel with fresh benzene. The resulting solution is refluxed for 4 h. The warm alkoxide solution is then siphoned into an ice bath-cooled and stirred solution of 3.35×10^{-2} mol of allyl methyl chlorophosphate in 100 mL of benzene. After siphoning and rinsing are complete the solution is allowed to stir at room temperature for $^1/_2$ h. Sodium chloride is removed by centrifugation at 8000 rpm for 45 min. The clear supernatant is drawn off and the solvent evaporated. The triester methyl allyl 2-(dimethylamino)ethyl phosphate is placed in a 500-mL round-bottom flask and dried on a vacuum line overnight: ^{1}H NMR ($CDCl_3$/Me_4Si) δ 2.32 (s, 6 H, $-N(CH_3)_2$), 2.63 (t, 2 H, $-CH_2NMe_2$), 3.78 (d, 3 H, J = 11 Hz, $-OCH_3$), 4.18 (m, 2 H, $-OCH_2CH_2NMe_2$), 4.58 (m, 2 H, $-OCH_2CH=CH_2$), 5.42 (m, 2 H, $-CH=CH_2$), 6.02 (m, 1 H, $-CH=CH_2$).

The triester is allowed to stand in the vacuum-sealed round-bottom flask for 4 weeks before being covered with methylene chloride (distilled from P_2O_5). After standing overnight the product is filtered off by suction in a glove box and washed with fresh methylene chloride and anhydrous ether. The fine white powder is transferred to a preweighed vial, placed in a desiccator and dried under vacuum overnight. The yield of diester **6** is 60% from allyl methyl chlorophosphate: ^{1}H NMR (D_2O/DSS) δ 3.30 (s, 9 H, $-N^+(CH_3)_3$), 3.72 (m, 2 H, $-CH_2N^+(Me_3)$, 4.42 (m, 4 H, $OCH_2CH_2N^+Me_3$ and $-OCH_2CH=CH_2$), 5.40 (m, 2 H, $-CH=CH_2$), 6.10 (m, 1 H, $-OCH_2CH=CH_2$); ^{13}C NMR (D_2O/DSS) δ 52.7 (t, J_{N-C} = 4 Hz, N^+CH_3), 58.1 (d, J_{P-C} = 5 Hz, OCH_2CH_2N), 64.6 (m, CH_2N), 65.5 (d, J_{P-C} = 5 Hz, $OCH_2CH=$), 116.0 (s, $H_2C=$), 132.4 (d, J_{P-C} = 6 Hz, $-CH=$). Anal. Calcd for $[C_8H_{18}NO_4P]_2[CdCl_2]_3$: C, 19.29; H, 3.64; N, 2.81; P, 6.22. Found: C, 19.04; H, 3.81; N, 2.73; P, 6.37.

1-Palmitoyl-2-bromo-2-deoxyglycero-3-phosphorylcholine (BLL) (8). To a solution of 3.50 g of the cadmium chloride addition complex of **6** (7.03×10^{-3} mol as phosphate) and 37 mL of doubly distilled water is added 7.03×10^{-3} mol (1.25 g) of *N*-bromosuccinimide (NBS). The mixture is stirred and the NBS is dissolved within 1 h. The solution is allowed to stir for a total of 4 h. The water is removed on the rotary evaporator until a viscous slurry remains. Absolute ethanol is added dropwise while swirling the flask. Several drops of water may be added if severe clumping results. After addition of ethanol is complete, a total volume of 100 mL, the mixture is warmed on a steam bath and the white precipitate triturated. Stirring is continued overnight. The mixture is placed in a refrigerator for $^1/_2$ h. The product is filtered off and washed first with absolute ethanol followed by anhydrous ether. The dense white solid is placed in a desiccator and dried under vacuum overnight. A yield of 94.5%, 3.95 g, of a mixture (1:1.6) of 1-bromo-1-deoxy- and 2-bromo-2-deoxyglycero-3-phosphorylcholine, **9** and **7**, respectively, is obtained in the cadmium chloride addition complex form. See Figure 1a for the ^{13}C NMR spectrum of this mixture.

Into a 50-mL round-bottom flask is placed 2.78×10^{-3} mol (3.31 g) of a mixture of the cadmium chloride addition complex of **7** and **9** and 5 mL of dry and alochol free chloroform. The flask is equipped with a stirring bar and an addition funnel, placed in an ice bath, and kept under a positive N_2 pressure. Freshly distilled palmitoyl chloride (2.78×10^{-2} mol or 7.64 g, 5 molar

equiv) and 2,6-lutidine (1.95×10^{-2} mol or 2.08 g, 3.5 molar equiv) are each dissolved in 15 mL of chloroform. The acid chloride solution is placed in the addition funnel and added dropwise to the stirred mixture. After addition is complete ($^1/_2$ h) the chloroform solution of 2,6-lutidine is placed in the addition funnel and added dropwise over a period of $^1/_2$ h. After this addition is complete, the ice bath is removed and the mixture is allowed to stir at room temperature for 2 h during which time the reaction mixture develops a light pink color. The solvent is removed by rotary evaporation. A 20-mL solution of 5:4:1 (v/v) $CHCl_3$–MeOH–H_2O is added dropwise to the residue while swirling the flask in an ice bath. The resulting solution is then passed through a mixed-bed ion exchange column containing 50 mequiv each of Rexyn 101 (H^+) and Rexyn 201 (OH^-). The total volume of resin is approximately 50 mL. The column is washed with 250 mL of a solution of 5:4:1 (v/v) $CHCl_3$–MeOH–H_2O. The combined eluate is placed in a 500-mL round-bottom flask and the solvents distilled off on a rotary evaporator. The residue is dried on a vacuum line overnight. The residue is dissolved in ~35 mL of chloroform. (*Note:* If all residue does not dissolve, passage through another mixed-bed ion exchange column is necessary.) Chromatography on a silica gel column is then performed. Approximately 10 g of silica gel per gram of material is suspended in chloroform and poured into a column (60 cm × 2.5 cm). Elution with ~600 mL of chloroform removes the fatty acid and fatty acid ester. A solution of 1:1 (v/v) $CHCl_3$–MeOH is then passed through the column at a rate of $^1/_2$ mL/minute to elute the product. The fractions containing pure BLL are combined and the solvent removed on the rotary evaporator. The colorless residue is dried on a vacuum line overnight and stored in a desiccator, containing P_2O_5, under vacuum. The yield of **8** is 29% or 0.91 g. Its R_f value of 0.14 on silica gel TLC plates lies between that of lyso-PC and PC in a solvent system of 65:25:4 $CHCl_3$–MeOH–H_2O. The ^{13}C NMR spectrum of **8** is displayed in Figure 2a and discussed in Results and Discussion. The $CdCl_2$ complex is not stoichiometric but should be close to 2:3. The analysis fit well for a stoichiometry of 2:2.7. Anal. Calcd for $[C_{24}H_{49}BrNO_4P]\cdot[CdCl_2]_{1.35}$: C, 35.65; H, 6.11; N, 1.74; P, 3.83. Found: C, 35.60; H, 6.32; N, 1.82; P, 3.95.

1-(10-Undecenoyl)-2-palmitoylglycero-3-phosphorylcholine (12). A slurry of 9.32 mequiv of AG1-X8 (Cl^-) resin in methanol is poured into a column (35 cm × 1 cm). The column is washed with 50 mL of distilled water. The hydroxide form of the resin is then prepared by passing 132 mL of aqueous 1 N NaOH solution (20 vol/vol of resin) through the column at a rate of ~1.3 mL/min. The column is washed with 100 mL of distilled water, 100 mL of methanol, and 50 mL of anhydrous ether. The column is finally purged with nitrogen.

A solution of 3.44 g (18.64 mequiv) of 10-undecenoic acid in 35 mL of MeOH and the dry resin prepared above are placed in a 50-mL round-bottom flask equipped with a stirring bar. The mixture is allowed to stir for 4 days at room temperature. The contents of the flask are poured back into a column (35 cm × 1 cm). The solution is drawn off, the resin washed with 5 × 40 mL portions of MeOH and 3 × 30 mL portions of anhydrous ether, and the resin purged with nitrogen. The combined eluents are evaporated and the residue dried under vacuum. A 78% conversion of the resin to its carboxylate form is obtained as determined by the amount of recovered acid.

The dried resin is placed in a 50-mL round-bottom flask containing 9.32×10^{-4} mol of **8** and 30 mL of freshly distilled benzene. The flask is equipped with a stirring bar and reflux condenser. Stirring and gentle refluxing are continued for 3 days under a positive nitrogen pressure. TLC is used as a convenient monitor of the reaction's progress. The resin is filtered off by suction onto a glass wool pad. The resin is washed several times with 10-mL portions of fresh benzene. The combined filtrate is evaporated and the residue dissolved in 5 mL of chloroform. The clear chloroform solution is placed on a column (60 cm × 2.5 cm) containing 95 g of Bio Sil A (100–200 mesh) in chloroform. Elution is begun with 250 mL of chloroform followed by 400 mL of 8:2 (v/v) $CHCl_3$–MeOH, ~400 mL of 6:4 (v/v) $CHCl_3$–MeOH, and 1600–1700 mL of 1:1 (v/v) $CHCl_3$–MeOH. The fractions containing pure PC are combined and the solvent stripped off. The product is dried in a desiccator, containing P_2O_5, under vacuum overnight. The mixed acid phosphatidylcholine has an R_f value of 0.19, identical to dipalmitoylphosphatidylcholine, on silica gel plates developed in a solvent system of 65:25:4 $CHCl_3$–MeOH–H_2O. The yield of **12** is 0.19 g or 30.0%: ^{13}C NMR ($CDCl_3/Me_4Si$) δ 14–35 (m, fatty acid saturated carbons), 54.4 (br s, N^+CH_3), 59.4 (d, J_{P-C} = 5 Hz, OCH_2CH_2N), 63.1 (s, CH_2OCOR), 63.3 (d, J_{P-C} = 7 Hz, $POCH_2CH$–), 66.4 (d, J_{P-C} = 6 Hz, CH_2N), 70.7 (d, J_{P-C} = 7 Hz, –CHO–), 114.2 (s, H_2C=), 139.1 (s, –HC=), 173.1 (s, CH–OCOR), 173.5 (s, CH_2OCOR). A 360 MHz ^1H NMR was obtained at the Syracuse University NIH Resource. ^1H NMR ($CDCl_3/Me_4Si$) δ 0.88 (t, J = 7 Hz, $-CH_3$), 1.1–1.6 (m, $(CH_2)_n$), 2.03 (d of t, J = 7 Hz, $-CH_2C$=), 2.28 (overlapping t, J = 7 Hz, $-CH_2COO$–), 3.35 (s, $N^+(CH_3)_3$), 3.77–3.97 (m, NCH_2CH_2OP), 4.1–4.4 (m, glyceryl protons), 4.9–5.2 (m, $=CH_2$), 5.75–5.86 (m, –CH=).

1-Lauroyl-2-palmitoylglycero-3-phosphorylcholine (13). A volume of 7.7 mL (10.8 mequiv) of ion exchange resin AG1-X8 (Cl^-) is dispersed in methanol and poured into a column (35 cm × 1 cm). The column is then washed with 50 mL of distilled water. Conversion to the hydroxide form of the resin is achieved by passing 50 mL of 1 N NaOH solution through the resin. The resin is washed with 50 mL of distilled water and 75 mL of methanol. Lauric acid (21.6 mequiv, 4.33 g) is placed in a flask with ~35 mL of methanol, and the resin is added. The mixture is allowed to stir for 2 days. The methanol solution is drawn off and the resin washed with 5 × 40 mL portions of methanol. All methanol solutions are combined. The resin is washed with 3 × 30 mL portions of anhydrous ether. The solvents are stripped off on the rotary evaporator and the residue dried on a vacuum line. Benzene (40 mL) is added to the resin and stripped off on the rotary evaporator. This procedure is performed two times to aid drying off the resin. Compound **8** (BLL, 1.08×10^{-3} mol, 0.60 g) is added to the flask containing the carboxylate form of the resin, and dry benzene is added to give a total volume of ~40 mL. Heating (~50 °C) is commenced and continued for 115 h under a positive N_2 pressure. Refluxing is then performed for 45 h. The benzene solution is drawn off, and the resin washed with fresh benzene and filtered. All benzene solutions are combined and concentrated on the rotary evaporator. The crude product is dissolved in several milliliters of chloroform and placed on a column (55 cm × 1.8 cm) containing 30 g of Bio Sil A (100–200 mesh) and chloroform. Elution with 60 mL of chloroform is performed first followed by 330 mL of 8:2 (v/v) $CHCl_3$–MeOH, 335 mL of 6:4 (v/v) $CHCl_3$–MeOH, and 800 mL of 1:1 (v/v) $CHCl_3$–MeOH. All fractions containing only pure PC are combined and concentrated and the residue dried in a desiccator under vacuum overnight. The purified PC, **13**, R_f 0.19 on silica gel plates in a solvent system of 65:25:4 $CHCl_3$–MeOH–H_2O, is obtained in 29% yield. The R_f value is identical with that of dipalmitoylphosphatidylcholine used as a standard. The ^{13}C NMR spectrum is also identical to that of dipalmitoyl PC (see Figure 2b).

1-Dipalmitoyl-*1*-^{13}C-phosphatidylcholine (14). A column of resin AG1-X8 (Cl^-) (3.89×10^{-3} equiv, 2.8 mL) is poured with methanol and rinsed with 30 mL of distilled water. The resin is converted to the hydroxide form by eluting with 17.5 mL of 1 N NaOH solution. The resin is washed with 50 mL of distilled water, 50 mL of methanol, and 50 mL of anhydrous ether. The resin is then purged with nitrogen. To a 100-mL round-bottom flask containing 1.00 g (3.89×10^{-3} mol) of palmitic-*1*-^{13}C acid in 40 mL of methanol is added the dry resin. The flask is equipped with a reflux condenser and heating commenced. After 1 day methanol is evaporated via a rotary evaporator, anhydrous ether is added to the flask, and refluxing is begun and continued overnight. The ether solution is drawn off and the resin rinsed with 2 × 40 mL portions of ether. Dry benzene (40 mL) is placed over the resin and evaporated on the rotary evaporator. The resin is dried under vacuum for 0.5 h. A 54% conversion of the resin to the carboxylate form is obtained. To a flask containing 0.39 g (6.99×10^{-4} mol) of **8** and 20 mL of dry benzene is added the dry resin. Refluxing is begun immediately under a positive N_2 pressure. Refluxing is stopped after 70 h. The resin is filtered off and washed with dry benzene. All filtrates are combined and evaporated on the rotary evaporator. The residue is dissolved in 5 mL of chloroform and placed on a column (55 cm × 1.8 cm) of 25 g of silica gel (60–200 mesh, Baker Analyzed) in chloroform. Elution is performed with chloroform and 8:2 (v/v) $CHCl_3$–MeOH.

Appropriate fractions are combined and concentrated. The product is dried in a desiccator under vacuum. The yield is less than 0.05 g. The ^{13}C NMR spectrum is identical with that of unenriched dipalmitoyl-PC (Figure 2b) except for the intensities of the downfield carbonyl resonances. The latter are discussed in Results and Discussion.

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Registry No. 1, 87728-50-5; 2, 87728-51-6; 4, 21991-64-0; 5, 59414-94-7; 6, 77075-58-2; 7, 87728-52-7; 8, 87728-53-8; 9, 87728-54-9; 10, 77075-52-6; 11, 34688-34-1; 12, 87728-55-0; 13, 87728-56-1; 14, 87760-76-7; dimethylethanolamine, 108-01-0; methyl dichlorophosphate, 677-24-7; methyl propyl 2-(dimethylamino)ethyl phosphate, 87728-57-2; methyl 2-(dimethylamino)ethyl 1,2-*O*-isopropylideneglyceryl phosphate, 77075-57-1; allyl methyl chlorophosphate, 77075-53-7; methyl allyl 2-(dimethylamino)ethyl phosphate, 77075-56-0; palmitoyl chloride, 112-67-4; 10-undecenoic acid, 112-38-9; lauric acid, 143-07-7; palmitic-*1*-^{13}C acid, 57677-53-9.

Chelation Control of Enolate Geometry. Acyclic Diastereoselection via the Enolate Claisen Rearrangement

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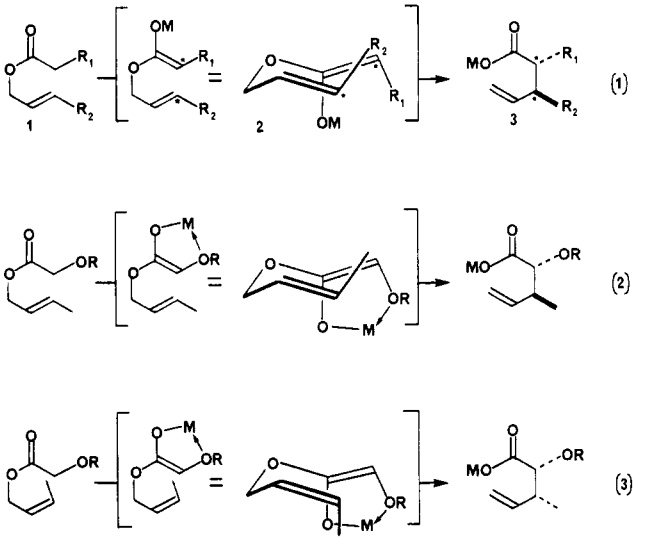
The Ireland–Claisen rearrangements of a variety of O-protected allylic glycolate esters are described. Vicinal diastereoselectivities ranging from 7.2:1 to >20:1 were observed, indicating that chelation control of enolate geometry is operational in the conversion of substrates **4a–c**, **6a–c**, and **8a,b** to the corresponding methyl 2-alkoxy-3-methyl-4-pentenoates **5a–c** and **7a–c** and to the sesquiterpene synthons **9a,b**. Four methods were developed for the preparation of the O-protected (*E*)- and (*Z*)-2-butenyl glycolate esters **4a–c** and **6a–c** and of the substrates **8a,b**. The assignment of relative vicinal stereochemistry in the rearrangement products **5a–c**, **7a–c**, and **9a,b** was accomplished by a combination of chemical and spectroscopic correlations, including a synthesis of (±)-verrucarinolactone (**12**).

The concept of "acyclic stereoselection" has recently received substantial experimental study, with impressive results.[1] A common rationale in many of the diastereoselective reactions thus developed is the coupling of sp^2-hybridized carbon centers via cyclic transition states. Accordingly, advantage is drawn from two sources: (1) the ready availability of reactive trigonal carbon sites (carbonyls, enolates, olefins), often with controlled local geometry; (2) the well-known conformational and stereochemical biases associated with cyclic structures, especially six-centered transition states.

The [3,3]-sigmatropic rearrangement of enolates (or trialkylsilyl ketene acetals) derived from esters of allylic alcohols is such a reaction and enjoys the stated advantages. In these Ireland–Claisen rearrangements (eq 1),[2] the sp^2 geometry at remote olefin and enolate carbons (asterisks in **2**) is transformed into vicinal sp^3-carbon stereochemistry (asterisks in **3**) via a chairlike pericyclic transition state.[3,4] We felt that if R_1 in **1** was a heteroatomic substituent, the enolate geometry would be controlled by intramolecular coordination, as illustrated in eq 2 and 3. With the enolate geometry thus set, selective entry into either diastereomeric series would depend only upon the geometry about the olefin linkage, as shown. A systematic study of such "chelation-controlled" Ireland–Claisen rearrangements on a variety of O-protected allylic glycolate ester substrates is herein reported in full detail. Several reports have appeared recently describing related



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