Analogs of natural lipids. IV. Synthesis and properties of cyclopentanoid analogs of phosphatidic acid[1]

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Abstract A new series of phosphatidic acid analogs has been synthesized in which the glycerol moiety of diacylglycerophosphoric acid is replaced by each of the three isomeric cyclopentane-1,2,3-triols (1,3/2, DL-1,2/3, and 1,2,3/0). Of the seven possible configurational and positional phosphatidic acid analogs of this series, five isomers have been obtained and characterized by spectroscopic methods and microanalysis. Four of the five isomers are 1-(or 3-)phosphoryl derivatives, while the fifth is a 2-phosphate.

The analogs were prepared in configurationally pure form by unequivocal synthetic procedures involving selectively blocked intermediates; acyl migration was avoided by the use of mild deblocking procedures. The anhydrous lipid products, all of which are dipalmitoyl esters, are solids indefinitely stable at room temperature in the free acid or potassium salt form; they have chromatographic mobility and melting points similar to dipalmitoyl glycerophosphoric acid. The dipotassium salts bind water of hydration tenaciously, remaining hydrated after drying in vacuo at 100°C. NMR spectra of dimethyl esters of some of the analogs show nonequivalence of the two methyl groups, consistent with the diastereotopic nature of those groups.

In addition to their intrinsic interest as conformationally restricted acidic lipids, the analogs are now available as starting materials for the synthesis of the more complex acidic and amphoteric lipids required for our exploitation of these cyclopentanoid analogs as unique probes for the study of lipid–lipid and protein–lipid interactions.

Supplementary key words lipid analogs · conformation of phosphoglycerides · hydration of phosphatides · nuclear magnetic resonance spectroscopy · diastereotopic groups · cyclitols

This communication is part of a series that describes the systematic synthesis and study of a new class of analogs of natural lipids. Previously (2), we reported the synthesis of three homologous series of triglyceride analogs, derived from each of the three diastereoisomeric cyclopentane-1,2,3-triols *1*, *2*, and *3* (**Fig. 1**). This work has now been extended to include the synthesis of five (*4–8*) of the seven possible phosphatidic acid analogs (*4–10*) in which the glycerol moiety of naturally occuring PA is replaced by one or the other of the three cyclopentane-1,2,3-triols. The rationale for the program of synthesis we have undertaken is the expectation that the lipid analogs will provide an original probe into the conformational aspects of lipid–lipid and lipid–protein interaction in biological situations.

Because there is no covalent restriction of the rotation of the glycerol backbone of natural glycerides, it has been impossible hitherto to assess the contribution of the rotameric state of that backbone to lipid–lipid and lipid–protein interactions. On the other hand, the cyclopentanoid ring imposes severe restrictions, so that each of the analogs may correspond to only a small number of rotameric states of the backbone of corresponding glycerides and one may therefore hope to observe preferential behavior of one or more analogs in model systems for the interactions noted.

In addition, the analogs may be substrates for or inhibitors of lipid metabolizing enzymes, again sug-

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Abbreviations and nomenclature: $CHCl_3$, chloroform; d, doublet; 2,2-DMP, 2,2-dimethoxypropane; DPPC, diphenylphosphoryl chloride; EtOAc, ethyl acetate; EtOH, ethanol; Et_2O, diethyl ether; GLC, gas–liquid chromatography; HOAc, acetic acid; Ip, isopropylidene [$(CH_3)_2C=$]; m, multiplet; MeOH, methanol; NMR, nuclear magnetic resonance; PA, phosphatidic acid; PC, phosphatidylcholine; Pd–C, palladium–charcoal (10%); ppm, parts per million; s, singlet; TLC, thin-layer chromatography; TMS, tetramethylsilane; TROC, 2,2,2-trichloroethoxycarbonyl.

Cyclic compounds described in this paper are named according to the Tentative Rules for Nomenclature of Cyclitols (1). The names are derived from those of the parent cyclanes of which they are formal derivatives. A summary of these rules has been presented in an earlier communication (2).

[1] For part III, see ref. (30)

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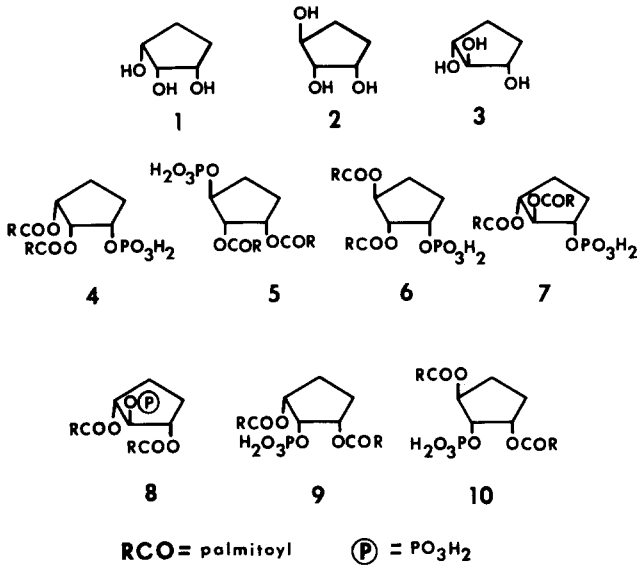


Fig. 1. Configuration of cyclopentanetriols and of cyclopentanoid analogs of phosphatidic acid. *1*: (1,2,3/0)-cyclopentane-1,2,3-triol; *2*: DL-(1,2/3)-cyclopentane-1,2,3-triol; *3*: (1,3/2)-cyclopentane-1,2,3-triol.

gesting the rotameric condition of the true substrates. Evidence supporting this contention has recently been obtained by Morrisett et al.[4] who found marked differences in the physical properties of the five analogs *4–8* and also in their ability to bind to apolipoprotein-C-III from human serum. The conformational rationale of the analogs has been published (2). Finally, the PA analogs are now available as starting materials for the synthesis of more complex cyclopentanoid phospholipid analogs. The synthetic routes developed allow the preparation of gram quantities of each of the five compounds in an analytically and stereochemically pure state. In each case, however, the compound has been synthesized from DL- or *meso*-starting material, so that the unsymmetrical products (*4–7*) are DL mixtures while *8* is a *meso* compound. The synthesis of compounds *4–8* is described in this paper.

MATERIALS AND METHODS

Melting points were measured on a Kofler micro hot-stage (Arthur H. Thomas and Co., Philadelphia, PA) and are uncorrected. Refractive index was measured with an Abbé refractometer. Infrared spectra were measured with a Perkin-Elmer 237B spectrophotometer (Perkin-Elmer Corp., Norwalk, CT) and were calibrated with polystyrene. NMR spectra were recorded on Varian A-60 and A-60A spectrometers for dilute solutions (Varian Associates, Palo Alto, CA), with TMS as internal standard. Unless otherwise stated, the solvent used was ^{2}H-chloroform. Chemical shifts are reported on the δ-scale in ppm downfield from TMS; chemical shifts are positive in this direction. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Analysis of reaction products by TLC and GLC was performed as described earlier (2); phosphates were visualized on TLC plates by spraying with the reagent of Dittmer and Lester (3).

Solutions of reaction products in organic solvents were dried with Na_2SO_4 before evaporation under reduced pressure on a rotary evaporator. Products of acylation and phosphorylation reactions were extracted into $CHCl_3$ and washed successively with water, ice-cold 1 N H_2SO_4, 5% $NaHCO_3$ and water.

Diphenylphosphorylchloride (DPPC) and 2,2,2-trichloroethyl chloroformate were obtained from Aldrich Chemical Co. Inc., Milwaukee, WI. Palmitoyl chloride and palmitic anhydride were products of Nu-Chek Prep., Elysian, MN. Celite 545 was supplied by Fisher Scientific Co., Pittsburgh, PA, and was washed with chloroform–methanol 1:1 before use. Platinum oxide was obtained from Engelhard Industries Co., Newark, N. J. Acylation reactions were generally carried out in anhydrous pyridine as described earlier for triacyl derivatives (2); in one case (1,3/2-isomer, *26*) the yield was marginally improved by using the fatty acid anhydride method of Cubero Robles and Van Den Berg (4). The dipalmitates were purified by silicic acid chromatography and recrystallization from methanol (2). *O*-Isopropylidene derivatives of diols were prepared as described previously (2). Epoxidations were carried out in wide-mouth brown bottles (2). Diphenyl esters of PA were hydrogenolyzed in quantitative yield over platinum in acetic acid. After centrifugation and evaporation of solvent, the PA analog was partitioned to remove cations according to a modification (5) of the procedure of Bligh and Dyer (6). Free PA was thus obtained as a sharply-melting white solid (**Table 1**). PA analogs (ca. 50 mg in $CHCl_3$, ca. 2 ml) were converted into potassium salts by titration to the phenolphthalein end point with KOH (0.2 N in MeOH–H_2O 98:2), and isolated in 90–95% yield as described by Kates et al. for phytanyl-ether PA analogs (5).

[4] J. D. Morrisett, A. M. Gotto, K-Y Hong, L. C. Smith, A. J. Hancock, and H. Z. Sable. *Federation Proc.* **35,** 1506 (1976), Abstract No. 746. Presented at the 67th Annual Meeting, American Society of Biological Chemists, San Francisco, June 1976. A full manuscript is in preparation.

TABLE 1. Analytical data for analogs of phosphatidic acid and potassium phosphatidate

		Free Acids $C_{37}H_{71}O_8P$ (674.9)			K_2 Salts, Trihydrates[a] $C_{37}H_{69}O_8PK_2 \cdot 3H_2O$ (805.2)					K_2 Salts, Dihydrates[c] $C_{37}H_{69}O_8PK_2 \cdot 2H_2O$ (787.1)		
		C	H	P	C	H	P	K	K/P[b]	C	H	H_2O[d]
Theory:		65.84	10.60	4.59	55.19	9.39	3.85	9.71	2.00	56.46	9.35	4.58
Compound	Configuration	Found			Found					Found		
4	1,2,3/0-(1P)	65.98	10.70	4.42	55.55	9.43	3.79	9.08	1.90	56.85	9.76	5.10[d]
5	1,2/3-(3P)	65.91	10.70	4.45	55.50	9.60	3.78	9.40	1.97	56.41	9.55	
6	1,2/3-(1P)	65.94	10.51	4.49	55.00	9.05	3.71	9.17	1.96	56.50	9.75	
7	1,3/2-(1P)	66.08	10.55	4.36	55.51	9.85	3.53	9.40	2.11	56.70	9.91	
8	1,3/2-(2P)	66.29	10.27	4.38	55.10	9.65	3.66	9.25	2.00	55.65	9.51	

[a] Compounds dried over P_2O_5 (12 hr at room temperature, 0.5 mm).
[b] K/P is ratio (gram-atoms K)/(gram-atoms P).
[c] Compounds dried over P_2O_5 (12 hr at room temperature, 0.5 mm), then dried further over P_2O_5 for 12 hr at 100°C (0.5 mm).
[d] Analysis by Karl Fischer method.

Methylation of PA analogs

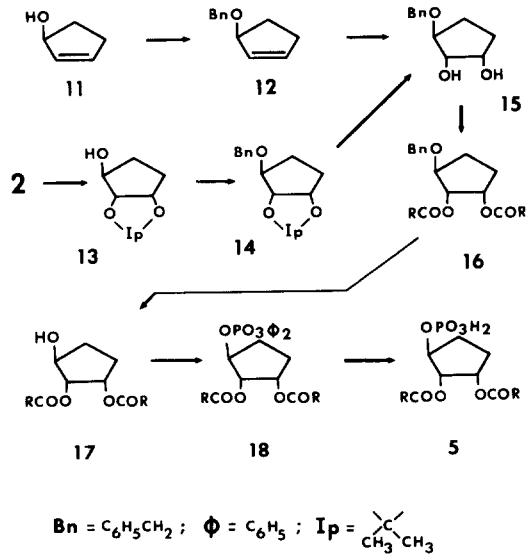
Each free PA analog was treated with excess diazomethane (7) to give the dimethyl ester. Evaporation gave the esters in quantitative yield. All five esters were sharply melting, gave one spot on TLC, and were stable on storage at room temperature, unlike related esters (8).

RESULTS AND DISCUSSION

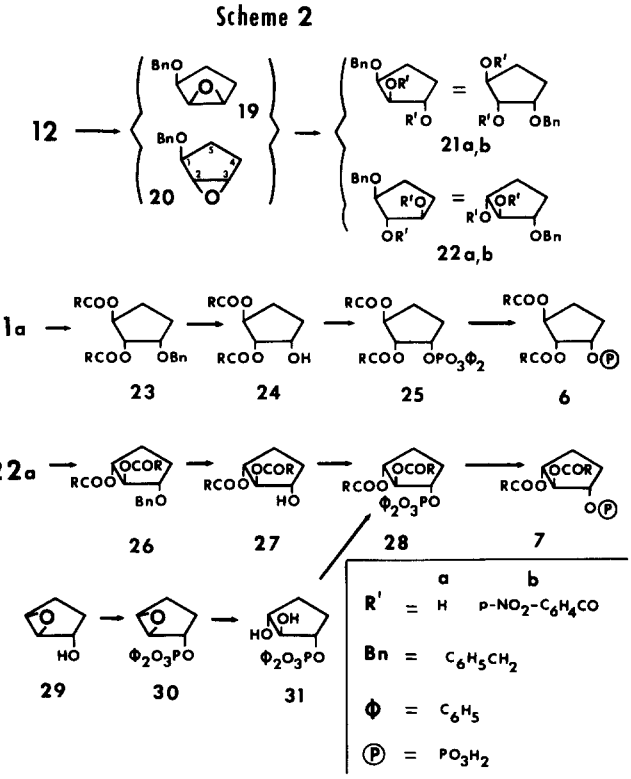
Monobenzyl ethers of cyclopentanetriols were key intermediates in several of the synthetic sequences, i.e., *13* → *14* (**Scheme 1**); *32* → *33* (**Scheme 3**). The acid stability of benzyl ethers allowed removal of the isopropylidene group (e.g., *14* → *15*); the resulting diols were acylated directly either with palmitoyl chloride or with palmitic anhydride (4). The benzyl group was removed by hydrogenolysis over Pd, and the resulting unisomerized diglyceride analog was phosphorylated to give the diphenyl ester of the PA analog.

Two benzyl ethers (*21a* and *22a*) were prepared by an indirect route. Epoxidation of *O*-benzyl-2-

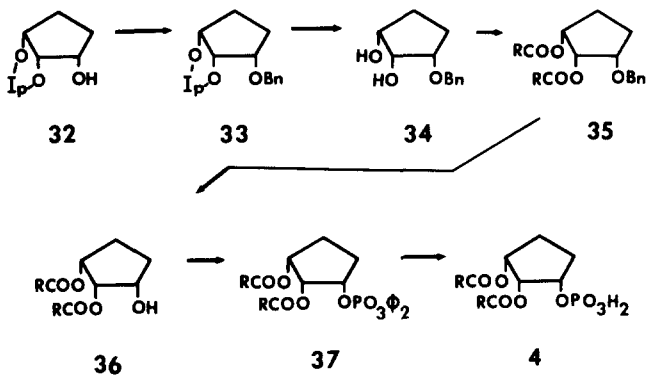
Scheme 1



Scheme 2



Scheme 3



cyclopenten-1-ol *12* gave a mixture of the isomeric epoxides *19* and *20* in a ratio of 1:2. This selectivity is unexpectedly low (9, 10). Since acid hydrolysis of each of the epoxides gave both *21a* and *22a*, the mixture was not separated, but was hydrolyzed directly and the diols converted to the *bis-O-p*-nitrobenzoate esters; the latter were separated by fractional crystallization and the purified substances were saponified as needed. For study of the regioselectivity (11) of hydrolysis of *19* and *20* the isomers were separated by preparative TLC. Hydrolysis of *19* gave *21a* and *22a* in a ratio of 9:91, while *20* gave a ratio of 95:5. This selectivity is similar to that seen (11) in related systems.

The synthesis of *8*, a symmetrical 2-phosphate, required a 1,3-blocked (1,3/2)-triol. The 1,3-benzylidene acetals of both glycerol (12) and *cis*-1,3-cyclopentanediol (13), as well as the 1,3-isobutylidene acetal[5] are known. However, in this series the *p*-nitrobenzylidene acetal *38* offered the advantages of both crystallinity and susceptibility to mild deblocking conditions. In this sequence, intramolecular migration is not possible since the diphenylphosphoryl group of *40* (**Scheme 4**) is *anti* to the regenerated hydroxyl groups.

DL-(1,2/3)-3-Phosphoryl analog

The benzyl diol *15* was synthesized by two routes (Scheme 1): one route required the triol acetonide *13* (14) and its benzyl derivative *14*. A more direct route to *15* involved direct hydroxylation of the allylic benzyl ether *12*, which is readily prepared from *11*. Hydroxylation with alkaline $KMnO_4$ was highly selective, less than 1% of the (1,2,3/0) isomer being formed. All four benzyl diols (*15*, *21a*, *22a*, and *34*) are thermally stable and can be distilled in nitrogen without decomposition; however, they are prone to deterioration on storage in air at room temperature. Ideally, each diol was used in the next stage of the synthesis without delay, but the diols could be stored over nitrogen at −20°C, or as the *bis-p*-nitrobenzoates at room temperature.

Diol *15* was acylated as described for the synthesis of the *tris*-acylates (2). The *bis*-palmitate was a stable solid; hydrogenolysis over Pd–C gave the analog *17*, which was phosphorylated to give *18*. The latter was stored at 4°C since, for some monophenyl esters (15), phenol is liberated on prolonged storage at room temperature. Catalytic dephenylation of *18* with PtO_2 in acetic acid gave *5* smoothly, while PtO_2 in ethanol gave complex mixtures. The free acid form of *5* melted in the range reported for glycerophosphatidic acids (5, 16).

DL-(1,3/2)-1-phosphoryl analog

Two (1,3/2)-PA analogs were synthesized. The all-*trans* isomer *7* was synthesized by two independent routes (**Scheme 2**). The high regioselectivity (11) of hydrolysis of epoxide *30* gave pure *31*, and the latter was acylated directly to give *28*.

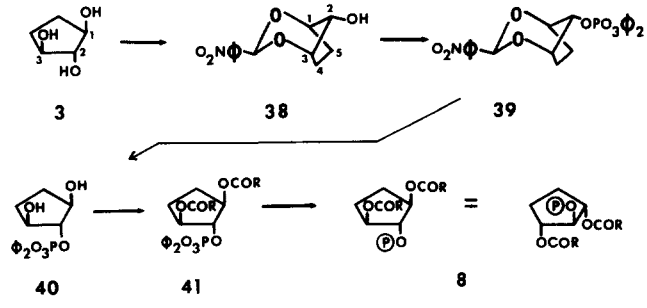
DL-(1,3/2)- and DL-(1,2/3)-1-phosphoryl analogs

A second route to *7* involves the intermediate benzyl ether *22a*, which is a by-product in the formation of 1,2/3-isomer *21a* (Scheme 2). The respective benzyl diols were acylated, debenzylated, and phosphorylated to give *28* and *25* in good yield. The phenyl groups were removed by hydrogenolysis over Pt.

DL-(1,2,3/0)-1-phosphoryl analog

The all-*cis* analog *4* was synthesized by a route (Scheme 3) resembling that for analog *5*. 1,2,3/0-Cyclopentanetriol acetonide *32* was obtained by reductive ring opening of DL-(1,2,3,4/0)-1,2-anhydro-

Scheme 4



Φ = C_6H_5 ; $O_2N\Phi$ = p-NO_2-C_6H_4 ; Ⓟ = PO_3H_2

[5] N. Dennis and E. L. Eliel. Unpublished experiments. We thank Professor Eliel for providing this information.

cyclopentane-1,2,3,4-tetrol (2) and purified via its benzoate ester. Benzylation and hydrolysis gave *34*, which was acylated and then converted into the pseudodiglyceride *36* without concomitant acyl group migration, as judged by TLC and melting behavior. However, prolonged exposure of *36* to unbuffered silicic acid did promote acyl migration, a property shared by the 1,2/3 isomer *24* (Scheme 2), as well known in glyceride chemistry (12).

2-*O*-Phosphoryl analog of PA

The symmetrical isomer *8*, one of the three possible "abnormal" analogs having the phosphoryl moiety at position 2 of the ring (Fig. 1), has been synthesized via the *p*-nitrobenzylidene acetal *38*. The synthetic sequence differed from that used for most of the other isomers, but resembled the route to the other all-*trans* isomer *7* (via *31*) in that the diphenylphosphorylation step preceded all the others. Hydrogenolysis of *39* over Pd–C removed the acetal blocking group without affecting the phenyl groups (17, 18). Acylation followed by catalytic dephenylation gave *8*.

Hydration of potassium salts

Elemental analyses showed that the free acid forms of *4*–*8* were anhydrous (Table 1). The equivalent weight of each isomer, determined by titration, agreed closely with the theoretical values. On the other hand, the elemental analysis showed that the vacuum-dried potassium salts exist as the trihydrates (Table 1). The water of hydration was particularly strongly bound: overnight drying at 100°C/0.5 mm removed only 1 mole of water. Confirmation was obtained by Karl Fischer analysis of the salt of the all-*cis* isomer *4* (Table 1). The tenacity of the hydration may be related to other observations on amphoteric lipids. Chapman and Fluck (19) related the temperature at which the lipid formed smectic mesophases in water to the major peaks observed in differential thermal analysis of the dry compounds. In effect this relates the degree of liquidity of the hydrocarbon side chains to the ease of disruption of phospholipid crystals by water. Williams and Chapman (20) showed that, for each molecule of PC, 10 molecules of water do not freeze at 0°C, and Bangham, deGier, and Greville (21) found that about 35 molecules of water, per molecule of PC, are osmotically inactive.

Melting point behavior of the PA analogs

The PA analogs melt in the range 73–84°C (**Table 2**), while dipalmitoyl glycerophosphoric acid acid and its distearyl ether analog melt at 70–71°C (16) and 69°C (5), respectively. Configurational differences among the analogs have a greater effect on the melting points of the dimethyl and diphenyl esters than on the melting points of the free acids themselves (Table 2). Similarly, the chromatographic behavior of the esters is more affected than is that of the free acids (see below). The 1,2,3/0 esters, with one exception, are lower melting than the corresponding members of the other two series, a characteristic observed also for the 1,2,3/0 benzyl ether *35*, and noted previously for the 1,2,3/0 tris-*homo*acylcyclopentanetriols (2).

TABLE 2. Melting points of isomeric cyclopentanoid analogs of phosphatidic acid (free acids and esters)

Compound	Configuration	Melting Point °C		
		Free Acid	Diphenyl Ester	Dimethyl Ester
4	1,2,3/0-(1P)	76–78	52–53	34–36
5	1,2/3-(3P)	77.5–78.5	56–57	53–54
6	1,2/3-(1P)	78–80	43–44	68–71
7	1,3/2-(1P)	82–83.5	57–58	59–60
8	1,3/2-(2P)	73–74.5	69–70	61–63

Spectroscopic analysis

(*i*) Structural and conformational assignments for epoxides *19* and *20* (Scheme 2) were based on earlier observations (14) that in pairs of *syn* or *anti* substituted cyclopentane epoxides, the frequency of a strong band in the 830–855 cm^{-1} region of the IR spectrum is diagnostic. Bands at 854 cm^{-1} for *19* and 843 cm^{-1} for *20* established the configurations. This was confirmed by NMR (14) by measurement of the coupling of the cyclopentanoid ring proton on C-1 with the vicinal oxirane proton of C-2. For *19* and *20* this coupling was 1.2 Hz and 0.6 Hz, respectively, in agreement with the assignment. In both compounds, the conformation, as determined from the coupling of the cyclopentanoid ring proton on C-1 with the vicinal methylenic protons on C-5 (14), showed the expected *endo*, or boat, conformation. The chemical shifts of the benzylic CH_2 resonances in *19* and *20* differed, respectively, by 0.19 ppm (C_6D_6) and 0.08 ppm ($CDCl_3$). Similar differences were observed in the *bis-p*-nitrobenzoates *21b* and *22b* (0.14 ppm in $CDCl_3$). These differences permitted the determination of the isomeric composition of mixtures and the isomeric purity of each of the four compounds after separation.

(*ii*) *O*-Isopropylidene monobenzyl ethers *14* and *33*. The NMR spectra were consistent with the proposed structures. The gem-dimethyldioxolane moieties in both compounds gave signals for *exo*- and *endo*-CH_3 groups within the ranges reported earlier (22).

(*iii*) Di-*O*-palmitoyl monobenzyl ethers *16, 23, 26,*

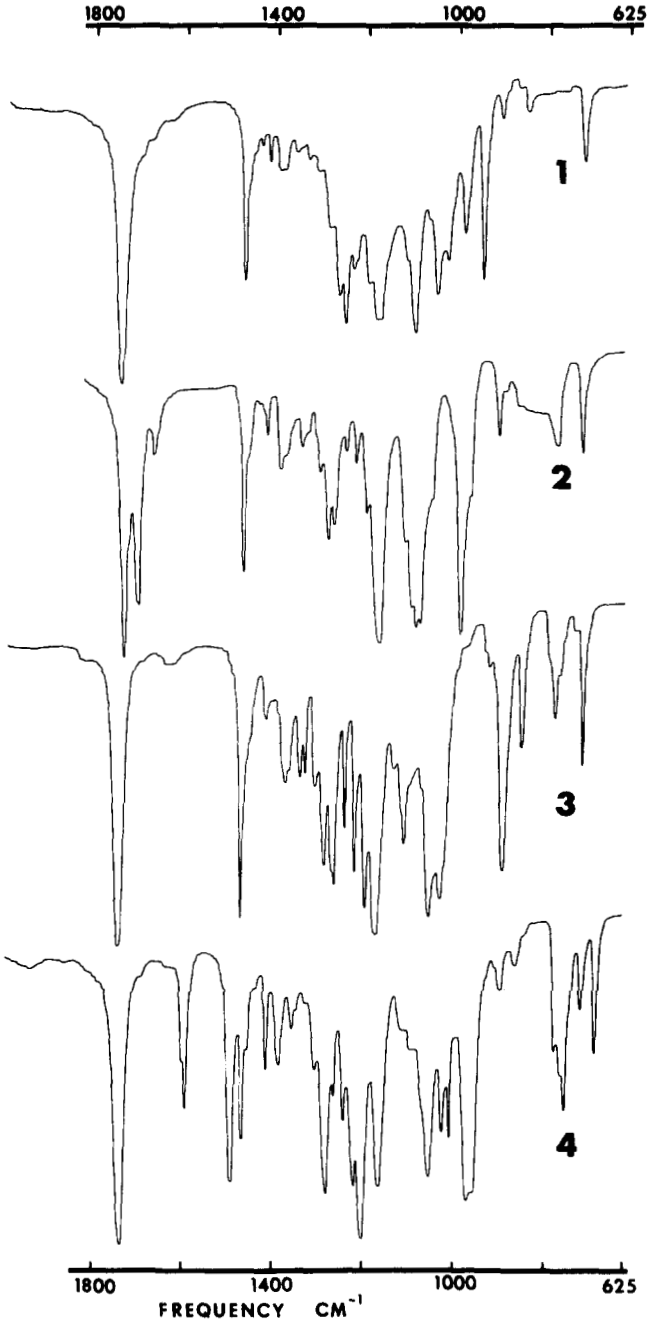


Fig. 2. Infrared spectra of KBr dispersions of the (1,3/2)-2P analog *8* and some of its derivatives. Spectrum 1 is of the free acid; 2 is of the dipotassium salt trihydrate (see text and Table 1); 3 is of the dimethyl ester; 4 is of the diphenyl ester.

and *35*. In the spectra of *26* and *35*, the nonequivalence (23, 24) of the benzylic CH_2 protons is just enough to produce a narrow doublet representing the inner lines of the expected AB quartet (25). 100 MHz spectra show the AB quartet clearly.

(*iv*) PA analogs and PA dimethyl and diphenyl esters. The NMR spectra of *4–8* showed the high field resonance signals expected for the aliphatic chains: δ 0.89, CH_3; δ 1.26, CH_2. Signals for ring CH_2 and ring O–C–*H* protons were not resolved, the spectra showing only broad lines. Much of the line broadening may be due to phosphate chelated paramagnetic ions (26), probably derived from the platinum catalyst used for cleavage of the phenyl groups. The spectra of the corresponding methyl and phenyl diesters of PA are significantly sharper, and the signals of some of the ring O–C –*H* protons are resolved. Both *28* and the corresponding dimethyl ester give a signal representing the ring proton (C-2)–H, as a well-resolved triplet, $J_{average}$ = 4.0 Hz. This coupling shows that the conformational equilibrium of the ring backbone of this lipid analog is identical with that deduced in the earlier work (27) for the tribenzoate of *3*. From this we infer that conformational preference deduced for the simpler compounds is a reasonable basis for predicting the conformation of ring skeletons of the phospholipid analogs.

The NMR spectra of the dimethyl esters of *4*, *5*, and *6* showed fine structure in the signals of the P–O–CH_3 protons centered at δ 3.80. In addition to the ^{31}P–O–C–H coupling of 11.3 Hz there was a further splitting of 0.5–1 Hz, similar to that observed in another system (28, 29). The multiplicity in the signal reflects the chemical nonequivalence of the diastereotopic methyl groups in the PA analogs (30). In the earlier case (23, 24) the prochiral phosphorus atom (23, 31) gave rise to diastereomeric methyl esters.

Infrared spectroscopy

The infrared spectra of KBr dispersions of the PA analogs, their salts, and their dimethyl and diphenyl esters show well-resolved absorption bands (**Fig. 2**). In general, these spectra agree with what is expected for such compounds (32). Details of these spectra will be discussed in a future publication.

Thin-layer chromatography

The chromatographic mobility of the PA analogs was, in general, slightly greater in acid or neutral solvent systems than that of dipalmitoyl glycerophosphoric acid; in an alkaline system the analogs, in common with glycero-PA, did not migrate (**Table 3**). The dependence of mobility on the ring configuration of the isomers was marginally evident in the chromatography of the free acids, but more marked for the dimethyl and diphenyl esters, where the (1,2,3/0) isomers (e.g., *37*) showed greater apparent polarity (Table 3). The PA analogs gave well-defined spots on chromatography in acid or neutral solvent systems, unlike other PA analogs such as the diether

TABLE 3. Chromatographic mobility of isomeric cyclopentanoid analogs of phosphatidic acid (free acids and esters)

Compound	Configuration	R_f Free Acid Solvent A	Free Acid Solvent B	Free Acid Solvent C	Diphenyl Esther Solvent D	Dimethyl Esther Solvent E
4	1,2,3/0-(1P)	0.36	0.62	0.00	0.40	0.29
5	1,2/3-(3P)	0.39	0.67	0.00	0.44	0.41
6	1,2/3-(1P)	0.44	0.70	0.00	0.40	0.39
7	1,3/2-(1P)	0.44	0.70	0.00	0.46	0.41
8	1,3/2-(2P)	0.46	0.71	0.00	0.54	0.48
	Dipalmitoylglycero-phosphoric acid	0.36	0.62	0.00		

Solvent systems: A, $CHCl_3$–MeOH–H_2O 65:35:5; B, $CHCl_3$–$(CH_3)_2CO$–MeOH–HOAc–H_2O 6:8:2:2:1; C, $CHCl_3$–MeOH–30%NH_4OH 65:35:5; D, CCl_4–EtOAc 8:2; E, $CHCl_3$–Et_2O 3:1.

glycero-analogs reported by Kates et al. (5), for which these systems were less suitable.

Rationale

The synthesis of the five PA analogs provides us with reasonable routes to the synthesis of more complex cyclopentanoid lipids. Our ultimate goal is to study the biological behavior of these lipid analogs, and of compounds derived from them. It is clear that, as with other lipid systems (33, 34), physical properties such as the gel-to-liquid crystal transition temperatures should be determined before such studies are undertaken. With this provision, we believe that study of the physical and biological properties of these phospholipid analogs can provide kinds of insight into the molecular organization of lipid and lipoprotein assemblies that are not available with the existing lipid repertoire.

EXPERIMENTAL SECTION

DL-2-Cyclopenten-1-ol[6] *11*

A solution of 450 g $NaHCO_3$ in 2 l of water in a 5-l, three-neck flask was chilled to 0°C and 140 g of freshly prepared DL-3-chloro-1-cyclopentene (2, 35) was added over a period of 1 hr. The reaction mixture was then stirred for an additional 2 hr at 0°C, the product was salted out with solid NaCl (500 g) and recovered by extraction with ether. The extract was dried, the solvent was evaporated, and the oil distilled bp 62–65°C/36 mm; n_D^{28} 1.4692; R_f 0.30 in $CHCl_3$–Et_2O 20:1. The TLC showed traces of dicyclopentenyl ether (R_f 0.75) in all fractions of the distillate, but the impurity did not interfere in subsequent steps. IR spectra were measured on solutions in CS_2. The ether side-product was purified by TLC. IR (CS_2) showed strong bands at 1160, 1315, and 1360 cm^{-1}, none of which were given by the allylic alcohol. The alcohol gave bands at 965 and 775 cm^{-1} which were weak or absent in the spectrum of the ether.

1-*O*-Benzyl-2-cyclopentenol *12*

A solution of 2-cyclopenten-1-ol *11* (21 g, 25 mmoles) and benzyl chloride (68.3 g, 39 mmoles) in benzene (100 ml) was refluxed with powdered KOH (18 g) in an apparatus equipped with a Dean-Stark phase separator until 5.0 ml of H_2O were collected. The mixture was poured over ice (200 g), the aqueous phase was extracted with $CHCl_3$, and the extracts were combined with the benzene phase. The solution was washed (ice-cold 1 M H_2SO_4, water, 5% $NaHCO_3$, water), dried, and evaporated. Excess benzyl chloride was removed by distillation at 30°C (50–60 mm) and *12* was distilled (bp 72–75°C/0.6 mm); (27.2 g; 15.6 mmoles, 62.5%). Spectroscopic data were consistent with the proposed structure, but acceptable elemental analyses could not be obtained. Similar difficulties in the case of an *O*-isopropylidene cyclopentenediol were reported by Young, Hall, and Winstein (36).

NMR: δ 7.30 [5], s, aromatic; δ 5.95 [2], m, olefinic; δ 4.68 [1], m, ring O–C–H; δ 4.54 [2], s, benzyl CH_2; δ 1.65–2.60 [4], m, ring CH_2.

Benzyl ethers of triols

DL-*(1,2/3)-1,2-O-Isopropylidene-3-O-benzylcyclopentane-1,2,3-triol 14*. Isopropylidenetriol *13* (3.0 g, 19.0

[6] We thank Dr. Henry C. Stevens for the details of this procedure.

mmoles) and benzyl chloride (4.8 g, 38 mmoles) were reacted in refluxing benzene in the presence of powdered KOH (3.0g) for 8 hr. Benzyl ether *14* was isolated as described for *12* (3.60 g, 14.5 mmoles, 77%; bp 126–129°C/0.5 mm, mp 15–16°C).

Anal. Calc. for $C_{15}H_{20}O_3$ (248.3): C, 72.55; H, 8.12. Found: C, 72.46; H, 8.29.

NMR: δ 1.28, 1.39 [6], d, *endo* and *exo*-CH_3 (22); δ 1.85 [4], s, ring CH_2; δ 4.50 [2], s, benzyl CH_2; δ 7.30 [5], s, C_6H_5; δ 3.87 [1], s (broad), CH–O–$CH_2C_6H_5$; δ 4.42–4.82 [2], m, ring CH–OIp.

IR (CS_2): 3030, 3060, 3090, 735, 695 cm^{-1} (aromatic); 1360, 1370, 1375 cm^{-1} (*gem*-dimethyl).

DL-*(1,2,3/0)-1-O-benzyl-2,3-O-isopropylidenecyclopentane-1,2,3-triol 33*. Isopropylidenetriol *32* (2) (12.0 g, 75.9 mmoles) was benzylated in refluxing benzene (120 ml) with benzyl chloride (20 g; 158 mmoles) and KOH (14 g) and the benzyl ether was isolated as described for *12*. The product *33* (16.9 g, 68.1 mmoles, 90%, bp 122–125°C/0.4 mm) had GLC retention 1.10 relative to *14*.

Anal. Calc. for $C_{15}H_{20}O_3$ (248.3): C, 72.55; H, 8.12. Found: C, 72.82; H, 8.50.

NMR: δ 1.32, 1.53 [6], d, *endo*- and *exo*-CH_3, (22); δ 4.66 [2], s, benzyl CH_2; δ 1.55–2.08 [4], m, ring CH_2; δ 7.33 [5], s, C_6H_5; δ 4.45–4.60 [2], m, ring CH–O–Ip; δ 3.36–3.75 [1], m (unresolved), ring CH-O-$CH_2C_6H_5$.

IR (liquid film): 3030, 3060, 3090, 1495, 735, 700 cm^{-1} (aromatic); 1365, 1377 (doublet, shoulder at 1360) cm^{-1}, *gem*-dimethyl.

(1,2/3)-3-O-Benzylcyclopentane-1,2,3-triol 15. METHOD I. Isopropylidenebenzyltriol *14* (2.36 g, 950 mmoles) was hydrolyzed by stirring for 2 hr in refluxing 0.1 N H_2SO_4 (200 ml). The cooled mixture was stirred with 10 g $BaCO_3$ for 1 hr, filtered through Celite and evaporated (1.65 g, 7.93 mmoles, 84%). TLC ($CHCl_3$–MeOH–H_2O, 90:10:1) showed one spot, R_f 0.50, GLC showed the presence of 1% of *34*, and 1% unindentified impurities. Preparative TLC on silica ($CHCl_3$–MeOH–H_2O 90:10:1) gave an analytical sample.

Anal. Calc. for $C_{12}H_{16}O_3$ (208.3): C, 69.21; H, 7.75. Found: C, 68.98; H, 7.87.

NMR: δ 7.30 [5], s, C_6H_5, δ 4.54 [2], s, benzyl CH_2; δ 3.10 [2], s (broad), OH; δ 1.30–2.40 [4], m, ring CH_2; δ 3.80–4.20 [3], m, ring O–C–H.

METHOD II. A solution of 1-*O*-benzylcyclopentenol *12* (30 g; 0.17 moles) in 900 ml of EtOH–dioxane–H_2O 1:1:1 containing NaOH (12.5 g; 0.31 mole) was maintained at −20°C while a cool solution of $KMnO_4$ (19 g; 0.2 moles) in water (700 ml) was added (4 hr). After a further hour, MnO_2 was reduced with SO_2 gas. The solution was filtered, concentrated, and continuously extracted with CH_2Cl_2 (2 days) to give a yellow oil (21.0 g, 0.11 mole, 64%) that cochromatographed with *15* as prepared above. The product was purified by conversion to *14*, which was then distilled; the fraction bp 95–100°C/0.5 mm (16.5 g) was >96% pure (GLC) and free from *33*. The *bis-p*-nitrobenzoate derivative (mp 117–118°C) was analyzed.

Anal. Calc. for $C_{26}H_{22}O_9N_2$ (506.5): C, 61.66; H, 4.38; N, 5.53. Found: C, 61.70; H, 4.32; N, 5.31.

(1,2,3/0)-1-O-Benzylcyclopentane-1,2,3-triol 34. Compound *33* (6.2 g, 25 mmoles) was hydrolyzed in refluxing 0.1 N H_2SO_4 (300 ml) for 3 hr. Workup as described for *15* gave *34* in quantitative yield. TLC ($CHCl_3$–MeOH–H_2O 90:10:1) showed one spot (R_f 0.60); 97% pure by GLC. The *bis-p*-nitrobenzoate derivative melted at 107–109°C.

Anal. Calc. for $C_{26}H_{22}O_9N_2$ (506.5): C, 61.66; H, 4.38; N, 5.53. Found: C, 61.73; H, 4.38; N, 5.61.

NMR: δ 7.30 [5], s, C_6H_5; δ 4.52 [2], s, benzyl CH_2; δ 1.80 [4], s, ring CH_2; δ 3.17 [2], s, OH; δ 3.85 [3], ring O–C–H.

DL-*(1,2,3/0)-1-O-Benzyl-2,3-epoxy-1-cyclopentanol 19* and DL-*(1/2,3)-1-O-benzyl-2,3-epoxy-1-cyclopentanol 20*. A solution of *m*-chloroperoxybenzoic acid (19 g; 110 mmoles) in $CHCl_3$ (300 ml) was cooled to 3–5°C and stirred while DL-1-*O*-benzyl-2-cyclopenten-1-ol *12* (15 g; 86 mmoles) in 15 ml of $CHCl_3$ was added during 30 min. Four such reactions were carried out simultaneously. After standing overnight in the dark at 5°C, the suspensions were filtered, combined, concentrated, and the residue was extracted with cool benzene (100 ml). The extract was filtered and washed with 5% $NaHCO_3$ and water, dried, and evaporated. Distillation (117–120°C/0.5 mm) gave an oil (45 g, 24 mmoles; 69%) containing two epoxides *20* and *19*. A portion was separated by preparative TLC. R_f ($CHCl_3$–Et_2O 20:1): *20*, 0.70; *19*, 0.80. Ratio *anti*/*syn* 2:1 by GLC.

Anal. Calc. for $C_{12}H_{14}O_2$ (190.2): C, 75.76; H, 7.42. Found: C, 75.84; H, 7.58.

(1,3/2)-1-O-Benzylcyclopentane, 1,2,3-triol 22a and *(1,2/3)-1-O-benzyl-cyclopentane-1,2,3-triol 21a*. The mixture of *19* and *20* (25 g, 0.19 moles) was suspended in 500 ml of 0.1 N H_2SO_4 and stirred at reflux temperature (3 hr). The solution was neutralized with $BaCO_3$ (15 g), filtered, and continuously extracted with CH_2Cl_2 (24 hr). The extract was concentrated to an oil (19.8 g, 73%). TLC ($CHCl_3$–MeOH–H_2O 90:10:1) showed two major components (R_f 0.40 and 0.55). GLC (trimethylsilyl derivatives) showed that *21a* and *22a* were formed in a ratio of 35:65.

DL-*(1,2/3)-1-O-Benzyl-2,3-bis-O-(p-nitrobenzoyl)-cyclopentane-1,2,3-triol 21b* and DL-*(1,3/2)-1-O-benzyl-2,3-bis-O-(p-nitrobenzoyl)-cyclopentane-1,2,3-triol 22b*. *p*-Nitrobenzoyl chloride (55 g, 0.30 moles) was added to a solution of *21a* and *22a* (20 g, 0.13 moles) in pyridine

(50 ml), chilled to 0°C and the mixture was left overnight. Ice (100 g) was added and after 1 hr the slurry was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ solution, worked up as usual, gave a solid product (55 g). TLC (hexane–Et_2O 60:40) showed a single spot (R_f 0.40) containing *21b* and *22b*, and a minor spot (R_f 0.35) (*p*-nitrobenzoic anhydride). The isomers were separated by fractional recrystallization from EtOAc; the rate of crystallization was adjusted for optimum separation (several crops of approximately 2 g each were collected over a period of a week). Isomeric distribution was assayed by integration of the NMR signals at δ 4.5–4.6 (benzylic CH_2). Early crops were almost pure *21b* (mp 159–162°C) while later crops were enriched in *22b*. Subsequent recrystallization of the later crops from acetonitrile gave pure *22b* (mp 122–123°C).

Anal. Calc. for $C_{26}H_{22}O_9N_2$ (506.5): C, 61.66; H, 4.38; N, 5.53. Found: *22b*: C, 61.76; H, 4.15; N, 5.50. Found *21b*: C, 61.76; H, 4.48; N, 5.48.

NMR *22b*: δ 4.6, benzyl CH_2; δ 7.3, C_6H_5; *21b*: δ 4.5, benzyl CH_2; δ 7.2, C_6H_5.

DL-*(1,3/2)-1-O-Benzylcyclopentane-1,2,3-triol 22a* or DL-*(1,2/3)-1-O-benzylcyclopentane, 1,2,3-triol 21a.* The appropriate *bis-p*-nitrobenzoate *21b* or *22b* was refluxed for 2 hr in 250 ml of 10% KOH in MeOH–H_2O 40:60. After cooling and neutralization with 6 N H_2SO_4, K_2SO_4 was removed; the filtrate was concentrated and then extracted continuously with CH_2Cl_2 for 24 hr. The extract, dried and concentrated to an oil, gave yields of 95–99%. Each diol was isomerically pure and was used at once for the next stage of the synthesis.

O-Benzyl-di-*O*-palmitoyl triols

DL-*(1,2/3)-3-O-Benzyl-1,2-di-O-palmitoylcyclopentane-1,2,3-triol 16.* Benzyl diol *15* (3.33 g, 16 mmoles) in 20 ml of pyridine at 0°C was acylated with palmitoyl chloride (10 g, 36 mmoles) (2). The oily product *16* crystallized on treatment with ethanol at 5°C (10.9 g, 15.9 mmoles, 99%). TLC (hexane–Et_2O–HOAc 90:10:1) showed a major component, R_f 0.23. Trituration with cold acetone removed the color; traces of fatty acid were removed by recyrstallization at 4°C (1 g in 30 ml CH_3OH); mp 52–53°C).

Anal. Calc. for $C_{44}H_{76}O_5$ (685.1): C, 77.14; H, 11.18. Found: C, 77.27; H, 11.26.

NMR: δ 4.56 [2], s, benzylic CH_2.

DL-*(1,3/2)-1-O-Benzyl-2,3-di-O-palmitoylcyclopentane-1,2,3-triol 26.* Benzyl diol *22a* (2.38 g, 11.9 mmoles) was acylated in 25 ml of pyridine with palmitoyl chloride (5.0 g, 18 mmoles) (2) to give 6.30 g of an oil that could not be induced to crystallize. TLC showed a relatively polar impurity and traces of fatty acid. Purification by chromatography on silica gel in hexane–benzene 1:1 gave an oil that crystallized in vacuo mp. 42–43°C (3.54g, 5.17 mmoles, 44%).

Anal. Calc. for $C_{44}H_{76}O_5$ (685.1): C, 77.14; H, 11.18. Found: C, 77.10; H, 11.09.

NMR: δ 4.58, 4.60 [2], "doublet", benzylic CH_2.

DL-*(1,2/3)-1-O-Benzyl-2,3-di-O-palmitoylcyclopentane-1,2,3-triol 23.* Benzyl diol *21a* (1.38 g, 6,63 mmoles) in 10 ml of pyridine was acylated with palmitoyl chloride (5.0 g, 18 mmoles) (2) to give 4.0 g of an oil, which was then purified by silica chromatography in hexane–benzene 1:1 giving *23* (3.67 g, 5.36 mmoles, 81%) mp 44–45°C.

Anal. Calc. for $C_{44}H_{76}O_5$ (685.1): C, 77.14; H, 11.18. Found: C, 77.22; H, 10.94.

NMR: δ 4.50 [2], s, benzylic CH_2.

DL-*(1,2,3/0)-1-O-Benzyl-2,3-di-O-palmitoylcyclopentane-1,2,3-triol 35.* Diol *34* (3.33 g, 16 mmoles) in 20 ml of pyridine was acylated with palmitoyl chloride (10 g, 36 mmoles) (2). Purification by column chromatography gave *35* (7.18 g, 10.5 mmoles, 66%) which crystallized slowly in vacuo and was recrystallized from MeOH at 4°C (mp. 38–39°C).

Anal. Calc. for $C_{44}H_{76}O_5$ (685.1): C, 77.14; H, 11.18. Found: C, 77.16; H, 11.32.

NMR: δ 4.50, 4.55 [2] "doublet", benzylic CH_2.

Di-*O*-palmitoyl triols

DL-*(1,2/3)-1,2-Di-O-palmitoylcyclopentane-1,2,3-triol 17.* Diacylmonobenzyl triol *16* (8.0 g; 11.7 mmoles) in 90 ml of $CHCl_3$–MeOH 75:15 was vigorously stirred under hydrogen with 2 g of 10% Pd–C. After 2 hr the catalyst was removed by filtration over Celite; evaporation gave *17* in quantitative yield; recrystallization (hexane) gave an analytical sample mp 63–64°C.

Anal. Calc. for $C_{37}H_{70}O_5$ (594.9): C, 74.69; H, 11.86. Found: C, 74.51; H, 11.89.

DL-*(1,2,3/0)-1,2-Di-O-palmitoylcyclopentane-1,2,3-triol 36.* Diacylmonobenzyl triol *35* (4.62 g, 6.75 mmoles) in 20 ml of EtOAc was hydrogenolyzed as above (1.5 g Pd–C; 90 min). Recrystallization from hexane gave *36* (3.98 g, 99%; mp 64–65°C).

Anal. Calc. for $C_{37}H_{70}O_5$ (594.9): C, 74.69; H, 11.86. Found: C, 74.61; H, 11.74.

DL-*(1,2/3)-2,3-Di-O-palmitoylcyclopentane-1,2,3-triol 24.* Compound *23* (3.67 g; 5.36 mmoles) in 15 ml of EtOAc was hydrogenolyzed (1 g Pd–C, 2.5 hr). TLC ($CHCl_3$–Et_2O 20:1) on sodium acetate-impregnated plates gave one spot (R_f 0.55), but unbuffered silica caused acyl migration as evidenced by a second spot (R_f 0.65). The product *24* (3.11 g, 5.23 mmole; 98%) was recrystallized from hexane (mp 52–53°C).

Anal. Calc. for $C_{37}H_{70}O_5$ (594.9): C, 74.69; H, 11.86. Found: C, 74.59; H, 11.66.

DL-*(1,3/2)-1,2-Di-O-palmitoylcyclopentane-1,2,3-triol 27*. Compound *26* (3.12 g, 4.55 mmoles) in 20 ml of EtOAc was hydrogenolyzed (1 g Pd–C) for 2 hr. The product crystallized during evaporation (2.70 g, 4.56 mmoles, 100%). Recrystallization (hexane) gave *27*, mp 57–59°C.

Anal. Calc. for $C_{37}H_{70}O_5$ (594.9): C, 74.69; H, 11.86. Found: C, 74.65; H, 11.72.

Diphenyl esters of phosphatidic acids

DL-*(1,2/3)-3-O-(Diphenylphosphoryl)-1,2-di-O-palmitoylcyclopentane-1,2,3-triol 18*. Diacyl triol *17* (6.0 g, 11 mmoles) in 1:1 anhydrous pyridine–Et_2O (25 ml) was stirred at 0°C while DPPC (5.37 g, 20 mmoles) was added; stirring was continued overnight at room temperature. Ice (2 g) was added and after 30 min the mixture was diluted with 100 ml each of $CHCl_3$ and water. The $CHCl_3$ phase was washed with water, dried, and evaporated to an oil that crystallized upon addition of EtOH (7.64 g, 9.24 mmoles; 84%); TLC (CCl_4–EtOAc 80:20) showed one major spot, R_f 0.44; recrystallization from MeOH gave *18*, mp 56–57°C.

Anal. Calc. for $C_{49}H_{79}O_8P$ (827.1): C, 71.15; H, 9.63; P, 3.75. Found: C, 71.09; H, 9.50; P, 3.76.

DL-*(1,2/3)-1-O-(Diphenylphosphoryl)-2,3-di-O-palmitoylcyclopentane-1,2,3-triol 25*. Diacyl triol *24* (2.77 g, 4.66 mmoles) in 20 ml of pyridine was phosphorylated (DPPC 2.70 g, 10 mmoles) as described for *18*. The oily product, which crystallized slowly (3.62 g; 6.09 mmoles, 94%), was chromatographically pure, R_f 0.40 (CCl_4–EtOAc 80:20). Recrystallization from MeOH gave *25*, mp 43–44°C.

Anal. Calc. for $C_{49}H_{79}O_8P$ (827.1): C, 71.15; H, 9.63; P, 3.75. Found: C, 71.33; H, 9.86; P, 3.72.

DL-*(1,2,3/0)1-O-(Diphenylphosphoryl)-2,3-di-O-palmitoylcyclopentane-1,2,3-triol 37*. Diacyl triol *36* (3.60 g, 6.05 mmoles) in 25 ml of pyridine was phosphorylated (DPPC 3.80 g, 14.1 mmoles) as described for *18*, giving chromatographically pure 37 (4.80 g, 5.81 mmoles; 96%); R_f 0.36 (CCl_4–EtOAc 80:20). Recrystallization from MeOH gave mp 52–53°C.

Anal. Calc. for $C_{49}H_{79}O_8P$ (827.1): C, 71.15; H, 9.63; P, 3.75. Found: C, 71.43; H, 9.68; P, 3.73.

DL-*(1/2,3)-1-O-(diphenylphosphoryl)-2,3-Epoxy-1-cyclopentanol 30*. To epoxyalcohol *29* (2) (3.0 g; 30 mmoles) in 50 ml of pyridine at 0°C, DPPC (10.8 g; 40 mmoles) in 15 ml Et_2O was added, and the solution was stirred at room temperature overnight. Ice (10 g) was added, stirred for 1 hr, and 200 ml each of $CHCl_3$ and water were added. The aqueous phase was extracted with $CHCl_3$ and the combined $CHCl_3$ solution was washed with water and dried. Evaporation gave an oil *30* (9.30 g, 28 mmoles; 93%); TLC ($CHCl_3$–Et_2O 3:1) showed a major phosphate-positive spot, R_f 0.80. An analytical sample was obtained by preparative TLC on silica with $CHCl_3$–Et_2O 3:1 as developing solvent and $CHCl_3$–MeOH–Et_2O 1:1:1 as eluant.

Anal. Calc. for $C_{17}H_{17}O_5P$ (332.3): C, 61.45; H, 5.16; P, 9.32. Found: C, 61.63; H, 5.23; P, 9.58.

The slightly impure product was used for hydrolysis to *31*.

DL-*(1,3/2)-1-O-(Diphenylphosphoryl)-cyclopentane-1,2,3-triol 31*. The phosphorylated epoxide *30* (5.55 g, 16.7 mmoles) in a mixture of 0.4 N H_2SO_4 (40 ml) and dioxane (50 ml), was refluxed for 90 min, cooled, and stirred with 1.4 g $NaHCO_3$ for 1 hr. Evaporation gave an oily solid, which was triturated with $CHCl_3$ and filtered. The filtrate was dried and evaporated to give an oil 31 (5.71 g, 16.3 mmoles; 98%); TLC, R_f 0.35 ($CHCl_3$–MeOH–H_2O 90:10:1). The product was used directly for acylation to *28*. For analytical purposes, a portion of *31* was converted to the dibenzoate (14); recrystallization from aqueous EtOH gave needles mp 132–133°C.

Anal. Calc. for $C_{31}H_{27}O_8P$ (558.5): C, 66.66; H, 4.87; P. 5.55. Found: C, 66.57; H, 4.73; P, 5.33.

DL-*(1,3/2)-1-O-(Diphenylphosphoryl)-2,3-di-O-palmitoylcyclopentane-1,2,3-triol 28*. METHOD 1. Diacyl triol *27* (2.60 g, 4.37 mmoles) in 25 ml of anhydrous pyridine was phosphorylated (DPPC 2.30 g, 8.56 mmoles) and worked up as described for *18*. The product (3.39 g, 4.10 mmoles, 94%) was chromatographically pure, R_f 0.46 (CCl_4–EtOAc 80:20). Recrystallization from MeOH gave *28* mp 57.5–58°C. METHOD 2. The phosphorylated triol *31* (1.07 g; 3.05 mmoles) in pyridine (30 ml) was acylated with palmitoyl chloride (2.20 g; 8.0 mmoles), and worked up as described for tris-*homo*acyl triols (2). TLC (CCl_4–EtOAc 80:20) showed a major spot R_f 0.46. Purification by silicic acid chromatography gave *28*, 1.40 g (75%) mp 56–57°C.

Anal. Calc. for $C_{49}H_{79}O_8P$ (827.1): C, 71.15; H, 9.63; P, 3.75. Found: C, 71.25; H, 9.37; P, 3.86.

(1,3/2)-1,3-O-Nitrobenzylidenecyclopentane-1,2,3-triol 38. Triol *3* (15 g, 127 mmoles) in 250 ml of toluene was refluxed for 2.5 hr with *p*-nitrobenzaldehyde (22.6 g, 150 mmoles) and *p*-toluenesulfonic acid (50 mg) in an apparatus fitted with a phase-separating head. The hot solution, decanted from the tarry residue, crystallized (25 g) on cooling, and yielded a second crop (1.5 g) on concentration to 100 ml. The crystals were dissolved in 120 ml toluene at 80–85°C, and the clear solution was decanted from a small quantity of dark oil and allowed to crystallize (14.6 g, 58.1 mmoles, 46%); TLC showed a major spot R_f 0.35 ($CHCl_3$–Et_2O 3:1). For analytical purposes the TROC ester was prepared: acetal *38* (200 mg; 0.80 mmoles) in Et_2O (5 ml) and pyridine (1 ml) was

stirred at 0°C with 2,2,2-trichloroethoxychloroformate (200 mg; 0.94 mmoles) for 16 hr. Ice (2 g) was added; the mixture was stirred for 30 min, and the ester was extracted with Et_2O (340 mg; 0.80 mmoles, 100%). TLC ($CHCl_3$–Et_2O 20:1) showed one spot, R_f 0.70. Recrystallization from ether gave yellow crystals, mp 143–144°C.

Anal. Calc. for $C_{15}H_{14}O_7NCl_3$ (426.6): C, 42.23; H, 3.31; N, 3.28; Cl, 24.99. Found: C, 42.31; H, 3.44; N, 3.18, Cl, 24.90.

NMR *38*: δ 2.15 [4], s, ring CH_2; δ 1.90 [1] broad, OH; δ 4.20 [1] s, (broad) ring HOC*H*; δ 4.52 [2] s (broad), ring ethereal–O–CH; δ 5.82 [1], s, benzylidene CH; 7.55–8.26 [4] quartet, aromatic. TROC ester of *38*: δ 2.23 [4] s, (broad) ring CH_2; δ 5.88 [1], s, benzylidene CH; δ 5.05 [1], ester–O–CH; δ 4.78 [4], $COOCH_2CCl_3$ and ring ethereal O–C–H.

IR: *38*: (CCl_4), 3640 cm^{-1}, OH. (KBr) 3350 cm^{-1} (broad), OH; 1350, 1525 cm^{-1}, NO_2; 3060, 1610, 750, 700 cm^{-1}, aromatic.

(1,3/2)-1,3-O-(p-Nitrobenzylidene)-2-O-(diphenylphosphoryl)-cyclopentane-1,2,3-triol 39. Acetal *38* (4.0 g; 16.2 mmoles) was phosphorylated in 30 ml of pyridine with DPPC (6.46 g; 24 mmoles), and *39* was isolated as described above. The oil (7.73 g; 16 mmoles, 99%) was decolorized with charcoal in hot benzene; evaporation gave an oil that crystallized in vacuo, mp 83–88°C. TLC ($CHCl_3$–Et_2O 20:1) showed a major spot R_f 0.60. Recrystallization of a portion (MeOH) removed traces of *p*-nitrobenzaldehyde and gave yellow plates, *39* mp 88–89°C.

Anal. Calc. for $C_{24}H_{22}O_8PN$ (483.4): C, 59.63; H, 4.59; P, 6.41; N, 2.90. Found: C, 59.96; H, 4.57; P, 6.27; N, 2.80.

NMR: δ 7.55–8.26 [4], quartet, $C_6H_4NO_2$; δ 7.30 [10], s, C_6H_5; δ 5.82 [1], s, benzylidene CH; δ 4.92 [1], doublet of triplets, ring POC–H; δ 4.70 [2], s, ring (C-1 and C-3)–H; δ 2.10 [4] s, ring CH_2.

(1,3/2)-2-O-(Diphenylphosphoryl)-cyclopentane-1,2,3-triol 40. The phosphorylated acetal *39* (2.75 g; 5.69 mmoles) in 50 ml EtOH–$CHCl_3$ 3:2 was hydrogenolyzed (Pd–C, 4.0 g). Filtration through Celite and concentration gave a yellow solid that was partitioned between $CHCl_3$ and ice-cold 1 N H_2SO_4. The $CHCl_3$ phase was washed with 5% $NaHCO_3$, dried, and evaporated to give *40* as an oily solid (1.75 g, 88%). TLC ($CHCl_3$–MeOH–H_2O 90:10:1) showed a major spot R_f 0.50. For analytical purposes, a sample was converted to the *bis*-(*p*-nitrobenzoate) derivative: recrystallization (EtOAc) gave yellow needles, mp 195–196°C (partial sublimation at 170°C).

Anal. Calc. for $C_{31}H_{25}O_{12}PN_2$ (648.5): C, 57.41; H, 3.89; N, 4.32, P, 4.78. Found: C, 57.64; H, 3.80; N, 4.31; P, 4.79.

The diol discolored on standing and was therefore used at once in the next stage of synthesis.

(1,3/2)-2-O-(Diphenylphosphoryl)-1,3-di-O-palmitoylcyclopentane-1,2,3-triol 41. The phosphorylated triol *40* (2.63 g, 7.50 mmoles) in 20 ml pyridine was acylated with palmitoyl chloride (5.0 g; 18.2 mmoles) at 0°C. Ice was added (10 g) and after 1 hr *41* was isolated as described for the benzyl diacyl derivative *16*. The oil crystallized on storage (5.71 g, 6.90 mmoles; 92%). TLC (CCl_4–EtOAc 80:20) showed *41* (R_f 0.54), traces of *40* and palmitic acid. An analytical sample was obtained by preparative TLC; the eluted product was recrystallized from MeOH (mp 69–70°C).

Anal. Calc. for $C_{49}H_{79}O_8P$ (827.1): C, 71.15, H, 9.63; P, 3.75. Found: C, 71.39; H, 9.56; P, 3.61.

This work was supported in part by grants AM-07719 and 5TO-GM-35 from the National Institutes of Health and from the American Heart Association, Northeast Ohio Chapter, Inc.. The capable technical assistance of Mary C. Djordjevic and Linda R. Berger in preparing synthetic intermediates is acknowledged. We thank Dr. A. A. Gallo for valuable discussions of some of the stereochemical aspects of these studies.

Manuscript received 25 August 1975 and in revised form 13 September 1976; accepted 11 October 1976.

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