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An Enantioselective Synthesis of Platelet-Activating Factors, Their Enantiomers, and Their Analogues from D- and L-Tartaric Acids

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Acetyl glyceryl ether phosphorylcholines (platelet-activating factors; PAFs), their enantiomers, and their analogues were efficiently synthesized in a stereochemically unambiguous manner starting from D- and L-tartaric acids as chiral synthons. The enantiomer of C_{16}-PAF (*S*-configuration) showed far less activity than the natural PAF (*R*-configuration), and the *N*-methylpiperidine and *N*-methylpyrrolidine analogues were found to possess much higher activity than natural C_{16}-PAF.

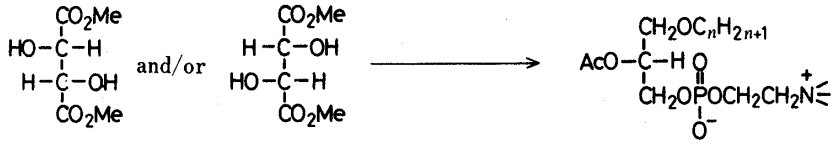
Keywords——platelet-activating factor; enantiomer; platelet-activating factor homologue; D-tartaric acid; L-tartaric acid; hydrogenolysis of benzylidene acetal; D- threitol derivative; L-threitol derivative; 2,3-*O*-isopropylidene-*sn*-glycerol alkylation

Since their isolation and characterization by Hanahan *et al.*[1] and Benveniste *et al.*[2] in 1979, the platelet-activating factors (PAF), acetyl glyceryl ether phosphorylcholines (**2** and **3**), have been the subjects of a great deal of synthetic study, because they act as powerful mediators in such physiological processes as anaphylaxis and inflammation.[3] However, PAFs of animal origin are elusive,[1] and even their chiral synthesis consists of multistep reactions containing some ambiguity in the stereochemistry at the C-2 position of the glycerol, and affording the target molecules in low overall yields. In fact, there is conflicting evidence about the biological activity of natural PAFs and their enantiomers.[4-6] These problems must be resolved in order to understand the mode of action of PAFs, which may involve stereospecific receptors.[7] The previous synthetic methods have used (*R*)-glycerol acetonide as the common intermediate, and D-mannitol,[8] L-ascorbic acid,[9] or L-serine[10] as starting materials, but McClure *et al.*[11] showed that optically active glycerol acetonide easily undergoes acid-catalyzed racemization during the work-up. Therefore, the requirement for a simple, high-yielding, and stereochemically unambiguous synthesis of glyceryl ether phosphorylcholines having the desired absolute configuration remains. We reported in a previous communication[12] an efficient methodology for the preparation of PAF in natural and unnatural forms starting from D- and/or L- tartaric acids. We wish to present here the details of the synthesis of natural PAFs, their enantiomers, and some homologues.

Synthetic Strategy (Chart 1)

The key feature of our approach is the selective transformation of D- and/or L-tartaric acids to the chiral phospholipid skeleton or the chiral glycerol moiety by using one of the two equivalent asymmetric carbons. Both acids are well-known chiral synthons and are readily available. However, synthetic routes which generate the glycerol acetonide[11] must, if possible, be avoided or carefully treated during the work-up in order to retain the stereochemical

integrity of D- and L-tartaric acids in the target molecules. Therefore, it was considered to be essential to protect one of the two hydroxyl groups of the starting acids, since the two hydroxyl groups are equivalent because of the C_2 symmetry of **1a** and **1b**.

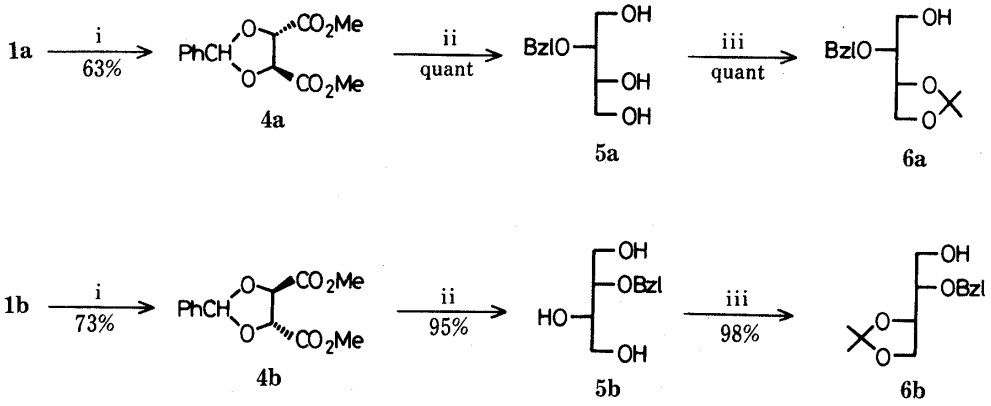


dimethyl D-tartrate **1a** | dimethyl L-tartrate **1b** | **2a**: $n=16$, **3a**: $n=18$

Chart 1

Synthesis of D- and L-Threitol Derivatives (Chart 2)

A two-step procedure was undertaken to protect one of the two equivalent hydroxyl groups. Thus, the dimethylesters, **1a** and **1b**, were separately treated with benzaldehyde to afford dimethyl 2,3-*O*-benzylidene D- and L-tartrates, **4a** and **4b**, respectively, in reasonable yields. Reductive cleavage[13] with $LiAlH_4$–$AlCl_3$ proceeded smoothly at room temperature to afford 2-*O*-benzyl-D- and L-threitols, **5a** and **5b**, almost quantitatively.[14] The vicinal glycols of **5a** and **5b** were protected with 2,2-dimethoxypropane in the presence of *p*-TsOH according to Rapoport's procedure[15] to afford 2-*O*-benzyl-3,4-*O*-isopropylidene D- and L-threitols, **6a** and **6b**, in 63 and 68% overall yields, respectively.



i) PhCHO, *p*-TsOH ii) $LiAlH_4$–$AlCl_3$ (1:1) iii) $\times^{OMe}_{OMe}$, *p*-TsOH

Chart 2

Synthesis of Natural PAF from D-Threitol Derivative 6a (Chart 3)

Now, all of the four hydroxyl groups of **6a** can be differentiated chemically and treated separately. The most straightforward and useful synthesis of natural PAF was achieved by starting with **6a**. This route was designed to incorporate the asymmetric carbon at C-2 of **6a** in the chiral center of natural PAF. The alkylation of the primary alcohol of **6a** proceeded smoothly with *n*-$C_{16}H_{33}OMs$ (1.25 eq) and KH (2.5 eq) in benzene under reflux to afford **7a** in an 88% yield. After the removal of the isopropylidene group with 2 N HCl in tetrahydrofuran (THF) (**7a**→**9a**, 91% yield), the resulting glycol **9a** was subjected to oxidative cleavage with $Pb(OAc)_4$, followed by reduction with $NaBH_4$, affording 2-*O*-benzyl-1-*O*-hexadecyl-*sn*-glycerol

(**11a**) in 80% yield. The final phase of the synthesis was accomplished by the known 4-step procedure:[5,16] (a) $Cl_2P(O)OCH_2CH_2Br$–KCl, (b) Me_3N–AgOAc, (c) H_2–Pd/C, and (d) Ac_2O–Et_3N, resulting in an overall yield of 48% (**11a**→**13a**→**15a**→**17a**→**2a**). The present synthesis consists of 11 steps, and results in overall yields of about 21—25% from **1a** to **2a**; it can be said that the methodology developed here is greatly superior to that from D-mannitol (15 steps, about 5—6% overall yields). C_{18}-PAF **3a** was also prepared from **1a** in an overall yield of about 32% according to the procedures shown in Chart 3 (**6a**→**8a**, 94%; **8a**→**10a**, 95%; **10a**→**12a**, 82%; **12a**→**14a**→**16a**, 78%, **16a**→**18a**, 98%; **18a**→**3a**, 91%). The synthetic PAF **2a** and **3a** showed $[\alpha]_D^{20}$ −3.30° (c=0.53, $CHCl_3$: MeOH=1:1) and $[\alpha]_D^{20}$ −3.46° (c=0.80, $CHCl_3$: MeOH=1:1), respectively.

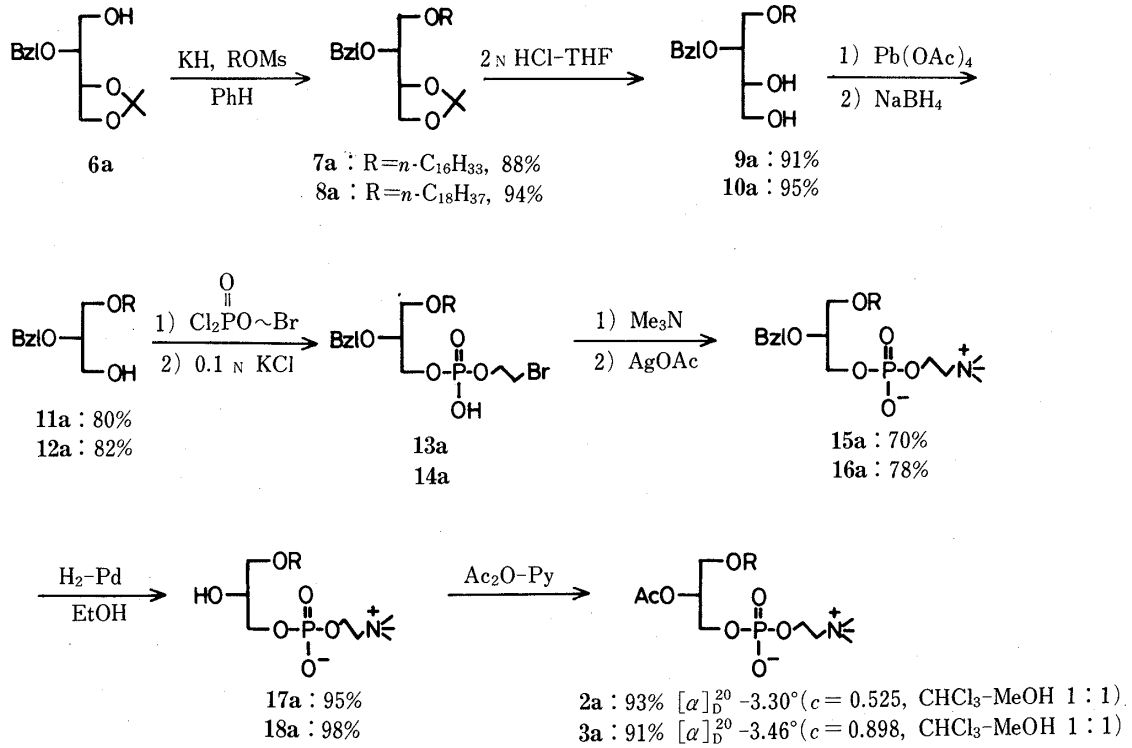


Chart 3. Synthesis of Natural PAF from 2-*O*-Benzyl-3,4-*O*-isopropylidene D-Threitol (**6a**)

Synthesis of Natural PAF from L-Threitol Derivative 6b (Chart 4)

Next, the synthetic routes from the L-tartaric acid series were investigated, since L-tartaric acid is more easily obtainable from argol. There are two reasonable ways to obtain natural PAF from **6b**. One of them is an approach using the asymmetric carbon at C-2 of **6b** by alkylation at O-3 and the introduction of the phosphocholine group at O-1 after the removal of the C-4 carbon. The other is an approach using the asymmetric carbon at C-3 of **6b** by alkylation at O-2 and the introduction of the phosphocholine group at O-3 after the removal of the C-1 carbon. The latter route eventually generates (*R*)-glycerol acetonide as an intermediate; this should be carefully treated during the work-up.[11] Thus, the L-threitol derivative **6b** was tritylated to afford **7b** in 86% yield, but the selective removal of the isopropylidene group proceeded inefficiently to give **8b** in only 32% yield, along with a 52% recovery of **7b**. This difficulty was overcome by employing cyclopentylidene acetal instead of isopropylidene acetal. The glycol of 2-*O*-benzyl-L-threitol (**5b**) was protected with cyclopentylidene acetal, and the primary hydroxyl group of **7c** was further protected with the trityl group to afford **8c** in 57% yield from **5b**. The cyclopentylidene acetal **8c** was easily converted to the

glycol **8b** by treatment with acetic acid. The cleavage of the vicinal glycol of **8b** with $NaIO_4$, followed by reduction with $NaBH_4$, gave **9b** in 92% yield. The alkylation of **9b** (alkylation at O-3 of **6b**) gave **10b** in 85% yield. The subsequent selective removal of the trityl group with *p*-TsOH and successive application of known 4-step procedures[5,16] gave natural C_{16}-PAF in about 14% overall yield from **1b** (13 steps). On the other hand, the glycol **11b** obtained by hydrogenolysis with Pd–C (85% yield) was cleaved with $Pb(OAc)_4$ in benzene at 50 °C for 2 h, and the resulting aldehyde was directly reduced with $NaBH_4$ at room temperature; after work-up with NaOH, the extract was distilled under reduced pressure (2 mm Hg) to afford a colorless oil with $[\alpha]_D^{20}$ −11.0° (c=1.72, MeOH). The optical purity of **12b** was confirmed to be equivalent to that of the (*R*)-glycerol acetonide obtained from L-ascorbic acid.[9] The alkylation of **12b** (alkylation at O-2 of **6b**) gave **13b** in 80% yield, and the isopropylidene group was removed to afford the chiral glycol **14b** in 78% yield. The secondary alcohol was selectively protected by a 3-step procedure (a, TrCl–Py; b, BzlCl–KH; c, *p*-TsOH in MeOH) to afford **16b** in 92% yield. Then, the known 4-step procedure was applied to **16b** to yield natural C_{16}-PAF **2a** from **1b** in about 7% overall yield (15 steps). These procedures are not only as efficient as those shown in Chart 3, but the sequence outlined here may possess a great deal of synthetic flexibility for a wide range of structurally related ether phospholipids.

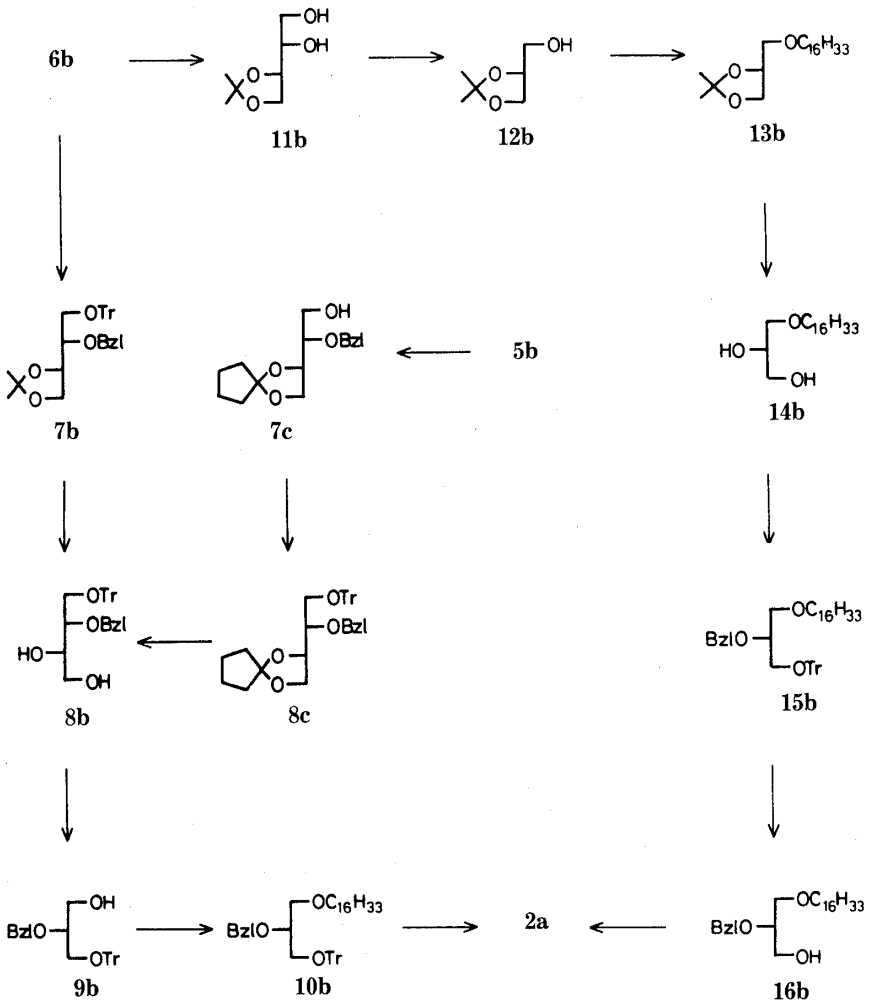


Chart 4. Synthesis of C_{16}-PAF from L-Tartaric Acid

Synthesis of PAF Enantiomers 2b and 3b from L-Tartaric Acid

Now, it is clear that the most straightforward and enantioselective method for the

synthesis of the antipodes of **2a** and **3a** is to start with **6b**. Thus, the enantiomers of C_{16}- and C_{18}-PAF were prepared from **6b** in the manner shown in Chart 3 (11 steps from **1b**; about 20% overall yields). The enantiomers, **2b** and **3b**, of C_{16}- and C_{18}-PAF showed $[\alpha]_D^{20}$ +3.12° (c=2.09, $CHCl_3$: MeOH=1:1) and $[\alpha]_D^{20}$ +3.38° (c=1.60, $CHCl_3$: MeOH=1:1), respectively.

Synthesis of PAF Analogues from 6a and 13a (Charts 5 and 6)

The present methodology can be applied to the synthesis of various PAF analogues[14] with ease and efficiency. Thus, four new analogues (**19a**, **20a**, **21a** and **22a**) of C_{16}-PAF were obtained in 4 steps (30% overall yields) by a modification of the phosphorylcholine moiety starting from **13a**. The 2-*O*-methyl derivative **27a**, which has growth-inhibitory activity on cultured myeloid leukemia cells[17,18] was also prepared in 9 steps (74% overall yield; see the experimental section) from **7a**.

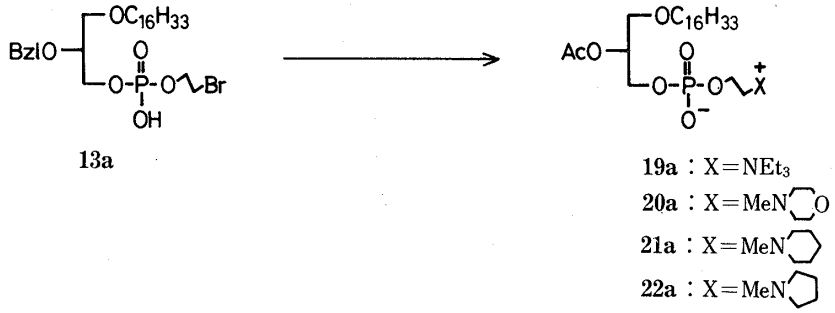


Chart 5. Synthesis of PAF Analogues

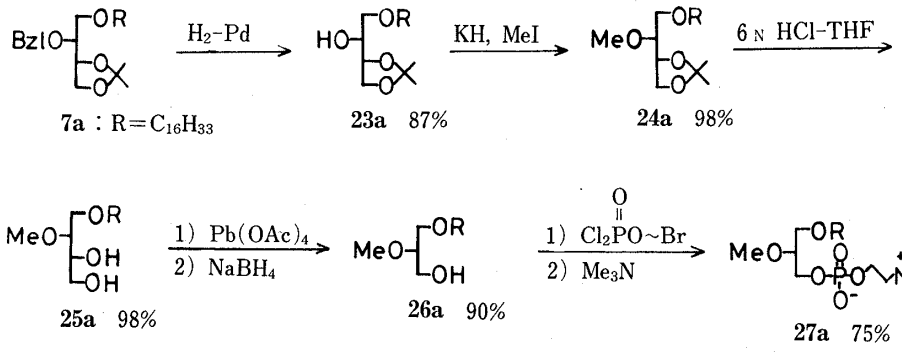


Chart 6. Synthesis of 2-*O*-Methyl Analogue

Biological Activity of Synthetic PAF and the Analogues[19,20]

The biological activities (platelet activation and antihypertension) of synthetic PAF and PAF analogues were investigated. Synthetic analogues were assessed for activity to induce platelet activation by measuring aggregation and the release of ^{14}C-serotonin from rabbit platelets. The preliminary results are summarized in Fig. 1 and Fig. 2.[20]

As shown in Fig. 1 and Fig. 2, the activity of synthetic C_{16}-PAF to induce aggregation and the release of serotonin were found to be equal to that of natural PAF. The C_{16}-PAF enantiomer was far less active than natural PAF. This result clearly demonstrates that the absolute configuration (*R*-form) of PAF is biologically significant.

Table I lists the relative biological activities of various synthetic phospholipids, along with their ability to induce irreversible platelet aggregation and their antihypertension activity[19] in male Wistar strain rats. The activities of the analogues are expressed relative to

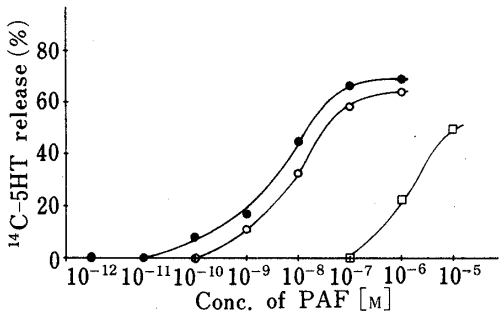


Fig. 1. ^{14}C-Serotonin Release from Rabbit Platelets Induced by Various PAFs

—●—, C_{16}-PAF; —○—, C_{18}-PAF; —□—, C_{16}-PAF enantiomer.

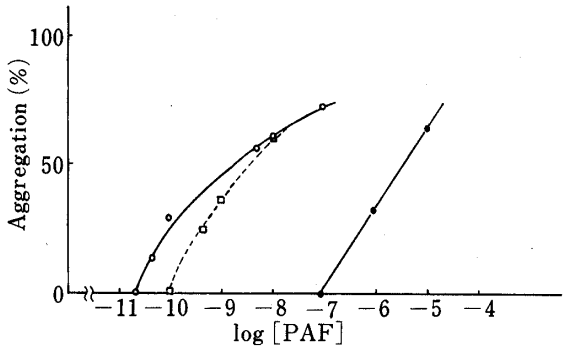


Fig. 2. Platelet Aggregating Activity of Synthetic PAF and Its Enantiomer

---□---, natural PAF; —○—, synthetic C_{16}-PAF; —●—, synthetic C_{16}-PAF enantiomer.

TABLE I. Biological Activities of Synthetic PAFs

	Relative activity	
	Platelet activation	Antihypertension
(−)-C_{16}-PAF	1	1
(+)-C_{16}-PAF	10^{-3}	$\sim 10^{-2}$
19a	10^{-2}	10^{-1}
20a	1	1
21a	10	3
22a	10	3

that of C_{16}-PAF (reciprocals of the concentrations required). Compounds **21a** and **22a** were about 10 times more active than the parent C_{16}-PAF in inducing platelet activation. The activity of the triethyl analogue (**19a**) was much less than that of C_{16}-PAF.[20]

Experimental Section

All the reactions were performed under an argon atmosphere unless otherwise specified, using a standard syringe technique for the transfer of materials. The solvents were generally redistilled before use. Tetrahydrofuran and ether were dried over sodium and distilled before use, with benzophenone ketyl as an indicator. Thin-layer chromatography (TLC) was performed on Merck 60 F_{254} (0.25 mm) sheets, and spots were visualized with molybdophosphoric acid in sulfuric acid. Wako-gel C200 was employed for the column chromatography. The melting points were determined with a Yamato MP-21 apparatus and are uncorrected. The infrared (IR) spectra were recorded with a JEOL A-102 spectrometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at 60 MHz (Hitachi R-600), 100 MHz (JEOL J-NM-FX100), or 400 MHz (JEOL J-NM-FX400). Unless otherwise indicated, the spectra were measured at 100 MHz; the chemical shift values (δ) are reported in parts per million downfield from tetramethylsilane as the internal standard. The coupling constants (J) are given in hertz (Hz), with the following abbreviations used for the splitting patterns: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The optical rotations were measured with a JASCO DIP-140 polarimeter. The mass spectra (MS) were recorded with a JEOL JMS-DX300 apparatus.

4*S*, 5*S*-4,5-Bis(methoxycarbonyl)-2-phenyl-1,3-dioxolane (4a)——A mixture of dimethyl D-tartrate (17.8 g, 0.1 mol), benzaldehyde (159 g, 1.5 mol), and *p*-toluenesulfonic acid monohydrate (380 mg, 2 mmol) in dry toluene (50 ml) was heated under reflux, with the azeotropic removal of water, for 2 h. After the addition of triethylamine (1 ml) to the cooled reaction mixture, the toluene and benzaldehyde were distilled off under reduced pressure. The resulting solid residue was recrystallized from chloroform–hexane to afford 16.8 g (63%) of **4a** as white crystals; mp 73—74.5 °C; bp 147—149 °C (0.15 mmHg), $[\alpha]_D^{23}$ +46.3° (c = 1.02, MeOH). NMR ($CDCl_3$): 3.83 (s, 3H), 4.85 (d, J = 5 Hz, 1H), 4.97 (d, J = 5 Hz, 1H), 6.12 (s, 1H), 7.3—7.6 (m, 5H). IR (KBr): 2970, 2940, 2840, 1740 cm^{-1}. *Anal.*

Calcd for $C_{13}H_{14}O_6$: C, 58.62; H, 5.30. Found: C, 58.85; H, 5.17.

2-*O*-Benzyl-D-threitol (5a)——The acetal **4a** (10 g, 0.038 mol) in dry dichloromethane (80 ml) was added, over a 30 min period, to a vigorously stirred suspension of $LiAlH_4$ (9.1 g, 0.24 mol) in dry ether (100 ml)–dry dichloromethane (50 ml) at 0 °C. The resulting suspension was stirred for an additional 30 min, then aluminum trichloride (31.9 g, 0.24 mol) in dry ether (200 ml) was added over a 10 min period at room temperature. After being heated under reflux for 1 h, the reaction mixture was cooled to 0 °C, diluted with tetrahydrofuran (500 ml), and quenched with water (18 ml), a 15% aqueous solution of NaOH (100 ml), and water (54 ml). The suspension was stirred for 1 h, and the resulting white precipitate was filtered with celite and washed with tetrahydrofuran (500 ml). The filtrate and washings were combined, and dried over anhydrous sodium sulfate. Removal of the solvent gave 8.0 g (99%) of **5a** as white crystals, which were used for the following step without any further purification. To obtain an analytical sample, **5a** was recrystallized from benzene; mp 69—72 °C, $[\alpha]_D^{23}$ −15.2° (c=0.96, MeOH). NMR ($CDCl_3$): 3.3—3.6 (m, 4H), 3.6—3.9 (m, 5H), 4.46 (d, J=12 Hz, 1H), 4.63 (d, J=12 Hz, 1H), 7.27 (s, 5H). IR (KBr): 3300, 1450 cm^{-1}. *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.37; H, 7.72.

2-*O*-Benzyl-3,4-*O*-isopropylidene-D-threitol (6a)——A mixture of **5a** (1.06 g, 5 mmol), 2,2-dimethoxypropane (0.78 g, 7.5 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) was heated under reflux, using a Soxhlet extractor containing freshly prepared molecular sieves 4A (2 g), for 1 h. Then triethylamine (1 ml) was added, and the reaction mixture was cooled, then concentrated to afford crude **6a**, which was subsequently purified by silica-gel column chromatography to afford 1.26 g (98%) of **6a** as a colorless oil; $[\alpha]_D^{22}$ +16.6° (c=1.30, $CHCl_3$). NMR ($CDCl_3$): 1.38 (s, 3H), 1.44 (s, 3H), 2.24 (br s, 1H), 3.4—3.76 (m, 3H), 3.89 (dd, J=8, 7.1 Hz, 1H), 4.01 (dd, J=8, 6.5 Hz, 1H), 4.28 (m, 1H), 4.72 (d, J=11.8 Hz, 1H), 7.33 (s, 5H). IR (neat): 3450, 2900, 2860, 1380, 1370 cm^{-1}. MS m/e: 252 (M^+).

2-*O*-Benzyl-3,4-*O*-isopropylidene-L-threitol (6b)——The threitol derivative **6b** was prepared in a manner similar to that described for the preparation of the D-threitol derivative **6a**. All of the spectral data of the L-series compounds were confirmed to be identical with those of the D-series except for the optical rotations. The yields and optical rotations were as follows; 3*S*,4*S*-3,4-bis(methoxycarbonyl)-2-phenyldioxolane (**4b**): yield, 73%, $[\alpha]_D^{20}$ −47.2° (c=1.00, MeOH); 2-*O*-benzyl-L-threitol (**5b**): yield, 95%, $[\alpha]_D^{22}$ +15.7° (c=1.00, MeOH); 2-*O*-benzyl-3,4-*O*-isopropylidene-L-threitol (**6b**): yield, 98%, $[\alpha]_D^{22}$ −16.8° (c=1.31, $CHCl_3$). MS m/e: 252 (M^+).

1-*O*-Alkyl-2-*O*-benzyl-3,4-*O*-isopropylidene-D-threitol, 7a and 8a——A 22% potassium hydride oil dispersion (5 ml, 25 mmol) was slowly added to a solution of **6a** (2.52 g, 10 mmol) dissolved in benzene (20 ml) at room temperature. The reaction mixture was stirred at room temperature for an additional 30 min, and then hexadecylmethanesulfonate (4 g, 12.5 mmol) in benzene (10 ml) was added. The reaction mixture was heated under reflux for 2 h, cooled to 0 °C, diluted with hexane (10 ml), and quenched by the successive addition of EtOH (1 ml) and water (5 ml). The organic layer was separated, and the aqueous layer was washed with benzene. The combined organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography (benzene) to afford 4.14 g (88%) of **7a** as a colorless oil. NMR ($CDCl_3$): 0.88 (t, J=7 Hz, 3H), 1.26 (s, 26H), 1.37 (s, 3H), 1.42 (s, 3H), 1.42—1.68 (m, 2H), 3.41 (t, J=7 Hz, 2H), 3.48—4.10 (m, 5H), 4.10 (m, 1H), 4.74 (s, 2H), 7.24—7.42 (m, 5H). IR (neat): 3450, 2920, 2860, 1455, 1370 cm^{-1}. MS m/e: 476 (M^+).

In a similar manner, **8a** was obtained from **6a** and octadecylmethanesulfonate in 94% yield. $[\alpha]_D^{24}$ +0.73° (c=1.15, $CHCl_3$). NMR ($CDCl_3$): 0.88 (t, J=7 Hz, 3H), 1.27 (s, 30H), 1.37 (s, 3H), 1.42 (s, 3H), 1.48—1.74 (m, 2H), 3.41 (t, J=7 Hz, 2H), 3.55—4.07 (m, 5H), 4.2 (m, 1H), 4.75 (s, 2H), 7.32 (s, 5H). IR (neat): 2920, 2860, 1455, 1370 cm^{-1}. MS m/e: 504 (M^+).

1-*O*-Alkyl-2-*O*-benzyl-D-threitol, 9a and 10a——The *O*-alkylated derivative **7a** (3.65 g, 7.7 mmol) was stirred in tetrahydrofuran (300 ml) and 2 N HCl (150 ml) at room temperature for 3 h. The solution was concentrated to a small volume (30 ml) under reduced pressure. After water (20 ml) had been added, the mixture was extracted with ethyl acetate (50 ml × 3). The combined extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica gel to give 3.04 g (91%) of **9a** as white crystals. mp 40—44 °C (hexane), $[\alpha]_D^{20}$ −6.19° (c=1.0, MeOH). NMR ($CDCl_3$): 0.88 (t, J=7 Hz, 3H), 1.27 (s, 26 H), 1.38—1.70 (m, 2H), 3.42 (t, J=7 Hz, 2H), 3.5—3.9 (m, 6H), 4.55 (d, J=12 Hz, 1H), 4.72 (d, J=12 Hz, 1H), 7.32 (s, 5H). IR (KBr): 3300, 2920, 2860, 1460 cm^{-1}. MS m/e: 436 (M^+).

In a similar manner, **10a** was obtained in 95% yield from **8a**. mp 44—46 °C, $[\alpha]_D^{17}$ −6.21° (c=1.62, MeOH). NMR ($CDCl_3$): 0.88 (t, J=7 Hz, 3H), 1.27 (s, 3OH), 1.4—1.7 (m, 2H), 2.4 (br s, 2H), 3.3—4.0 (m, 8H), 4.66 (d, J=12 Hz, 1H), 4.73 (d, J=12 Hz, 1H), 7.35 (s, 5H). MS m/e: 464 (M^+).

1-*O*-Alkyl-2-*O*-benzyl-*sn*-glycerol, 11a and 12a——Under vigorous stirring, **10a** (1.69 g, 4 mmol) in benzene (50 ml) was added to a solution of lead tetraacetate (2.58 g, 5.8 mmol) in benzene (50 ml) over a 2 h period at room temperature. After being stirred for an additional hour, the reaction mixture was cooled to 0 °C and saturated aqueous sodium bicarbonate was added. The resulting insoluble material was filtered on celite and washed with benzene. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated to afford 1.6 g (quant.) of the crude aldehyde as a colorless oil. This was used without further purification for the next step. Sodium borohydride (300 mg, 8 mmol) was slowly added to a solution of the crude aldehyde (1.6 g, 4 mmol) in methanol (10 ml) and tetrahydrofuran (20 ml) at room temperature. The reaction mixture was then allowed to stand at room

temperature overnight, cooled to 0 °C, acidified with dil. hydrochloric acid, and concentrated to dryness under reduced pressure. The product was extracted with ethyl acetate (30 ml × 3), and the organic layer was dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was chromatographed on silica gel to afford 1.30 g (80%) of **11a** as a colorless oil. $[\alpha]_D^{21}$ −1.15° (c=0.95, MeOH). NMR ($CDCl_3$): 0.88 (t, J=7 Hz, 3H), 1.27 (s, 26H), 1.38—1.73 (m, 2H), 2.20 (br s, 1H), 3.43 (t, J=7 Hz, 2H), 3.5—3.76 (m, 5H), 4.58 (d, J=12 Hz, 1H), 4.75 (d, J=12 Hz, 1H), 7.32 (s, 5H). IR (neat): 3400, 2910, 2840, 1460, 1450 cm^{-1}. MS m/e: 406 (M^+).

In a similar manner, **12a** was prepared from **10a** in 82% yield. mp 25—27 °C, $[\alpha]_D^{20}$ −1.02° (c=2.88, MeOH), −8.51° (c=7.20, C_6H_6). NMR ($CHCl_3$): 0.88 (t, J=7 Hz, 3H), 1.27 (s, 30H), 1.38—1.74 (m, 2H), 2.14 (br s, 1H), 3.2—3.8 (m, 7H), 4.66 (s, 1H), 4.69 (s, 1H), 7.33 (s, 5H). IR ($CHCl_3$): 3300, 2910, 2840 cm^{-1}. MS m/e: 434 (M^+).

2-Bromoethyl 2-*O*-Benzyl-L-1-*O*-hexadecyl-glyceryl Hydrogen Phosphate (13a)——A mixture of **11a** (128 mg, 0.32 mmol), 2-bromoethyl phosphoryl dichloride (116 mg, 0.48 mmol) and triethylamine (202 mg, 2 mmol) in chloroform (7 ml) was stirred at room temperature for 6 h and then at 40 °C for 12 h. After cooling, the reaction mixture was treated with 10 ml of 0.1 N KCl; the mixture was then vigorously stirred for 1 h. After the addition of 10 ml of methanol, the organic layer was separated. The aqueous layer was acidified to pH 3.0 with conc. hydrochloric acid and extracted again with chloroform. The combined organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent, the residue was chromatographed on silica gel to afford 135 mg (71%) of **13a** as a slightly yellowish oil. NMR ($CDCl_3$): 0.88 (t, °J=7 Hz, 3H), 1.27 (s, 26H), 1.38—1.73 (m, 2H), 2.0 (br, 1H), 3.2—3.9 (m, 7H), 4.0—4.4 (m, 4H), 4.65 (s, 2H), 7.33 (s, 5H). IR (neat): 3400, 2940, 2860, 1680 cm^{-1}.

1-*O*-Alkyl-2-*O*-benzyl-*sn*-glycero(3)phosphocholines, 15a and 16a——A solution of **13a** (135 mg, 2.27 mmol) and trimethylamine (2 ml) in methanol (4 ml) was heated to 55 °C in a sealed tube overnight. After the removal of the solvent, silver acetate (500 mg, 3.0 mmol) in 90% aqueous methanol (20 ml) was added, and the reaction mixture was stirred for 2 h. The resulting precipitate was removed by filtration, and the filtrate was concentrated to give crude **15a**. This product was purified by silica gel column chromatography to afford 132 mg (quant.) of the hexadecyl derivative **15a** as a white, amorphous solid. mp *ca.* 200 °C, $[\alpha]_D^{20}$ +2.41° (c=2.32, MeOH). NMR ($CDCl_3$: CD_3OD=5:1): 0.88 (t, J=7 Hz, 3H), 1.26 (s, 26H), 1.38—1.7 (m, 2H), 3.09 (s, 9H), 3.28—3.64 (m, 9H), 3.88—4.10 (m, 2H), 4.69 (s, 2H), 7.23 (s, 5H). IR (KBr): 3390, 3070, 3040, 2930, 2860, 1660, 1460, 1230 cm^{-1}. FD-MS m/e: 675 (M^+ + choline), 594 (M^+ + Na), 572 (M^+ + 1), 104 (choline).

In a similar manner, the octadecyl derivative **16a** was prepared from **12a** through **14a** in 78% yield. mp 220 °C (dec.), $[\alpha]_D^{20}$ +2.24° (c=2.18, MeOH). NMR ($CDCl_3$: CD_3OD=4:1) 0.88 (t, J=7 Hz, 3H), 1.27 (s, 30H), 1.38—1.70 (m, 2H), 3.09 (s, 9H), 3.28—3.64 (m, 9H), 3.88—4.1 (m, 2H), 4.69 (s, 2H), 7.23 (s, 5H). IR (KBr): 3400, 2920, 2850, 1660, 1460, 1230 cm^{-1}.

1-*O*-Alkyl-*sn*-glycero(3)phosphocholine (Lyso PAF), 17a and 18a——A mixture of **15a** (120 mg, 0.2 mmol) and palladium black (15 mg) in ethanol (10 ml) was vigorously stirred under a hydrogen atmosphere (1 atm) for 3 d at 50 °C. The catalyst was then filtered off. The filtrate was concentrated, and the residue was chromatographed on silica gel to give 97 mg (95%) of **17a** as a white powder. $[\alpha]_D^{20}$ −6.03° (c=1.04, $CHCl_3$: MeOH=1:1), −400° (c=2.08, MeOH). NMR ($CDCl_3$: CD_3OD=3:1): 0.88 (t, J=7 Hz, 3H), 1.26 (s, 26H), 1.38—1.7 (m, 2H), 3.21 (s, 9H), 3.3—3.76 (m, 9H), 3.94 (m, 2H). IR (KBr): 3420, 2940, 2850, 1465^{-1}. FD-MS m/e: 482 (M^+ + 1).

In a similar manner, **18a** was prepared in 98% yield from **16a**. mp 240 °C (dec.), $[\alpha]_D^{20}$ −4.65° (c=1.00, $CHCl_3$: MeOH=1:1), −3.84° (c=2.00, MeOH). NMR ($CDCl_3$: CD_3OD=3:1): 0.88 (t, J=7 Hz, 3H), 1.26 (s, 30H), 1.38—1.7 (m, 2H), 3.21 (s, 9H), 3.3—3.76 (m, 9H), 3.94 (m, 2H). IR (KBr): 3400, 2900, 2840, 1650, 1460, 1230, 1050 cm^{-1}. FD-MS m/e: 510 (M^+ + 1).

2-*O*-Acetyl-1-*O*-hexadecyl-*sn*-glycero(3)phosphocholine (2a) and 2-*O*-Acetyl-1-*O*-octadecyl-*sn*-glycero(3)phosphocholine (3a)——A solution of **17a** (100 mg, 0.2 mmol) in acetic anhydride (2 ml) was mixed with 0.5 ml of pyridine at 0 °C, after which the reaction mixture was heated to 70 °C for 2 h, then cooled to 50 °C. Pyridine and acetic anhydride were removed under reduced pressure, and the resulting residue was chromatographed on silica gel to afford 100 mg (93%) of C_{16}-PAF (**2a**) as a white, amorphous solid. mp 247 °C (dec.), $[\alpha]_D^{21}$ −3.30° (c=0.53, $CHCl_3$: MeOH=1:1), −3.66° (c=0.71, $CHCl_3$), NMR (400 MHz, CD_3OD): 0.89 (t, J=7 Hz, 3H), 1.28 (s, 26H), 1.54 (m, 2H), 2.07 (s, 3H), 3.22 (s, 9H), 3.45 (t, J=7 Hz, 2H), 3.59 (d, J=5 Hz, 2H), 3.64 (m, 2H), 4.00 (m, 2H), 4.26 (m, 2H), 5.13 (quintet, J=5 Hz, 1H). IR (KBr): 3420, 2920, 2850, 1732, 1627, 1465, 1374, 1235 cm^{-1}. FD-MS m/e: 627 (M^+ + choline), 525 (M^+ + 2), 104 (choline).

In a similar manner, C_{18}-PAF (**3a**) was prepared in 91% yield. mp 212—215 °C (dec.), $[\alpha]_D^{20}$ −4.00° (c=0.71, $CHCl_3$), −3.46° (c=0.90, $CHCl_3$: MeOH=1:1). NMR ($CDCl_3$: CD_3OD=3:1): 0.89 (t, J=7 Hz, 3H), 1.28 (s, 30H), 1.38—1.66 (m, 2H), 2.07 (s, 3H), 3.22 (s, 9H), 3.28—3.70 (m, 6H), 3.88—4.10 (m, 2H), 4.10—4.4 (m, 2H), 5.13 (quintet, J=5 Hz, 1H). IR (KBr): 3400, 2910, 2840, 1730 cm^{-1}. FD-MS m/e: 552 (M^+ + 1), 104 (choline).

2-*O*-Acetyl-3-*O*-hexadecyl-*sn*-glycero(1)phosphocholine (2b) and 2-*O*-Acetyl-3-*O*-octadecyl-*sn*-glycero(1)phosphocholine (3b) (PAF Enantiomers)——The (PAF) enantiomers, **2b** and **3b**, were prepared from **6b** by methods similar to these described for the preparation of the natural PAFs, **2a** and **3a**. The spectral data of the intermediates were identical with those of the D-series. Therefore, only the yields and important optical rotations of the intermediates will be described here. 2-*O*-Benzyl-1-*O*-hexadecyl-3,4-*O*-isopropylidene L-threitol, 90%; 2-*O*-benzyl-1-*O*-hexadecyl L-threitol, 100%, $[\alpha]_D^{20}$ +6.16° (c=0.99, MeOH); 2-*O*-benzyl-1-*O*-hexadecyl D-glyceraldehyde,

100%; 2-*O*-benzyl-3-*O*-hexadecyl-*sn*-glycerol, 98%, $[\alpha]_D^{20}$ +1.10° (*c*=0.85, MeOH); 2-*O*-benzyl-3-*O*-hexadecyl-*sn*-glycero(1)phosphocholine, 65%, $[\alpha]_D^{20}$ −2.68° (*c*=1.78, MeOH); 3-*O*-hexadecyl-*sn*-glycero(1)phosphocholine, 100%, $[\alpha]_D^{20}$ +6.07° (*c*=1.99, $CHCl_3$: MeOH=1:1); C_{16}-enantiomer **2b**, 74%, $[\alpha]_D^{20}$ +3.12° (*c*=2.09, $CHCl_3$: MeOH=1:1); 2-*O*-benzyl-3,4-*O*-isopropylidene-1-*O*-octadecyl L-threitol, 94%, $[\alpha]_D^{20}$ −0.44°(*c*=1.16, $CHCl_3$); 2-*O*-benzyl-1-*O*-octadecyl L-threitol, 91%, $[\alpha]_D^{20}$ +6.21° (*c*=1.62, MeOH); 2-*O*-benzyl-3-*O*-octadecyl-*sn*-glycerol, 80%; 2-*O*-benzyl-3-*O*-octadecyl-*sn*-glycero(1)phosphocholine, 78%, $[\alpha]_D^{20}$ −3.51° (*c*=1.00, $CHCl_3$: MeOH=1:1) and $[\alpha]_D^{20}$ −2.55° (*c*=1.62, MeOH); 3-*O*-octadecyl-*sn*-glycero(1)phosphocholine, 100%, $[\alpha]_D^{20}$ +4.40° (*c*=1.23, MeOH); C_{18}-enantiomer **3b**, 100%, $[\alpha]_D^{20}$ +3.38° (*c*=1.60, $CHCl_3$: MeOH=1:1).

3,4-*O*-Isopropylidene-L-threitol (11b)——A mixture of **6b** (504 mg, 2 mmol) and palladium black (10 mg) in ethanol (10 ml) was stirred under a hydrogen atmosphere for 2 h at room temperature. The catalyst was then filtered off, and the filtrate was concentrated to afford **11b** (277 mg, 85%) as a colorless oil. NMR ($CDCl_3$): 1.37 (s, 3H), 1.45 (s, 3H), 3.22 (br s, 2H), 3.44—4.28 (m, 6H). IR (neat): 3400, 2960, 2910, 2850, 1450, 1375, 1365 cm^{-1}.

2,3-*O*-Isopropylidene-*sn*-glycerol (12b)——A solution of **11b** in ethyl acetate (3 ml) and benzene (17 ml) was slowly added to a solution of lead tetraacetate (1.72 g, 3.9 mmol) in benzene at 50 °C. The reaction mixture was stirred at 50 °C for 1 h, then cooled to 10 °C. The insoluble materials were filtered off, and the filtrate was treated with sodium borohydride (980 mg, 26 mmol) in ethanol (80 ml). The reaction mixture was stirred at room temperature for 5 h, then sodium hydroxide (100 mg) was added, and the mixture was stirred for 30 min more. Next, 40 ml of a 1 N sodium hydroxide solution was added, and the product was extracted with ether (100 ml × 3). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was subjected to distillation to afford **12b** (104 mg, 46%); a colorless oil. bp 110—130 °C (bath temp.)/2 mmHg, $[\alpha]_D^{21}$ −11.0° (*c*=1.72, MeOH). NMR ($CDCl_3$): 1.39 (s, 3H), 1.44 (s, 3H), 2.43 (br s, 1H), 3.5—4.5 (m, 5H). IR (neat): 3400, 2960, 2910, 2850, 1375, 1365 cm^{-1}.

1-*O*-Hexadecyl-2,3-*O*-isopropylidene-*sn*-glycerol (13b)——A solution of **12b** (86 mg, 0.65 mmol) in benzene (5 ml) was added to a suspension of sodium hydride (60% in mineral oil, 40 mg, 0.98 mmol) in benzene (5 ml). After the evolution of hydrogen had stopped, hexadecylmethanesulfonate (250 mg, 0.78 mmol) in benzene (7 ml) was added, and the reaction mixture was heated under reflux overnight. The excess sodium hydride was treated with ethanol (1 ml), and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to afford **13b** (186 mg, 80%) as a white wax. mp 70—71 °C, $[\alpha]_D^{20}$ −16.4° (*c*=1.77, hexane). NMR ($CDCl_3$): 0.90 (t, *J*=7 Hz, 3H), 1.27 (s, 26H), 1.39 (s, 3H), 1.46 (s, 3H), 1.50—1.65 (m, 2H), 3.4—4.2 (m, 7H). IR (KBr): 2910, 2840, 1460, 1380, 1370, 1120 cm^{-1}.

1-*O*-Hexadecyl-*sn*-glycerol (14b)——The hexadecyl derivative **13b** (72 mg, 0.2 mmol) in tetrahydrofuran (3 ml) was treated with 2 N HCl at room temperature overnight. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to afford **14b** (50 mg, 78%) as white crystals. mp 64—66 °C (recrystallized from acetone), $[\alpha]_D^{20}$ +2.52° (*c*=0.92, $CHCl_3$). NMR ($CDCl_3$): 0.90 (br t, 3H), 1.28 (s, 26H), 1.4—1.7 (m, 2H), 3.3—4.0 (m, 7H), 4.26 (br s, 2H). IR (KBr): 3400, 3320, 3240 cm^{-1}. *Anal.* Calcd for $C_{19}H_{40}O_3$: C, 72.10; H, 12.74. Found: C, 71.88: H, 12.98.

1-*O*-Hexadecyl-3-*O*-trityl-*sn*-glycerol (14c)——A mixture of **14b** (90 mg, 0.28 mmol), trityl chloride (396 mg, 1.42 mmol), and 4,4-dimethylaminopyridine (15 mg) in pyridine (20 ml) was heated to 100 °C for 3 h. The cooled reaction mixture was poured into ice water, and the product was extracted with ether (20 ml × 3). The ethereal layer was successively washed with cold 0.2 N hydrochloric acid, water, and 5% aqueous sodium bicarbonate, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to afford a trityl derivative **14c** (146 mg, 92%) as a syrup. NMR ($CDCl_3$): 0.90 (br t, 3H), 1.26 (s, 26H), 1.4—1.72 (m, 2H), 2.46 (d, *J*=6 Hz, 1H), 3.08—3.65 (m, 6H), 3.76—4.10 (m, 1H), 6.9—7.6 (m, 15H). IR (neat): 3400, 3050, 3020, 2910, 2840, 1600 cm^{-1}.

2-*O*-Benzyl-1-*O*-hexadecyl-3-*O*-trityl-*sn*-glycerol (15b)——A 22% potassium hydride oil dispersion (0.72 ml, 0.48 mmol) was added to a solution of **14c** (134 mg, 0.24 mmol) in benzene at room temperature. The reaction mixture was stirred at room temperature for 30 min and then treated with benzyl chloride (54 mg, 0.48 mmol). The whole was heated underreflux overnight. The mixture was cooled to room temperature, and ethanol (1 ml) was added to destroy the excess potassium hydride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica gel to afford **15b** (156 mg, quant.) as a colorless syrup. NMR ($CDCl_3$): 0.90 (br t, *J*=7 Hz, 3H), 1.26 (s, 26H), 1.4—1.72 (m, 2H), 3.0—3.8 (m, 7H), 4.60 (s, 2H), 7.18—7.52 (m, 20H). IR (neat): 3040, 3010, 2940, 2860, 1950, 1820 cm^{-1}. MS *m/e*: 647 (M^+-1).

2-*O*-Benzyl-1-*O*-hexadecyl-*sn*-glycerol (16b)——A mixture of **15b** (90 mg, 0.14 mmol) and *p*-toluenesulfonic acid monohydrate (7 mg) in 95% methanol was heated under reflux overnight, then cooled to room temperature, and the insoluble materials were filtered off and washed with methanol. The combined methanol solution was concentrated, and the residue was chromatographed on silica gel to afford **16b** (56 mg, 92%). This was confirmed to be identical with the product obtained from the D-threitol derivative **6a**.

2-*O*-Benzyl-3,4-*O*-cyclopentylidene-L-threitol (7c)——Triethylorthoformate (1.5 ml, 9 mmol) in toluene (10 ml) was reacted with cyclopentanone (6 ml) in the presence of *p*-TsOH at 0 °C, after which the reaction mixture was

stirred at room temperature for 2 h. Next, **5b** (1.2 g, 5.7 mmol) was added, and the whole was stirred at room temperature for 24 h. Triethylamine (1 ml) was added, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to afford **7c** (1.22 g, 77%) as a slightly yellowish oil. $[\alpha]_D^{20}$ −4.03° (c=1.34, $CHCl_3$). NMR ($CDCl_3$): 1.5—2.0 (m, 8H), 2.20 (br s, 1H), 3.48—4.5 (m, 6H), 4.72 (s, 1H), 7.32 (s, 5H). IR (neat): 3400, 2940, 2860, 1450, 1430, 1335, 1200, 1100 cm^{-1}. MS m/e: 278 (M^+).

2-*O*-Benzyl-3,4-*O*-cyclopentylidene-1-*O*-trityl-L-threitol (8c)——A mixture of **7c** (278 mg, 1 mmol), trityl chloride (557 mg, 2 mmol), and 4,4-dimethylaminopyridine (10 mg) in pyridine (5 ml) was stirred overnight at 50 °C. The reaction mixture was cooled and poured into ice water, and the product was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on silica gel to afford **8c** (387 mg, 74%) as white crystals. mp 90—92 °C. NMR ($CDCl_3$): 1.5—2.0 (m, 8H), 3.12—4.50 (m, 6H), 7.10—7.64 (m, 20H). IR (neat): 3070, 3040, 2960, 2890, 1600, 1495, 1450, 1317 cm^{-1}. MS m/e: 520 (M^+).

2-*O*-Benzyl-1-*O*-trityl-L-threitol (8b)——A solution of **8c** (222 mg, 0.43 mmol) in ethanol (15 ml) and acetic acid (15 ml) was stirred at room temperature for 2 d. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to afford **8b** (173 mg, 90%), along with **8c** (11 mg, 5%). NMR ($CDCl_3$): 2.16 (br s, 2H), 3.14—4.08 (m, 6H), 4.42 (d, J=12 Hz, 1H), 4.72 (d, J=12 Hz, 1H), 7.04—7.62 (m, 20H). IR (neat): 3360, 3020, 2980, 2880, 2830, 1480, 1435, 1205 cm^{-1}.

2-*O*-Benzyl-3-*O*-trityl-*sn*-glycerol (9b)——Sodium metaperiodate (208 mg, 0.97 mmol) was added to a solution of **8b** (296 mg, 0.65 mmol) in 90% aqueous methanol at 0 °C. The mixture was stirred at 0 °C for 2 h, then sodium borohydride (50 mg, 1.32 mmol) was added in small portions. The reaction mixture was stirred at 0 °C for 2 h and quenched with water (10 ml). The product was extracted with ethyl acetate (30 ml × 4), and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to afford **9b** (254 mg, 92%) as a colorless syrup. NMR ($CDCl_3$): 2.0 (br s, 1H), 3.15—3.45 (m, 2H), 3.50—3.86 (m, 3H), 4.57 (d, J=12 Hz, 1H), 4.61 (d, J=12 Hz, 1H), 7.07—7.70 (m, 20H). IR (neat): 3360, 3020, 2980, 2880, 2830, 1480, 1435, 1205, 1160 cm^{-1}. MS m/e: 347 (M^+ − Ph).

2-*O*-Benzyl-1-*O*-hexadecyl-*sn*-glycerol (10b)——The hexadecyl derivative **10b** was prepared from **9b** in a manner similar to that described for the alkylation of **6a**. It was confirmed to be identical with the product obtained from **14b**.

PAF Analogues, 19a, 20a, 21a, and 22a——These analogues were prepared from **13a** in a manner similar to that described for the preparation of natural C_{16}-PAF (**2a**). The overall yields and spectral data were as follows. Triethylamine homologue **19a**: 30%, mp 183—185 °C (dec.), $[\alpha]_D^{20}$ −3.37° (c=0.80, $CHCl_3$: MeOH=1:1). NMR ($CDCl_3$): 0.88 (t, J=7 Hz, 3H), 1.28 (s, 26H), 1.40 (t, J=7 Hz, 9H), 1.40—1.60 (m, 2H), 2.08 (s, 3H), 3.11 (m, 6H), 3.34—4.40 (m, 10H), 5.12 (m, 1H). IR (KBr): 3450, 2910, 2840, 1730, 1235, 1085 cm^{-1}. MS (FAB, 6KV, glycerine): 566 (M^++1). *N*-Methylmorpholine homologue **20a**: 28%, $[\alpha]_D^{21}$ −1.40° (c=1.0, $CHCl_3$: MeOH=1:1). NMR ($CDCl_3$): 0.89 (t, J=7 Hz, 3H), 1.27 (s, 26H), 1.40—1.70 (m, 2H), 2.09 (s, 3H), 3.32, (s, 3H), 3.35—3.48 (m, 4H), 3.48—3.70 (m, 6H), 3.70—3.86 (m, 2H), 3.88—4.16 (m, 4H), 4.16—4.88 (m, 2H), 5.16 (m, 1H). IR (neat): 3350, 2900, 2840, 1720 cm^{-1}. MS (FAB, 6KV, glycerine): 566 (M^++1). *N*-Methylpiperidine homologue **21a**: 20%, $[\alpha]_D^{21}$ −0.44° (c=1.25, $CHCl_3$: MeOH=1:1). NMR ($CDCl_3$: CD_3OD=3:1): 0.88 (t, J=7 Hz, 3H), 1.27 (s, 26H), 1.34—1.60 (m, 4H), 1.64—2.12 (m, 4H), 2.08 (s, 3H), 3.11 (s, 3H), 3.2—3.78 (m, 10H), 3.94 (m, 2H), 4.26 (m, 2H), 5.10 (m, 1H). IR (KBr): 3400, 2910, 2840, 2590, 2480, 1727, 1460, 1370, 1235, 1060 cm^{-1}. MS (FAB, 6KV, glycerine): 564 (M^++1). *N*-Methylpyrrolidine homologue **22a**: 44%, $[\alpha]_D^{20}$ −4.12° (c=0.38, $CHCl_3$: MeOH=1:1). NMR ($CDCl_3$: CD_3OD=10:1): 0.89 (t, J=7 Hz, 3H), 1.27 (s, 26H), 1.40—1.70 (m, 2H), 2.08 (s, 3H), 2.10—2.40 (m, 4H), 3.15, (s, 3H), 3.25—3.80 (m, 11H), 3.94—4.08 (m, 2H), 4.18—4.26 (m, 2H). IR (KBr): 3400, 2910, 2840, 2590, 2480, 1728, 1460, 1370, 1235, 1065 cm^{-1}. MS (FAB, 6KV, glycerine): 550 (M^++1).

1-*O*-Hexadecyl-3,4-*O*-isopropylidene-D-threitol (23a)——A mixture of **7a** (306 mg, 0.64 mmol) and palladium black (10 mg) in 2% acetic acid-methanol (10 ml) was stirred under a hydrogen atmosphere (1 atm) at room temperature overnight. The catalyst was then filtered off, and triethylamine (1 ml) was added to the filtrate. After the removal of the solvent under reduced pressure, the residue was chromatographed on silica gel to afford **23a** (216 mg, 87%) as a colorless oil. NMR ($CDCl_3$): 0.89 (t, J=7 Hz, 3H), 1.27 (s, 26H), 1.38 (s, 3H), 1.44 (s, 3H), 1.4—1.6 (m, 2H), 2.30 (br s, 1H), 3.35—4.18 (m, 8H). IR (neat): 3440, 2960, 2910, 2840, 1460, 1375, 1365, 1245 cm^{-1}. MS m/e: 386 (M^+).

1-*O*-Hexadecyl-3,4-*O*-isopropylidene-2-*O*-methyl-D-threitol (24a)——A potassium hydride oil dispersion (0.13 ml, 0.7 mmol) was added to **23a** (180 mg, 0.47 mmol) in benzene (5 ml) at room temperature. After the evolution of hydrogen had stopped, methyl iodide (0.2 ml, 3.2 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. Hexane (5 ml), ethanol (1 ml), and water (0.5 ml) were added successively, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to afford **24a** (182 mg, 98%) as a colorless oil. $[\alpha]_D^{18}$ +4.18° (c=3.17, $CHCl_3$). NMR ($CDCl_3$): 0.89 (t, J=7 Hz, 3H), 1.27 (s, 26H), 1.38 (s, 3H), 1.44 (s, 3H), 1.50—1.75 (m, 2H), 3.20 —4.42 (m, 8H), 3.52 (s, 3H). IR (neat): 2960, 2900, 2840, 1455, 1373, 1365, 1243, 1207, 1150 cm^{-1}. MS m/e: 385 (M^+ − CH_3).

1-*O*-Hexadecyl-2-*O*-methyl-D-threitol (25a)——The methoxy derivative **24a** (160 mg, 10.4 mmol) in tetrahydrofuran (3 ml) and 6 N hydrochloric acid (1.5 ml) was stirred at room temperature for 5 min. The solvent was removed under pressure, and the residue was chromatographed on silica gel to afford **25a** (142 mg, 98%) as white crystals.

mp 44—46 °C, $[\alpha]_D^{20}$ −8.60 °(c=2.09, MeOH). NMR ($CDCl_3$): 0.90 (t, J=7 Hz, 3H), 1.27 (s, 26H), 1.5—1.6 (m, 2H), 2.92 (br s, 2H), 3.32—3.98 (m, 8H), 3.48 (s, 3H). IR (KBr): 3350, 2920, 2840, 1465, 1375, 1120 cm^{-1}. *Anal.* Calcd for $C_{21}H_{44}O_4$: C, 69.95; H, 12.20. Found: C, 69.68; H, 12.50.

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol (26a)——The glycerol derivative **26a** was prepared from **25a** in 90% yield in a manner similar to that described for the preparation of **11a** from **9a**. mp 29—30 °C, $[\alpha]_D^{20}$ −9.92° (c=1.64, $CHCl_3$). NMR ($CDCl_3$): 0.89 (t, J=7 Hz, 3H), 1.27 (s, 26H), 1.52 (m, 2H), 2.28 (br s, 1H), 3.03—4.02 (m, 7H), 3.48 (s, 3H). IR (neat): 3400, 2930, 2840, 1640, 1460, 1375, 1195, 1100 cm^{-1}.

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycero(3)phosphocholine (27a)——The methoxy homologue of PAF **2a** was prepared in 75% yield from **26a** in a manner similar to that described for the preparation of **15a**. $[\alpha]_D^{20}$ −5.41° (c= 0.95, $CHCl_3$: MeOH = 1 : 1). NMR ($CDCl_3$: CD_3OD = 1 : 1) 0.89 (t, J=7 Hz, 3H), 1.27 (s, 26H), 1.54 (m, 2H), 3.26 (s, 9H), 3.5—3.81 (m, 9H), 3.47 (s, 3H), 4.05 (m, 2H). MS (FAB, 6KV, glycerine): 496 (M^++1).

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