Analogues of Platelet Activating Factor (PAF). 2.[1] Some Modifications of the Glycerine Backbone

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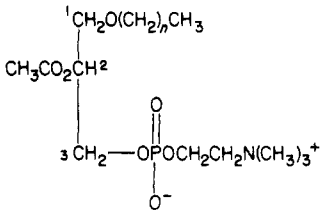
Racemic analogues of platelet activating factor (PAF) that contain a methylene group between the C_2 and C_3 carbon atoms (**39**) or between the C_1 and C_2 carbon atoms (**40**) have been synthesized. These compounds show reduced platelet aggregation and hypotensive activity as measured against racemic C_{16} PAF. Compounds in which the C_1 carbon atom of PAF is substituted with one or two methyl groups (**41** and **42**, respectively) or the C_3 carbon is substituted with a single methyl group (**43**) have been synthesized. Platelet aggregation and hypotensive responses produced by these compounds are significantly less than those obtained with racemic C_{16} PAF. None of the above compounds exhibit a separation of the platelet aggregation and hypotensive activities.

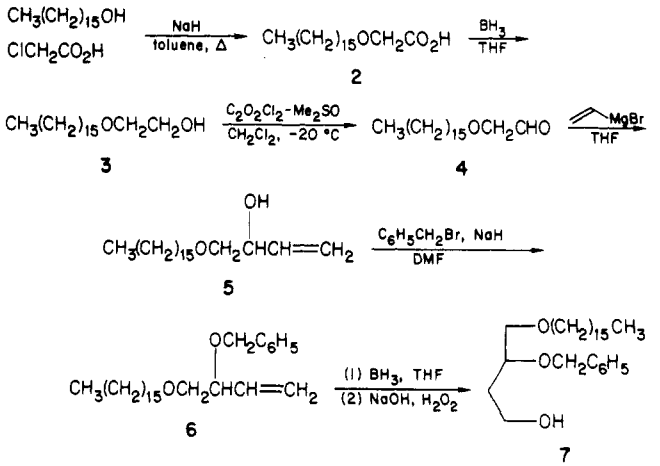
Platelet activating factor (PAF), an alkyl ether phospholipid comprised primarily of C_{16} and C_{18} homologues (**1a** and **1b**), has a variety of interesting biological properties among which is its ability to activate various inflammatory cell types (e.g., platelets, neutrophils, and basophils) and to lower blood pressure.[2]



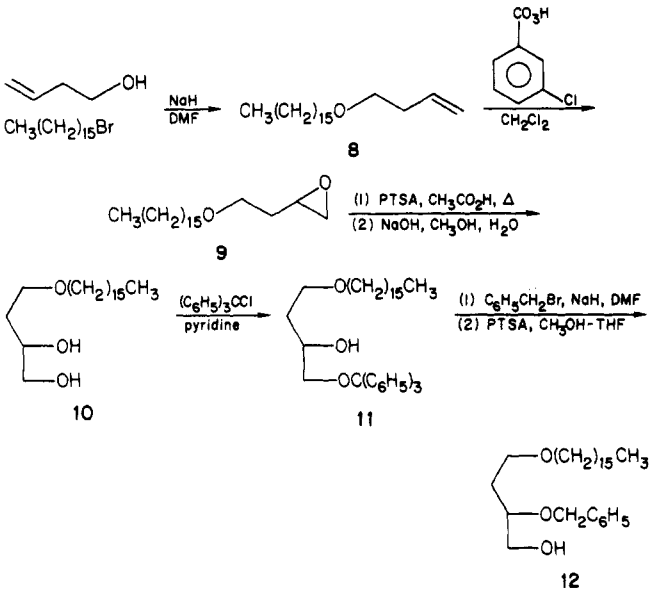
1a, n=15
b, n=17

Previous research on PAF analogues have involved the preparation of compounds in which the length of the alkyl chain was varied[3] or substituted with an aromatic ring.[1] We have reported a deoxy analogue in which the ether oxygen has been removed,[1] while others have described a compound in which a sulfur atom replaces the ether oxygen.[4] Compounds have been prepared in which the 2-acetyl group[3,5] or the phosphocholine[3,6] portion of the molecule has been modified. In a continuation of our effort to prepare a more selective analogue that maintains good antihypertensive activity and has diminished potency as a platelet aggregating agent, we have prepared a number of analogues that incorporate alterations of the glycerine backbone of the molecule. Specifically, we report the syntheses and biological activities of racemic analogues in which the glycerine backbone has been substituted at the C_1 or C_3 carbon atoms with methyl groups and molecules in which the length of the backbone has been increased by the addition of a methylene group between the C_1–C_2 or C_2–C_3 bonds.

Scheme I



Scheme II



Chemistry. The various synthetic strategies developed for the preparation of the PAF analogues all converge to similar intermediates (**7**, **12**, **23**, **24**, **27**) that contain the alkyl ether chain, a secondary benzyloxy group, and a free

(1) For previous publication in this series, see: Wissner, A.; Sum, P.-E.; Schaub, R. E.; Kohler, C. A.; Goldstein, B. M. *J. Med. Chem.* **1984**, *27*, 1174.
(2) For recent review of the biological properties of PAF see: (a) Snyder, F. *Annu. Rep. Med. Chem.* **1982**, *17*, 243. (b) Pinckard, R. N.; McManus, L. M.; Hanahan, J. *Adv. Inflammation Res.* **1982**, *4*, 147. (c) Vargaftig, B. B.; Chignard, M.; Benveniste, J.; Lefort, J.; Wal, F. *Ann. N.Y. Acad. Sci.* **1981**, *370*, 119.
(3) (a) Hanahan, D. J.; Munder, P. G.; Sartouchi, K.; McManus, L.; Pinckard, R. N. *Biochem. Biophys. Res. Commun.* **1981**, *99*, 183. (b) Tence, M.; Coeffier, E.; Heymans, F.; Polonsky, J.; Godfroid, J.; Benveniste, J. *Biochim.* **1981**, *63*, 723.
(4) Hillmar, I.; Muramatsu, T.; Zollner, N. *Z. Phys. Chem.* **1984**, *365*, 33.
(5) (a) O'Flaherty, J. T.; Salzer, W. L.; Cousort, S.; McCall, C. E.; Piantadosi, C.; Suries, J. R.; Hammett, M. J.; Wykle, R. L. *Res. Commun. Chem. Pathol. Pharmacol.* **1983**, *39*, 291. (b) Blank, M. L.; Cress, E. A.; Lee, T.-C.; Malone, B.; Surles, J. R.; Piantadosi, C.; Hajdu, J.; Snyder, F. *Res. Commun. Chem. Pathol. Pharmacol.* **1982**, *38*, 3. (c) Wykle, R. L.; Surles, J. R.; Piantadosi, C.; Salzer, W. L.; O'Flaherty, J. T. *FEBS Lett.* **1982**, *141*, 29. (d) Chandrakumar, N. S.; Hajdu, J. *J. Org. Chem.* **1982**, *48*, 1197.
(6) Sartouchi, K.; Pinckard, R. N.; McManus, L. M.; Hanahan, J. T. *J. Biol. Chem.* **1981**, *256*, 4425. (b) Moschidis, M. C.; Demopoulos, C. A.; Kritikou, L. G. *Chem. Phys. Lipids* **1983**, *33*, 87.

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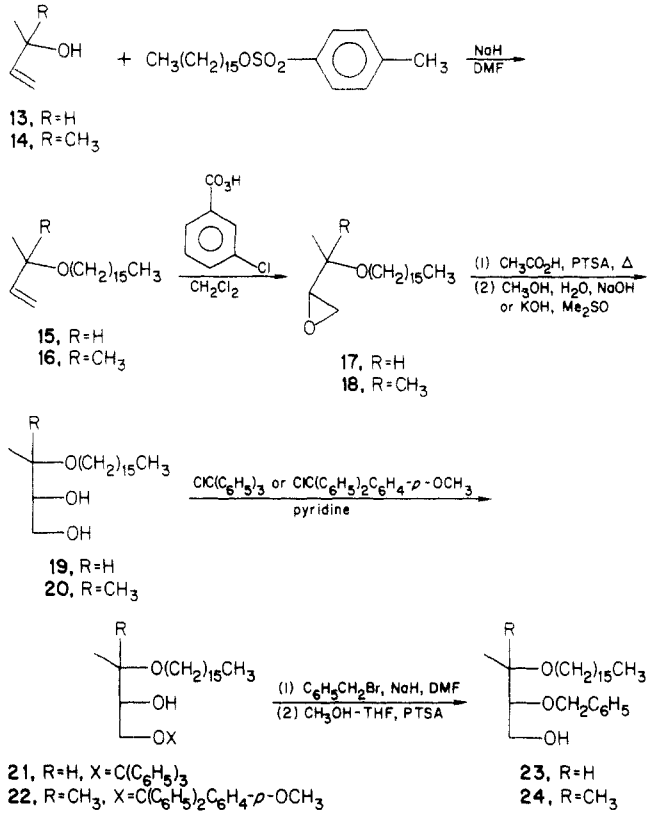
Scheme III



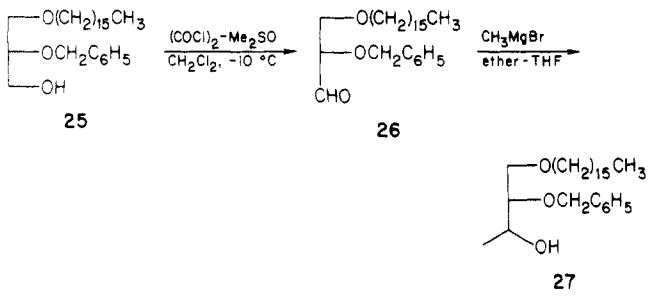
hydroxyl group. The syntheses of these precursors are detailed below.

Introduction of a Methylene Group between the C_2 and C_3 Carbon Atoms (Scheme I). Alkylation of 1-hexadecanol with chloroacetic acid is accomplished by the prior formation of the sodium salt of the acid by its addition to a suspension of sodium hydride in toluene; addition of the alcohol and refluxing for 40 h give the carboxylic acid **2**. The aldehyde **4** is prepared by reduction of **2** with borane–THF to give alcohol **3** followed by oxidation of **3** with oxalyl chloride–Me_2SO at −20 °C. We have found **4** to be a rather unstable substance that is best stored at low temperature in solution (petroleum ether, 30–60 °C) prior to use. The reaction of **4** with vinylmagnesium bromide gives the allylic alcohol **5**. Protection of the hydroxyl group as a benzyl ether (**6**) followed by hydroboration–oxidation then gives the desired precursor **7**.

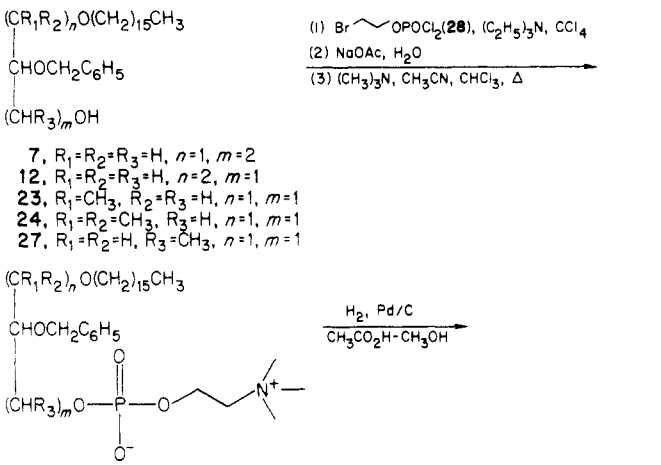
Introduction of a Methylene Group between the C_1 and C_2 Carbon Atoms (Scheme II). Alkylation of 3-buten-1-ol with 1-bromohexadecane using sodium hydride in DMF gives the ether **8**. Oxidation of **8** with *m*-chloroperbenzoic acid furnishes the epoxide **9** that is then converted to diol **10** in a two-step process involving an acid-catalyzed epoxide ring opening in acetic acid followed by hydrolysis of the resulting mixture of monoacetates with methanolic sodium hydroxide. The primary hydroxyl group of **10** is selectively protected with trityl chloride in pyridine. Alkylation of the hydroxyl group of **11** with benzyl bromide and sodium hydride in DMF followed by removal of the trityl protecting group in an acidified mixture of MeOH and THF then gives the desired precursor **12**.

Mono- and Dimethyl Substitution at the C_1 Carbon Atom (Scheme III). Alkylation of 3-buten-2-ol or 2-methyl-3-buten-2-ol with the tosylate of 1-hexadecanol using sodium hydride in dimethylformamide gives the allylic ethers **15** and **16**, respectively. Both were oxidized

Scheme IV



Scheme V

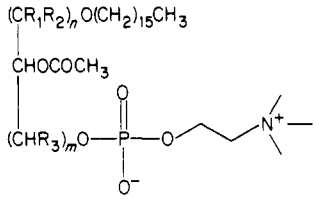


to the respective epoxides **17** and **18** with *m*-chloroperbenzoic acid in methylene chloride. Refluxing an acetic acid solution of **17** in the presence of of a catalytic amount of *p*-toluenesulfonic acid followed by basic hydrolysis of the resulting mixture of monoacetates gave the diol **19**. On attempted acid-catalyzed ring opening of the more hindered epoxide **18**, it was recovered unchanged. Successful ring opening was achieved however, using potassium hydroxide in Me_2SO at 110 °C for 8 h, giving the diol **20** along with a dimer side product (see Experimental Section). Diols **19** and **20** were then converted to the desired precursors **23** and **24**, respectively, by the protection–alkylation–deprotection sequence described above. It was evident, by thin-layer chromatography, that both possible diastereoisomers of **23** are present in about equal amounts.

Methyl Substitution at the C_3 Carbon Atom (Scheme IV). Oxidation of **25**[8] with oxalyl chloride–Me_2SO[7] in methylene chloride at −10 °C gave the aldehyde

(7) Mancuso, A. J.; Huang, S.-L.; Swenn, D. *J. Org. Chem.* **1978**, *43*, 2480.

Chart I



39, $R_1=R_2=R_3=H$, $n=1$, $m=2$
40, $R_1=R_2=R_3=H$, $n=2$, $m=1$
41, $R_1=CH_3$, $R_2=R_3=H$, $n=1$, $m=1$
42, $R_1=R_2=CH_3$, $R_3=H$, $n=1$, $m=1$
43, $R_1=R_2=H$, $R_3=CH_3$, $n=1$, $m=1$

26. The reaction of **26** with methylmagnesium bromide in ether–tetrahydrofuran furnished the desired intermediate **27**. Thin-layer chromatography indicated the presence of both possible diastereoisomers in about equal amounts.

Preparation of PAF Analogues 39–43 (Scheme V). The phosphocholine groups were introduced with 2-bromoethyl phosphorodichloridate (**28**) by a modification of the method of Hirt.[9] The reaction of a carbon tetrachloride solution of **7**, **12**, **23**, **24**, or **27** with an excess of **28** and triethylamine followed by hydrolysis in aqueous sodium acetate gave a series of bromoethyl phosphates that were converted to phosphocholines **29–33**, respectively, by refluxing in a solution of chloroform–acetonitrile containing a large excess of anhydrous trimethylamine. The reaction of **28** with the more hindered alcohol **27** required a considerably longer reaction time (48 h) than the reaction with the less hindered alcohols.

The benzyl protecting groups were removed from **29–33** by catalytic hydrogenolysis using 5% Pd/C in a mixture of acetic acid and MeOH. Finally, the alcohols **34–38** were acetylated with acetic anhydride and triethylamine in chloroform at reflux to give the PAF analogues **39–43** (Chart I).

Biology. We have proposed the hypothesis that the various biological effects of PAF need not be mediated by the same receptor and that the hypotensive activity of PAF is not a consequence of mediator cell (e.g., platelet) activation and release.[1] If this is true and if the receptor responsible for cell activation and that responsible for the hypotensive effect differ sufficiently in their structural requirements, then it may be possible to prepare an analogue that retains the hypotensive activity yet has diminished activity with respect to cell activation and release. Such a compound may be a therapeutically useful hypotensive agent. Evidence that at least some of the biological activities of PAF are receptor-mediated processes include its stereospecificity of action,[10] the discovery of a specific antagonist,[11] and the actual identification of PAF receptors.[12]

To examine the effect of our PAF analogues on mediator cell activation, we have chosen to study platelet aggregation using rabbit platelet-rich plasma. We have chosen the platelets of this species since they are known to be very sensitive to PAF.[2c,13] The data (Table I) are expressed as the molar concentration of the analogue required to obtain 50% of its maximum response (EC_{50}) and as the maximum aggregation response of the analogue obtained at the indicated molar concentration. This latter value is useful in order to distinguish partial from full agonists.

Table I. Blood Pressure and Platelet Aggregation Activities for PAF Analogues

compd	MABP[a]	platelet EC_{50}[b] (n)	max aggregation resp[c]	ratio[d]
1a	1.25 (0.30, 4.98)	1.94×10^{-8} (7)	75 (1.3×10^{-5})	0.65
39	47.5 (10.6, 197.8)	1.4×10^{-6} (1)	65 (5×10^{-5})	0.34
40	24.3 (9.3, 63.0)	1.5×10^{-6} (1)	50 (1.9×10^{-4})	0.16
41	7.12 (3.69, 13.9)	5.1×10^{-7} (1)	65 (5×10^{-4})	0.14
42	875.7 (229.2, 3564)	1.1×10^{-5} (1)	64 (5×10^{-5})	0.80
43	63.4 (13.2, 262.0)	3.2×10^{-6} (1)	70 (1.9×10^{-4})	0.20

[a] Dose (μg/kg, iv) required to decrease mean arterial blood pressure (MABP) 50 mmHg. Values in parentheses are 95% confidence limits. [b] Molar concentration required to produce 50% of maximum aggregation. The n values are the number of experiments in which a dose–response curve was determined from two to six replicates per dose level. [c] Maximum aggregation units at the specified molar concentration. [d] (MABP/platelet EC_{50}) $\times 10^{-8}$.

Spontaneously hypertensive rats were used for blood pressure studies. It is known that the platelets of this species do not respond well to PAF and that the hypotensive effect is not mediated by platelets.[2c] Blood pressure data (Table I) are expressed as the intravenous dose of the analogue needed to reduce the mean arterial blood pressure (MABP) 50 mmHg as determined from a least-squares regression line.

The last column in Table I gives the ratio of the blood pressure and platelet aggregation values and can be used as a measure of the degree of separation of the two activities for a particular compound relative to the standard compound (racemic C_{16} PAF, **1a**). A value of this ratio smaller than that observed for **1a** may indicate selectivity in favor of the hypotensive effect while a larger ratio would suggest selectivity in favor of platelet aggregation.

Results and Discussion

The blood pressure and platelet aggregation data obtained for racemic **1a** and analogues **39–43** are presented in Table I. Increasing the length of the glycerine backbone of PAF by the introduction of a methylene group between carbon atoms C_2 and C_3 (compound **39**) or between carbon atoms C_1 and C_2 (compound **40**) results in a decrease of both the hypotensive (38- and 19-fold) and platelet aggregation (73- and 77-fold) responses, respectively, when compared to **1a**.

Methyl substitution at both C_1 (compound **41**) and at C_3 (compound **43**) also result in a decreased response in both assays, and it is apparent that this effect is greatest for C_3 substitution. It should be pointed out that these results are complicated by the fact that **41** and **43** are both a mixture of two diastereomers, with each diastereomeric component of the mixture containing an enantiomer with the same configuration as the natural isomer, and consequently it is not known to what extent the activities reside in one or both of the enantiomers of the mixture. Substitution of C_1 with two methyl groups (compound **42**)

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(9) Hirt, R.; Berchtold, R. *Pharm. Acta Helv.* **1958**, *33*, 349.
(10) (a) Wykle, R. L.; Miller, C. H.; Lewis, J. C.; Schmitt, J. D.; Smith, J. A.; Surles, J. R.; Piantadosi, C.; O'Flaherty, J. T. *Biochem. Biophys. Res. Commun.* **1981**, *100*, 1651. (b) Tence, M.; Coeffies, E.; Polonsky, J.; Benveniste, J. *Biochim. Biophys. Acta* **1983**, *735*, 526.
(11) Terashita, Z.-i.; Tsushima, S.; Yoshioka, Y. Nomura, H.; Inada, Y.; Nishikawa, K. *Life Sci.* **1983**, *32*, 1975.
(12) (a) Valone, F. H.; Coles, E.; Reinhold, V. R.; Goetzl, E. J. *J. Immunol.* **1982**, *129*, 1637. (b) Valone, F. H.; Goetzl, E. J. *J. Immunol.* **1983**, *48*, 141. (c) Hwang, S.-B.; Lee, C.-S.; Cleah, M. J.; Shen, T. Y. *Biochemistry* **1983**, *22*, 4756.
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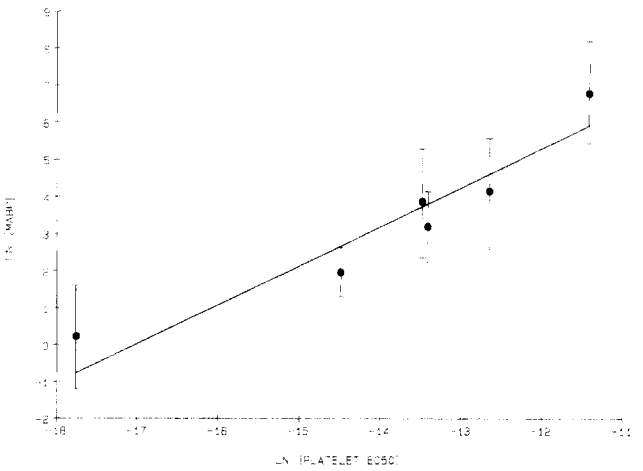

Figure 1. Relationship between the natural logarithms of the MABP and platelet EC_{50} values. Error bars are the natural logarithmic values of the 95% confidence limits for the MABP values. The regression equation is ln [platelet EC_{50}] = 0.925 ln [MABP] - 17.0.

results in an even larger decrease in the hypotensive (700-fold) and platelet-aggregating (567-fold) activities.

The ratios of the hypotensive and platelet-aggregating responses observed for **39–43** span a rather narrow range (0.14–0.80) and are comparable to that observed for the standard compound **1a** (0.65), suggesting that these strucutral modifications have resulted in little or no significant changes in selectivity. These results are presented graphically in Figure 1 in which the log values of the hypotensive and platelet-aggregating responses of **1a** and **39–43** are plotted. A linear correlation is observed with an R^2 value of 0.89.

While we have not observed the hoped for hypotensive selectivity in this series of compounds, we are, nevertheless, continuing with our efforts in this area.

Experimental Section

General Methods. Unless otherwise stated, the following are implied. Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected. The nuclear magnetic resonance (NMR) spectra were recorded on either a Varian EM 390 spectrometer or Varian FT-80 spectrometer, and chemical shifts in parts per million (ppm) are reported with tetramethylsilane (Me_4Si) or chloroform as internal references. Infrared spectra (IR) were recorded on a Nicolet FT 7000 spectrophotometer. Mass spectra were determined on a Finnegan-MAT Model CH 7 mass spectrometer. The field desorption (FD) (FD *p*-TSA), and fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS 50 mass spectrometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical value.

Biological Assays. The methods used in the platelet aggregation and blood pressure assays have been described previously.[1]

1-(Hexadecyloxy)acetic Acid (2). To a suspension of 44.5 g (0.93 mol) of washed (hexane) 50% NaH mineral oil dispersion in 50 mL of toluene was added with mechanical stirring under argon a solution of 46.8 g (0.49 mol) of chloroacetic acid in 200 mL of toluene over 1 h. A solution of 100 g (0.41 mol) of 1-hexadecanol in 200 mL of toluene was then added over 15 min. The mixture was stirred at reflux 40 h, cooled to room temperature, and acidified with dilute HCl. The mixture was heated until all solid dissolved. The hot organic layer was dried over $MgSO_4$, filtered, and cooled, giving 84.5 g (68%) of **2** as a colorless solid: mp 64–66 °C (lit.[14] mp 64.3 °C); NMR ($CDCl_3$) δ 7.78 (b s, 1 H, CO_2H), 4.18 (s, 2 H, OCH_2CO_2), 3.60 (t, 2 H, OCH_2CH_2), 1.30 (m, 28 H, $(CH_2)_{14}$), 0.93 (m, 3 H, terminal CH_3); IR (KBr) 1695 cm^{-1} (C=O); mass spectrum *m/z* 300 (M^+). Anal. ($C_{18}H_{36}O_3$) C; H: calcd, 12.08; found, 11.64.

2-(Hexadecyloxy)ethanol (3). To a solution of 80 g (0.27 mol) of **2** in 350 mL of THF was added, dropwise with stirring at 0 °C under argon, 799 mL of 1 M borane in THF over a 1-h period. After an additional 2 h, 50 mL of acetone was added dropwise to destroy the excess borane followed by 60 mL of H_2O. The THF was evaporated, and the residue was heated in a mixture of H_2O and $CHCl_3$ to dissolve the solids. The organic layer was separated and dried ($MgSO_4$). The solvent was removed. The residue was recrystallized from CH_3OH, giving 70.6 g (93%) of **3** as a colorless solid: mp 42–44 °C; NMR ($CDCl_3$) δ 3.7 (s, 1 H, OH), 3.50 (m, 6 H, OCH_2's), 2.18 (m, 2 H, CH_2CH_2O), 1.32 (m, 26 H, $(CH_2)_{13}$), 0.91 (m, 3 H, terminal CH_3); IR (KBr) 3275 (OH) cm^{-1}; mass spectrum *m/z* 255 (M = CH_2OH). Anal. ($C_{18}H_{38}O_2$) C, H.

(Hexadecyloxy)acetaldehyde (4). A solution of 49.4 g (0.39 mol) of oxalyl chloride in 900 mL of CH_2Cl_2 was cooled to −60 °C, and a solution of 60.8 g (0.78 mol) of Me_2SO in 175 mL of CH_2Cl_2 was added dropwise with stirring over 0.5 h so that the reaction temperature never exceeded −50 °C. The solution was warmed to −20 °C and maintained at this temperature as a solution of 44.6 g (0.16 mol) of **3** in 350 mL of CH_2Cl_2 was added dropwise over 20 min. The mixture was stirred another 20 min, and 98.2 g of $(C_2H_5)_3N$ was added. The mixture was allowed to warm to 25 °C, and H_2O was added. The organic layer was separated and washed first with dilute HCl and then with saturated $NaHCO_3$ solution until neutral. The solution was dried ($MgSO_4$–Norite) and filtered through a pad of silica gel. Solvent was removed at reduced pressure at 30 °C, giving 32 g (76%) of **4** as a yellow solid that was not purified further; **4** was stored at low temperature in petroleum ether (30–60 °C): NMR ($CDCl_3$) δ 9.67 (s, 1 H, CHO), 3.99 (s, 2 H, OCH_2CHO), 3.45 (t, 3 H, CH_2O), 1.23 (m, 28 H, $(CH_2)_{14}$), 0.88 (m, 3 H, terminal CH_3); mass spectrum *m/z* 420 (M^+).

1-(Hexadecyloxy)-3-buten-2-ol (5). A suspension of 5.67 g (0.23 mol) of Mg was stirred in 25 mL of THF. A few drops of dibromoethane were added. After the evolution of ethylene was observed, another 100 mL of THF was added, followed by the dropwise addition of a solution of 49.9 g (0.47 mol) of vinyl bromide in 250 mL of THF at a rate that maintained reflux. After all the Mg was consumed, the solution was cooled to 0 °C and a solution of 44.2 g (0.16 mol) of **4** in 125 mL of ether was added dropwise over 0.5 h. After stirring an additional 1 h at 25 °C, dilute HCl was added. The THF was removed, and the residue was extracted with ether. The ether solution was washed with brine and dried ($MgSO_4$). The solvent was removed, the residue was chromatographed via HPLC (silica gel, hexane–ether (9:1)), and the product was isolated. Short-path distillation (185–190 °C, 0.2 mm) gave 20.2 g (42%) of **5** as an oil that crystallized on standing: mp 28.5–30 °C; NMR ($CDCl_3$) δ 6.15–5.11 (m, 3 H, $CH{=}CH_2$), 4.33 (m, 1 H, CH), 3.70–3.15 (m, 4 H, CH_2OCH_2), 2.48 (d, 1 H, OH), 1.30 (m, 28 H, $(CH_2)_{14}$), 0.91 (m, 3 H, terminal CH_3): IR (KBr) 3450 (OH), 1650 ($CH{=}CH_2$ cm^{-1}; mass spectrum *m/z* 312 (M^+). Anal. ($C_{20}H_{40}O_2$) C, H.

[[[1-[(Hexadecyloxy)methyl]-2-propenyl]oxy]methyl]benzene (6). To a suspension of 3.35 g (69.9mmol) of NaH (50% mineral oil dispersion) in 75 mL of DMF was added 10.92 g (63.8 mmol) of benzyl bromide and dropwise a solution of 19 g (60.8 mmol) of **5** in 75 mL of DMF. The mixture was stirred overnight and quenched with H_2O. The mixture was extracted with ether. The ether solution was dried ($MgSO_4$). Solvent was removed, and the residue was chromatographed via HPLC (silica gel, hexane–$CHCl_3$ (8:1)), giving 12 g (49%) of **6** as an oil: NMR ($CDCl_3$ δ 7.37 (s, 5 H, C_6H_5), 6.13–5.18 (m, 3 H, $CH{=}CH_2$), 4.60 (AB q, 2 H, J = 15 Hz, $CH_2C_6H_5$), 4.05 (m, 1 H, CH), 3.80–3.28 (m, 4 H, CH_2OCH_2), 1.30 (m, 28 H, $(CH_2)_{14}$), 0.91 (m, 3 H, terminal CH_3); mass spectrum *m/z* 311 (M − $CH_2C_6H_4$). Anal. ($C_{27}H_{46}O_2$) C, H.

4-(Hexadecyloxy)-3-(phenylmethoxy)-1-butanol (7). To a solution of 11.5 g (28.6 mmol) of **6** in 50 mL of THF was added dropwise with stirring under argon 57.1 mL of 1 M borane in THF at 0 °C. After the mixture was stirred 3 h at 25 °C, H_2O was slowly added. The mixture was cooled in an ice bath, and 100 mL of 3 N NaOH solution and 100 mL of 30% H_2O_2 were added with stirring. After 10 min, the mixture was warmed to 25 °C and

(14) Hato, M.; Shinoda, K.; Miyagoma, T. *Bull. Chem. Soc. Jpn.* 1976, *49*, 1257.

stirred 0.5 h. The mixture was poured into ether. The ether solution was washed with brine and saturated $NaHSO_3$ solution and dried ($MgSO_4$). Solvent was removed, and the residue was chromatographed via HPLC (silica gel, hexane–ethyl acetate (9:1)) to give 7.8 g (65%) of **7** as an oil: NMR ($CDCl_3$) δ 7.38 (s, 5 H, C_6H_5), 4.70 (AB q, 2 H, J = 15 Hz, $CH_2C_6H_5$), 3.81 (m, 2 H, CH_2OH), 3.66–3.35 (m, 4 H, CH_2OCH_2), 2.50 (m, 1 H, OH), 2.00–1.11 (m, 28 H, $(CH_2)_{14}$), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3440 (OH) cm^{-1}; mass spectrum m/z 420 (M^+). Anal. ($C_{27}H_{48}O_3$) H; C: calcd 77.09; found, 78.18.

1-(3-Butenyloxy)hexadecane (8). An aliquot of 73.2 g (1.53 mol) of NaH (50% mineral oil dispersion) was washed with hexane to remove oil, and 1.25 L of DMF was added. The suspension was mechanically stirred under argon as a solution of 100 g (1.39 mol) of 3-buten-1-ol (Aldrich) in 300 mL of DMF was added dropwise over 1.5 h. After the mixture was stirred an additional 1 h, 423.5 g (1.39 mol) of 1-bromohexadecane was added dropwise. The mixture was stirred overnight at 25 °C. H_2O was slowly added to destroy excess NaH. The mixture was poured into 1.5 L of H_2O and extracted several times with ether. The combined ether solutions were washed with brine and dried ($MgSO_4$). Solvent was removed. The residue was distilled first through a short Vigreux column to remove lower boiling side products and then with a Kugelrohr apparatus (145 °C, 0.05 mm) to give 131.6 g (32%) of **8** as an oil: NMR ($CDCl_3$) δ 6.18–4.87 (m, 3 H, $CH{=}CH_2$), 3.38 (m, 4 H, CH_2OCH_2), 2.28 (m, 2 H, allylic CH_2), 1.23 (m, 28 H, $(CH_2)_{14}$), 0.86 (m, 3 H, terminal CH_3); IR (neat) 1635 ($CH{=}CH_2$) cm^{-1}; mass spectrum m/z 255 (M – C_3H_5). Anal. ($C_{20}H_{40}O$) C, H.

1-[(1-Methyl-2-propenyl)oxy]hexadecane (15). A suspension of 10.57 g (0.22 mol) of NaH (50% mineral oil dispersion, washed with hexane to remove oil) was stirred in 150 mL of DMF under argon as a solution of 16.58 g (0.23 mol) of 3-buten-2-ol (**13**) in 100 mL of DMF was added dropwise over 0.5 h. After gas evolution ceased, 76 g (0.19 mol) of the tosylate of 1-hexadecanol was added, followed by 70 mL of DMF. After stirring overnight, the mixture was poured into water and extracted with petroleum ether. The solution was dried ($MgSO_4$), and solvent was removed. The residue was distilled in a Kugelrohr apparatus (180–185 °C, 0.35 mm) to give 50.9 g (90%) of **15** as a colorless liquid: NMR ($CDCl_3$) δ 6.05–4.98 (m, 3 H, $CH{=}CH_2$), 3.83 (m, 1 H, HCO), 3.40 (m, 2 H, CH_2O), 1.28 (m, 28 H, $(CH_2)_{14}$), 1.22 (s, 3 H, CH_3), 0.91 (m, 3 H, terminal CH_3); IR (neat) 1643 ($CH{=}CH_2$) cm^{-1}; mass spectrum m/z 296 (M^+). Anal. ($C_{20}H_{40}O$) C, H.

1-[(1,1-Dimethyl-2-propenyl)oxy]hexadecane (16). This compound was prepared by a procedure identical with the above using 150 g (0.38 mol) of the tosylate of 1-hexadecanol, 23.6 (0.49 mol) of NaH (50% dispersion), and 55.4 g (0.64 mol) of **14**, giving 75.6 g of **16** as a colorless liquid: NMR ($CDCl_3$) δ 5.80 (m, 1 H, $CH{=}CH_2$), 5.1 (m, 2 H, $CH{=}CH_2$), 3.25 (t, 2 H, CH_2O), 1.25 (m, 34 H, $(CH_2)_{14}$, $C(CH_3)_2$), 0.89 (m, 3 H, terminal CH_3). Anal. ($C_{21}H_{42}O$) C, H.

[1-(Hexadecyloxy)ethyl]oxirane (17). A solution of 46.9 g (0.16 mol) of **15** and 32.2 g (0.21 mol) of *m*-chloroperbenzoic acid was stirred in 300 mL of CH_2Cl_2 overnight, and the mixture was filtered. The solvent was removed from the filtrate. The residue was dissolved in a petroleum ether–ether mixture, and the solution was washed with a saturated solution of $NaHCO_3$. Solvent was removed, and the residue was chromatographed via HPLC (silica gel, hexane–ether (9:1)) to give 33 g (67%) of **17** as a colorless oil. TLC (hexane–ether (9:1)) showed two isomers in comparable amounts: NMR ($CDCl_3$) δ 3.85–2.35 (m, 6 H, CH_2O's, CHO's), 1.8–1.08 (m, 31 H, $(CH_2)_{14}$, CH_3), 0.90 (m, 3 H, terminal CH_3). Anal. ($C_{20}H_{40}O_2$) C, H.

[1-(Hexadecyloxy)-1-methylethyl]oxirane (18). This compound was prepared by a method similar to the above from 36.5 g (0.12 mol) of **16** and 23.9 g (0.15 mol) of *m*-chloroperbenzoic acid, giving 36 g (97%) of **18** which was used in the next step without purification.

[2-(Hexadecyloxy)ethyl]oxirane (9). This compound was prepared by a similar method from 100 g (0.34 mol) of **8** and 69 g (0.44 mol) of *m*-chloroperbenzoic acid, giving 83.4 g (79%) of **9** as an oil: NMR ($CDCl_3$) δ 3.70–3.30 (m, 4 H, CH_2OCH_2), 3.05, 2.78 (m, 3 H, epoxide), 2.50 (m, 2 H, CH_2CH_2O), 1.30 (m, 28 H, $(CH_2)_{14}$), 0.90 (m, 3 H, terminal CH_3); mass spectrum m/z 312 (M^+). Anal. ($C_{20}H_{40}O_2$) C, H.

3-(Hexadecyloxy)-1,2-butanediol (19). A solution of 30 g (0.10 mmol) of **17** was refluxed in 200 mL of acetic acid containing 0.2 g of *p*-toluenesulfonic acid (PTSA) for 4.5 h. The solvent was removed at reduced pressure. The residue was stirred in 22 mL of CH_3OH, and a solution of 13.44 g (0.34 mol) of NaOH in 14 mL of H_2O was added. After stirring for 0.5 h, the solvent was removed and the residue was diluted with H_2O. The mixture was extracted with ether. The ether solution was washed with brine and dried ($MgSO_4$). Solvent was removed, and the residue was distilled in a Kugelrohr apparatus (200 °C, 0.5 mm) to give 28.9 g (91%) of **19** as a sticky solid: NMR ($CDCl_3$) δ 4.08–3.08 (m, 8 H, OCH_2's, OCH's, OH's), 1.73–1.05 (m, 31 H, $(CH_2)_{14}$, CH_3), 0.90 (m, 3 H, terminal CH_3); IR (KBr) 3300, 3425 (OH) cm^{-1}. Anal. ($C_{20}H_{42}O_3$) C, H.

4-(Hexadecyloxy)-1,2-butanediol (10). This compound was prepared by a method similar to the above using 40 g (0.13 mol) of **9**, 270 mL of acetic acid, 0.27 g of PTSA, and 17.9 g of NaOH, giving 32 g, (76%) of **10** as a colorless solid: mp 60–61 °C; NMR ($CDCl_3$) δ 4.10–3.18 (m, 9 H, CH_2O's, CHO, OH's), 2.25 (m, 2 H, CH_2CH_3), 2.05–1.05 (m, 28 H, $(CH_2)_{14}$), 0.90 (m, 3 H, terminal CH_3); IR (KBr) 3360 (OH) cm^{-1}; mass spectrum m/z 299 (M – CH_2OH). Anal. ($C_{20}H_{42}O_3$) C, H.

3-(Hexadecyloxy)-3-methyl-1,2-butanediol (20). A solution of 35 g (0.11 mol) of **18** in 450 mL of Me_2SO was stirred, and a solution of 30.1 g (0.54 mol) of KOH in 700 mL of H_2O was added. The solution was maintained at 110 °C for 8 h. The mixture was cooled, poured into H_2O, and extracted with ether. The ether solution was dried ($MgSO_4$), and solvent was removed. The residue was chromatographed via HPLC (silica gel, hexane–ethyl acetate (4:1)), giving as the more polar component 18.2 g (49%) of **20** as a colorless solid: mp 30–31 °C; NMR ($CDCl_3$) δ 3.83–3.23 (m, 5 H, CH_2O's, CHO), 2.73 (b s, 2 H, OH's), 1.88–1.08 (m, 34 H, $(CH_2)_{14}$, $(CH_3)_2$), 0.90 (m, 3 H, terminal CH_3); mass spectrum m/z 283 (M – CH_2OH); IR (KBr) 3290 (OH) cm^{-1}. Anal. ($C_{21}H_{44}O_3$) C, H.

From the earlier fractions was obtained 13 g of a less polar component $(CH_3(CH_2)_{15}OC(CH_3)_2CH(OH)CH_2)_2O$: mp 40–42 °C; mass spectrum m/z 637 (M – H_2O, CH_3). Anal. ($C_{42}H_{86}O_5$) C, H.

3-(Hexadecyloxy)-2-(phenylmethoxy)-1-butanol (23). A solution of 27.5 g (83.2 mmol) of **19** and 34.8 g (120 mmol) of trityl chloride in 125 mL of dry pyridine was allowed to stand at room temperature for 48 h. The mixture was poured into H_2O and extracted with a mixture (1:1) of ether and petroleum ether (30–60 °C). The organic solution was washed with brine and dried ($MgSO_4$). Solvent is removed, giving 46.6 g (98%) of crude **21** which is used in the next step without additional purification.

To a suspension of 5.01 g (100 mmol) of NaH (50% oil dispersion), which was prewashed with hexane, in 200 mL of DMF was added 15.8g (92.3 mmol) of benzyl bromide. The mixture was stirred under argon at 0 °C, and a solution of 46 g (80.3 mmol) of **21** in 50 mL of DMF was added over 0.5 h. The mixture was stirred at 25 °C overnight, poured into H_2O, and extracted with petroleum ether (30–60 °C). The organic layer was dried ($MgSO_4$), and solvent was removed. The residue was dissolved in 190 mL of CH_3OH and 100 mL of THF containing 0.4 g of PTSA. After the mixture was allowed to stand at 25 °C overnight, the solvent was removed. The residue was dissolved in petroleum ether (30–60 °C); the solution was washed with saturated $NaHCO_3$ solution and dried (Na_2SO_4). Solvent was removed, and the residue was chromatographed via HPLC (silica gel, hexane–ethyl acetate (9:1)) to give 21.8 g (65%) of **23** as an oil. TLC (hexane–ethyl acetate, silica gel) showed two isomers in comparable amounts: NMR ($CDCl_3$) δ 7.40 (s, 5 H, C_6H_5), 4.71 (m, 2 H, $CH_2C_6H_5$), 3.98–3.20 (m, 6 H, CH_2O's, CHO's), 2.43 (m, 1 H, OH), 2.10–1.08 (m, 31 H, $(CH_2)_{14}$, CH_3), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3450 (OH) cm^{-1}. Anal. ($C_{27}H_{48}O_3$) C, H.

4-(Hexadecyloxy)-2-(phenylmethoxy)-1-butanol (12). This compound was prepared by a method similar to the above from 30 g (90.8 mmol) of **10** and 37.95 g (130 mmol) of trityl chloride to give 56.7 g of **11** which, on alkylation with 6.17 g (128.5 mmol) of 50% NaH dispersion and 19.5 g (114 mmol) of benzyl bromide, gave, after deprotection, 23 g (61%) of **12** as an oil: NMR ($CDCl_3$) δ 7.35 (s, 5 H, C_6H_5), 4.60 (s, 2 H, $CH_2C_6H_5$), 3.91–3.30 (m, 8 H, CH_2O's, CHO, OH), 2.39 (m, 2 H, CH_2CH_2O), 2.18–1.11 (m, 28 H, $(CH_2)_{14}$), 0.89 (m, 3 H, terminal CH_3); IR (neat) 3340 (OH)

cm^{-1}; mass spectrum m/z 391 (M − CH_2OH). Anal. ($C_{27}H_{48}O_3$) C, H.

3-(Hexadecyloxy)-3-methyl-2-(phenylmethoxy)-1-butanol (24). This compound was prepared in a similar manner to the above from **20** (17.5 g, 50.8 mmol) except that protection of the primary hydroxyl group was accomplished with *p*-anisylchlorodiphenylmethane (17.9 g, 57.9 mmol) instead of trityl chloride, giving **22** which was alkylated with benzyl bromide (13.5g, 78.9 mmol) and deblocked with Amberlyst 15 ion-exchange resin in methanol–THF, giving 12.1 g (53%) of **24** as an oil: NMR ($CDCl_3$) δ 7.35 (s, 5 H, C_6H_5), 4.70 (s, 2 H, $CH_2C_6H_5$), 3.82, 3.45 (m, 5 H, CH_2O's, CHO), 3.00 (m, 1 H, OH), 1.80–1.18 (m, 28 H, $(CH_2)_{14}$), 0.96 (m, 3 H, terminal CH_3). Anal. ($C_{28}H_{50}O_3$) C, H.

4-(Hexadecyloxy)-3-(phenylmethoxy)-2-butanol (27). A solution of 9.4 g (73.7 mmol) of oxalyl chloride in 130 mL of CH_2Cl_2 was stirred under argon at −70 °C as 11.5 g (147.5 mmol) of Me_2SO was added dropwise so that the reaction temperature never exceeded −65 °C. A solution of 10 g (24.6 mmol) of **25**[8] in 60 mL of CH_2Cl_2 was added rapidly. The mixture was allowed to warm slowly to −10 °C. The solution was then recooled to −50 °C, and 16.2 g (159.8 mmol) of triethylamine was added. The reaction mixture was warmed to 25 °C and poured into 100 mL of H_2O. The organic layer was washed with dilute HCl and a saturated solution of $NaHCO_3$. The organic layer was dried ($MgSO_4$) and solvent was removed, giving 10 g of **26** as an oil that was used without additional purification.

To a solution of **26** in 120 mL of dry THF was added, at 5 °C, under argon with stirring, 16.4 mL (49.2 mmol) of 3 M CH_3MgBr in ether at a rate such that the temperature never exceeded 8 °C. After 15 min, the mixture was warmed to 25 °C and stirred for 3 h. The solution was cooled to 5 °C, and 50 mL of 1 N HCl was added at a rate that maintained the temperature at 10 °C. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic solutions were washed with saturated $NaHCO_3$ solution and brine and dried ($MgSO_4$). Solvent was removed, and the residue was chromatographed via HPLC (silica gel, hexane–ether (5:1)) to give 6.16 g (60%) of **27** as an oil which showed two isomers on TLC in comparable amounts: NMR ($CDCl_3$) δ 7.43 (s, 5 H, C_6H_5), 4.73 (m, 2 H, $CH_2C_6H_5$), 4.20–3.30 (m, 6 H, CH_2O's, CHO's), 2.63 (s, 1 H, OH), 1.81–1.06 (m, 31 H, $(CH_2)_{14}$, CH_3), 0.91 (m, 3 H, terminal CH_3); IR (neat) 3415 (OH) cm^{-1}. Anal. ($C_{27}H_{48}O_3$) C, H.

4-Hydroxy-*N*,*N*,*N*-trimethyl-8-(phenylmethoxy)-3,5,10-trioxa-4-phosphahexacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (29). A solution of 7.3 g (17.4 mmol) of **7**, 7.3g (30.4 mmol) of **28**, and 3.07 g (30.4 mmol) of triethylamine in 160 mL of CCl_4 was stirred for 1.5 h. The mixture was filtered, and solvent was removed. The residue was stirred in a mixture of 300 mL of 0.5 M NaOAc and 300 mL of THF for 3 h. The THF was removed at reduced pressure, and the aqueous solution was acidified with HCl and extracted with ether. The ether solution was washed with brine and dried ($MgSO_4$). The solvent was removed, and the residue was dissolved in a mixture of 100 mL of CH_3CN, 90 mL of $CHCl_3$ and 50 g of anhydrous $(CH_3)_3N$. The solution was refluxed for 20 h. The solvent was removed, and the residue was stirred in 100 mL CH_3OH containing 2.7 g of Ag_2CO_3 for 2 h. The mixture was filtered, and the solvent was removed. The residue was chromatographed on silica gel, eluting first with $CHCl_3$–CH_3OH (7:3) to remove the more mobile impurities and then with $CHCl_3$–CH_3OH–H_2O (70:30:5) to elute product that was triturated with ether to give 6.31 g (62%) of **29** as a white powder with no well-defined melting point: NMR ($CDCl_3$–CD_3OH) δ 7.30 (m, 5 H, C_6H_5), 4.60 (AB q, 2 H, J = 15Hz, $CH_2C_6H_5$), 4.38–3.21 (7, 11 H, α to O and N), 3.10 (s, 9 H, $N(CH_3)_3$), 1.85 (m, 2 H, CH_2CH_2O), 1.23 (m, 28 H, $(CH_2)_{14}$), 0.84 (m, 3 H, terminal CH_3); mass spectrum (FAB) m/z 586 (M + H). Anal. ($C_{32}H_{60}O_6PN{\cdot}H_2O$) C, H, N, P.

4-Hydroxy-*N*,*N*,*N*-trimethyl-7-(phenylmethoxy)-3,5,10-trioxa-4-phosphahexacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (30). This compound was prepared by a method similar to the above from 10.0 g (23.8 mmol) of **12** to give 9.33 g (67%) of **30** as a white powder with no well-defined melting point: NMR ($CDCl_3$–CD_3OD) δ 7.35 (m, 5 H, C_6H_5), 4.62 (AB q, 2 H, $CH_2C_6H_5$), 4.17 (m, 2 H, $POCH_2$), 4.03, 3.89 (m, 2 H, CH_2OP), 3.78 (m, 1 H, CH), 3.56–3.29 (m, 6 H, CH_2OCH_2, CH_2N), 3.09 (s, 9 H, $N(CH_3)_3$), 1.83 (m, 2 H, $CHCH_2CH_2$), 1.53 (m, 2 H, OCH_2CH_2), 1.25 (m, 26 H, $(CH_2)_{13}$), 0.88 (m, 3 H, terminal CH_3); mass spectrum (FAB) m/z 586 (M + H). Anal. ($C_{32}H_{60}O_6N$-$P{\cdot}H_2O$) C, H, P, N.

4-Hydroxy-*N*,*N*,*N*,8-tetramethyl-7-(phenylmethoxy)-3,5,9-trioxa-4-phosphapentacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (31). This compound was prepared by a method similar to the above from 20 g (47.5 mmol) of **23** to give 10.4 g (39%) of **31** as a colorless foam: NMR ($CDCl_3$–CD_3OD) δ 7.28 (m, 5 H, C_6H_5), 4.70 (m, 2 H, $CH_2C_6H_5$), 4.00–3.30 (m, 10 H, α to O and N), 3.15 (s, 9 H, $N(CH_3)_3$), 1.64 (m, 2 H, CH_2CH_2O), 1.24 (m, 29 H, $(CH_2)_{13}$, CH_3), 0.89 (m, 3 H, terminal CH_3); mass spectrum (FAB) m/z 586 (M + H). Anal. ($C_{32}H_{60}O_6PN{\cdot}4H_2O$) C, N, P; H: calcd, 10.42; found, 9.10.

4-Hydroxy-*N*,*N*,*N*,8,8-pentamethyl-7-(phenylmethoxy)-3,5,9-trioxa-4-phosphapentacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (32). This compound was prepared by a similar method from 11 g (25.3 mmol) of **24** to give 5.4 g (36%) of **32** as a white powder with no well-defined melting point: NMR ($CDCl_3$–CD_3OD) δ 7.37 (m, 5 H, C_6H_5), 4.80 (AB q, 2 H, $CH_2C_6H_5$), 4.16 (m, 2 H, $POCH_2$), 4.25, 3.92 (m, 2 H, CH_2OP), 3.60 (m, 1 H, CHO), 1.25 (m, 26 H, $(CH_2)_{13}$), 1.25 (s, 3 H, CH_3), 0.88 (m, 3 H, terminal CH_3); mass spectrum (FAB) m/z 600 (M + H). Anal. ($C_{33}H_{62}O_6PN{\cdot}{}^1/_2H_2O$) C, H, N.

4-Hydroxy-*N*,*N*,*N*,6-tetramethyl-7-(phenylmethoxy)-3,5,9-trioxa-4-phosphapentacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (33). This compound was prepared by a similar method from 4.8 g (11.4 mmol) of **27** except that the reaction with **28** was allowed to proceed for 48 h, giving 3.6 (54%) of **33** as a colorless powder with no well-defined melting point: NMR ($CDCl_3$–CD_3OD) δ 7.20–7.52 (m, 5 H, C_6H_5), 4.78–4.60 (AB q, 2 H, $CH_2C_6H_5$), 4.54–4.12 (m, 3 H, $CHOPO_3CH_2$), 4.00–3.36 (m, 7 H, CH_2N, CHO, CH_2OCH_2), 3.12 (s, 9 H, $N(CH_3)_3$), 1.59 (m, 2 H, CH_2CH_2O), 1.26 (m, 29 H, $(CH_2)_{13}$, CH_3), 0.88 (m, 3 H, terminal CH_3); mass spectrum (FAB) m/z 586 (M + H). Anal. ($C_{32}H_{60}O_6PN{\cdot}3H_2O$) C, H, N, P.

4,8-Dihydroxy-*N*,*N*,*N*-trimethyl-3,5,10-trioxa-4-phosphahexacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (34). A solution of 5.6 g (9.6 mmol) of **29** in 35 mL of CH_3CO_2H and 35 mL of CH_3OH containing 0.5 g of 5% Pd/C catalyst was subjected to hydrogenolysis in a Parr shaker for 17 h. The catalyst was removed by filtration, and the solvent was removed, giving 4.7 g (99%) of **34** that was used in the next step without additional purification.

4,7-Dihydroxy-*N*,*N*,*N*-trimethyl-3,5,10-trioxa-4-phosphahexacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (35). This compound was prepared from 8.8 g (15 mmol) of **30** and 0.9 g of 5% Pd/C by a similar method to give 7.5 g (100%) of **35** as a white powder after trituration with ether: NMR ($CDCl_3$–CD_3OD) δ 4.30 (m, 2 H, $POCH_2$), 4.08–3.71 (m, 3 H, CH_2OP, CH), 3.66 (m, 2 H, CH_2N), 3.60–3.32 (m, 4 H, CH_2OCH_2), 3.25 (s, 9 H, $N(CH_3)_3$), 1.71 (m, 2 H, $CHCH_2CH_2$), 1.53 (m, 2 H, OCH_2CH_2), 1.25 (m, 26 H, $(CH_2)_{13}$), 0.88 (m, 3 H, terminal CH_3); IR (KBr) 3210 (OH) cm^{-1}; mass spectrum (FAB) m/z 496 (M + H). Anal. ($C_{25}H_{54}NPO_6{\cdot}1{}^1/_2H_2O$) C, H, N, P.

4,7-Dihydroxy-*N*,*N*,*N*,8-tetramethyl-3,5,9-trioxa-4-phosphapentacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (36). This compound was prepared by a similar method from 10 g (17.1 mmol) of **31** and 1.0 g of 5% Pd/C to give 7.4 g (88%) of **36** as a thick oil: mass spectrum (FAB) m/z 496 (M + H); IR (neat) 3230 (OH) cm^{-1}.

4,7-Dihydroxy-*N*,*N*,*N*,8,8-pentamethyl-3,5,9-trioxa-4-phosphapentacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (37). This compound was prepared by a similar method from 5 g (8.3 mmol) of **32** and 0.5 g of 5% Pd/C to give after precipitation with ether 3.93 g (92%) of **37** as a white powder with no well-defined melting point: NMR ($CDCl_3$–CD_3OH) δ 4.28 (m, 2 H, $POCH_2$), 4.13, 3.82 (m, 2 H, CH_2OP), 3.64 (m, 3 H, CHO, CH_2N), 3.36 (t, 2 H, OCH_2), 3.06 (s, 9 H, $N(CH_3)_3$), 1.49 (m, 2 H, CH_2CH_2O), 1.24 (m, 26 H, $(CH_2)_{13}$), 1.23 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 0.88 (m, 3 H, terminal CH_3); mass spectrum (FAB) m/z 552 (M + H). Anal. ($C_{28}H_{58}O_7PN{\cdot}H_2O$) C, H, P, N.

4,7-Dihydroxy-*N*,*N*,*N*,6-tetramethyl-3,5,9-trioxa-4-phosphapentacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (38). This compound was prepared by a similar method from 3.5 g (5.97 mmol) of **33** and 0.6 g of 5% Pd/C, giving after precipitation with ether 2.69 g (91%) of **38** as a white powder with

no well-defined melting point: IR (KBr) 3420 (OH) cm^{-1}; mass spectrum (FAB) m/z 496 (M + H). Anal. ($C_{25}H_{54}O_6PN \cdot {}^1/_2H_2O$) C, H, N, P.

8-(Acetyloxy)-4-hydroxy-*N*,*N*,*N*-trimethyl-3,5,10-trioxa-4-phosphahexacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (39). A solution of 4.5 g (9.1 mmol) of **34**, 23.2 g (230 mmol) of acetic anhydride, and 9.2 g (90.8 mmol) of triethylamine in 250 mL of $CHCl_3$ was refluxed for 4 h. Solvent and excess anhydride were removed at reduced pressure. The residue was chromatographed on silica gel (250 mL dry volume), eluting first with $CHCl_3$–CH_3OH (7:3) to remove more mobile impurities and then with $CHCl_3$–CH_3OH–H_2O (70:30:5) to elute product. The product was precipitated with ether, giving 3.6 g (74%) of **39** as a white powder with no well-defined melting point: NMR ($CDCl_3$–CD_3OD) δ 5.16 (m, 1 H, CHO), 4.25 (m, 2 H, $POCH_2$), 3.93 (m, 2 H, CH_2OP), 3.63 (m, 2 H, CH_2N), 3.50 (m, 4 H, CH_2OCH_2), 3.24 (s, 9 H, $N(CH_3)_3$), 2.07 (s, 3 H, $COCH_3$), 1.92 (m, 2 H, $CHCH_2CH_2$), 1.54 (m, 2 H, CH_2CH_2O), 1.26 (m, 26 H, $(CH_2)_{13}$), 0.88 (m, 3 H, terminal CH_3); IR (KBr) 1730 (C=O) cm^{-1}; mass spectrum (FAB) m/z 538 (M + H). Anal. ($C_{27}H_{56}O_7PN \cdot {}^1/_2H_2O$) C, H, N, P.

7-(Acetyloxy)-4-hydroxy-*N*,*N*,*N*-trimethyl-3,5,10-trioxa-4-phosphahexacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (40). This compound was prepared by a similar method from 5.0 g (10.0 mmol) of **35**, 25 g (245 mmol) of acetic anhydride, and 10.2 g (100 mmol) of triethylamine, giving 2.88 g (53%) of **40** as a colorless powder with no well-defined melting point: NMR ($CDCl_3$–CD_3OD) δ 5.14 (m, 1 H, CH), 4.28 (m, 2 H, $POCH_2$), 3.93 (m, 2 H, CH_2OP), 3.65 (m, 2 H, CH_2N), 3.40 (m, 4 H, CH_2OCH_2), 3.23 (s, 9 H, $N(CH_3)_3$), 2.05 (s, 3 H, $COCH_3$), 1.87 (m, 2 H, $CHCH_2CH_2$), 1.52 (m, 2 H, OCH_2CH_2), 1.26 (m, 26 H, $(CH_2)_{13}$), 0.88 (m, 3 H, terminal CH_3); IR (KBr) 1735 (C=O) cm^{-1}; mass spectrum (FAB) m/z 538 (M + H). Anal. ($C_{27}H_{56}O_7NP \cdot H_2O$) C, H, N; P: calcd, 5.57; found, 6.20.

7-(Acetyloxy)-4-hydroxy-*N*,*N*,*N*,8-tetramethyl-3,5,9-trioxa-4-phosphapentacosan-1-aminium 4-Oxide, Hydroxide, Inner Salt (41). This compound was prepared from 6.4 g (12.9 mmol) of **36**, 32.95 g (320 mmol) of acetic anhydride, and 13.1 g (130 mmol) of triethylamine, giving, after precipitation with ether, 4.6 g (66%) of **41**, a mixture of two isomers in equal amounts, as a white powder with no well-defined melting point: NMR ($CDCl_3$–CD_3OD) δ 5.12, 5.02 (m, 1 H, CHOAc), 4.33–3.35 (m, 9 H, α to O and N), 3.34 (s, 9 H, $N(CH_3)_3$), 2.09, 2.08 (s, 3 H, CH_3CO), 1.49 (m, 2 H, CH_2CH_2O), 1.06 (m, 28 H, $(CH_2)_{14}$), 1.14, 1.12 (d, 3 H, CH_3), 0.88 (m, 3 H, terminal CH_3); IR (KBr) 1725 (C=O) cm^{-1}; mass spectrum (FAB) m/z 538 (M + H). Anal. ($C_{27}H_{56}O_7PN$) C, H, N, P.

7-(Acetyloxy)-4-hydroxy-*N*,*N*,*N*,8,8-pentamethyl-3,5,9-trioxa-4-phosphapentacosan-1-aminium 4-Oxide, Hydroxide, Inner salt (42). This compound was prepared by a similar method from 3 g (5.9 mmol) of **37**, 15 g (150 mmol) of acetic anhydride, and 5.96 g (58.9 mmol) of triethylamine except that the reaction mixture was refluxed for 15 h, giving, after precipitation with ether, 1.0 g (31%) of **42** as a colorless powder with no definite melting point: NMR ($CDCl_3$–CD_3OD) δ 5.12 (m, 1 H, CHO), 4.24, 3.97 (m, 4 H, $CH_2OPO_3CH_2$), 3.59 (m, 2 H, CH_2N), 3.57 (s, 9 H, $N(CH_3)_3$), 3.24 (t, 2 H, OCH_2), 3.21 (s, 3 H, $COCH_3$), 1.46 (m, 2 H, OCH_2CH_2), 1.26 (m, 29 H, $(CH_2)_{13}$, CH_3), 1.17 (s, 3 H, CH_3), 0.88 (m, 3 H, terminal CH_3); IR (KBr) 1735 (C=O) cm^{-1}; mass spectrum (FAB) m/z 552 (M + H). Anal. ($C_{28}H_{58}O_7PN \cdot H_2O$) C, H, N, P.

7-(Acetyloxy)-4-hydroxy-*N*,*N*,*N*,6-tetramethyl-3,5,9-trioxa-4-phosphapentacosan-1-aminium 4-Oxide, Hydroxide, Inner salt (43). This compound was prepared by a similar method from 2 g (4 mmol) of **38**, 10.3 g (101 mmol) pf acetic anhydride, and 4.08 g (40.3 mmol) of triethylamine to give, after precipitation with ether, 1.13 g of (52%) of **43**, a mixture of isomers, as a colorless powder with no definite melting point: NMR ($CDCl_3$–CD_3OD) δ 5.17, 5.03 (m, 1 H, CHOAc), 4.44, 4.24 (m, 3 H, $CHOPO_3CH_2$), 3.72–3.33 (m, 6 H, CH_2N, CH_2OCH_2), 3.22, 3.21 (s, 9 H, $N(CH_3)_3$), 2.09, 2.08 (s, 3 H, $COCH_3$), 1.52 (m, 2 H, CH_2CH_2O), 1.23 (m, 29 H, $(CH_2)_{13}$, CH_3), 0.88 (m, 3 H, terminal CH_3); IR (KBr) 1738 (C=O) cm^{-1}; mass spectrum (FAB) m/z 538 (M + H). Anal. ($C_{27}H_{56}O_7PN \cdot 2{}^1/_2H_2O$) C, H, N, P.

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