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Lactone and Cyclic Ether Analogues of Platelet-Activating Factor. Synthesis and Biological Activities

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Six-membered lactone and tetrahydropyran analogues of platelet-activating factor (PAF), 4—11, and related antagonistic derivatives 41—46 were synthesized. None of the δ-lactones 4—7 showed PAF-like activities, while the corresponding cyclic ethers 8, 9 and 11 were slightly active. Some of the cyclic antagonists showed more potent inhibitory activities than the open chain antagonist CV-3988 against platelet aggregation (rabbit platelet-rich plasma, IC_{50}) and hypotension (rat, ID_{50}) induced by C_{16}-PAF: *e.g.* *dl*-3-{6-[*O*-(*trans*-3-heptadecylcarbamoyloxytetrahydropyran-2-yl)methyl]phosphonoxy}hexylthiazolium (inner salt) (41d) (IC_{50} 5.5×10^{-7} M, ID_{50} 0.046 mg/kg, i.v.); *dl*-3-{5-[*O*-(*cis*-3-heptadecylcarbamoylthiotetrahydropyran-2-yl)methyl]phosphonoxy}pentylthiazolium (inner salt) (43c) (IC_{50} 5.7×10^{-7} M, ID_{50} 0.076 mg/kg, i.v.).

Keywords platelet-activating factor; PAF antagonist; platelet aggregation; hypotension; lactone PAF analogue; cyclic ether PAF analogue

In view of the importance of platelet-activating factor[1] (PAF) (**1**) in biological and pathological processes,[2] a number of its analogues[3-7] have been synthesized to clarify the structure–activity relationships of this remarkable ether phospholipid and to find effective PAF antagonists. Based on the accumulated data, a putative structure of the PAF binding site has been proposed.[6] Nevertheless, information about the conformation of PAF binding to the specific receptor(s)[8] is still scarce, although several conformationally restricted analogues[4] including cyclic agonistic[4e] and antagonistic derivatives[3c,4a,f] have been reported.

In this paper, we describe the synthesis of the δ-lactone PAF analogues, *dl*-**4**—**7** (Fig. 1). These compounds represent the conformationally restricted glycerol backbone of the propionyl PAF (**2**), which has nearly equipotent biological activities with **1**.[1d,7] Imaginary connection of the propionyl group with C(1) led to the structure of **4** and **5** (type A compounds), while combination with C(3) gave **6** and **7** (type B compounds). Corresponding cyclic ether derivatives **8**—**11** (Fig. 1) were also prepared, because the 2-ethoxy analogue **3** has considerable PAF-like activities.[7] In order to examine the influence of the constrained backbone on antagonistic activities against PAF, cyclic ether derivatives **41**—**46** (Chart 4), with antagonistic side chains like those of the first PAF antagonist CV-3988,[5a] were synthesized. The PAF-agonistic and antagonistic properties of these newly synthesized compounds are also described.

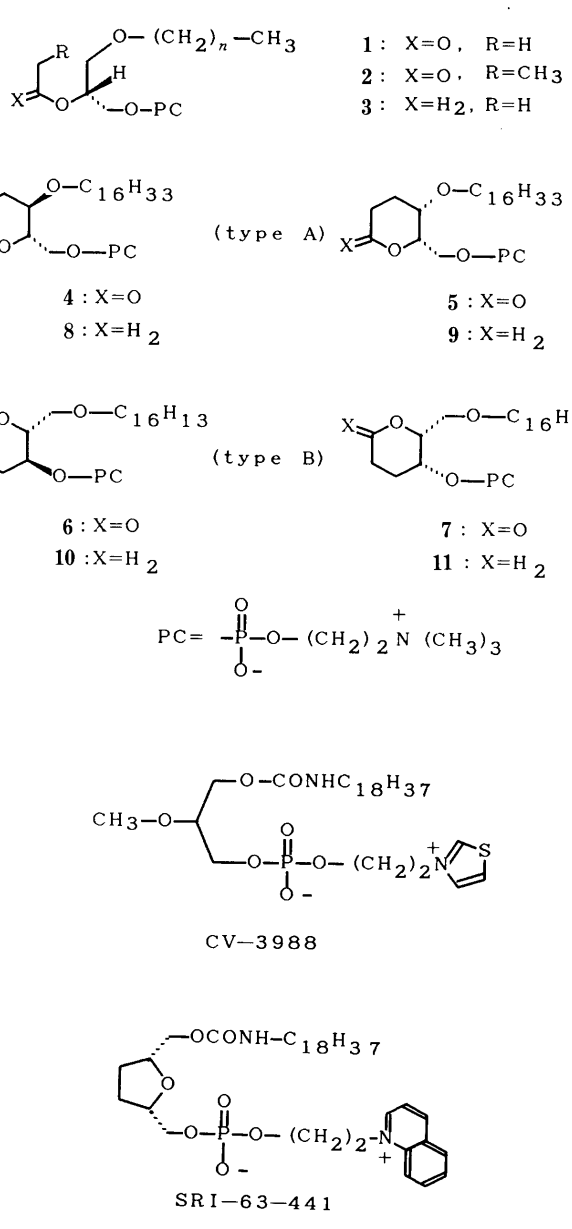
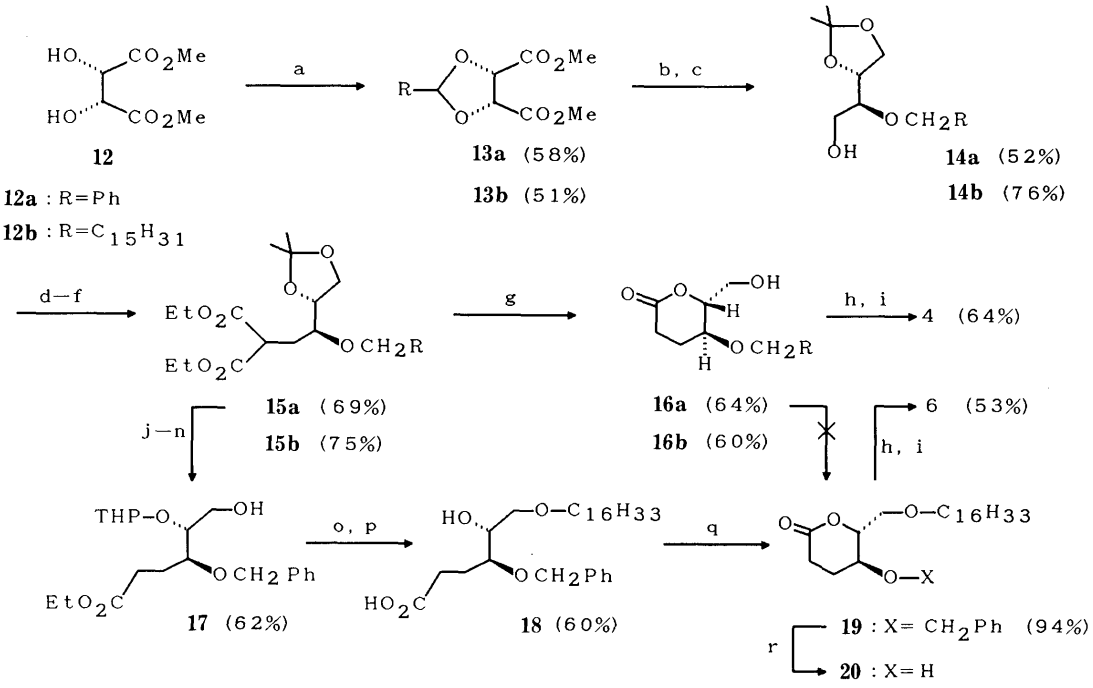


Fig. 1

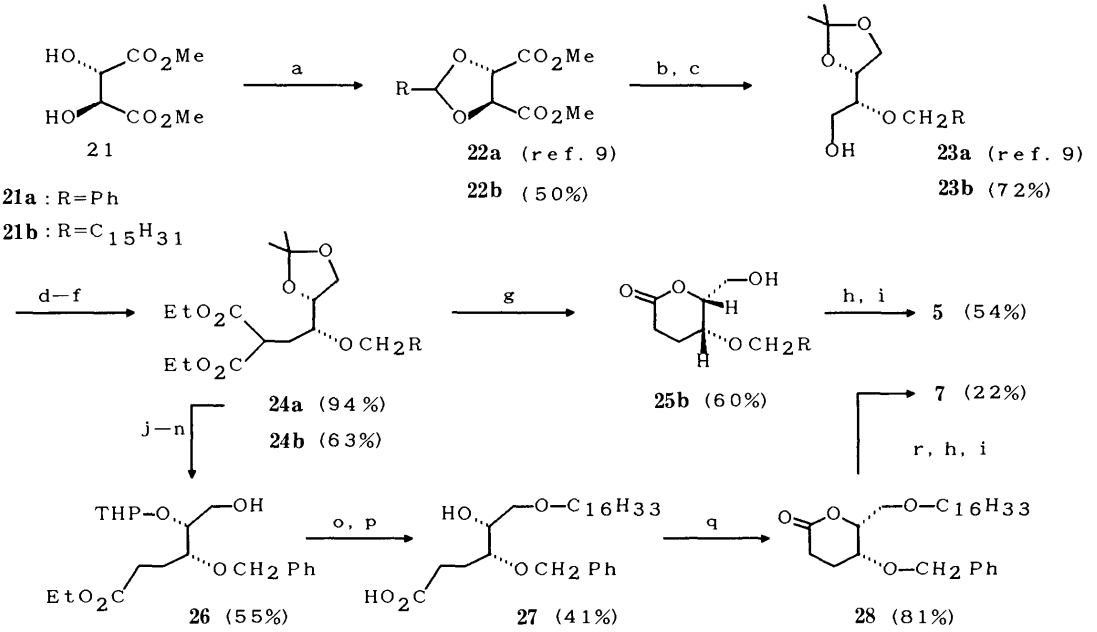
Syntheses of the Lactone Derivatives of PAF The *trans* lactone derivatives **4** and **6** were prepared from dimethyl *meso*-tartrate (**12**) as illustrated in Chart 1. Acetalization of **12** with benzaldehyde gave **13a** as an isomeric mixture, which was converted into the racemic 2-*O*-benzylerythritol derivative **14a** according to Ohno's procedure for the corresponding threitol derivative.[9] The methanesulfonate of **14a** was treated with sodium iodide, and the resulting iodide was condensed with diethyl malonate to afford the acetal diester **15a**. Treatment of **15a** with magnesium chloride (hexahydrate) in *N*,*N*-dimethylacetamide (DMA)[10] yielded the six-membered *trans*-lactone **16a**. Starting from the reaction of **12** with hexadecanal, *trans*-4-hexadecyloxy-6-hydroxy-5-hexanolide (**16b**) was prepared similarly. The

trans configuration of **16b** was evidenced by its proton nuclear magnetic resonance (^{1}H-NMR) signals [400 MHz: δ 3.69 (1H, ddd, J=6.8, 6.8, and 5.4 Hz, C(4)-H), 4.23 (1H, dt, J=6.8, and 3.4 Hz, C(5)-H)], showing a coupling constant of 6.8 Hz between the two methine protons. Introduction of the phosphocholine moiety into **16b** by a modification of Chandrakumar and Hajdu's method[11] (see Experimental) yielded the PAF analogue **4**.



a) RCHO, TsOH; b) $LiAlH_4$—$AlCl_3$; c) $Me_2C(OMe)_2$, H^+; d) MsCl, NEt_3; e) NaI, $NaHCO_3$; f) $CH_2(CO_2Et)_2$, NaH; g) $MgCl_2$, DMA; h)  , iso-Pr_2NEt; i) NMe_3; j) NaCl, DMSO—H_2O; k) aq. AcOH; l) *tert*-$BuMe_2SiCl$, NEt_3, DMAP; m) dihydropyran, PPTS; n) Bu_4NF; o) $C_{16}H_{33}Br$, NaH; p) aq. HCl; q) Ac_2O—pyridine; r) H_2, Pd—C

Chart 1



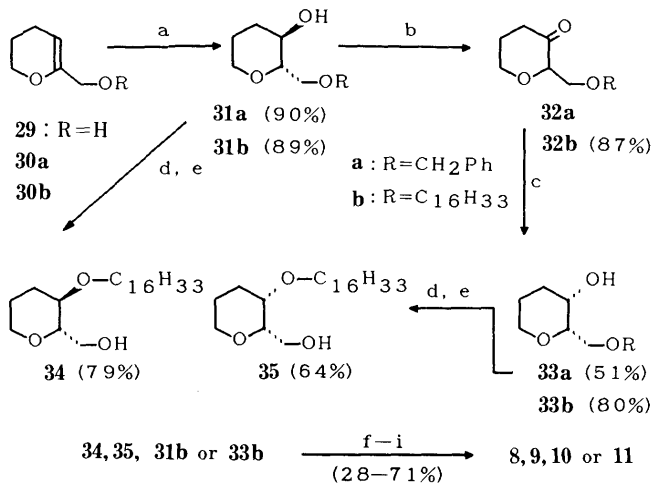
(a—r: same as in Chart 1)

Chart 2

On the other hand, the synthesis of the type B compound **6** was not straightforward. The attempted alkylation of **16a** with hexadecyl bromide to **19** resulted in cleavage of the lactone ring under the basic conditions. Therefore, introduction of the hexadecyl side chain at C(6) before lactonization became necessary. Thus, **15a** was converted into the 6-hydroxyhexanoate **17** in five steps: i) deethoxycarbonylation, ii) deacetalization, iii) *tert*-butyldimethylsilylation of the primary hydroxy group, iv) tetrahydropyranylation, v) desilylation. Alkylation of **17** with hexadecyl bromide followed by removal of the tetrahydropyranyl group gave the hydroxy-acid **18**, which, on treatment with acetic anhydride, afforded the lactone **19**. The benzyl group of **19** was removed by catalytic hydrogenation, and the resulting hydroxy-lactone **20** was phosphorylated as described above to give the final product **6**. The coupling constant (7.8 Hz) between the two methine protons proved the *trans* configuration of the lactone **20**.

The *cis*-lactones **5** and **7** were similarly prepared from dimethyl *dl*-tartrate (**21**), as illustrated in Chart 2. The *cis* configuration of the lactones in this series was proved by the small coupling constant (2.0 Hz) between the C(4) and C(5) protons of **28** in its 400 MHz NMR spectra [δ 4.43 (1H, ddd, J=7.3, 5.4 and 2.0 Hz, C(5)-H)].

Synthesis of the Cyclic Ether Derivatives of PAF All of the four racemic cyclic ether derivatives **8**—**11** were synthesized from the common starting material, 3,4-dihydro-6-hydroxymethyl-2*H*-pyran[12] (**29**), as outlined in Chart 3. Alkylation of **29** with benzyl chloride or hexadecyl bromide gave **30a** or **30b**, respectively. Hydroboration of the dihydropyran ring[12,13] afforded the *trans* alcohols **31a, b**, which were oxidized with Jones' reagent or pyridinium chlorochromate to the ketones **32a, b**. Stereoselective reduction of **32a, b** with L-Selectride yielded the *cis* alcohols **33a, b**. The benzyl derivatives **31a** and **33a** were alkylated with hexadecyl bromide and debenzylated to afford the 3-hexadecyloxy compounds **34** and **35**, respectively. By the standard method to introduce the phosphocholine side chain,[14] the four alcohols **34**, **35**, **31b** and **33b** were converted into the PAF analogues **8**, **9**, **10** and **11**, respectively.



a) BH_3—THF, H_2O_2, aq. NaOH; b) CrO_3;
c) L—Selectride; d) $C_{16}H_{33}Br$, KOH or NaH;
e) H_2, 10% Pd–C; f) $BrCH_2CH_2OPOCl_2$;
g) H_2O; h) NMe_3; i) Ag_2CO_3

Chart 3

The antagonists **41**—**45** with side chains like those of CV-3988 were also prepared from the same precursors **31a** and **33a** as illustrated in Chart 4. Carbamoylation of **31a** and **33a** with octadecyl isocyanate, prepared from nonadecanoic acid and diphenylphosphoryl azide (DPPA),[15] and subsequent debenzylation gave the primary alcohols **36a** and **37**, respectively. The heptadecylcarbamoyloxy derivative **36b** was similarly prepared using heptadecyl isocyanate. Phosphorylation of **36a, b** or **37** with 2-bromoethyl phosphorodichloridate and the reaction of the resulting 2-bromoethyl phosphate with thiazole were carried out as described by Tsushima *et al.*[5a] The products, **41a, b** and **42**, were obtained as inner salts after treatment with the ion-exchanger Amberlite MB-3.[16] Compounds with longer methylene chains, **41c** and **41d**, were similarly prepared using corresponding ω-bromophosphorochloridates.[17]

As the *cis* antagonist **42** showed weak agonistic activities (*vide infra*), the corresponding carbamoylthio derivatives **43a**—**d** were prepared in order to eliminate this undesirable effect. Reaction of the methanesulfonate of **31a** with sodium thioacetate, after deacetylation, yielded the *cis*-thiol **38** with inversion of the configuration at C(3). By a similar procedure to that described above, **38** was converted into the final products **43a**—**d** (inner salts). Removal of the benzyl group in the presence of the sulfur atom (step j in Chart 4) was achieved by the hard acid–soft base combination method developed by Fuji *et al.*,[18] whereas the usual catalytic hydrogenation procedure was unsuccessful.

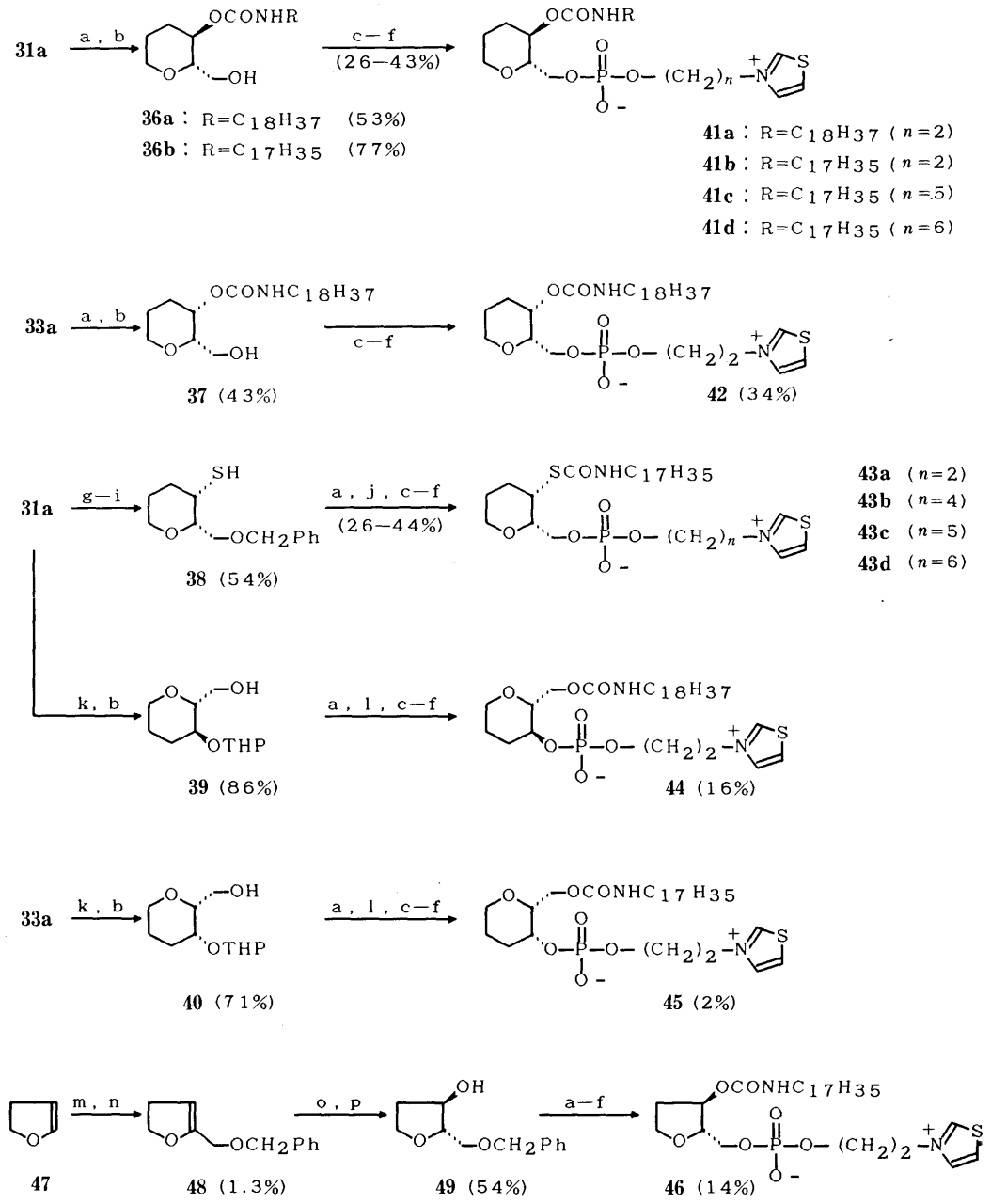
To synthesize type B antagonists **44** and **45**, **31a** and **33a** were tetrahydropyranylated and subsequently debenzylated to afford the primary alcohols **39** and **40**, respectively.

Table I. Agonistic Activities of Cyclic PAF Analogues

Compound	Type	Platelet aggregation (Rabbit, EC_{50} μM)	Hypotension (Rat, relative ratio)
8	A, *trans*	>400	3×10^{-5}
9	A, *cis*	70	$<3\times10^{-5}$
10	B, *trans*	>100	$<3\times10^{-5}$
11	B, *cis*	4.6	3×10^{-4}
C_{16}-PAF		0.009	1.0

Table II. Antagonistic Activities of Cyclic PAF Analogues

Compound	Type	Platelet aggregation (Rabbit, IC_{50} μM)	Hypotension (Rat, ID_{50} mg/kg, i.v.)
41a	A, *trans*	3.8	0.46
41b	A, *trans*	1.5	0.57
41c	A, *trans*	0.55	0.044
41d	A, *trans*	0.55	0.046
42	A, *cis*	9.6	0.09
43a	A, *cis*	3.1	0.22
43b	A, *cis*	1.1	0.24
43c	A, *cis*	0.57	0.076
43d	A, *cis*	0.78	0.19
44	B, *trans*	>100	Inactive
45	B, *cis*	24	2.0
46	A, *trans*	21	0.41
CV-3988		9.8	0.49



a) $C_{17}H_{35}COOH$ or $C_{18}H_{37}COOH$, DPPA, Et_3N; b) H_2, Pd—C; c) Br $(CH_2)_nOPOCl_2$; d) H_2O; e) thiazole; f) Amberlite MB—3; g) MsCl, Et_3N; h) AcSNa; i) MeONa, MeOH; j) NaI, $AlCl_3$, MeCN; k) dihydropyran, PPTS; l) H^+; m) BuLi, $(CH_2O)_3$; n) $PhCH_2Br$, Et_3N; o) BH_3; p) H_2O_2, aq. NaOH

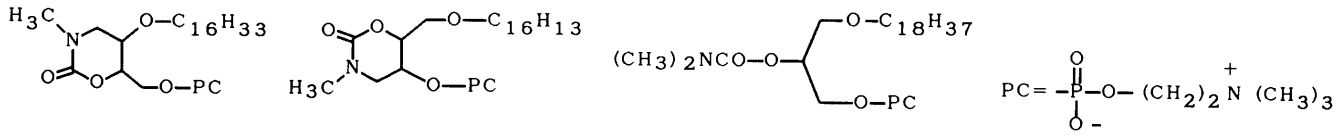
Chart 4

Introduction of the two side chains into **39** and **40** was carried out as described above to yield **44** and **45**.

The five membered analogue **46** was also synthesized, starting from dihydrofuran (**47**). Hydroxymethylation of **47** as reported for the synthesis of **29**[12] afforded unstable 2-hydroxymethyldihydrofuran, which was in turn converted into the final product **46**, following the procedure described for preparation of **41b**.

Biological Results The agonistic activities of the PAF analogues **4**—**11** were evaluated in hypotension (rat) and rabbit platelet aggregation tests according to the methods described earlier.[19] All of the four lactone derivatives **4**—**7** were inactive in both tests. On the other hand, the cyclic ether analogues **8**, **9** and **11** were weakly active, as summarized in Table I. Only the type B *cis* compound **11** was active in both hypotension and platelet aggregation tests. The corresponding type B *trans* isomer **10** was totally inactive.

Antagonistic activities of the compounds **41**—**46** were measured against rabbit platelet aggregation and hypotension in the rat induced by C_{16}-PAF, and the results are summarized in Table II. The *trans* type B derivative **44** showed no antagonistic activities, whereas the *cis* compound **45** was weakly active. On the other hand, both *trans*



50 (*cis*) 51 (*trans*) 52 (*cis*) 53 (*trans*) 54

Fig. 2

and *cis* isomers of type A cyclic ether derivatives with the thiazolioethylphosphoryl side chain, **41a, b** and **42**, showed antagonistic potencies comparable to that of the reference compound CV-3988. The *cis* compound **42**, in addition, exhibited weak agonistic activities in platelet aggregation ($EC_{50} = 10^{-4}$—10^{-3} M) and hypotension (relative potency: 1/300000 against C_{16}-PAF). In contrast, the corresponding *cis* thio-compound **43a** was devoid of these disadvantageous effects.

The potency of the antagonistic activities was influenced by the methylene chain length between the phosphoryl and thiazolium residues in the side chain.[3d] Best results were obtained when five or six methylene groups linked the two residues (compounds **41d** and **43c**).

The five-membered *trans* type A analogue **46** was much less active than the six-membered homologue **41b**.

Discussion

Unexpectedly, all of the lactone analogues **4**—**7**, with all the functional groups of PAF in their molecules, were totally inactive, whereas the corresponding cyclic ether analogues showed PAF-like activities to some extent. One tentative explanation is the lability of the lactone ring to hydrolysis. During the synthesis of the compounds **4**—**7**, we found that the δ-lactone ring was gradually hydrolyzed even under neutral conditions. During the biological tests, the lactones **4**—**7** might have been cleaved. To examine this possibility, we prepared water-stable cyclic urethane derivatives **50**—**53**,[20] whose non-cyclic form **54** is known to be a potent PAF agonist.[5c] These compounds, however, were totally inactive, suggesting that ring cleavage was not the reason for the loss of activity. An alternative explanation is that the orientation of the carbonyl group in the ring might not be appropriate to exert the agonistic activities.

Results on the activities of antagonistic compounds can be interpreted more clearly. The fact that cyclic derivatives **41a** and **43a** exhibited more potent antagonistic activities than CV-3988 seems to show the existence of an active conformation of the open chain antagonist. Related tetrahydrofuran compounds (*e.g.* SRI-63-441) with potent PAF-antagonistic activities have been reported,[3c] although their structures do not exactly correspond to the glycerol backbone of PAF. As the specific binding of PAF to the receptor is competitively inhibited by CV-3988,[5d,8] the partially constrained structures of **41a** and **43a** might be correlated to the "active conformation" of PAF itself. From this point of view, it would be interesting to investigate whether the enantiomers of these cyclic antagonists show different activities or not. The following paper[21] will describe the results of our attempt to answer this question.

Experimental

All melting points and boiling points are uncorrected. ^{1}H-NMR spectra were obtained with a Varian EM-390 (90 MHz), a JEOL JNM-GX270 (270 MHz), or a JEOL JNM-GX400 (400 MHz) instrument. The solvent was $CDCl_3$ and the frequency was 90 MHz unless otherwise noted. Infrared (IR) spectra were taken in $CHCl_3$ solutions on a JEOL IR-A2 spectrometer if not otherwise specified. Mass spectra (MS) were obtained with a JEOL JMS-01SG spectrometer. Fast atom bombardment (FAB)-MS were taken with a JMS-HX100 spectrometer.

Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Dimethylformamide (DMF) was refluxed over CaH_2 and distilled. Other aprotic solvents for reactions were passed through a short column of neutral alumina (ICN Alumina N-Super I) just before use. All reactions in aprotic solvents were carried out under a nitrogen atmosphere. For silica gel column chromatography, Kieselgel 60 (Merck, 60—230 mesh) was used.

Dimethyl *meso*-2,3-*O*-Benzylidenetartrate (13a) A mixture of dimethyl *meso*-tartrate (48.20 g, 271 mmol), benzaldehyde (31.60 g, 307 mmol), *p*-TsOH (H_2O) (1.00 g, 5.26 mmol) and toluene (500 ml) was heated under reflux for 8 h. After cooling, the mixture was poured into water and the organic layer was washed with saturated aqueous $NaHCO_3$ and aqueous NaCl solution, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel (750 g). Elution with hexane–EtOAc (4 : 1—2 : 1) yielded **13a** (41.88 g, 58%) as a crystalline isomeric mixture (ratio, *ca.* 1 : 1), which was used in the next step without separation. ^{1}H-NMR δ: 3.76 (6H, s), 4.84 and 4.97 (2H, s × 2), 5.87 and 6.36 (1H, s × 2), 7.15—7.65 (5H, m).

Dimethyl *meso*-2,3-*O*-Hexadecylidenetartrate (13b) In a similar manner to that described above, dimethyl *meso*-tartrate was allowed to react with hexadecanal to afford **13b** (51%) as a crystalline isomeric mixture (ratio, *ca.* 1 : 1, mp 52 °C). ^{1}H-NMR δ: 0.7—2.0 (31H, m), 3.74 (6H, s), 4.72 and 4.86 (2H, s × 2), 5.10 and 5.52 (1H, t × 2, J = 7 Hz). IR cm^{-1}: 1750. MS *m/z*: 401 ($M^+ + 1$), 400 (M^+), 399 ($M^+ - 1$), 341 ($M^+ - CO_2Me$). *Anal.* Calcd for $C_{22}H_{40}O_6$: C, 66.00; H, 10.07. Found: C, 65.90; H, 10.21.

***dl*-2-*O*-Benzyl-3,4-*O*-isopropylideneerythritol (14a)** A solution of $AlCl_3$ (70.00 g, 525 mmol) in Et_2O (900 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (20.00 g, 527 mmol) in Et_2O–CH_2Cl_2 (1 : 1, 800 ml) under ice-water cooling. A solution of **13a** (41.80 g, 157 mmol) in CH_2Cl_2 (100 ml) was then added during a period of 40 min under ice-water cooling, and the mixture was stirred at room temperature for 3 h. Under ice-water cooling, 4% aqueous NaOH solution (160 ml) was added, and the mixture was filtered through a layer of Celite. The filtrate was evaporated *in vacuo*, and the residue was chromatographed on silica gel (300 g). Elution with CH_2Cl_2–EtOAc (5 : 1—0 : 1) gave *dl*-2-*O*-benzylerythritol (21.75 g, 65%) as a white waxy substance, mp 30—34 °C. ^{1}H-NMR δ: 3.2—4.3 (9H, m), 4.49 (1H, d, J = 11 Hz), 4.58 (1H, d, J = 11 Hz), 7.32 (5H, m). IR cm^{-1}: 3400. MS *m/z*: 213 ($M^+ + 1$), 212 (M^+). *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 61.98; H, 7.80.

A mixture of the above compound (21.75 g, 102 mmol), 2,2-dimethoxypropane (10.67 g, 102 mmol), *p*-TsOH (H_2O) (200 mg) and benzene (200 ml) was heated under reflux for 3 h, in a flask equipped with a Soxhlet extractor containing molecular sieves (4 A, 10 g). After cooling, the mixture was poured into water, and the organic layer was washed with saturated aqueous $NaHCO_3$ and aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The oily residue was chromatographed on silica gel (500 g). Elution with hexane–CH_2Cl_2–EtOAc (8 : 1 : 1) yielded **14a** (20.65 g, 80%) as a colorless oil, bp 135—140 °C (bath temperature)/2 mmHg. ^{1}H-NMR δ: 1.33 (3H, s), 1.43 (3H, s), 2.10 (1H, t, J = 6 Hz), 3.4—4.3 (6H, m), 4.67 (2H, s), 7.37 (5H, m). IR cm^{-1}: 3600. MS *m/z*: 252 (M^+). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.39; H, 7.82.

***dl*-2-*O*-Hexadecyl-3,4-*O*-isopropylideneerythritol (14b)** A solution of $AlCl_3$ (80.0 g, 600 mmol) in Et_2O (900 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (22.76 g, 600 mmol) in Et_2O–CH_2Cl_2 (1 : 1, 800 ml)

under ice-water cooling. A solution of **13b** (58.60 g, 147 mmol) in CH_2Cl_2 (100 ml) was added, and the cooling bath was removed. The mixture was stirred at room temperature for 2 h, then heated under reflux for 2 h, and allowed to cool. Aqueous 10% HCl (1.5 l) was added, and the mixture was extracted ten times with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated to dryness. The crystalline residue was recrystallized from Et_2O–hexane to give *dl*-2-*O*-hexadecylerythritol (40.77 g, 80%), mp 41.0—42.0 °C. ^{1}H-NMR δ: 0.8—1.8 (31H, m), 2.8—4.0 (11H, m). IR cm^{-1}: 3400. MS *m/z*: 347 ($M^+ + 1$). *Anal.* Calcd for $C_{20}H_{42}O_4$: C, 69.32; H, 12.21. Found: C, 69.03; H, 12.01.

Acetalization of the above diol, as described for the synthesis of **14a**, yielded **14b** (95%) as a colorless oil. ^{1}H-NMR δ: 0.7—1.8 (31H, m), 1.34 (3H, s), 1.41 (3H, s), 2.08 (1H, dd, J=7.0, 4.5 Hz), 3.2—4.3 (8H, m). IR cm^{-1}: 3510. MS *m/z*: 386 (M^+), 371 ($M^+ - Me$). *Anal.* Calcd for $C_{23}H_{46}O_4$: C, 71.45; H, 11.99. Found: C, 71.24; H, 12.07.

Ethyl *dl-erythro*-4-Benzyloxy-2-ethoxycarbonyl-5,6-isopropylidenedioxyhexanoate (15a) A solution of MsCl (3.70 ml, 47.8 mmol) in benzene (50 ml) was added to a stirred solution of **14a** (10.03 g, 39.8 mmol) and Et_3N (7.80 ml, 56.0 mmol) in benzene (150 ml) under ice-water cooling. After being stirred at room temperature for 1 h, the mixture was poured into ice water, and the organic layer was washed with aqueous NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*, yielding the methanesulfonate of **14a** as a colorless oil (13.11 g). ^{1}H-NMR δ: 1.30 (3H, s), 1.36 (3H, s), 2.93 (3H, s), 3.4—4.5 (6H, m), 4.53 (1H, d, J=11 Hz), 4.67 (1H, d, J=11 Hz), 7.24 (5H, m).

A mixture of the above methanesulfonate (13.11 g), $NaHCO_3$ (20.00 g) and NaI (29.74 g) in acetone (200 ml) was heated under reflux for 14 h. After cooling, the mixture was diluted with EtOAc and poured into ice water. The organic layer was washed with aqueous NaCl solution, dried over Na_2SO_4, evaporated to dryness, and the residue was chromatographed on silica gel (250 g). Elution with hexane–EtOAc (95 : 5) afforded *dl-erythro*-3-*O*-benzyl-4-iodo-1,2-*O*-isopropylidenebutane-1,2,3-triol (13.70 g, 95%) as a colorless oil. ^{1}H-NMR δ: 1.34 (3H, s), 1.40 (3H, s), 3.12 (1H, dt, J=7, 4 Hz), 3.48 (2H, d, J=4 Hz), 3.8—4.3 (3H, m), 4.48 (1H, d, J=11 Hz), 4.75 (1H, d, J=11 Hz), 7.40 (5H, m). IR cm^{-1}: 520. MS *m/z*: 362 (M^+), 347 ($M^+ - Me$).

A solution of diethyl malonate (6.351 g, 39.7 mmol) in DMF (20 ml) was added to a stirred suspension of NaH (55% dispersion in mineral oil, 1.802 g, 41.3 mmol) in DMF (100 ml) under ice-water cooling. The mixture was stirred at room temperature for 30 min, and then a solution of the above iodide (12.95 g, 35.8 mmol) in DMF (30 ml) was added dropwise under ice-water cooling. The reaction mixture was heated at 95 °C for 3 h, cooled, diluted with EtOAc and poured into water. The organic layer was washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was subjected to medium-pressure liquid chromatography (MPLC) using a Lobar C column (Merck). Elution with hexane–EtOAc (9 : 1) gave **15a** (10.37 g, 73%) as a colorless oil. ^{1}H-NMR δ: 1.22 (6H, t, J=7.5 Hz), 1.34 (3H, s), 1.41 (3H, s), 2.04 (1H, ddd, J=14.5, 7.5, 6.0 Hz), 2.30 (1H, ddd, J=14.5, 8.5, 5.0 Hz), 3.45—4.1 (4H, m), 3.65 (1H, dd, J=8.5, 6 Hz), 4.15 (4H, q, J=7.5 Hz), 4.56 (1H, d, J=12 Hz), 4.65 (1H, d, J=12 Hz), 7.36 (5H, m). IR cm^{-1}: 1725. MS *m/z*: 394 (M^+), 379 ($M^+ - Me$). *Anal.* Calcd for $C_{21}H_{30}O_7$: C, 63.94; H, 7.67. Found: C, 63.75; H, 7.73.

Ethyl *dl-erythro*-2-Ethoxycarbonyl-4-hexadecyloxy-5,6-isopropylidenedioxyhexanoate (15b) By a similar procedure to that described above, **14b** was converted into its methanesulfonate [^{1}H-NMR δ: 0.7—1.8 (31H, m), 1.32 (3H, s), 1.39 (3H, s), 3.01 (3H, s), 3.2—4.7 (8H, m)], and then into the corresponding iodide (colorless oil, 96%). ^{1}H-NMR δ: 0.6—1.8 (31H, m), 1.34 (3H, s), 1.40 (3H, s), 2.93 (1H, dt, J=3.5, 3.5 Hz), 3.35 (1H, dt, J=9.0, 6.0 Hz), 3.45 (2H, d, J=3.5 Hz), 3.65 (1H, dt, J=9.0, 6.0 Hz), 3.9—4.2 (3H, m). IR cm^{-1}: 515. MS *m/z*: 481 ($M^+ - Me$). *Anal.* Calcd for $C_{25}H_{45}IO_3$: C, 55.64; H, 9.14; I, 25.56. Found: C, 55.71; H, 8.93; I, 25.72.

Alkylation of diethyl malonate with this iodide in the same way as described above afforded **15b** (colorless oil, 78%). ^{1}H-NMR δ: 0.6—1.8 (37H, m), 1.34 (3H, s), 1.41 (3H, s), 1.8—2.5 (2H, m), 3.2—4.2 (7H, m), 4.21 (4H, q, J=8.0 Hz). IR cm^{-1}: 1725. MS *m/z*: 529 ($M^+ + 1$), 513 ($M^+ - Me$). *Anal.* Calcd for $C_{30}H_{56}O_7$: C, 68.14; H, 10.67. Found: C, 67.92; H, 10.68.

***dl-trans*-4-Benzyloxy-6-hydroxy-5-hexanolide (16a)** A mixture of **15a** (9.354 g, 23.7 mmol), $MgCl_2(6H_2O)$ (5.018 g, 24.7 mmol) and *N*,*N*-dimethylacetamide (95 ml) was heated under reflux for 22 h. After cooling, the mixture was diluted with EtOAc, poured into water and extracted six times with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (180 g). Elution with hexane–EtOAc (2 : 1) gave a crude product, which was further purified by MPLC using a Lobar C column to yield crystalline **16a** (3.605 g, 64%), mp 61.0—63.0 °C (Et_2O–hexane). ^{1}H-NMR (400 MHz) δ: 2.01 (1H, dddd, J=13.6, 6.8, 6.8, 6.8 Hz), 2.07 (1H, t, J=6.8 Hz), 2.13 (1H, dddd, J=13.6, 8.3, 5.4, 5.4 Hz), 2.51 (1H, ddd, J=17.6, 6.8, 5.4 Hz), 2.74 (1H, ddd, J=17.6, 8.3, 6.8 Hz), 3.79 (1H, ddd, J=12.8, 6.8, 3.6 Hz), 3.85 (1H, ddd, J=6.8, 6.8, 5.4 Hz), 3.89 (1H, ddd, J=12.8, 6.8, 3.6 Hz), 4.31 (1H, dt, J=6.8, 3.6 Hz), 4.54 (1H, d, J=11.2 Hz), 4.65 (1H, d, J=11.2 Hz), 7.28—7.40 (5H, m). IR cm^{-1}: 3420, 1735. MS *m/z*: 237 ($M^+ + 1$), 236 (M^+). *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.92; H, 6.93.

***dl-trans*-4-Hexadecyloxy-6-hydroxy-5-hexanolide (16b)** From **15b**, **16b** was similarly prepared (60%), mp 45.5—46.5 °C (Et_2O–hexane). ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (26H, m), 1.52—1.60 (2H, m), 1.93 (1H, dddd, J=13.6, 6.8, 6.8, 6.8 Hz), 2.03 (1H, br s), 2.11 (1H, dddd, J=13.6, 8.3, 5.4, 5.4 Hz), 2.50 (1H, ddd, J=17.1, 6.8, 5.4 Hz), 2.72 (1H, ddd, J=17.1, 8.3, 6.8 Hz), 3.41 (1H, dt, J=9.0, 6.5 Hz), 3.58 (1H, dt, J=9.0, 6.5 Hz), 3.69 (1H, ddd, J=6.8, 6.8, 5.4 Hz), 3.80 (1H, br d, J=12.3 Hz), 3.90 (1H, br d, J=12.3 Hz), 4.23 (1H, dt, J=6.8, 3.4 Hz). IR cm^{-1}: 3450, 1740. MS *m/z*: 371 ($M^+ + 1$), 370 (M^+). *Anal.* Calcd for $C_{22}H_{42}O_4$: C, 71.31; H, 11.42. Found: C, 71.32; H, 11.37.

Ethyl *dl-erythro*-4-Benzyloxy-6-hydroxy-5-(tetrahydropyran-2-yloxy)-hexanoate (17) A mixture of **15a** (8.591 g, 21.8 mmol), NaCl (1.535 g, 26.3 mmol) and dimethylsulfoxide (DMSO) (170 ml) was heated under reflux for 2 h on an oil bath at 210 °C. After cooling, the mixture was diluted with EtOAc and poured into water. The organic layer was washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (140 g). Elution with hexane–EtOAc (95 : 5) afforded ethyl *dl-erythro*-4-benzyloxy-5,6-isopropylidenedioxyhexanoate (6.404 g, 91%) as a colorless oil, bp 165—170 °C (bath temperature)/3 mmHg. ^{1}H-NMR δ: 1.23 (3H, t, J=7.5 Hz), 1.35 (3H, s), 1.41 (3H, s), 1.96 (2H, dt, J=7.5, 4.5 Hz), 2.44 (2H, t, J=7.5 Hz), 3.56 (1H, dt, J=6.0, 4.5 Hz), 3.7—4.2 (3H, m), 4.10 (2H, q, J=7.5 Hz), 4.62 (2H, s), 7.35 (5H, m). IR cm^{-1}: 1725. MS *m/z*: 307 ($M^+ - Me$).

A mixture of the above ester (3.275 g, 10.2 mmol), AcOH (20 ml) and water (10 ml) was stirred at room temperature for 1 h, and at 50 °C for 2 h. After cooling, the mixture was evaporated to dryness, and the residue was subjected to flash chromatography using silica gel (30 g). Elution with hexane–EtOAc (1 : 1) gave ethyl *dl-erythro*-4-benzyloxy-5,6-dihydroxyhexanoate (2.675 g, 93%) as a colorless oil, bp 200—205 °C (bath temperature)/3 mmHg. ^{1}H-NMR δ: 1.23 (3H, t, J=7.5 Hz), 1.97 (2H, dt, J=7.5, 7.0 Hz), 2.43 (2H, t, J=7.5 Hz), 2.69 (2H, s), 3.4—4.0 (4H, m), 4.10 (2H, q, J=7.5 Hz), 4.58 (2H, s), 7.36 (5H, m). IR cm^{-1}: 3460, 1730. MS *m/z*: 236 ($M^+ - C_2H_6O$).

tert-Butyldimethylsilyl chloride (2.351 g, 15.6 mmol) was added to a stirred solution of the above dihydroxy ester (3.663 g, 13.0 mmol), Et_3N (2.20 ml, 15.8 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.399 g, 3.26 mmol) in CH_2Cl_2 (76 ml) under ice-water cooling. The mixture was stirred at room temperature for 6 h and poured into water. The organic layer was washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on a Lobar C column. Elution with hexane–EtOAc (6 : 1) afforded ethyl *dl-erythro*-4-benzyloxy-6-(*tert*-butyldimethylsiloxy)-5-hydroxyhexanoate (4.299 g, 83%) as a colorless oil. ^{1}H-NMR δ: 0.04 (3H, s), 0.07 (3H, s), 0.91 (9H, s), 1.23 (3H, t, J=7.5 Hz), 1.8—2.2 (2H, m), 2.3—2.6 (2H, m), 2.50 (1H, br s), 3.4—3.9 (4H, m), 4.10 (2H, q, J=7.5 Hz), 4.58 (2H, s), 7.35 (5H, m). IR cm^{-1}: 3560, 1725. MS *m/z*: 339 ($M^+ - C_4H_9$). *Anal.* Calcd for $C_{21}H_{36}O_5Si$: C, 63.60; H, 9.15. Found: C, 63.62; H, 9.00.

A mixture of the above compound (4.140 g, 10.4 mmol), 3,4-dihydro-2*H*-pyran (1.318 g, 15.7 mmol), pyridinium *p*-toluenesulfonate (0.263 g, 1.05 mmol) and CH_2Cl_2 (80 ml) was stirred at room temperature for 14 h, and poured into ice water. The organic layer was washed with saturated aqueous $NaHCO_3$ and aqueous NaCl solutions, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on a Lobar C column. Elution with hexane–EtOAc (9 : 1) yielded ethyl *dl-erythro*-4-benzyloxy-6-(*tert*-butyldimethylsiloxy)-5-(tetrahydropyran-2-yloxy)hexanoate (4.477 g, 90%) as a colorless oil. ^{1}H-NMR δ: 0.04 (3H, s), 0.07 (3H, s), 0.91 (9H, s), 1.22 (3H, t, J=7.5 Hz), 1.3—1.8 (6H, m), 1.7—2.1 (2H, m), 2.3—2.6 (2H, m), 3.3—4.1 (6H, m), 4.09 (2H, q, J=7.5 Hz), 4.46 and 4.52 (1H, d × 2, J=12 Hz), 4.68 and 4.74 (1H, d × 2, J=12 Hz), 4.90 (1H, m), 7.36 (5H, m). IR cm^{-1}: 1725. MS *m/z*: 479 ($M^+ - 1$), 423 ($M^+ - C_4H_9$). *Anal.* Calcd for $C_{26}H_{44}O_6Si$: C, 64.96; H, 9.23. Found: C, 64.86; H, 8.98.

A solution of Bu_4NF in THF (1.0 M, 5.00 ml, 5.00 mmol) was added to a

stirred solution of the above silyl ether (2.011 g, 4.18 mmol) in THF (40 ml) at room temperature. After stirring for 3 h, the mixture was diluted with EtOAc and poured into water. The organic layer was washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (40 g). Elution with hexane–EtOAc (5 : 1) afforded **17** (1.502 g, 98%) as a colorless oil. ^{1}H-NMR δ: 1.22 (3H, t, J=7.5 Hz), 1.4—1.9 (6H, m), 1.8—2.1 (2H, m), 2.3—2.6 (2H, m), 3.3—4.1 (7H, m), 4.10 (2H, q, J=7.5 Hz), 4.59 (1H, d, J=11 Hz), 4.73 (1H, d, J=11 Hz), 4.81 (1H, m), 7.37 (5H, m). IR cm^{-1}: 3440, 1725. MS m/z: 282 ($M^+ - C_5H_9O$). *Anal.* Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.51; H, 8.08

***dl-erythro*-4-Benzyloxy-6-hexadecyloxy-5-hydroxyhexanoic Acid (18)** A solution of **17** (1.762 g, 4.81 mmol) in THF (9 ml) was added to a stirred suspension of NaH (55% dispersion in mineral oil, 0.516 g, 11.8 mmol) in THF (27 ml) under ice-water cooling. The mixture was stirred at room temperature for 15 h, and the solvent was evaporated off. The residue was dissolved in DMF (15 ml), and this solution was added to a stirred suspension of NaH (55% dispersion in mineral oil, 0.780 g, 17.9 mmol) in DMF (16 ml) under ice-water cooling. The mixture was stirred at room temperature for 30 min. A solution of hexadecyl bromide (3.571 g, 11.7 mmol) in DMF (16 ml) was added and stirring was continued at room temperature for 16 h. A mixture of 1,4-dioxane (50 ml) and 10% aqueous HCl (100 ml) was then added under ice-water cooling, and the reaction mixture was stirred at 50 °C for 4 h. After cooling, the mixture was extracted ten times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, evaporated to dryness, and the residue was chromatographed on silica gel (27 g). Elution with EtOAc gave **18** (1.381 g, 60%) as a colorless oil. ^{1}H-NMR δ: 0.8—1.8 (31H, m), 1.8—2.1 (2H, m), 2.3—2.6 (2H, m), 3.3—4.0 (7H, m), 4.60 (2H, s), 6.30 (1H, br s), 7.37 (5H, m). IR cm^{-1}: 3000, 1710. MS m/z: 460 ($M^+ - H_2O$).

***dl-trans*-4-Benzyloxy-6-hexadecyloxy-5-hexanolide (19)** Pyridine (0.43 ml, 5.32 mmol) and Ac_2O (0.25 ml, 2.65 mmol) were added to a solution of **18** (1.406 g, 2.18 mmol) in CH_2Cl_2 (14 ml) under ice-water cooling. The mixture was stirred at room temperature for 4 h, and then poured into water. The organic layer was washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (25 g). Elution with hexane–EtOAc (4 : 1) afforded crystalline **19** (0.942 g, 94%), mp 63.0—64.0 °C (Et_2O–hexane). ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=6.8 Hz), 1.25 (26H, m), 1.48—1.57 (2H, m), 1.99 (1H, dddd, J=13.7, 5.4, 5.4, 5.4 Hz), 2.12 (1H, dddd, J=13.7, 9.5, 5.4, 4.4 Hz), 2.47 (1H, ddd, J=17.1, 5.4, 5.4 Hz), 2.71 (1H, ddd, J=17.1, 9.5, 5.4 Hz), 3.40 (1H, dd, J=9.3, 6.8 Hz), 3.46 (1H, dd, J=9.3, 6.8 Hz), 3.60 (1H, dd, J=10.7, 3.9 Hz), 3.65 (1H, dd, J=10.7, 3.9 Hz), 3.87 (1H, ddd, J=5.4, 5.4, 4.4 Hz), 4.44 (1H, ddd, J=5.4, 3.9, 3.9 Hz), 4.55 (1H, d, J=11.7 Hz), 4.62 (1H, d, J=11.7 Hz), 7.28—7.40 (5H, m). IR cm^{-1}: 1735. MS m/z: 460 (M^+). *Anal.* Calcd for $C_{29}H_{48}O_4$: C, 75.61; H, 10.50. Found: C, 75.54; H, 10.26.

***dl-trans*-6-Hexadecyloxy-4-hydroxy-5-hexanolide (20)** A mixture of **19** (0.701 g, 1.52 mmol), 10% Pd–C (0.492 g) and THF (50 ml) was hydrogenated in a Paar apparatus at 4 atm for 8 h. The catalyst was filtered through a layer of Celite, and the filtrate was evaporated to dryness. The residue was subjected to flash chromatography on silica gel (13 g). Elution with hexane–EtOAc (4 : 1) recovered unreacted **19** (0.328 g). Further elution with hexane–EtOAc (1 : 1) gave crystalline **20** (0.282 g, 94% based on recovered **19**), mp 49.0—50.0 °C (Et_2O–hexane). ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (26H, m), 1.53—1.63 (2H, m), 1.91 (1H, dddd, J=13.5, 8.0, 7.8, 6.8 Hz), 2.17 (1H, dddd, J=13.5, 6.8, 6.3, 5.2 Hz), 2.52 (1H, ddd, J=17.6, 8.0, 6.3 Hz), 2.73 (1H, ddd, J=17.6, 6.8, 6.8 Hz), 2.87 (1H, d, J=2.3 Hz), 3.51 (2H, t, J=6.8 Hz), 3.61 (1H, dd, J=9.8, 7.1 Hz), 3.81 (1H, dd, J=9.8, 4.0 Hz), 4.04 (1H, dddd, J=7.8, 7.8, 5.2, 2.3 Hz), 4.24 (1H, ddd, J=7.8, 7.1, 4.0 Hz). IR cm^{-1}: 3500, 1740. MS m/z: 371 (M^++1), 370 (M^+). *Anal.* Calcd for $C_{22}H_{42}O_4$: C, 71.31; H, 11.42. Found: C, 71.02; H, 11.36.

***dl-O*-{[*O*-(*trans*-3-Hexadecyloxy-6-oxotetrahydropyran-2-yl)methyl]-phosphono}choline (Inner Salt) (4)** An attempt to synthesize **4** from **16b** under the conditions described by Chandrakumar and Hajdu[11] failed. The following modifications in the base and the solvent were necessary.

A solution of 2-chloro-2-oxo-1,3,2-dioxaphospholane (0.678 g, 4.76 mmol) in 1,2-dichloroethane (3 ml) was added in one portion to a stirred solution of **16b** (0.886 g, 2.39 mmol) and *N*,*N*-diisopropylethylamine (0.83 ml, 4.76 mmol) in 1,2-dichloroethane (17 ml). The mixture was stirred at 80 °C for 24 h, cooled and concentrated to dryness under N_2. The residue was dissolved in acetonitrile (6 ml), mixed with a solution of Me_3N (7.00 g, 118 mmol) in acetonitrile (10 ml) in a sealed tube, and heated on an oil bath at 70—80 °C for 65 h. After cooling, the mixture was evaporated to dryness, and the residue was chromatographed on silica gel (20 g). The crude product eluted with CH_2Cl_2–MeOH–H_2O (65 : 35 : 5) was further subjected to MPLC using a Lobar B column. Elution with the same solvent gave **4** (0.817 g, 64%) as an amorphous powder of mp 70 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD, 1 : 1) δ: 0.8—1.7 (31H, m), 1.8—2.2 (2H, m), 2.3—2.7 (2H, m), 3.23 (9H, s), 3.3—4.9 (10H, m). IR cm^{-1}: 1730. FAB-MS: 536 ($M+H)^+$. *Anal.* Calcd for $C_{27}H_{54}NO_7P \cdot H_2O$: C, 58.57; H, 10.19; N, 2.53; P, 5.59. Found: C, 58.42; H, 10.42; N, 2.46; P, 5.34.

***dl-O*-[*O*-(*trans*-2-Hexadecyloxymethyl-6-oxotetrahydropyran-3-yl)phosphono]choline (Inner Salt) (6)** In the same manner as described above, **6** (53%) was prepared from **20**, as an amorphous powder of mp 209—211 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD, 1 : 1) δ: 0.7—1.8 (31H, m), 1.8—2.3 (2H, m), 2.3—2.8 (2H, m), 3.23 (9H, s), 3.3—4.9 (10H, m). IR cm^{-1}: 1730. FAB-MS: 536 ($M+H)^+$. *Anal.* Calcd for $C_{27}H_{54}NO_7P \cdot 1.5H_2O$: C, 57.63; H, 10.21; N, 2.49; P, 5.50. Found: C, 57.76; H, 10.03; N, 2.45; P, 5.40.

According to the above sequences **12**→**13a**, **b**→**14a**, **b**→**15a**, **b**→**16a**, **b** and **15a**→**17**→**18**→**19**, the following compounds **22**—**28** of the threitol series were similarly synthesized from dimethyl *dl*-tartrate (**21**).

Dimethyl *dl*-2,3-*O*-Hexadecylidenetartrate (22b) White crystals (50%), mp 39.5—40.5 °C (Et_2O–hexane). ^{1}H-NMR δ: 0.7—2.0 (31H, m), 3.82 (6H, s), 4.71 (1H, d, J=9 Hz), 4.77 (1H, d, J=9 Hz), 5.26 (1H, t, J=7 Hz). IR cm^{-1}: 1750. MS m/z: 401 (M^++1), 400 (M^+), 399 (M^+−1), 341 ($M^+ - CO_2Me$). *Anal.* Calcd for $C_{22}H_{40}O_6$: C, 66.00; H, 10.07. Found: C, 65.82; H, 10.10.

***dl*-2-*O*-Hexadecyl-3,4-*O*-isopropylidenethreitol (23b)** Synthesized *via* *dl*-2-*O*-hexadecylthreitol [white crystals (80% from **22b**) of mp 54.0—56.0 °C (Et_2O–hexane); ^{1}H-NMR δ: 0.8—2.1 (31H, m), 2.72 (1H, t, J=6 Hz), 2.8—3.2 (2H, m), 3.3—4.0 (8H, m); MS m/z: 347 (M^++1); *Anal.* Calcd for $C_{20}H_{42}O_4$: C, 69.32; H, 12.21; Found: C, 69.26; H, 12.08], in 90% yield as white crystals of mp 41.0—43.0 °C (hexane). ^{1}H-NMR δ: 0.7—1.8 (31H, m), 1.36 (3H, s), 1.42 (3H, s), 2.31 (1H, t, J=6 Hz), 3.3—4.4 (8H, m). IR cm^{-1}: 3500. MS m/z: 371 ($M^+ - Me$). *Anal.* Calcd for $C_{23}H_{46}O_4$: C, 71.45; H, 11.99. Found: C, 71.31; H, 11.96.

Ethyl *dl-threo*-4-Benzyloxy-2-ethoxycarbonyl-5,6-isopropylidenedioxyhexanoate (24a) According to Ohno *et al.*'s method,[9a] **21** was converted into *dl*-2-*O*-benzyl-3,4-*O*-isopropylidenethreitol[9] (**23a**). The methanesulfonate of **23a** [^{1}H-NMR δ: 1.32 (3H, s), 1.40 (3H, s), 2.92 (3H, s), 3.4—4.5 (6H, m), 4.65 (2H, s), 7.25 (5H, m)] was iodinated to *dl-threo*-3-*O*-benzyl-4-iodo-1,2-*O*-isopropylidenebutane-1,2,3-triol [^{1}H-NMR δ: 1.36 (3H, s), 1.44 (3H, s), 3.16 (1H, dd, J=10.5, 7.0 Hz), 3.34 (1H, dd, J=10.5, 5.0 Hz), 3.57 (1H, ddd, J=7.0, 5.0, 5.0 Hz), 3.78 (1H, dd, J=8.0, 6.5 Hz), 4.00 (1H, dd, J=8.0, 6.5 Hz), 4.33 (1H, dt, J=6.5, 5.0 Hz), 4.69 (1H, d, J=11 Hz), 4.79 (1H, d, J=11 Hz), 7.40 (5H, m)], which was then converted into **24a** [94% from **23a**, colorless oil, bp 170—180 °C (bath temperature)/1 mmHg]. ^{1}H-NMR δ: 1.22 (3H, t, J=7.5 Hz), 1.24 (3H, t, J=7.5 Hz), 1.38 (3H, s), 1.46 (3H, s), 2.01 (2H, t, J=6.5 Hz), 3.4—4.4 (9H, m), 4.57 (1H, d, J=11 Hz), 4.80 (1H, d, J=11 Hz), 7.38 (5H, m). IR cm^{-1}: 1730. MS m/z: 379 ($M^+ - Me$). *Anal.* Calcd for $C_{21}H_{30}O_7$: C, 63.94; H, 7.67. Found: C, 64.21; H, 7.86.

Ethyl *dl-threo*-2-Ethoxycarbonyl-4-hexadecyloxy-5,6-isopropylidenedioxyhexanoate (24b) The methanesulfonate of **23b** [colorless oil; ^{1}H-NMR δ: 0.5—1.8 (31H, m), 1.34 (3H, s), 1.41 (3H, s), 3.01 (3H, s), 3.4—4.6 (8H, m)] was iodinated to *dl-threo*-3-*O*-hexadecyl-4-iodo-1,2-*O*-isopropylidenebutane-1,2,3-triol (colorless oil, 97% from **23b**). ^{1}H-NMR δ: 0.7—1.8 (31H, m), 1.35 (3H, s), 1.42 (3H, s), 3.0—3.7 (5H, m), 3.90 (1H, dd, J=7.5, 6.5 Hz), 4.00 (1H, dd, J=7.5, 6.5 Hz), 4.32 (1H, dt, J=6.5, 4.5 Hz). IR cm^{-1}: 518. MS m/z: 481 ($M^+ - Me$). *Anal.* Calcd for $C_{25}H_{45}IO_3$: C, 55.64; H, 9.14. Found: C, 55.64; H, 8.97. This iodide was converted into **24b** (a colorless oil) in 65% yield. ^{1}H-NMR δ: 0.6—1.8 (37H, m), 1.34 (3H, s), 1.41 (3H, s), 1.97 (2H, m), 3.2—3.5 (1H, m), 3.66 (2H, dt, J=7.5, 7.5 Hz), 3.8—4.2 (4H, m), 4.16 (2H, q, J=7.5 Hz), 4.21 (2H, q, J=7.5 Hz). IR cm^{-1}: 1730. MS m/z: 513 ($M^+ - Me$). *Anal.* Calcd for $C_{30}H_{56}O_7$: C, 68.14; H, 10.67. Found: C, 68.04; H, 10.72.

***dl-cis*-4-Hexadecyloxy-6-hydroxy-5-hexanolide (25b)** White crystals of mp 54.0—55.0 °C (Et_2O–hexane). ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (26H, m), 1.53—1.63 (2H, m), 1.90 (1H, dddd, J=14.4, 11.2, 6.8, 2.4 Hz), 2.22 (1H, dddd, J=14.4, 6.8, 3.4, 3.4 Hz), 2.26 (1H, br s), 2.53 (1H, ddd, J=18.1, 6.8, 3.4 Hz), 2.66 (1H, ddd, J=18.1, 11.2, 6.8 Hz), 3.33 (1H, dt, J=8.8, 6.5 Hz), 3.57 (1H, dt, J=8.8, 6.5 Hz), 3.80 (1H, ddd, J=3.4, 2.4, 2.4 Hz), 3.81 (1H, dd, J=12.2, 4.3 Hz), 3.99 (1H, dd, J=12.2, 6.4 Hz), 4.40 (1H, ddd, J=6.4, 4.3, 2.4 Hz). IR cm^{-1}: 3500, 1735. MS m/z: 370 (M^+). *Anal.* Calcd for $C_{22}H_{42}O_4$: C, 71.31; H, 11.42. Found: C, 71.14; H, 11.36.

Ethyl *dl-threo*-4-Benzyloxy-6-hydroxy-5-(tetrahydropyran-2-yloxy)-hexanoate (26) Deethoxycarbonylation of **24a** gave ethyl *dl-threo*-4-

benzyloxy-5,6-isopropylidenedioxyhexanoate as a colorless oil (87%), bp 150—160 °C (bath temperature)/1 mmHg. ^{1}H-NMR δ: 1.23 (3H, t, J=7.5 Hz), 1.38 (3H, s), 1.45 (3H, s), 1.6—2.0 (2H, m), 2.43 (2H, t, J=7.5 Hz), 3.35—3.6 (1H, m), 3.6—4.35 (3H, m), 4.10 (2H, q, J=7.5 Hz), 4.61 (1H, d, J=11 Hz), 4.79 (1H, d, J=11 Hz), 7.38 (5H, m). MS m/z: 322 (M^+), 307 ($M^+ - Me$). *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.10; H, 8.11.

Deacetalization of the above compound yielded ethyl *dl-threo*-4-benzyloxy-5,6-dihydroxyhexanoate (90%) as a colorless oil, bp 170—180 °C (bath temperature)/2 mmHg. ^{1}H-NMR δ: 1.23 (3H, t, J=7.5 Hz), 1.8—2.2 (2H, m), 2.41 (2H, t, J=7.5 Hz), 2.60 (2H, br s), 3.4—3.8 (4H, m), 4.11 (2H, q, J=7.5 Hz), 4.53 (1H, d, J=11 Hz), 4.65 (1H, d, J=11 Hz), 7.37 (5H, m). IR cm^{-1}: 3550, 3460, 1725. MS m/z: 236 ($M^+ - C_2H_6O$). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.80; H, 7.85. Found: C, 63.66; H, 7.78.

Subsequent silylation gave ethyl *dl-threo*-4-benzyloxy-6-(*tert*-butyldimethylsiloxy)-5-hydroxyhexanoate (90%) as a syrup. ^{1}H-NMR δ: 0.04 (3H, s), 0.07 (3H, s), 0.91 (9H, s), 1.23 (3H, t, J=7.5 Hz), 1.8—2.1 (2H, m), 2.42 (2H, t, J=7.5 Hz), 2.4 (1H, br s), 3.5—3.8 (4H, m), 4.11 (2H, q, J=7.5 Hz), 4.63 (2H, s), 7.38 (5H, m). IR cm^{-1}: 3560, 1725. MS m/z: 396 ($M^+ - C_4H_9$). *Anal.* Calcd for $C_{21}H_{36}O_5Si$: C, 63.60; H, 9.15. Found: C, 63.64; H, 9.01.

Tetrahydropyranylation of this substance followed by desilylation afforded **26** (78%) as a syrup. ^{1}H-NMR δ: 1.23 (3H, t, J=7.5 Hz), 1.4—1.9 (6H, m), 1.8—2.1 (2H, m), 2.3—2.6 (2H, m), 3.4—4.1 (7H, m), 4.11 (2H, q, J=7.5 Hz), 4.58 (1H, d, J=11 Hz), 4.72 (1H, d, J=11 Hz), 4.85 (1H, m), 7.30 (5H, m). IR cm^{-1}: 3450, 1725. MS m/z: 282 ($M^+ - C_5H_9O$). *Anal.* Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.26; H, 8.50.

***dl-threo*-4-Benzyloxy-6-hexadecyloxy-5-hydroxyhexanoic Acid (27)** Alkylation and deprotection of **26** gave **27** (41%) as a colorless syrup. ^{1}H-NMR δ: 0.8—1.8 (31H, m), 1.8—2.2 (2H, m), 2.3—2.8 (2H, m), 3.3—4.0 (6H, m), 4.35—4.55 (1H, m), 4.51 (1H, d, J=11 Hz), 4.65 (1H, d, J=11 Hz), 6.44 (1H, br s), 7.38 (5H, m). IR cm^{-1}: 1710. MS m/z: 460 ($M^+ - H_2O$). The following lactone **28** was formed as a minor product (14%) in this step.

***dl-cis*-4-Benzyloxy-6-hexadecyloxy-5-hexanolide (28)** Lactonization of **27** yielded **28** (81%) as white crystals of mp 51.0—52.0 °C (Et_2O–hexane). ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=6.8 Hz), 1.25 (26H, m), 1.49—1.59 (2H, m), 1.90 (1H, dddd, J=14.2, 10.7, 6.8, 2.0 Hz), 2.21 (1H, dddd, J=14.2, 7.3, 3.9, 3.9 Hz), 2.53 (1H, ddd, J=18.1, 6.8, 3.9 Hz), 2.70 (1H, ddd, J=18.1, 10.7, 7.3 Hz), 3.40 (1H, dt, J=9.3, 6.6 Hz), 3.48 (1H, dt, J=9.3, 6.6 Hz), 3.63 (1H, dd, J=9.3, 5.4 Hz), 3.73 (1H, dd, J=9.3, 7.3 Hz), 3.90 (1H, ddd, J=3.9, 2.0, 2.0 Hz), 4.43 (1H, ddd, J=7.3, 5.4, 2.0 Hz), 4.50 (1H, d, J=12.0 Hz), 4.65 (1H, d, J=12.0 Hz), 7.30—7.40 (5H, m). IR cm^{-1}: 1735. MS m/z: 460 (M^+). *Anal.* Calcd for $C_{29}H_{48}O_4$: C, 75.61; H, 10.50. Found: C, 75.66; H, 10.54.

***dl-O*-{*O*-[(*cis*-3-Hexadecyloxy-6-oxotetrahydropyran-2-yl)methyl]phosphono}choline (Inner Salt) (5)** The introduction of the phosphonocholine side chain into **25b** was carried out as described for **4**, yielding **5** (54%) as an amorphous powder, mp 168—170 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD, 1 : 1) δ: 0.8—1.8 (31H, m), 1.6—2.2 (2H, m), 2.42 (2H, m), 3.24 (9H, s), 3.3—4.8 (10H, m). IR cm^{-1}: 1730. FAB-MS: 536 $(M+H)^+$. *Anal.* Calcd for $C_{27}H_{54}O_7NP \cdot H_2O$: C, 58.57; H, 10.19; N, 2.53; P, 5.59. Found: C, 58.29; H, 10.33; N, 2.44; P, 5.33.

***dl-O*-[*O*-(*cis*-2-Hexadecyloxymethyl-6-oxotetrahydropyran-3-yl)phosphono]choline (7)** Debenzylation of **28** was carried out as described for **20** to afford crystalline *dl-cis*-6-hexadecyloxy-4-hydroxy-5-hexanolide (55%), mp 63.0—64.0 °C (Et_2O–hexane). ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=6.8 Hz), 1.25 (26H, m), 1.53—1.64 (2H, m), 1.95 (1H, ddddd, J=14.4, 10.7, 7.8, 2.9, 1 Hz), 2.09 (1H, dddd, J=14.4, 7.8, 2.9, 2.9 Hz), 2.52 (1H, ddd, J=18.6, 7.8, 2.9 Hz), 2.84 (1H, ddd, J=18.6, 10.7, 7.8 Hz), 3.50 (1H, dt, J=9.3, 6.6 Hz), 3.55 (1H, dt, J=9.3, 6.6 Hz), 3.80 (1H, s), 3.86 (2H, d, J=3.4 Hz), 4.26—4.30 (2H, m). IR cm^{-1}: 3480, 1740. MS m/z: 370 (M^+). *Anal.* Calcd for $C_{22}H_{42}O_4$: C, 71.31; H, 11.42. Found: C, 71.19; H, 11.27.

Phosphorylation of the above alcohol as described for **4** gave **7** (22%) as an amorphous powder, mp 119—122 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD, 1 : 1) δ: 0.7—1.7 (31H, m), 1.94 (2H, dt, J=7.5, 6.5 Hz), 2.52 (2H, t, J=7.5 Hz), 3.22 (9H, s), 3.3—4.9 (10H, m). IR cm^{-1}: 1730. FAB-MS: 536 $(M+H)^+$. *Anal.* Calcd for $C_{27}H_{54}O_7NP \cdot H_2O$: C, 58.57; H, 10.19; N, 2.53; P, 5.59. Found: C, 58.61; H, 10.23; N, 2.45; P, 5.31.

6-Benzyloxymethyl-3,4-dihydro-2*H*-pyran (30a) A solution of 3,4-dihydro-6-hydroxymethyl-2*H*-pyran[12] (**29**) (5.71 g, 50 mmol) in DMF (100 ml) was added to a stirred suspension of NaH (55% dispersion in mineral oil, 2.18 g, 50 mmol) in DMF (100 ml) under ice-water cooling. Stirring was continued at room temperature for 1 h, and benzyl chloride (6.33 g, 50 mmol) was added under ice-water cooling. The mixture was stirred at room temperature for 16 h, poured into water (1 l), and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (200 g). Elution with hexane–Et_2O (100 : 4—100 : 5) afforded **30a** (9.40 g, 92%) as a colorless oil, bp 125—130 °C (bath temperature)/1 mmHg. ^{1}H-NMR δ: 1.65—2.20 (4H, m), 3.87 (2H, s), 4.03 (2H, m), 4.57 (2H, s), 4.80 (1H, t, J=3.5 Hz), 7.2—7.6 (5H, m). MS m/z: 205 ($M^+ + 1$). *Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.36; H, 7.90.

3,4-Dihydro-6-hexadecyloxymethyl-2*H*-pyran (30b) A mixture of **29** (5.71 g, 50 mmol), hexadecyl bromide (16.79 g, 55 mmol), finely powdered KOH (85% purity, 8.22 g, 125 mmol) and toluene (160 ml) was heated under reflux for 2 h. After cooling, the reaction mixture was washed with water and aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (400 g). Elution with hexane–Et_2O (5 : 1) gave **30b** (14.38 g, 85%) as a colorless syrup. ^{1}H-NMR δ: 0.7—2.2 (35H, m), 3.42 (2H, t, J=6 Hz), 3.80 (2H, s), 4.01 (2H, m), 4.77 (1H, t, J=3.5 Hz). MS m/z: 328 (M^+). *Anal.* Calcd for $C_{22}H_{42}O_2$: C, 78.04; H, 12.50. Found: C, 77.84; H, 12.39.

***dl-trans*-2-Benzyloxymethyltetrahydropyran-3-ol (31a)** A 1 M solution of BH_3 in THF (Aldrich, 29.33 ml) was added dropwise to a stirred solution of **30a** (9.00 g, 44 mmol) in THF (30 ml) at −5—0 °C. Stirring was continued at room temperature for 3 h, and then 10% aqueous NaOH solution (13 ml) was slowly added to the reaction mixture. The inner temperature rose to 40 °C. Then 30% aqueous H_2O_2 solution (10.8 ml) was added dropwise at a rate sufficient to keep the inner temperature at 32—40 °C. The mixture was stirred at room temperature for 1 h, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The organic solutions were combined, washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue (10.5 g) was chromatographed on silica gel (250 g). Elution with CH_2Cl_2–EtOAc (100 : 5) afforded **31a** (8.82 g, 90%) as a colorless oil, bp 130—135 °C (bath temperature)/1 mmHg. ^{1}H-NMR δ: 1.15—2.25 (4H, m), 2.83 (1H, d, J=3 Hz), 3.1—3.6 (3H, m), 3.68 (2H, d, J=5 Hz), 3.75—4.05 (1H, m), 4.58 (2H, s), 7.2—7.5 (5H, m). IR cm^{-1}: 3500. MS m/z: 222 (M^+). *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 70.24; H, 8.16. Found: C, 70.07; H, 8.04.

***dl-trans*-2-Hexadecyloxytetrahydropyran-3-ol (31b)** Hydroboration of **30b** was carried out as described above, yielding crystalline **31b** (89%), mp 41.5—43 °C (hexane). ^{1}H-NMR δ: 0.7—2.3 (35H, m), 3.0—3.1 (1H, m), 3.1—4.1 (8H, m). IR cm^{-1}: 3500. MS m/z: 357 ($M^+ + 1$). *Anal.* Calcd for $C_{22}H_{44}O_3$: C, 74.10; H, 12.43. Found: C, 73.83; H, 12.51.

***dl*-2-Benzyloxymethyltetrahydropyran-3-one (32a)** Jones' reagent (6.00 ml, containing 1.60 g of CrO_3) was added to a solution of **31a** (2.22 g, 10 mmol) in acetone (20 ml) under ice-water cooling. After stirring at room temperature for 1 h, 2-propanol (1 ml) was added, and the mixture was poured into water and extracted with EtOAc. The extract was washed twice with water, dried over Na_2SO_4 and concentrated *in vacuo*, leaving oily crude **32a** (2.08 g). ^{1}H-NMR δ: 1.8—2.7 (4H, m), 3.4—4.3 (5H, m), 4.50 (2H, s), 7.23 (5H, m).

2-Hexadecyloxymethyltetrahydropyran-3-one (32b) Similarly, **31b** (4.30 g, 12.1 mmol) was oxidized with Jones' reagent and worked up as described above. The crude product thus obtained was chromatographed on silica gel (100 g). Elution with hexane–EtOAc (10 : 1—20 : 3) afforded crystalline **32b** (3.73 g, 87%), mp 42.0—43.5 °C (hexane). ^{1}H-NMR δ: 0.7—2.4 (33H, m), 2.4—2.7 (2H, m), 3.3—4.3 (7H, m). IR cm^{-1}: 1725. MS m/z: 354 (M^+). *Anal.* Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.41; H, 12.01.

***dl-cis*-2-Benzyloxymethyltetrahydropyran-3-ol (33a)** A 1 M solution of L-Selectride in THF (Aldrich, 12.0 ml) was added dropwise to a solution of crude **32a** (2.00 g) in THF (10 ml) during a period of 10 min at 0—5 °C. The mixture was stirred at 5 °C for 30 min and at room temperature for 2 h. Then, 10% aqueous NaOH solution (6.0 ml, at 5—15 °C) and 35% aqueous H_2O_2 solution (6.0 ml, at 15—30 °C) were successively added under ice-water cooling. After being stirred at room temperature for 2 h, the mixture was poured into water and extracted twice with Et_2O. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The oily residue was chromatographed on silica gel (60 g). Elution with hexane–EtOAc (5 : 1—4 : 1) yielded **33a** (1.135 g, 51% from **31a**) as a colorless oil, bp 130—140 °C (bath temperature)/1 mmHg. ^{1}H-NMR δ: 1.25—2.3 (4H, m), 2.68 (1H, d, J=6 Hz), 3.3—3.7 (4H, m), 3.80 (1H, m), 4.03 (1H, m), 4.59 (2H, s), 7.2—7.5 (5H, m). IR cm^{-1}: 3480. MS m/z: 222 (M^+).

***dl-cis*-2-Hexadecyltetrahydropyran-3-ol (33b)** Reduction of **32b** was carried out as described above to afford crystalline **33b** (80%), mp 67.5—68.5 °C (EtOAc). ^{1}H-NMR δ: 0.7—2.2 (35H, m), 2.89 (1H, d, J=6 Hz),

3.2—4.2 (8H, m). IR cm^{-1}: 3480. MS *m/z*: 357 ($M^+ + 1$). *Anal.* Calcd for $C_{22}H_{44}O_3$: C, 74.10; H, 12.44. Found: C, 73.86; H, 12.63.

***dl*-(*trans*-3-Hexadecyloxytetrahydropyran-2-yl)methanol (34)** A solution of **31a** (2.22 g, 10 mmol) in DMF (10 ml) was added to a stirred suspension of NaH (55% dispersion in mineral oil, 0.48 g, 11 mmol) in DMF (10 ml) under ice-water cooling. Stirring was continued at room temperature for 1 h, and then hexadecyl bromide (5.49 g, 18 mmol) was added under ice-water cooling. The mixture was stirred at room temperature for 4 h and at 60 °C for 1 h. After cooling, the mixture was poured into water and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (100 g). Elution with hexane–Et_2O (20:1—10:1) gave *dl-trans*-2-benzyloxymethyl-3-hexadecyloxytetrahydropyran (3.82 g, 86%) as a low-melting solid, mp 28.5—29.5 °C (MeOH). ^{1}H-NMR δ: 0.7—2.4 (35H, m), 3.0—4.2 (8H, m), 4.60 (2H, s), 7.2—7.45 (5H, m). MS *m/z*: 446 (M^+). *Anal.* Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.06; H, 11.31.

A mixture of the above compound (3.757 g, 8.41 mmol), 10% Pd–C (1.50 g) and MeOH (150 ml) was hydrogenated in a Paar apparatus at 4 atm for 20 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to yield crystalline **34** (2.749 g, 92%), mp 41.0—42.0 °C (hexane). ^{1}H-NMR δ: 0.7—2.4 (35H, m), 2.18 (1H, m), 3.1—4.1 (8H, m). IR cm^{-1}: 3600, 3470. MS *m/z*: 357 ($M^+ + 1$), 356 (M^+). *Anal.* Calcd for $C_{22}H_{44}O_3$: C, 74.10; H, 12.43. Found: C, 74.12; H, 12.11.

***dl*-(*cis*-3-Hexadecyloxytetrahydropyran-2-yl)methanol (35)** Alkylation of **33a** (1.037 g, 4.67 mmol) with hexadecyl bromide was carried out and the reaction mixture was worked up as described for **30b**. The crude product was chromatographed on silica gel (50 g). Elution with hexane–Et_2O (10:1) afforded *dl-cis*-2-benzyloxymethyl-3-hexadecyloxytetrahydropyran (1.455 g, 70%) as a colorless oil. ^{1}H-NMR δ: 0.7—2.3 (35H, m), 3.1—3.8 (5H, m), 3.61 (2H, s), 3.85—4.15 (1H, m), 4.51 (1H, d, J = 13 Hz), 4.59 (1H, d, J = 13 Hz), 7.2—7.5 (5H, m). MS *m/z*: 447 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 77.68; H, 11.16.

A mixture of the above compound (1.409 g, 3.15 mmol), 10% Pd–C (0.70 g) and MeOH–EtOH (1:1, 100 ml) was hydrogenated in a Paar apparatus at 4 atm for 20 h. The catalyst was filtered off, and the solvents were evaporated *in vacuo*. The residue was chromatographed on silica gel (30 g). Elution with hexane–Et_2O (20:1—5:1) afforded crystalline **35** (1.031 g, 92%), mp 42.0—43.0 °C (hexane). ^{1}H-NMR δ: 0.7—2.3 (35H, m), 2.40 (1H, m), 3.1—4.2 (8H, m). IR cm^{-1}: 3600, 3460. MS *m/z*: 357 ($M^+ + 1$), 356 (M^+). *Anal.* Calcd for $C_{22}H_{44}O_3$: C, 74.10; H, 12.44. Found: C, 73.85; H, 12.13.

***dl*-*O*-{*O*-[(*trans*-3-Hexadecyloxytetrahydropyran-2-yl)methyl]phosphono}-choline (Inner Salt) (8)** A mixture of **34** (1.253 g, 3.51 mmol), 2-bromoethyl phosphorodichloridate (1.275 g, 5.27 mmol) and Et_3N (0.97 ml, 7.02 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 5 h. Water (2.0 ml) was then added, and the mixture was heated under reflux for 1 h, cooled, and poured into cold 10% aqueous HCl solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic solutions were dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (50 g). Elution with CH_2Cl_2–MeOH (100:5) afforded 2-bromoethyl (*dl-trans*-3-hexadecyloxytetrahydropyran-2-yl)methyl phosphate (1.504 g, 77%) as a syrup. This substance was dissolved in DMF–isopropanol–$CHCl_3$ (5:5:3, 26 ml), and gaseous Me_3N (*ca.* 5 g) was introduced into the solution under ice-water cooling. The mixture was heated on an oil bath at 50 °C for 7 h, and cooled to the room temperature. Silver carbonate (0.572 mg, 2.08 mmol) was then added, and the mixture was heated again at 65 °C for 1.5 h, cooled, and filtered through a layer of Celite. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel (50 g). Elution with CH_2Cl_2–MeOH–H_2O (65:35:5) afforded **8** (1.089 g, 75%) as an amorphous powder, mp 85—92 °C. ^{1}H-NMR (CD_3OD) δ: 0.7—1.85 (34H, m), 2.0—2.55 (1H, m), 3.23 (9H, s), 3.3—4.15 (10H, m), 4.15—4.5 (2H, m). *Anal.* Calcd for $C_{27}H_{56}NO_6P \cdot 2H_2O$: C, 58.14; H, 10.84; N, 2.51; P, 5.55. Found: C, 58.61; H, 10.46; N, 2.68; P, 5.53.

Similar introduction of the phosphonocholine side chain into **35**, **31b** or **33b** gave **9**, **10** or **11**, respectively.

***dl*-*O*-{*O*-[(*cis*-3-Hexadecyloxytetrahydropyran-2-yl)methyl]phosphono}-choline (Inner Salt) (9)** An amorphous powder (71%), mp 213—220 °C. ^{1}H-NMR (CD_3OD) δ: 0.8—1.8 (33H, m), 1.8—2.3 (2H, m), 3.23 (9H, s), 3.4—3.75 (5H, m), 3.8—4.2 (3H, m), 4.1—4.45 (2H, m). *Anal.* Calcd for $C_{27}H_{56}NO_6P \cdot H_2O$: C, 60.08; H, 10.83; N, 2.60; P, 5.74. Found: C, 59.71; H, 10.68; N, 2.56; P, 6.05.

***dl*-*O*-[*O*-(*trans*-2-Hexadecyloxymethyltetrahydropyran-3-yl)phosphono]-choline (Inner Salt) (10)** An amorphous powder (44%), mp 220—224 °C. ^{1}H-NMR (CD_3OD) δ: 0.7—1.9 (34H, m), 2.2—2.55 (1H, m), 3.23 (9H, s), 3.3—4.1 (10H, m), 4.27 (2H, m). FAB-MS: 522 $(M+H)^+$. *Anal.* Calcd for $C_{27}H_{56}NO_6P \cdot H_2O$: C, 60.08; H, 10.83; N, 2.60; P, 5.74. Found: C, 59.97; H, 10.59; N, 2.48; P, 5.68.

***dl*-*O*-[*O*-(*cis*-2-Hexadecyloxymethyltetrahydropyran-3-yl)phosphono]-choline (Inner Salt) (11)** An amorphous powder (28%), mp 225—231 °C. ^{1}H-NMR (CD_3OD) δ: 0.7—1.7 (32H, m), 1.7—2.4 (3H, m), 3.25 (9H, s), 3.4—3.8 (9H, m), 3.8—4.15 (1H, m), 4.15—4.45 (2H, m). *Anal.* Calcd for $C_{27}H_{56}NO_6P \cdot H_2O$: C, 60.08; H, 10.83; N, 2.60; P, 5.74. Found: C, 59.97; H, 10.59; N, 2.48; P, 5.66.

***dl-trans*-2-Hydroxymethyltetrahydropyran-3-yl *N*-Octadecylcarbamate (36a)** A mixture of nonadecanoic acid (5.405 g, 18.1 mmol), Et_3N (2.52 ml, 18.1 mmol), DPPA (3.25 ml, 15.1 mmol) and benzene (180 ml) was heated under reflux for 3 h. After cooling, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and aqueous NaCl solution, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in benzene (150 ml), and **31a** (1.118 g, 5.03 mmol) and Et_3N (2.52 ml, 18.1 mmol) were added. After being heated under reflux for 6 d, the mixture was cooled, diluted with EtOAc, washed with aqueous $NaHCO_3$ and aqueous NaCl solution, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (120 g). Elution with hexane–EtOAc (9:1—4:1) yielded *dl-trans*-2-benzyloxymethyltetrahydropyran-3-yl *N*-octadecylcarbamate (1.417 g, 54%), as a solid substance. ^{1}H-NMR δ: 0.7—2.5 (39H, m), 2.6—4.1 (7H, m), 4.4—4.9 (2H, m), 4.50 (2H, s), 7.21 (5H, m). A mixture of this carbamate (1.395 g), 10% Pd–C (0.70 g) and THF (30 ml) was hydrogenated in a Paar apparatus at 4 atm for 7 h. The catalyst was filtered through a layer of Celite, and the filtrate was evaporated to dryness to give crystalline **36a** (1.128 g, 98%), mp 84.0—86.0 °C (Et_2O). ^{1}H-NMR δ: 0.7—2.4 (39H, m), 2.80 (1H, m), 3.0—4.2 (7H, m), 4.5—4.9 (2H, m). IR cm^{-1}: 3600, 3460, 1710. MS *m/z*: 427 (M^+), 396 ($M^+ - CH_3O$). *Anal.* Calcd for $C_{25}H_{49}NO_4$: C, 70.21; H, 11.55; N, 3.28. Found: C, 69.91; H, 11.55; N, 3.19.

***dl-trans*-2-Hydroxymethyltetrahydropyran-3-yl *N*-Heptadecylcarbamate (36b)** Using stearic acid in place of nonadecanoic acid, *dl-trans*-2-benzyloxymethyltetrahydropyran-3-yl *N*-heptadecylcarbamate (87%, mp 61.0—63.0 °C) was similarly prepared from **31a**. ^{1}H-NMR δ: 0.7—2.5 (37H, m), 2.6—4.1 (7H, m), 4.4—4.8 (2H, m), 4.57 (2H, s), 7.33 (5H, m). IR cm^{-1}: 3460, 1720. MS *m/z*: 503 (M^+), 412 ($M^+ - C_7H_7$). *Anal.* Calcd for $C_{31}H_{53}NO_4$: C, 73.91; H, 10.60; N, 2.78. Found: C, 74.27; H, 10.70; N, 2.71.

Debenzylation of this compound was carried out as described for **36a**, to give crystalline **36b** (88%), mp 84.0—86.0 °C (Et_2O). ^{1}H-NMR δ: 0.7—2.4 (37H, m), 2.4—2.7 (1H, m), 3.0—4.2 (7H, m), 4.5—4.9 (2H, m). IR cm^{-1}: 3570, 3450, 1710. MS *m/z*: 413 (M^+), 382 ($M^+ - CH_3O$). *Anal.* Calcd for $C_{24}H_{47}NO_4$: C, 69.69; H, 11.45; N, 3.39. Found: C, 69.38; H, 11.35; N, 3.52.

***dl*-3-{2-[*O*-(*trans*-3-Octadecylcarbamoyloxytetrahydropyran-2-yl)methyl]phosphonoxy}ethylthiazolium (Inner Salt) (41a)** A solution of 2-bromoethyl phosphorodichloridate (0.891 g, 3.68 mmol) in CH_2Cl_2 (5 ml) was added to a stirred solution of **36a** (1.050 g, 2.46 mmol) and Et_3N (0.58 ml, 4.17 mmol) in CH_2Cl_2 (15 ml) under ice-water cooling. Stirring was continued at room temperature for 2 h. Pyridine (2.0 ml) and water (1.0 ml) were added and the mixture was further stirred at room temperature for 2 h. The solvent was evaporated off, and the residue was treated with 10% aqueous HCl solution and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (30 g). Elution with CH_2Cl_2–MeOH (98:2—1:1) gave resinous *dl*-[*trans*-3-(*N*-octadecylcarbamoyloxy)tetrahydropyran-2-yl]methyl 2-bromoethyl phosphate (1.157 g, 77%). A solution of this compound (0.655 g, 1.07 mmol) and thiazole (0.76 ml, 10.7 mmol) in toluene (0.8 ml) was heated on an oil bath at 80 °C for 60 h. The solvent was evaporated off *in vacuo*, and the residue was chromatographed on silica gel (15 g). Elution with CH_2Cl_2–MeOH (3:1—0:1) gave the bromide of **41a** (0.382 g), which was dissolved in THF–H_2O (95:5, 4 ml) and passed through a column containing Amberlite MB-3 (4 ml) and the same solvent. The eluate was repeatedly (six times) passed through the same column, and finally the column was washed with the same solvent. The eluate and the washing were combined, and evaporated to dryness. The residue was subjected to MPLC on a Lobar B column. Elution with CH_2Cl_2–MeOH–H_2O (65:35:5) gave **41a** (0.284 g, 43% from **36a**) as an amorphous powder. ^{1}H-NMR (CD_3OD) δ: 0.8—2.5 (39H, m), 2.9—5.1 (12H, m), 8.30 (1H,

m), 8.53 (1H, d, $J=3$ Hz), 10.20 (1H, m). *Anal.* Calcd for $C_{30}H_{55}N_2O_7PS\cdot H_2O$: C, 56.58; H, 9.02; N, 4.40; P, 4.86. Found: C, 56.71; H, 8.65; N, 4.38; P, 4.41.

***dl*-3-{2-[*O*-(*trans*-3-Heptadecylcarbamoyloxytetrahydropyran-2-yl)methyl]phosphonoxy}ethylthiazolium (Inner Salt) (41b)** According to a similar procedure to that described for **41a**, **41b** (an amorphous powder, 26%) was synthesized from **36b**. ^{1}H-NMR (CD_3OD) δ: 0.8—2.4 (37H, m), 3.05 (2H, m), 3.2—4.9 (10H, m), 8.27 (1H, m), 8.53 (1H, d, $J=3$ Hz), 10.17 (1H, m). *Anal.* Calcd for $C_{29}H_{53}N_2O_7PS\cdot 0.5H_2O$: C, 56.75; H, 8.87; N, 4.56. Found: C, 56.91; H, 8.80; N, 4.51.

Using 5-bromopentyl or 6-bromohexyl phosphorodichloridate in place of 2-bromoethyl phosphorodichloridate, **36b** was similarly converted into **41c** or **41d**, respectively.

***dl*-3-{5-[*O*-(*trans*-3-Heptadecylcarbamoyloxytetrahydropyran-2-yl)methyl]phosphonoxy}pentylthiazolium (Inner Salt) (41c)** Amorphous powder (43%), mp 101—104 °C. ^{1}H-NMR (CD_3OD) δ: 0.8—2.4 (43H, m), 3.05 (2H, m), 3.2—4.9 (10H, m), 8.30 (1H, d, $J=4$ Hz), 8.55 (1H, d, $J=4$ Hz), 10.23 (1H, m). FAB-MS: 647 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{59}N_2O_7PS\cdot 1.5H_2O$: C, 57.03; H, 9.27; N, 4.16; P, 4.60; S, 4.76. Found: C, 57.20; H, 9.17; N, 4.10; P, 5.00; S, 4.88.

***dl*-3-{6-[*O*-(*trans*-3-Heptadecylcarbamoyloxytetrahydropyran-2-yl)methyl]phosphonoxy}hexylthiazolium (Inner Salt) (41d)** An amorphous powder (43%), mp 117—120 °C. ^{1}H-NMR (CD_3OD) δ: 0.8—2.4 (45H, m), 3.05 (2H, m), 3.2—4.9 (10H, m), 8.30 (1H, d, $J=4$ Hz), 8.54 (1H, d, $J=4$ Hz). *Anal.* Calcd for $C_{33}H_{61}N_2O_7PS\cdot H_2O$: C, 58.38; H, 9.35; N, 4.13; P, 4.56; S, 4.72. Found: C, 58.09; H, 9.35; N, 4.15; P, 4.66; S, 4.94.

***dl-cis*-2-Hydroxymethyltetrahydropyran-3-yl *N*-Octadecylcarbamate (37)** Treatment of **33a** as described for the synthesis of **36a** gave crystalline **37** (43%), mp 85.0—86.0 °C (Et_2O–hexane). ^{1}H-NMR δ: 0.7—2.2 (39H, m), 2.9—3.8 (7H, m), 3.9—4.2 (1H, m), 4.65—5.1 (2H, m). IR cm^{-1}: 3600, 3450, 1700. MS *m/z*: 427 (M^+), 396 (M^+-CH_3O). *Anal.* Calcd for $C_{25}H_{49}NO_4$: C, 70.21; H, 11.55; N, 3.28. Found: C, 70.27; H, 11.73; N, 3.28.

***dl*-3-{2-[*O*-(*cis*-3-Octadecylcarbamoyloxytetrahydropyran-2-yl)methyl]phosphonoxy}ethylthiazolium (Inner Salt) (42)** Treatment of **37** as described for the synthesis of **41a** afforded **42** (34%) as an amorphous powder with no clear melting point. ^{1}H-NMR (CD_3OD) δ: 0.7—2.2 (39H, m), 2.9—4.9 (12H, m), 8.28 (1H, d, $J=3$ Hz), 8.51 (1H, d, $J=3$ Hz), 10.18 (1H, m). *Anal.* Calcd for $C_{30}H_{55}N_2O_7PS\cdot 1.5H_2O$: C, 55.79; H, 9.05; N, 4.34; P, 4.79. Found: C, 55.90; H, 8.65; N, 4.38; P, 4.78.

***dl-cis*-2-Benzyloxymethyltetrahydropyran-3-thiol (38)** Methanesulfonyl chloride (1.04 ml, 13.4 mmol) was added to a stirred solution of **31a** (2.00 g, 9.0 mmol) and Et_3N (2.51 ml, 18 mmol) in benzene (40 ml) under ice-water cooling. After being stirred at room temperature for 1 h, the mixture was poured into ice water and the organic layer was washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness to yield the methanesulfonate of **31a**.

A solution of thioacetic acid (0.77 ml, 10.8 mmol) in DMF (5 ml) was added to a stirred suspension of NaH (55% in mineral oil, 0.47 g, 10.8 mmol) in DMF (5 ml) under ice-water cooling. The mixture was stirred at room temperature for 1 h, and then a solution of the methanesulfonate described above in DMF (10 ml) was added. The reaction mixture was heated at 80 °C for 16 h, and at 100 °C for 10 h. The mixture was cooled, poured into water, and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (50 g). Elution with hexane–Et_2O (97:3—9:1) gave *dl-S*-(*cis*-2-benzyloxymethyltetrahydropyran-3-yl)thioacetate (1.448 g, 57%) as an oil. ^{1}H-NMR δ: 1.1—2.2 (4H, m), 2.30 (3H, s), 3.2—4.2 (6H, m), 4.47 (1H, d, $J=12$ Hz), 4.57 (1H, d, $J=12$ Hz), 7.2—7.5 (5H, m). IR cm^{-1}: 1685. MS *m/z*: 280 (M^+). *Anal.* Calcd for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19; S, 11.44. Found: C, 64.19; H, 6.96; S, 11.67.

A solution of NaOMe in MeOH (28%, 1.04 ml, 5.08 mmol) was added to a solution of the above compound (1.422 g, 5.07 mmol) in MeOH (30 ml) at −10 °C. After being stirred at −10—0 °C for 2 h, the mixture was acidified with methanesulfonic acid (0.33 ml, 5.08 mmol), poured into water, and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The oily residue was chromatographed on silica gel (30 g). Elution with hexane–Et_2O (97:3—95:5) gave **38** (1.146 g, 95%) as an oil. ^{1}H-NMR δ: 1.1—2.4 (4H, m), 1.66 (1H, d, $J=10$ Hz), 2.95—3.25 (1H, m), 3.25—3.85 (4H, m), 3.85—4.2 (1H, m), 4.51 (1H, d, $J=12$ Hz), 4.59 (1H, d, $J=12$ Hz), 7.1—7.5 (5H, m). MS *m/z*: 238 (M^+). *Anal.* Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.62; H, 7.83; S, 13.19.

***dl-S*-(*cis*-2-Hydroxymethyltetrahydropyran-3-yl) *N*-Heptadecylthiocarbamate (55)** Following the procedure described for the synthesis of **36a**, **38** was allowed to react with heptadecyl isocyanate to yield *dl-S*-(*cis*-2-benzyloxymethyltetrahydropyran-3-yl) *N*-heptadecylthiocarbamate (93%), mp 80.0—81.0 °C (Et_2O–hexane). ^{1}H-NMR δ: 0.8—2.2 (37H, m), 3.1—4.2 (8H, m), 4.51 (1H, d, $J=12$ Hz), 4.59 (1H, d, $J=12$ Hz), 5.31 (1H, m), 7.35 (5H, m). IR cm^{-1}: 3430, 1670. MS *m/z*: 518 (M^+-1). *Anal.* Calcd for $C_{31}H_{53}NO_3S$: C, 71.63; H, 10.28; N, 2.69; S, 6.17. Found: C, 71.73; H, 10.19; N, 2.64; S, 6.43.

A solution of this compound in CH_2Cl_2 (5.20 g, 10 mmol) was added to a cold mixture of $AlCl_3$ (6.67 g, 50 mmol), NaI (7.50 g, 50 mmol), acetonitrile (200 ml) and CH_2Cl_2 (100 ml).[18] After being stirred at room temperature for 4 h, the mixture was diluted with water, filtered through a layer of Celite, and extracted twice with CH_2Cl_2. The combined extracts were washed with aqueous $Na_2S_2O_3$ and aqueous NaCl solutions, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (90 g). Elution with hexane–CH_2Cl_2–EtOAc (10:10:1—2:2:1) gave **55** (4.04 g, 94%), mp 90.0—91.0 °C (hexane). ^{1}H-NMR δ: 0.7—2.3 (38H, m), 3.15—4.15 (8H, m), 5.53 (1H, m). IR cm^{-1}: 3430, 1650. *Anal.* Calcd for $C_{24}H_{47}NO_3S$: C, 67.08; H, 11.02; N, 3.26; S, 7.46. Found: C, 67.04; H, 10.98; N, 3.31; S, 7.63.

Starting from the above thiocarbamate **55**, compounds **43a**—**d** were synthesized in the same way as described for **41a**, using 2-bromoethyl, 4-bromobutyl, 5-bromopentyl and 6-bromohexyl phosphorodichloridate as the phosphorylating agent, respectively.

***dl*-3-{2-[*O*-(*cis*-3-Heptadecylcarbamoylthiotetrahydropyran-2-yl)methyl]phosphonoxy}ethylthiolium (Inner Salt) (43a)** An amorphous powder (28% from **55**). ^{1}H-NMR (CD_3OD) δ: 0.7—2.4 (37H, m), 2.9—4.2 (10H, m), 4.82 (2H, t, $J=7.5$ Hz), 8.30 (1H, d, $J=4$ Hz), 8.53 (1H, d, $J=4$ Hz). IR (KBr) cm^{-1}: 3400, 1650. *Anal.* Calcd for $C_{29}H_{53}N_2O_6PS_2\cdot 0.5H_2O$: C, 55.30; H, 8.64; N, 4.45. Found: C, 55.53; H, 8.42; N, 4.74.

***dl*-3-{4-[*O*-(*cis*-3-Heptadecylcarbamoylthiotetrahydropyran-2-yl)methyl]phosphonoxy}butylthiazolium (Inner Salt) (43b)** An amorphous powder (41%). ^{1}H-NMR (CD_3OD) δ: 0.7—2.4 (41H, m), 2.9—4.2 (10H, m), 4.71 (2H, t, $J=7.5$ Hz), 8.29 (1H, d, $J=4$ Hz), 8.55 (1H, d, $J=4$ Hz). IR (KBr) cm^{-1}: 3250, 1665. *Anal.* Calcd for $C_{31}H_{57}N_2O_6PS_2\cdot H_2O$: C, 57.38; H, 8.85; N, 4.32; P, 4.77; S, 9.88. Found: C, 57.58; H, 8.92; N, 4.20; P, 4.64; S, 9.62.

***dl*-3-{5-[*O*-(*cis*-3-Heptadecylcarbamoylthiotetrahydropyran-2-yl)methyl]phosphonoxy}pentylthiazolium (Inner Salt) (43c)** An amorphous powder (44%). ^{1}H-NMR (400 MHz, CD_3OD) δ: 0.90 (3H, t, $J=7.0$ Hz), 1.23—1.37 (28H, m), 1.43—1.53 (5H, m), 1.68 (2H, quintet, $J=7.0$ Hz), 1.84—2.05 (3H, m), 2.06 (2H, quintet, $J=7.3$ Hz), 3.11 (1H, dt, $J=13.4$, 6.8 Hz), 3.20 (1H, dt, $J=13.4$, 6.8 Hz), 3.49 (1H, ddd, $J=12.0$, 12.0, 2.8 Hz), 3.78—3.97 (7H, m), 4.62 (2H, t, $J=7.3$ Hz), 8.28 (1H, d, $J=3.8$ Hz), 8.52 (1H, d, $J=3.8$ Hz), 10.17 (1H, m). IR cm^{-1}: 3250, 1665. *Anal.* Calcd for $C_{32}H_{59}N_2O_6PS_2\cdot H_2O$: C, 56.44; H, 9.03; N, 4.11; P, 4.55; S, 9.42. Found: C, 56.48; H, 9.07; N, 4.14; P, 4.75; S, 9.64.

***dl*-3-{6-[*O*-(*cis*-3-Heptadecylcarbamoylthiotetrahydropyran-2-yl)methyl]phosphonoxy}hexylthiazolium (Inner Salt) (43d)** An amorphous powder (39%). ^{1}H-NMR (CD_3OD) δ: 0.7—2.4 (45H, m), 2.9—4.2 (10H, m), 4.61 (2H, t, $J=7.5$ Hz), 8.28 (1H, d, $J=4$ Hz), 8.52 (1H, d, $J=4$ Hz). IR cm^{-1}: 3250, 1665. *Anal.* Calcd for $C_{33}H_{61}N_2O_6PS_2\cdot H_2O$: C, 57.03; H, 9.14; N, 4.03; P, 4.46; S, 9.23. Found: C, 57.06; H, 9.18; N, 3.97; P, 4.30; S, 9.59.

***dl*-[*trans*-3-(Tetrahydropyran-2-yloxy)tetrahydropyran-2-yl]methanol (39)** A solution of **31a** (2.22 g, 10 mmol), 3,4-dihydro-2*H*-pyran (2.65 ml, 29 mmol) and pyridinium *p*-toluenesulfonate (0.05 g) in CH_2Cl_2 (40 ml) was stirred at room temperature for 4 h. The solvent was evaporated off and the residue was chromatographed on silica gel (80 g). Elution with hexane–Et_2O (6:1—5:1) gave *dl-trans*-2-benzyloxymethyl-3-(tetrahydropyran-2-yloxy)tetrahydropyran (2.93 g, 96%) as a colorless oil. ^{1}H-NMR δ: 1.1—2.4 (10H, m), 3.15—4.15 (8H, m), 4.49 (1H, d, $J=12$ Hz), 4.67 (1H, d, $J=12$ Hz), 4.78 (1H, m), 7.35 (5H, m). MS *m/z*: 306 (M^+). *Anal.* Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.65; H, 8.45.

A mixture of the above compound (2.93 g, 9.58 mmol), 10% Pd–C (1.30 g) and THF (130 ml) was hydrogenated in a Paar apparatus at 4 atm for 8 h. The catalyst was filtered off through a layer of Celite, and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel [50 g, elution with hexane–Et_2O (2:1—1:1)] to give **39** (1.87 g, 90%) as a colorless oil. ^{1}H-NMR δ: 1.15—2.4 (10H, m), 2.77 (1H, t, $J=7$ Hz), 3.1—4.1 (8H, m), 4.70 (1H, m). IR cm^{-1}: 3600, 3480. MS *m/z*: 216 (M^+), 115 ($M^+-C_5H_9O_2$). *Anal.* Calcd for $C_{11}H_{20}O_4$: C, 61.12; H, 9.33. Found: C, 60.75; H, 9.29.

***dl*-3-{2-[*O*-(*trans*-2-Octadecylcarbamoyloxymethyltetrahydropyran-3-yl)]phosphonoxy}ethylthiazolium (Inner Salt) (44)** As described for **36a**, **39** (1.809 g, 8.37 mmol) was allowed to react with octadecyl isocyanate in

benzene (reflux, 24 h), and the reaction mixture was worked up. The crude product was chromatographed on silica gel [100 g, elution with hexane–CH_2Cl_2–Et_2O (5:5:1)] to give *dl*-[*trans*-3-(tetrahydropyran-2-yloxy)-tetrahydropyran-2-yl]methyl *N*-octadecylcarbamate (4.200 g, a solid). A solution of this compound (4.200 g) and *dl*-10-camphorsulfonic acid (0.20 g) in THF–MeOH (1:2, 30 ml) was stirred at room temperature for 45 min. Saturated aqueous $NaHCO_3$ solution (10 ml) was added, and the solvents were evaporated off *in vacuo*. The residue was mixed with ice water and extracted twice with Et_2O. The combined extracts were washed with aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel (70 g). Elution with hexane–CH_2Cl_2–Et_2O (5:5:1) gave crystalline *dl*-(*trans*-3-hydroxymethyltetrahydropyran-2-yl)methyl *N*-octadecylcarbamate (3.289 g, 92% from **39**), mp 55.0—56.0 °C (Et_2O–hexane). ^{1}H-NMR δ: 0.75—2.3 (39H, m), 3.0—3.6 (5H, m), 3.69 (1H, d, J=4 Hz), 3.85—4.2 (2H, m), 4.75 (1H, dd, J=13, 3 Hz), 4.95 (1H, m). IR cm^{-1}: 3450, 1700. MS *m/z*: 427 (M^+), 409 ($M^+ - H_2O$). *Anal.* Calcd for $C_{25}H_{49}NO_4$: C, 70.21; H, 11.55; N, 3.28. Found: C, 70.31; H, 11.42; N, 3.27.

Introduction of the phosphate side chain into the above compound (1.050 g) was carried out as described for **41a** to give **44** (0.148 g, 17%) as an amorphous powder, mp 47—52 °C. ^{1}H-NMR (CD_3OD) δ: 0.7—2.4 (39H, m), 2.9—5.0 (12H, m), 8.27 (1H, d, J=4 Hz), 8.52 (1H, d, J=4 Hz), 10.20 (1H, m). *Anal.* Calcd for $C_{30}H_{55}N_2O_7PS \cdot 1.5H_2O$: C, 55.79; H, 9.05; N, 4.34; P, 4.79. Found: C, 55.60; H, 9.05; N, 4.21; P, 4.31.

***dl*-[*cis*-3-(Tetrahydropyran-2-yloxy)tetrahydropyran-2-yl]methanol (40)** Treatment of **33a** as described for **39** afforded **40** (71%) as a colorless oil. ^{1}H-NMR δ: 0.8—2.4 (10H, m), 2.94 (1H, s), 3.2—4.2 (8H, m), 4.58 (1H, m). MS *m/z*: 216 (M^+).

***dl*-3-{2-[*O*-(*cis*-2-Heptadecylcarbamoyloxymethyltetrahydropyran-3-yl)]-phosphonoxy}ethylthiazolium (Inner Salt) (45)** Reaction of **40** with heptadecyl isocyanate was carried out as described for **36a**, and the product was deprotected as described above to give *dl*-(*cis*-3-hydroxytetrahydropyran-2-yl)methyl *N*-heptadecylcarbamate (85% from **40**), mp 86.0—87.0 °C (Et_2O). ^{1}H-NMR δ: 0.7—2.3 (37H, m), 3.0—5.0 (10H, m). IR cm^{-1}: 3460, 1710. MS *m/z*: 414 (M^++1), 413 (M^+). *Anal.* Calcd for $C_{24}H_{47}NO_4$: C, 69.69; H, 11.45; N, 3.39. Found: C, 69.55; H, 11.42; N, 3.30.

Following the procedure described for **41a**, this compound was converted into **45** (an amorphous powder, 2.5%). ^{1}H-NMR (CD_3OD) δ: 0.7—2.5 (37H, m), 2.9—5.0 (12H, m), 8.29 (1H, d, J=4 Hz), 8.55 (1H, d, J=4 Hz), 10.29 (1H, m).

5-Benzyloxymethyl-2,3-dihydrofuran (48) A solution of butyllithium in hexane (15.08%, 358 g) was added dropwise to a solution of 2,3-dihydrofuran (58.7 g, 0.838 mol) in THF (350 ml) over a period of 30 min at 5—10 °C under ice-water cooling. The mixture was then heated at 50 °C for 2 h, and cooled to 0 °C. Paraformaldehyde (90% purity, 28.7 g, 0.838 mol) was then added all at once, and the mixture was heated at 50 °C for 2 h. After cooling, the mixture was washed with ice-water (500 ml). The organic layer was separated, and the aqueous layer was extracted five times with CH_2Cl_2. The combined organic solutions were dried and concentrated *in vacuo*. Distillation of the residue (14 g) gave 4,5-dihydrofurfuryl alcohol (8.97 g, 12%), bp 66—67 °C/7 mmHg. ^{1}H-NMR (C_6D_6) δ: 2.21 (2H, br t, J=9 Hz), 2.98 (1H, br t, J=6 Hz), 3.98 (2H, d, J=6 Hz), 4.00 (2H, t, J=9 Hz), 4.68 (1H, m). MS *m/z*: 200 ($M \times 2$)$^+$, 101 (M^++1), 100 (M^+). This substance was used in the next step immediately after distillation, as it dimerized easily.

A solution of the above alcohol (17.64 g, 0.176 mol) in DMF (30 ml) was added dropwise to a stirred suspension of NaH (55% in mineral oil, 7.69 g, 0.176 mol) in DMF (150 ml) at 10—15 °C under ice-water cooling over 30 min. The mixture was stirred at room temperature for 1 h, and then benzyl bromide (20.93 ml, 0.176 mmol) was added dropwise at 10—15 °C over a period of 30 min. The reaction mixture was stirred at room temperature for 1 h, poured into water (1 l), and extracted twice with EtOAc. The combined extracts were washed with aqueous NaCl solution, dried, and evaporated to dryness. The residue was chromatographed on silica gel (400 g). Elution with hexane–Et_2O (100:7) gave **48** (3.71 g, 11%) as a colorless oil. ^{1}H-NMR δ: 2.65 (2H, br t, J=10 Hz), 3.58 (2H, s), 4.03 (2H, m), 4.39 (2H, t, J=10 Hz), 4.93 (1H, m), 7.35 (5H, m). MS *m/z*: 190 (M^+).

***dl-trans*-2-Benzyloxymethyltetrahydrofuran-3-ol (49)** Hydroboration of **48** was carried out as described for **31a** to give **49** (54%) as a colorless oil. ^{1}H-NMR δ: 1.6—2.4 (2H, m), 2.28 (1H, m), 3.43 (1H, dd, J=10, 6 Hz), 3.60 (1H, dd, J=10, 4.5 Hz), 3.75—4.10 (3H, m), 4.27 (1H, m), 4.58 (2H, s), 7.30 (5H, s). MS *m/z*: 208 (M^+).

Starting from **49**, following compounds were successively synthesized in a similar manner to that used for the synthesis of **41c**.

***dl-trans*-2-Benzyloxymethyltetrahydrofuran-3-yl *N*-Heptadecylcarbamate** White flakes (80%), mp 54—56 °C (hexane). ^{1}H-NMR (270 MHz) δ: 0.8—1.7 (33H, m), 1.90—2.30 (2H, m), 3.15 (2H, dt, J=6.6, 6.6 Hz), 3.59 (2H, d, J=4.4 Hz), 3.88 (1H, m), 4.05 (2H, m), 4.56 (2H, s), 4.67 (1H, m), 5.10 (1H, m), 7.32 (5H, m). IR cm^{-1}: 3450, 1720. *Anal.* Calcd for $C_{30}H_{51}NO_4$: C, 73.57; H, 10.50; N, 2.86. Found: C, 73.09; H, 10.33; N, 2.87.

***dl-trans*-2-Hydroxymethyltetrahydrofuran-3-yl *N*-Heptadecylcarbamate** White leaflets (90%), mp 77—78 °C (Et_2O–hexane). ^{1}H-NMR (270 MHz) δ: 0.8—1.7 (33H, m), 1.95—2.25 (2H, m), 2.41 (1H, t, J=6.2 Hz), 3.16 (2H, dt, J=6.6, 6.6 Hz), 3.70 (2H, m), 3.80—4.10 (3H, m), 4.72 (1H, m), 5.01 (1H, m). IR cm^{-1}: 3600, 3450, 1710. MS *m/z*: 400 (M^++1), 399 (M^+), 368 ($M^+ - CH_3O$). *Anal.* Calcd for $C_{23}H_{45}NO_4$: C, 69.13; H, 11.35; N, 3.50. Found: C, 68.98; H, 11.22; N, 3.70.

***dl*-3-{2-[*O*-(*trans*-3-Heptadecylcarbamoyloxytetrahydrofuran-2-yl)-methyl]phosphonoxy}ethylthiazolium (Inner Salt) (46)** Viscous oil (19%). ^{1}H-NMR (270 MHz, CD_3OD) δ: 0.89 (3H, t, J=7.0 Hz), 1.2—1.6 (30H, m), 1.96 (1H, m), 2.20 (1H, m), 3.07 (2H, t, J=7.0 Hz), 3.75—4.10 (4H, m), 4.20—4.40 (2H, m), 5.05 (1H, dm, J=6.2 Hz), 8.26 (1H, dd, J=3.7, 2.2 Hz), 8.50 (1H, dd, J=3.7, 1.1 Hz), 10.14 (1H, m).

Inhibition of PAF-Induced Platelet Aggregation (*in Vitro*)[22] Rabbit blood drawn by heart puncture was immediately mixed with one-ninth volume of 3.8% aqueous sodium citrate solution. Platelet-rich plasma (PRP) was obtained as the upper layer by centrifugation of the blood at 150 × *g* for 15 min at room temperature. The remaining blood was further centrifuged for 15 min at 1000 × *g* to give platelet-poor plasma (PPP) as the supernatant. Appropriate proportions of PRP and PPP thus obtained were mixed to prepare plasma with a platelet count of $6 \times 10^5/\mu l$. Platelet aggregation was measured by Born's method[22] with an aggregometer. A saline solution (1 μl) of a test compound at an appropriate concentration was added to the above plasma (250 μl). After 1 min, a saline solution (25 μl) of synthetic C_{16}-PAF was added (final concentration: 1—3×10^{-8} M), and the aggregation was observed for 5 min. The IC_{50} values listed in Table II were calculated from the dose–response curves.

Inhibition of PAF-Induced Hypotension Under inactin anesthesia (90 mg/kg, i.p.) the left femoral artery and vein of a Wistar-Imamichi rat (350—450 g) were cannulated to allow continuous monitoring of the arterial pressure and for drug administration, respectively. At 5 min intervals, the animal was given a solution of C_{16}-PAF (10 ng/kg, i.v.) in saline containing 0.25% bovine serum albumin (BSA), until a steady hypotensive response was achieved. A solution of a test compound in saline containing 0.25% BSA or 20% (v/v) EtOH was intravenously administered. Within 1 min, the same amount of C_{16}-PAF was again administered, and the hypotensive response was compared with the responses before the test drug administration. The dose of the test compound was cumulatively increased by a factor of 3 at 5 min intervals. The ID_{50} values listed in Table II were calculated from the dose–response curves for the test compounds.

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