ethyl acetate–hexanes, to yield **22** (4.2 g, 77%) as an orange solid: ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1 H), 7.78–6.96 (m, 8 H), 3.10 (s, 6 H) ppm. Anal. ($C_{18}H_{15}FN_2O$) C, H, N.

Methyl (*E*)-3-[2-(dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]-2-propenoate (23) was prepared analogously to compounds **4a–e** in Scheme I: yield 92%; ^{1}H NMR ($CDCl_3$) δ 7.78–6.87 (m, 9 H), 5.98 (d, 1 H), 3.60 (s, 3 H), 2.95 (s, 6 H) ppm. Anal. ($C_{21}H_{19}FN_2O_2$) C, H, N.

(*E*)-3-[2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]-2-propen-1-ol (24) was prepared analogously to compounds **5a–e** in Scheme I: yield 98%; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1 H), 7.50–7.30 (m, 1 H), 7.20–6.98 (m, 6 H), 6.31 (d, 1 H), 5.72 (dt, 1 H), 3.99 (bd, 2 H), 2.96 (s, 6 H), 1.54 (bs, 1 H) ppm. Anal. ($C_{20}H_{19}FN_2O$) H; C: calcd, 74.51; found, 72.52; N: calcd, 8.69; found, 7.84.

(*E*)-3-[2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]-2-propenal (25) was prepared analogously to compounds **6a–e** in Scheme I: yield 92%; ^{1}H NMR ($CDCl_3$) δ 9.35 (d, 1 H), 7.75 (d, 1 H), 7.58–6.98 (m, 8 H), 6.32 (dd, 1 H), 2.99 (s, 6 H) ppm. Anal. ($C_{20}H_{17}FN_2O$) H, N; C: calcd, 74.98; found, 72.85.

[4α,6β(*E*)]-6-[2-[2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (26) was prepared in 29% overall yield from compound **25** in an analogous manner to the preparation of lactones **8a–e** from aldehydes **6a–e**: mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1 H), 7.57–7.50 (m, 1 H), 7.26–7.16 (m, 6 H), 6.49 (d, 1 H), 5.66 (dd, 1 H), 5.16–5.06 (m, 1 H), 4.28–4.25 (m, 1 H), 3.01 (s, 6 H), 2.75–2.60 (q, 2 H), 2.07 (bs, 1 H), 1.82–1.51 (m, 1 H) ppm. Anal. ($C_{24}H_{23}FN_2O_3 \cdot 0.5C_4H_8O_2$) C, H, N.

3-Methyl-4-quinolinemethanol (28) was prepared in 73% yield via a DIBAL-H reduction of **27**:[15] ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1 H), 8.17–7.90 (m, 2 H), 7.68–7.42 (m, 2 H), 5.05 (s, 2 H), 2.46 (s, 3 H), 2.20 (bs, 1 H) ppm.

3-Methyl-4-quinolinecarboxaldehyde (29) was prepared in 70% yield from **28** via a Swern oxidation: ^{1}H NMR ($CDCl_3$) δ 10.77 (s, 1 H), 8.68 (s, 1 H), 8.52–8.41 (m, 1 H), 8.03–7.87 (m, 1 H), 7.67–7.34 (m, 2 H), 2.67 (s, 3 H) ppm.

Methyl (*E*)-3-(3-methyl-4-quinolinyl)-2-propenoate (30) was prepared in 76% yield via treatment of **29** with methyl (triphenylphosphoranylidene)acetate in an analogous manner to the preparation of compounds **4a–e** in Scheme I: ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1 H), 8.10–7.34 (m, 5 H), 6.21 (d, 1 H), 3.80 (s, 3 H), 2.42 (s, 3 H) ppm. Anal. ($C_{14}H_{13}NO_2$) C, H, N.

(*E*)-3-(3-Methyl-4-quinolinyl)-2-propen-1-ol (31) was prepared in 71% yield from **30** via DIBAL-H reduction: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1 H), 8.10–7.85 (m, 2 H), 7.66–7.33 (m, 2 H), 6.92 (d, 1 H), 6.11 (dt, 1 H), 4.35 (bs, 3 H), 2.46 (s, 3 H) ppm.

(*E*)-3-(3-Methyl-4-quinolinyl)-2-propenal (32) was prepared in 71% yield from **31** via a Swern oxidation. ^{1}H NMR ($CDCl_3$) δ 9.75 (d, 1 H), 8.63 (s, 1 H), 8.02–7.14 (m, 5 H), 6.38 (dd, 1 H), 2.41 (s, 3 H) ppm.

[4α,6β(*E*)]-6-[2-(3-Methyl-4-quinolinyl)ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (34) was prepared in 10% overall yield from aldehyde **32**. The low yield is due to inefficient extraction of the dihydroxy acid from the aqueous phase during the acidification procedure: mp 198–200 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1 H), 7.94–7.87 (m, 2 H), 7.55–7.34 (m, 2 H), 6.87 (d, 1 H), 5.92 (dd, 1 H), 5.46–5.37 (m, 1 H), 4.90 (bs, 1 H), 4.26 (bs, 1 H), 2.62 (d, 2 H), 2.33 (s, 3 H), 2.15–2.03 (m, 1 H), 1.89–1.76 (m, 1 H) ppm.

In Vivo Acute Inhibition of Cholesterol Synthesis Assay (AICS). Male Sprague–Dawley rats (250 g body weight), previously fed 2.5% cholestyramine for 3 days, were randomly divided into groups (N = 5/group) and given a single dose of vehicle (controls) or compound by an oral gavage at the indicated doses. One hour after drug dosing, all rats were injected intraperitoneally with sodium [1-^{14}C]acetate (20.0 μCi/rat in 0.3 mL of saline). After 50 min, blood samples were taken, plasma was obtained by centrifugation, and plasma [^{14}C]cholesterol was measured after saponification and extraction.

Acknowledgment. We thank Dr. F. A. MacKellar and staff for analytical and spectral determinations, and last but not least Ms. Patty Elka for manuscript preparation.

Disubstituted Tetrahydrofurans and Dioxolanes as PAF Antagonists

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A new series of disubstituted tetrahydrofuran and dioxolane derivatives were prepared and evaluated for their PAF antagonist activity in the PAF-induced in vitro platelet-aggregation and in vivo hypotension tests. Several of these compounds exhibited more potent activity than the structurally related 2-[*N*-acetyl-*N*-[[[[2-methoxy-3-[(octadecylcarbamoyl)oxy]propoxy]carbonyl]amino]methyl]-1-ethylpyridinium chloride (CV-6209, **3**) in the in vitro assay, whereas all showed less potency in the in vivo test. The role of both the substituent nature and the placement and number of oxygen atoms in the ring are discussed. A qualitative SAR study was carried out on these nuclei.

Platelet activating factor (PAF, 1) is a naturally occurring phospholipid first described in 1972.[1] It is produced by stimulated basophils, neutrophils, platelets, macrophages, endothelial cells, and IgE-sensitized bone marrow cells.[2] PAF is involved in a wide range of biological actions such as stimulation of platelets and leukocytes, bronchoconstriction, hypotension, negative inotropic cardiac effects, and increase in vascular permeability.[3-5] In vivo experiments have demonstrated PAF's role in several pathological conditions,[6] such as asthma,[7] inflammation,[8] anaphylactic shock,[9] gastric ulceration,[10] and

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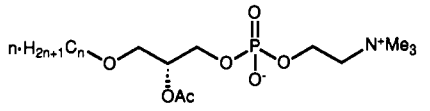
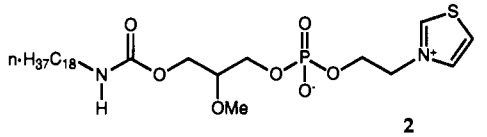
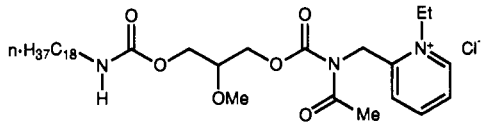
transplant rejection.[11] In view of all these properties, the search for PAF antagonists, potentially useful drugs for the treatment of these diseases, has attracted the attention of a large number of research groups in the industrial and academic worlds.[12]



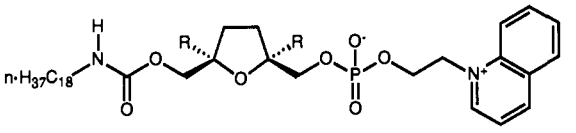
1: n=16 and 18



2

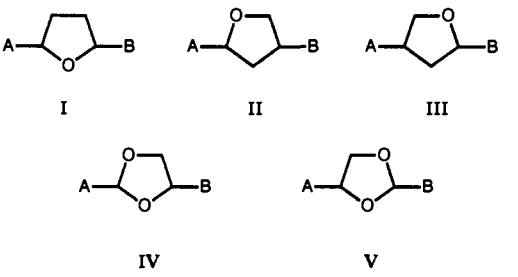


3



4: R=H
5: R=Me

Chemically, PAF was identified in 1979 as 1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine, the natural substance being a mixture of the C16 and C18 homologues.[13] Four years later, Takeda pharmaceuticals described the first PAF antagonist, 3-(4-hydroxy-7-methoxy-10-oxo-3,5,9-trioxa-11-aza-4-phosphanonacos-1-yl)thiazolium hydroxide, inner salt, *P*-oxide (CV-3988, **2**), a phospholipid derivative originally developed as a cytotoxic and antifungal agent.[14] This compound was further elaborated to a more potent substance, 2-[*N*-acetyl-*N*-[[[[2-methoxy-3-[(octadecylcarbamoyl)oxy]propoxy]carbonyl]-amino]methyl]-1-ethylpyridinium chloride (CV-6209, **3**).[15] Since the discovery of PAF, a large number of compounds belonging to a wide range of chemical structures have been reported to show PAF-antagonist activity. In a very general way, and despite their often unrelated chemical structure, all of these compounds can be regarded as belonging to one of the following two classes: ionic and nonionic. When this project was started, several PAF antagonists having an ionic, PAF-like structure had been described. In most of them, the fatty alkoxy group of PAF had been replaced by a long-chain carbamoyloxy group, the acetoxy radical by a lower alkoxy, and the phosphatidylcholine residue either modified at the quaternary nitrogen or completely replaced by an ester or ether carrying a quaternary nitrogen at the end of a methylene chain.[12] We were interested in exploring the effect on the activity that would cause the transformation of the glycerol backbone into an oxygen-containing five-membered ring. In this regard, two 2,5-disubstituted tetrahydrofurans (**4** and **5**) had been previously reported to be good PAF antagonists,[16] but nothing had been described about 2,4-disubstituted tetrahydrofurans or dioxolanes. We planned, thus, to construct all the tetrahydrofuran and dioxolane nuclei carrying two substituents of the type previously reported in the literature and having a 1,3-substitution relationship, as shown in Figure 1, whereby A stands for a long alkyl chain containing group and B represents a substituent carrying a quaternary nitrogen. Both substituents were varied in terms of length and chemical functionality. With regard to the fatty chain containing substituent, three functionalities were explored: alkyl, alkoxy, and alkyl carbamate. As to the charge-containing moiety, we first investigated the onium salts containing a phosphatidyl, an ether, or an ester function. However, we could soon verify that the acyl carbamate group present in **3** was a much better choice. We therefore did most of our ring optimization work on the compounds carrying this substituent.



I II III IV V

Figure 1.

Disubstitution in a five-membered ring raises the issue of relative stereochemistry (cis and trans diastereomers). It seemed to us that preparing each compound in its pure cis and trans forms would be too tedious for a long series study of this kind. In addition, it is reasonable to assume that the PAF antagonist activity of a 1:1 cis/trans mixture must be comprised between that of the most active diastereomer and half of it. These two factors, together with the observation that the mixtures were usually unresolvable on the TLC plate, led us to carry out the pharmacological tests on the final products as mixtures. However, in order to gain an insight into the structural features of the PAF receptor, we independently synthesized the cis and trans forms of two representative compounds.

In the present paper, we describe the synthesis and PAF antagonist activities of the above compounds, as monitored by their ability to inhibit PAF-induced platelet aggregation and hypotension. Finally, we discuss the importance of the different structural features of their skeleton in the attempt to find a logical structure–activity relationship.

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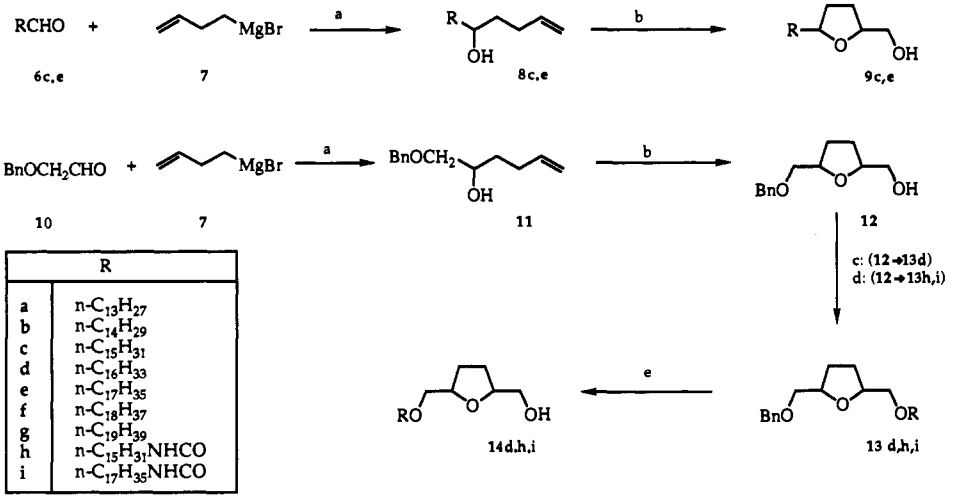
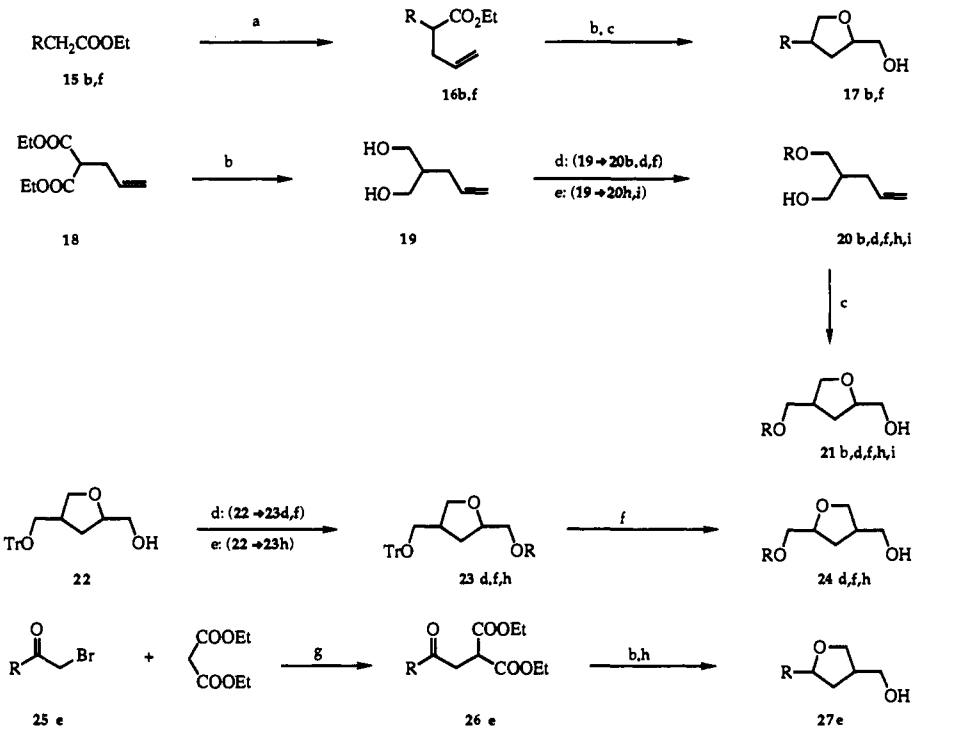
Scheme I. Class I[a]



R	
a	n-$C_{13}H_{27}$
b	n-$C_{14}H_{29}$
c	n-$C_{15}H_{31}$
d	n-$C_{16}H_{33}$
e	n-$C_{17}H_{35}$
f	n-$C_{18}H_{37}$
g	n-$C_{19}H_{39}$
h	n-$C_{15}H_{31}$NHCO
i	n-$C_{17}H_{35}$NHCO

[a] (a) Et_2O, reflux, 1 h; (b) MCPBA, CH_2Cl_2, room temperature, 24 h; (c) NaH, RBr, DMF, room temperature, 24 h; (d) RNCO, pyr, 70 °C, 4 h; (e) H_2, 5% Pd/C, CH_2Cl_2, EtOH, 100 psi, 18 h.

Scheme II. Classes II and III[a]



[a] (a) (1) LDA, THF, 1 h, 0 °C, (2) $BrCH_2CH{=}CH_2$, room temperature, 12 h; (b) LAH, THF, room temperature, 2 h; (c) MCPBA, CH_2Cl_2, room temperature, 16 h; (d) NaH, RBr, DMF, 60 °C, 6 h; (e) RNCO, pyr, 70 °C, 4 h; (f) TsOH, MeOH, room temperature, 15 h; (g) NaH, DMF, room temperature, 1 h; (h) (1) TsCl, pyr, CH_2Cl_2, 4 °C, 48 h, (2) K_2CO_3, MeOH, room temperature, 30 min.

Chemistry

The routes followed for the preparation of the five starting ring alcohols are outlined in Schemes I–IV. Scheme V shows the construction of substituent B from the mentioned alcohols.

According to Scheme I, cyclic alcohol **9** was prepared by reaction of the corresponding bis-homoallylic alcohol 8[17] with MCPBA in CH_2Cl_2.[18] In a similar way, alcohol 11 was converted to compound **12**, which then was reacted with either an *n*-alkyl bromide (via sodium alkoxide) or an *n*-alkyl isocyanate to give compound **13**. Catalytic hydrogenolysis afforded alcohol **14**. Compounds belonging to classes II and III were prepared according to Scheme II. Thus, enolate formation of a fatty acid ester (**15**) with LDA in THF and alkylation with allyl bromide afforded compound **16**. Reduction with LAH and oxidation–cyclization with MCPBA in CH_2Cl_2 gave alcohol **17**. In a similar fashion, diethyl allylmalonate (**18**) was reduced with LAH in THF to diol **19**, which was then converted to the corresponding ether or carbamate **20**. MCPBA oxidation–cyclization provided the desired alcohol **21**. When R was a trityl group (**22**), functionalization at the other

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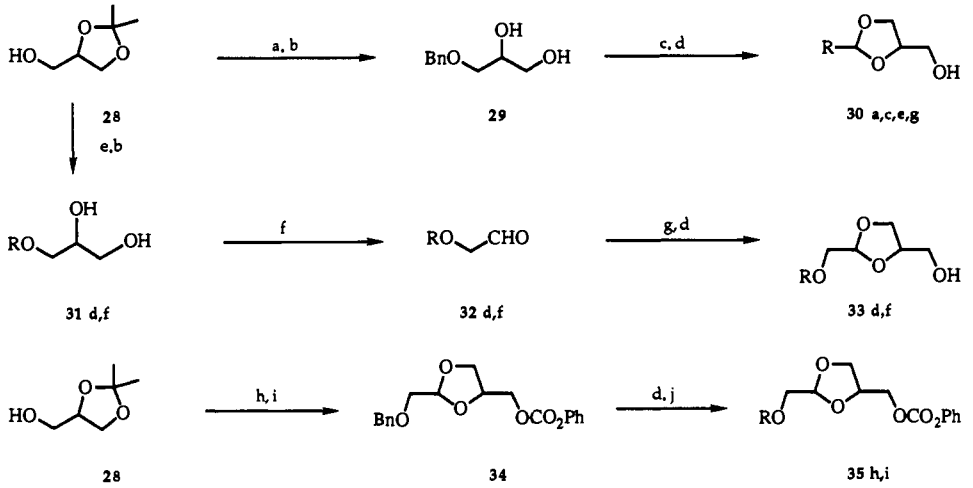
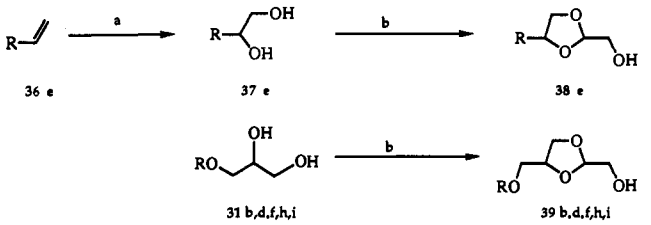
Scheme III. Class IV[a]



[a] (a) 50% NaOH, BnCl, cat. R_4NBr, 100 °C, 5 h; (b) aqueous H_2SO_4, THF, 100 °C, 2 h; (c) RCHO, cat. CSA, toluene, room temperature, 18 h; (d) H_2, 5% Pd/C, 100 psi, CH_2Cl_2, EtOH, room temperature, 18 h; (e) NaH, RBr, DMF, 60 °C, 6 h; (f) $NaIO_4$, H_2O, Me_2CO, room temperature, 1 h; (g) **29**, cat. CSA, toluene, room temperature, 18 h; (h) $ClCO_2Ph$, pyr, CH_2Cl_2, 0 °C, 2 h; (i) $BnOCH_2CHO$, cat. CSA, toluene, room temperature, 18 h; (j) RNCO, pyr, 70 °C, 4 h.

Scheme IV. Class V[a]



[a] (a) 70% aqueous TBHP, cat. OsO_4, H_2O, Me_2CO, room temperature, 24 h; (b) (1) $BnOCH_2CHO$, cat. CSA, toluene, 18 h, (2) H_2, 5% Pd/C, 100 psi, CH_2Cl_2, EtOH, room temperature, 18 h.

hydroxyl group and trityl deprotection provided a facile synthesis to the alcohols of class II (**24**). Alcohol **27** was obtained from compound **26** by reduction to the triol, selective tosylation of one of the primary hydroxyl groups, and internal nucleophillic displacement. Analysis by ^{13}C NMR indicated that tetrahydrofuranmethanols **12**, **17**, **21**, **24**, and **27** were roughly 1:1 cis/trans mixtures. Compound **9** showed a diastereomeric ratio of 2:1. None of the mixtures showed resolution on the TLC plate under a variety of eluent conditions. Alcohol **17** was obtained independently in its pure cis and trans forms by a diastereoselective process from the corresponding *trans*-butyrolactone.[19,20] The cis and trans isomers of alcohol **22** were obtained by a three-step procedure from the original 1:1 diastereomeric mixture. Thus, **22** was transformed into its palmitoyl ester, now separable by TLC (R_f sup: 0.25, R_f inf: 0.20; EtOAc/hexane 1:10). The mixture was carefully flash chromatographed, and the isomers were independently hydrolyzed under basic conditions to the alcohols *cis*-**22** and *trans*-**22**. To determine their relative stereochemistry, the faster TLC running palmitate of **22** was hydrolyzed to the alcohol and converted by a straightforward, six-step procedure into 2-hexyl-4-methyltetrahydrofuran.[21] The ^{13}C NMR spectra of the cis and trans isomers of the latter compound are reported in the literature.[22] In this way we could unambiguously assign the trans stereochemistry to the faster running palmitoyl ester of alcohol **22** and the cis stereochemistry to the slower isomer.

Scheme III shows the synthesis of dioxolanes IV starting from 1,2-isopropylideneglycerol (**28**). Alcohol **30** was obtained from condensation of 1-benzylglycerol[23] (**29**) with a fatty aldehyde in the presence of a catalytic amount of camphorsulfonic acid.[24] Similarly, alcohol **33** was prepared by condensation of diol **29** with aldehyde **32**, which, in turn, was readily obtained by oxidative cleavage of diol **31**. Catalytic hydrogenolysis provided alcohol **33**. A different route was followed in the obtention of dioxolanes IV containing a carbamate function. Thus, 1,2-isopropylideneglycerol was treated with phenyl chloroformate and pyridine, and then transacetalated to benzyl ether **34** under acid catalysis. Catalytic hydrogenolysis and reaction with the corresponding alkyl isocyanate provided compound **35**. Finally, the remaining dioxolane ring pattern (class V) (**38**) was prepared starting from long chain terminal olefin **36** (Scheme IV), via catalytic osmilation[25] of the double bond and condensation of the resulting diol **37**

(19) Submitted for publication.

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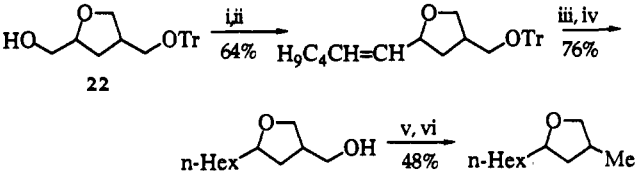
(21) Compound **22** was chemically converted to 2-hexyl-4-methyltetrahydrofuran by the following sequence:



(i) DMSO, $(COCl)_2$, CH_2Cl_2; (ii) $H_{11}C_5PPh_3I$, BuLi, toluene; (iii) H_2 (10% Pd/C), EtOH; (iv) HCl, H_2O, MeOH; (v) TsCl, TEA, CH_2Cl_2; (vi) LAH, THF.

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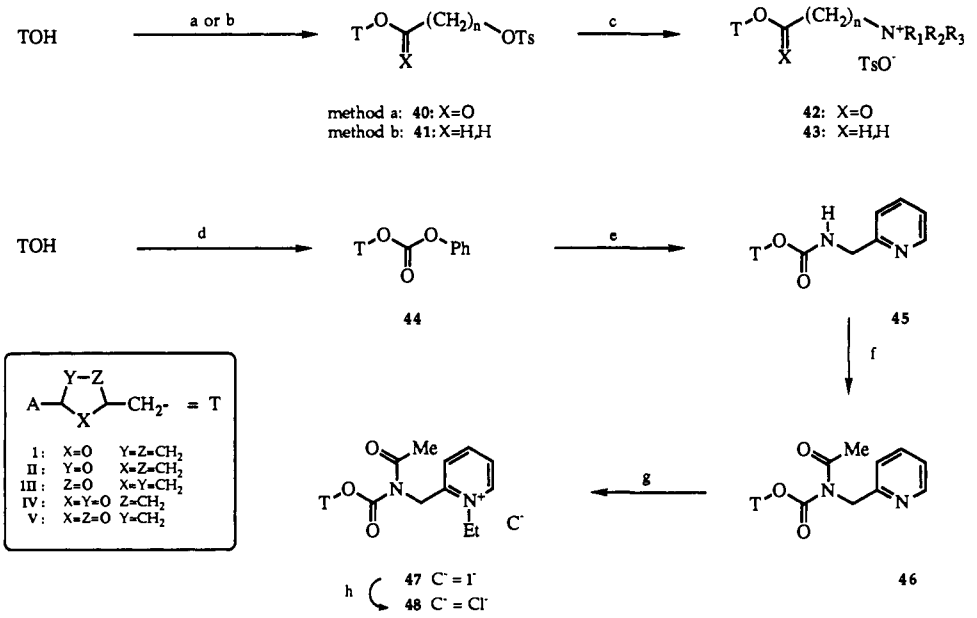
Scheme V. Introduction of the Charged Moiety[a]



[a] (a) $ClC(=O)(CH_2)_nOTs$, TEA, CH_2Cl_2, room temperature, 18 h; (b) (1) NaH, $TsO(CH_2)_nOTHP$, DMF, room temperature, 18 h; (2) CSA, MeOH, room temperature, 18 h; (3) TsCl, pyr, 4 °C, 12 h; (c) $NR_1R_2R_3$, reflux, 3–24 h; (d) $ClCO_2Ph$, pyr, CH_2Cl_2, 0 °C, 2 h; (e) 2-picolylamine, $CHCl_3$, reflux, 18 h; (f) AcCl, TEA, CH_2Cl_2, room temperature, 48 h; (g) EtI, CH_3CN, 70 °C, 24–72 h; (h) Amberlite IRA-410, Cl^- form.

with (benzyloxy)ethanal,[26] followed by benzyl removal. Alcohol **39** was prepared from the corresponding glycerol derivative **31** in a similar way. Analysis by ^{13}C and ^1H NMR spectroscopy of the ring formation crude reaction mixtures indicated that compounds **39h** and **39i** were roughly 2:1 mixtures of diastereomers, whereas all other dioxolanemethanols (**30**, **33**, **38**, and **39b,d,f**) proved to be 8–6:1 mixtures. As above, no TLC separation was observed for these compounds.

Scheme V shows the chemical transformations used for the introduction of the charged branch portion (substituent B). Tosylate **42** was obtained by the reaction of the corresponding alcohol with an ω-tosyloxy acid chloride in presence of triethylamine, followed by reaction with the appropriate amine. Compound **43** was prepared from the alcohol via alkylation of the corresponding sodium alkoxide with an ω-(tetrahydropyranyloxy)alkyl *p*-toluenesulfonate, followed by THP deprotection, conversion of the resulting alcohol to the *p*-toluenesulfonate ester, and final reaction with the appropriate amine. Acyl carbamate **48** (i.e. the compounds of Table VI) and the compounds of Table V were prepared according to the literature, with the appropriate (aminoalkyl)pyridine, acyl chloride, and alkyl iodide.[15b]

Results and Discussion

The optimization of substituents A and B was initially carried out mostly on compounds of classes III and IV bearing a thiazolium ring. For substituent A, three different types of long chain containing groups were prepared: *n*-alkyl, *n*-alkoxymethyl, and *n*-[(alkylcarbamoyl)oxy]-methyl. As far as the substituent B is concerned, compounds having phosphate, ether, ester, or carbamate functions, a medium size alkyl chain, and a quaternary nitrogen at one end were synthesized. Although the results in activity clearly indicated that the effect of these structural variables should not be handled separately, some general SARs are highlighted.

In relation to substituent A, the chain length for optimal activity was determined from the two mentioned biological assays (PAF-induced platelet aggregation and hypotension). The results in Table I show that this length depended on both the class of compound and the chemical functionality present in substituent A. Thus, in class IV we found that the optimal pure alkyl length was C_{17} (entries **71–75**), whereas in class III a C_{14} chain was slightly better than a C_{16} chain (entries **58** and **59**).

Regarding substituent B, in compounds bearing an ether functionality and a directly linked quaternary nitrogen at one end, aromatic heterocycles such as thiazolium and quinolinium (entries **69**, **81**, **57**, and **84**) showed higher potency than nonaromatic amines (e.g. *N*-methylmorpholinium and trimethylammonium; entries **82**, **83**, and **85**). This effect was most evident in the blood pressure test (Table II).

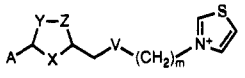
The optimal distance of the quaternary center to the ring was determined in classes III and IV for the thiazolium series. Table I (entries **56–58** and **60**) shows that maximum activity was found for a chain of 7 methylenes in class III. A similar optimal length was also found in class IV (entries **68–70**).

The effect of the chemical functionality present in substituent B proved to be much more dramatic. In classes I, II, and IV, esters and ethers showed similar activities (Table I, entries **49** vs **50**, **52** vs **53**, **69** vs **74**), whereas for class III there was a striking preference for the ether over the ester function (entries **55** vs **57**). Surprisingly, though, this latter class of compounds did not show large differences in activity when the alkyl substituent was replaced by an alkoxymethyl group (entries **61** and **63**).

Contrary to what we expected, phosphates displayed only weak activities (Table III). The decreases were of about 2 orders of magnitude in relation to comparable compounds. This contrasts sharply with the activities reported for other phosphate-containing compounds of the literature.[14,16]

(26) Walkup, R. D.; Cunningham, R. T. *Tetrahedron Lett.* **1987**, *28*, 4019.

Table I. PAF Antagonist Activities of Thiazolium Salts

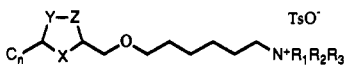


I: X=O Y=Z=CH_2
II: Y=O X=Z=CH_2
III: Z=O X=Y=CH_2
IV: X=Y=O Z=CH_2

cmpd	class	A	V	m	platelet aggregation: IC_{50},[a] μM	blood pressure: ID_{50},[b] mg/kg	formula[c]	anal.[d]
49	I	$C_{15}H_{31}$	O	6	1.3 (0.67-1.5)	2.0 (1.3-3.1)	$C_{36}H_{61}NO_5S_2 \cdot {}^3/_2H_2O$	C,H,N
50	I	$C_{15}H_{31}$	OC(=O)	5	3.1 (0.92-6.1)	1.2 (0.52-2.8)	$C_{36}H_{59}NO_6S_2$	C,H,N
51	II	$C_{18}H_{37}OCH_2$	O	5	2.1 (1.4-4.6)	2.5 (1.4-4.4)	$C_{39}H_{67}NO_6S_2 \cdot {}^1/_2H_2O$	C,H,N
52	II	$C_{18}H_{37}OCH_2$	OC(=O)	5	1.5 (0.87-3.5)	1.1 (0.77-1.5)	$C_{40}H_{67}NO_7S_2$	C,H,N
53	II	$C_{16}H_{33}OCH_2$	O	6	1.4 (0.66-3.5)	1.8 (0.15-22)	$C_{38}H_{65}NO_6S_2$	C,H,N
54	II	$C_{18}H_{37}OCH_2$	O	7	3.9 (2.2-6.8)	2.1 (1.8-2.6)	$C_{41}H_{71}NO_6S_2$	C,N; H[e]
55	III	$C_{14}H_{29}$	OC(=O)	5	>50.0	>5	$C_{35}H_{57}NO_6S_2$	C,N; H[f]
56	III	$C_{14}H_{29}$	O	4	39 (8.2-164)	>5	$C_{33}H_{55}NO_5S_2 \cdot {}^3/_4H_2O$	C,H,N
cis-**57**	III	$C_{14}H_{29}$	O	6	2.1 (1.3-3.4)	2.9 (2.2-3.6)	$C_{35}H_{59}NO_5S_2 \cdot H_2O$	C,H,N
trans-**57**	III	$C_{14}H_{29}$	O	6	2.6 (2.1-3.1)	2.5 (1.6-3.9)	$C_{35}H_{59}NO_5S_2 \cdot {}^1/_2H_2O$	C,H,N
58	III	$C_{14}H_{29}$	O	7	0.83 (0.42-1.7)	1.5 (0.61-3.5)	$C_{38}H_{61}NO_5S_2$	C,H,N
59	III	$C_{16}H_{33}$	O	7	1.7 (0.85-3.5)	2.0 (0.28-14)	$C_{38}H_{65}NO_5S_2 \cdot H_2O$	C,H,N
60	III	$C_{14}H_{29}$	O	8	1.1 (0.52-2.0)	2.3 (0.81-6.5)	$C_{37}H_{63}NO_5S_2$	C,H,N
61	III	$C_{16}H_{33}OCH_2$	OC(=O)	5	3.6 (2.9-4.6)	1.7 (0.95-3.2)	$C_{38}H_{63}NO_7S_2 \cdot {}^1/_4H_2O$	C,H,N
62	III	$C_{18}H_{37}OCH_2$	OC(=O)	5	9.2 (5.9-15)	2.4 (0.66-8.7)	$C_{40}H_{67}NO_7S_2$	C,H,N
63	III	$C_{16}H_{33}OCH_2$	O	6	0.54 (0.25-1.2)	1.2 (0.54-2.5)	$C_{38}H_{65}NO_6S_2$	C,H,N
64	III	$C_{14}H_{29}OCH_2$	O	6	1.4 (0.42-5.0)	3.1 (2.1-4.6)	$C_{38}H_{61}NO_6S_2 \cdot 2H_2O$	C,H,N
65	III	$C_{14}H_{29}OCH_2$	O	7	1.7 (1.4-2.1)	1.4 (0.83-2.5)	$C_{37}H_{63}NO_6S_2 \cdot {}^1/_2H_2O$	C,H,N
66	III	$C_{12}H_{25}OCH_2$	O	7	1.1 (0.56-1.8)	3.7 (1.3-10)	$C_{35}H_{59}NO_6S_2 \cdot {}^1/_2H_2O$	C,H,N
67	III	$C_{15}H_{31}NHCO_2CH_2$	OC(=O)	5	11 (2.0-58)	3.6 (1.5-8.3)	$C_{38}H_{62}N_2O_8S_2 \cdot {}^1/_2H_2O$	C,H,N
68	IV	$C_{17}H_{35}$	O	4	6.0 (0.38-51)	>5	$C_{35}H_{59}NO_6S_2 \cdot 2H_2O$	C,H,N
69	IV	$C_{17}H_{35}$	O	6	1.4 (0.63-3.2)	1.3 (0.90-1.9)	$C_{37}H_{63}NO_6S_2 \cdot H_2O$	C,N; H[g]
70	IV	$C_{17}H_{35}$	O	8	3.7 (2.0-6.9)	>5	$C_{39}H_{67}NO_6S_2 \cdot H_2O$	C,H,N
71	IV	CH_3	OC(=O)	5	150 (22-1900)	>5	$C_{21}H_{29}NO_7S_2 \cdot {}^1/_2H_2O$	C,H,N
72	IV	$C_{13}H_{27}$	OC(=O)	5	20 (7.9-50)	>5	$C_{33}H_{53}NO_7S_2 \cdot {}^1/_4H_2O$	C,H,N
73	IV	$C_{15}H_{31}$	OC(=O)	5	3.0 (1.5-6.1)	0.86 (0.38-1.9)	$C_{35}H_{57}NO_7S_2 \cdot {}^1/_2H_2O$	C,H,N
74	IV	$C_{17}H_{35}$	OC(=O)	5	1.1 (0.70-1.6)	0.88 (0.44-1.8)	$C_{37}H_{61}NO_7S_2 \cdot {}^1/_2H_2O$	C,H,N
75	IV	$C_{19}H_{39}$	OC(=O)	5	5.5 (2.7-11)	5.1 (3.4-7.8)	$C_{39}H_{65}NO_7S_2 \cdot {}^1/_2H_2O$	C,H,N
76	IV	$C_{16}H_{33}OCH_2$	O	4	1.2 (0.54-4.8)	2.7 (1.3-5.8)	$C_{35}H_{59}NO_7S_2$	C,H,N
77	IV	$C_{16}H_{33}OCH_2$	O	6	1.3 (0.61-2.8)	1.8 (1.3-2.6)	$C_{37}H_{63}NO_7S_2$	C,H,N
78	IV	$C_{16}H_{33}OCH_2$	OC(=O)	5	4.9 (3.8-6.4)	1.1 (0.65-1.8)	$C_{37}H_{61}NO_8S_2$	C,H,N

[a] Concentration required to inhibit PAF-induced maximum aggregation by 50%. Parentheses contain 95% confidence limits. [b] Dose required to reduce the lowering of the arterial blood pressure caused by PAF by 50%. Parentheses contain 95% confidence limits. [c] Empirical formula with amount of water of hydration. [d] Analytical results for the indicated elements are within ±0.4% of the calculated values, unless indicated otherwise. [e] H: calcd, 9.69; found, 10.23. [f] H: calcd, 8.81; found, 9.68. [g] H: calcd, 9.09; found, 9.68.

Table II. Nature of the Quaternary Nitrogen and PAF Antagonist Activity



III: Z=O X=Y=CH_2
IV: X=Y=O Z=CH_2

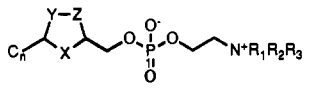
cmpd	class	$N^+R_1R_2R_3$	n	platelet aggregation: IC_{50},[a] μM	blood pressure: ID_{50},[b] mg/kg	formula[c]	anal.[d]
69	IV	thiazolium	17	1.4 (0.63-3.2)	1.3 (0.90-1.9)	$C_{37}H_{63}NO_6S_2 \cdot H_2O$	C,N; H[e]
79	IV	4-methylthiazolium	17	3.1 (1.4-6.9)	3.1 (0.47-20)	$C_{38}H_{65}NO_6S_2 \cdot 2H_2O$	C,H,N
80	IV	pyridinium	17	3.0 (2.4-3.7)	>5	$C_{39}H_{65}NO_6S \cdot {}^1/_2H_2O$	C,N; H[f]
81	IV	quinolinium	17	2.7 (1.5-4.9)	3.8 (2.2-6.4)	$C_{43}H_{67}NO_6S \cdot {}^1/_2H_2O$	C,H,N
82	IV	trimethylammonium	17	2.4 (1.5-3.8)	>5	$C_{37}H_{69}NO_6S \cdot {}^1/_2H_2O$	C,H,N
83	IV	*N*-methylmorpholinium	17	10 (6.3-17)	>5	$C_{39}H_{71}NO_7S \cdot H_2O$	C,H,N
cis-**57**	III	thiazolium	14	2.1 (1.3-3.4)	2.9 (2.2-3.6)	$C_{35}H_{59}NO_5S_2 \cdot H_2O$	C,H,N
84	III	quinolinium	14	1.9 (1.1-3.0)	3.0 (1.1-8.8)	$C_{41}H_{63}NO_5S \cdot {}^1/_4H_2O$	C,H,N
85	III	trimethylammonium	14	8.2 (4.8-11)	>5	$C_{35}H_{65}NO_5S$	C,N; H[g]
86	III	*N*-methylimidazolium	14	6.0 (5.1-7.1)	>5	$C_{36}H_{62}N_2O_5S \cdot 2H_2O$	C,H,N

[a] Concentration required to inhibit PAF-induced maximum aggregation by 50%. Parentheses contain 95% confidence limits. [b] Dose required to reduce the lowering of the arterial blood pressure caused by PAF by 50%. Parentheses contain 95% confidence limits. [c] Empirical formula with amount of water of hydration. [d] Analytical results for the indicated elements are within ±0.4% of the calculated values, unless indicated otherwise. [e] H: calcd, 9.09; found, 9.70. [f] H: calcd, 9.44; found, 10.17. [g] H: calcd, 10.70; found, 11.31.

In summary, the differences in the activities found for thiazolium compounds carrying the optimized A and B variables were relatively small for all the five-membered rings tested (compare entries **49**, **53**, **58**, **65**, **74**, and **77**, for example). Moreover, a clear correlation was found between the two pharmacological tests toward structural changes: increases in activity observed for the in vitro test were accompanied by increases in the in vivo test, in a linear fashion.

By the time this research project was being completed, Takeda laboratories reported an SAR study describing compound **3** in which a new polar substituent had been introduced.[15b] We were delighted to observe that the incorporation of this moiety in our compounds involved an important gain in activity. Thus, an increase of 1–2 orders of magnitude in potency was found when the previously described substituent B was replaced by the acetylcarbamate group B_2 (Table IV).

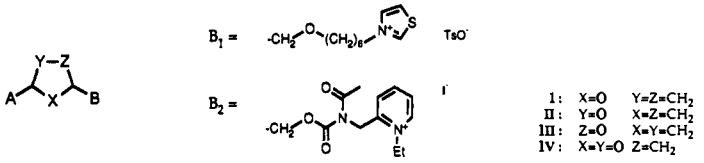
Table III. PAF Antagonist Activities of Phosphate Derivatives



cmpd	class	$N^+R_1R_2R_3$	*n*	platelet aggregation: IC_{50},[a] μM	blood pressure: ID_{50},[b] mg/kg	formula[c]	anal.[d]
87	IV	pyridinium	17	>100	>5	$C_{28}H_{50}NO_6P\cdot{}^3/_2H_2O$	C,H,N
88	IV	trimethylammonium	17	>100	>5	$C_{26}H_{54}NO_6P\cdot 2H_2O$	C,N; H[e]
89	III	thiazolium	14	>100		$C_{24}H_{44}NO_5PS\cdot H_2O$	C,H,N
90	III	pyridinium	14	>100	>5	$C_{26}H_{46}NO_5P\cdot H_2O$	C,N; H[f]
91	III	trimethylammonium	14	>200	>5	$C_{24}H_{50}NO_5P\cdot 3H_2O$	C,H,N

[a] Concentration required to inhibit PAF-induced maximum aggregation by 50%. [b] Dose required to reduce the lowering of the arterial blood pressure caused by PAF by 50%. [c] Empirical formula with amount of water of hydration. [d] Analytical results for the indicated elements are within ±0.4% of the calculated values, unless indicated otherwise. [e] H: calcd, 10.75; found, 11.28. [f] H: calcd, 9.64; found, 10.36.

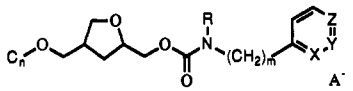
Table IV. Comparison of the 2-Pyridinium and Thiazolium Salts



cmpd	class	A	B	platelet aggregation: IC_{50},[a] μM	blood pressure: ID_{50},[b] mg/kg	formula[c]	anal.[d]
49	I	$C_{15}H_{31}$	B_1	1.3 (0.67-1.5)	2.0 (1.3-3.1)	$C_{36}H_{61}NO_5S_2\cdot{}^3/_2H_2O$	C,H,N
92	I	$C_{15}H_{31}$	B_2	0.080 (0.035-0.18)	0.15 (0.13-0.17)	$C_{31}H_{53}IN_2O_4$	C,H,N
53	II	$C_{16}H_{33}OCH_2$	B_1	1.4 (0.66-3.5)	1.8 (0.15-22)	$C_{38}H_{65}NO_6S_2$	C,H,N
93	II	$C_{16}H_{33}OCH_2$	B_2	0.0068 (0.0062-0.0075)	0.020 (0.013-0.031)	$C_{33}H_{57}IN_2O_5\cdot{}^1/_2H_2O$	C,H,N
***cis*-57**	III	$C_{14}H_{29}$	B_1	2.1 (1.3-3.4)	2.9 (2.2-3.6)	$C_{33}H_{59}NO_5S_2\cdot H_2O$	C,H,N
94	III	$C_{14}H_{29}$	B_2	0.14 (0.050-0.54)	0.24 (0.13-0.46)	$C_{30}H_{51}IN_2O_4$	C,H,N
63	III	$C_{16}H_{33}OCH_2$	B_1	0.54 (0.25-1.2)	1.2 (0.54-2.5)	$C_{38}H_{65}NO_6S_2$	C,H,N
95	III	$C_{16}H_{33}OCH_2$	B_2	0.018 (0.012-0.028)	0.035 (0.026-0.047)	$C_{33}H_{57}IN_2O_5\cdot H_2O$	C,H,N
77	IV	$C_{16}H_{33}OCH_2$	B_1	1.3 (0.61-2.8)	1.8 (1.3-2.6)	$C_{37}H_{63}NO_7S_2$	C,H,N
96	IV	$C_{16}H_{33}OCH_2$	B_2	0.083 (0.039-0.18)	0.024 (0.012-0.049)	$C_{32}H_{55}IN_2O_6\cdot{}^1/_2H_2O$	C,H,N
69	IV	$C_{17}H_{35}$	B_1	1.4 (0.63-3.2)	1.3 (0.9-1.9)	$C_{37}H_{63}NO_6S_2\cdot H_2O$	C,H,N
97	IV	$C_{17}H_{35}$	B_2	0.21 (0.13-0.33)	0.24 (0.11-0.53)	$C_{32}H_{55}IN_2O_5\cdot{}^3/_2H_2O$	C,H,N

[a] Concentration required to inhibit PAF-induced maximum aggregation by 50%. Parentheses contain 95% confidence limits. [b] Dose required to reduce the lowering of the arterial blood pressure caused by PAF by 50%. Parentheses contain 95% confidence limits. [c] Empirical formula with amount of water of hydration. [d] Analytical results for the indicated elements are within ±0.4% of the calculated values, unless indicated otherwise.

Table V. Optimization of the (Aminoalkyl)pyridinium Moiety

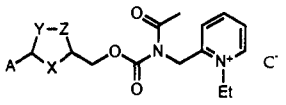


cmpd	*n*	*m*	R	X	Y	Z	A	platelet aggregation: IC_{50},[a] μM	blood pressure: ID_{50},[b] mg/kg	formula[c]	anal.[d]
95	16	1	$COCH_3$	N^+Et	CH	CH	I	0.018 (0.012-0.028)	0.035 (0.026-0.047)	$C_{33}H_{57}IN_2O_5\cdot H_2O$	C,H,N
98	16	1	H	N^+Et	CH	CH	I	5.3 (1.6-17)	>5	$C_{31}H_{55}IN_2O_4\cdot H_2O$	C,H,N
99	16	1	CO_2Et	N^+Et	CH	CH	I	0.073 (0.054-0.098)	0.035 (0.018-0.077)	$C_{34}H_{59}IN_2O_6\cdot{}^1/_2H_2O$	C,H,N
100	16	1	$COCH_3$	N	CH	CH		11 (0.66-150)	>5	$C_{31}H_{52}N_2O_5$	C,H,N
101	16	1	$COCH_3$	N^+Me	CH	CH	I	0.20 (0.075-0.55)	0.24 (0.12-0.47)	$C_{32}H_{55}IN_2O_5\cdot H_2O$	C,H,N
102	18	1	$COCH_3$	CH	N^+Et	CH	I	2.5 (1.7-4.9)	>5	$C_{33}H_{61}IN_2O_5\cdot H_2O$	C,H,N
103	18	1	$COCH_3$	CH	CH	N^+Et	I	1.6 (1.0-2.5)	1.6 (0.58-4.5)	$C_{35}H_{61}IN_2O_5\cdot H_2O$	C,H,N
104	18	1	H	CH	CH	N^+Et	I	8.0 (5.3-16)	>5	$C_{33}H_{59}IN_2O_4\cdot{}^1/_2H_2O$	C,H,N
105	16	2	$COCH_3$	N^+Et	CH	CH	I	2.6 (1.3-5.1)	>5	$C_{34}H_{59}IN_2O_5\cdot{}^1/_2H_2O$	C,H,N
106	16	2	H	N^+Et	CH	CH	I	2.8 (1.3-8.4)	>5	$C_{32}H_{57}IN_2O_4\cdot{}^1/_2H_2O$	C,H,N
107	18	0	H	CH	CH	N^+Et	I	1.9 (0.18-14)	>5	$C_{32}H_{57}IN_2O_4\cdot{}^1/_2H_2O$	C,H,N
108	16	0	$COCH_3$	CH	CH	N^+Et	I	0.86 (0.32-2.3)	>5	$C_{32}H_{55}IN_2O_5\cdot H_2O$	C,H,N
109	16	0	$COCH_3$	CH	N^+Et	CH	I	2.3 (1.3-4.3)	0.13 (0.12-0.14)	$C_{32}H_{55}IN_2O_5$	C,H,N

[a] Concentration required to inhibit PAF-induced maximum aggregation by 50%. Parentheses contain 95% confidence limits. [b] Dose required to reudce the lowering of the arterial blood pressure caused by PAF by 50%. Parentheses contain 95% confidence limits. [c] Empirical formula with amount of water of hydration.

This particular substituent seemed to be particularly well-suited (Table V). Indeed, we have unsuccessfully tried to optimize it by changing the *N*-alkyl group on the pyridine quaternary center (entry 101), the pyridine site substitution (entries 102 and 103), the carbamic nitrogen–pyridine ring distance (entries 105, 108, and 109)

Table VI. PAF Antagonist Activities of the 2-Pyridinium Salts



I: X=O Y=Z=CH_2
II: Y=O X=Z=CH_2
III: Z=O X=Y=CH_2
IV: X=Y=O Z=CH_2
V: X=Z=O Y=CH_2

cmpd	class	A	C	platelet aggregation: IC_{50},[a] μM	blood pressure: ED_{50},[b] mg/kg	formula[c]	anal.[d]
92	I	$C_{15}H_{31}$	I	0.080 (0.035–0.18)	0.15 (0.13–0.17)	$C_{31}H_{53}IN_2O_4$	C,H,N
110	I	$C_{17}H_{35}$	I	0.071 (0.070–0.073)	0.15 (0.12–0.19)	$C_{33}H_{57}IN_2O_4 \cdot {}^3/_2H_2O$	C,N; H[e]
111	I	$C_{16}H_{33}OCH_2$	I	0.099 (0.093–0.11)	0.036 (0.019–0.067)	$C_{33}H_{57}IN_2O_5 \cdot {}^1/_4H_2O$	C,H,N
112	I	$C_{15}H_{31}NHCO_2CH_2$	I	0.072 (0.039–0.13)	0.098 (0.032–0.30)	$C_{33}H_{56}IN_3O_6 \cdot {}^1/_2H_2O$	C,H,N
113	I	$C_{17}H_{35}NHCO_2CH_2$	I	0.033 (0.0033–0.35)	0.064 (0.036–0.12)	$C_{35}H_{60}IN_3O_6$	C,H,N
114	II	$C_{17}H_{35}$	I	0.21 (0.16–0.31)	0.052 (0.041–0.067)	$C_{33}H_{57}IN_2O_4 \cdot {}^1/_2H_2O$	C,H,N
93	II	$C_{16}H_{33}OCH_2$	I	0.0068 (0.0062–0.0075)	0.020 (0.013–0.031)	$C_{33}H_{57}IN_2O_5 \cdot {}^1/_2H_2O$	C,H,N
115	II	$C_{16}H_{33}OCH_2$	Cl	0.0086 (0.0071–0.012)	0.027 (0.023–0.033)	$C_{33}H_{57}ClN_2O_5 \cdot H_2O$	C,H,N; Cl[f]
trans-**116**	II	$C_{15}H_{31}NHCO_2CH_2$	I	0.011 (0.0082–0.015)	0.042 (0.033–0.055)	$C_{33}H_{56}IN_3O_6$	C,H,N
cis-**116**	II	$C_{15}H_{31}NHCO_2CH_2$	I	0.022 (0.014–0.034)	0.057 (0.040–0.082)	$C_{33}H_{56}IN_3O_6$	C,H,N
117	II	$C_{15}H_{31}NHCO_2CH_2$	Cl	0.014 (0.011–0.015)	0.049 (0.039–0.062)	$C_{33}H_{56}ClN_3O_6 \cdot {}^1/_2H_2O$	C,H,Cl,N
94	III	$C_{14}H_{29}$	I	0.14 (0.050–0.54)	0.24 (0.13–0.46)	$C_{30}H_{51}IN_2O_4$	C,H,N
118	III	$C_{18}H_{37}$	I	0.47 (0.33–0.65)	0.23 (0.14–0.38)	$C_{34}H_{59}IN_2O_4 \cdot {}^1/_2H_2O$	C,H,N
119	III	$C_{14}H_{29}OCH_2$	I	0.085 (0.051–0.14)	0.087 (0.044–0.17)	$C_{31}H_{53}ClN_2O_5 \cdot {}^1/_2H_2O$	C,H,N
95	III	$C_{16}H_{33}OCH_2$	I	0.018 (0.012–0.028)	0.035 (0.026–0.047)	$C_{33}H_{57}IN_2O_5 \cdot H_2O$	C,H,N
120	III	$C_{16}H_{33}OCH_2$	Cl	0.0082 (0.0011–0.059)	0.044 (0.035–0.055)	$C_{33}H_{57}ClN_2O_5 \cdot H_2O$	C,H,N
121	III	$C_{18}H_{37}OCH_2$	I	0.052 (0.042–0.068)	0.035 (0.018–0.066)	$C_{35}H_{61}IN_2O_5 \cdot {}^1/_2H_2O$	C,H,N
122	III	$C_{15}H_{31}NHCO_2CH_2$	I	0.0045 (0.0028–0.0069)	0.033 (0.021–0.053)	$C_{33}H_{56}IN_3O_6 \cdot H_2O$	C,H,N
123	III	$C_{15}H_{31}NHCO_2CH_2$	Cl	0.0080 (0.0050–0.013)	0.067 (0.038–0.12)	$C_{33}H_{56}ClN_3O_6 \cdot H_2O$	C,H,Cl,N
124	III	$C_{17}H_{35}NHCO_2CH_2$	I	0.027 (0.014–0.061)	0.043 (0.033–0.055)	$C_{35}H_{60}IN_3O_6 \cdot 2H_2O$	C,H,N
97	IV	$C_{17}H_{35}$	I	0.21 (0.13–0.33)	0.24 (0.11–0.53)	$C_{32}H_{55}IN_2O_5 \cdot {}^3/_2H_2O$	C,H,N
96	IV	$C_{16}H_{33}OCH_2$	I	0.083 (0.039–0.18)	0.024 (0.012–0.049)	$C_{32}H_{55}IN_2O_6 \cdot {}^1/_2H_2O$	C,H,N
125	IV	$C_{18}H_{37}OCH_2$	I	0.14 (0.10–0.20)	0.041 (0.020–0.080)	$C_{34}H_{59}IN_2O_6 \cdot H_2O$	C,H,N
126	IV	$C_{15}H_{31}NHCO_2CH_2$	I	0.026 (0.016–0.043)	0.11 (0.069–0.17)	$C_{32}H_{54}IN_3O_7 \cdot {}^3/_4H_2O$	C,H,N
127	V	$C_{17}H_{35}$	I	0.024 (0.017–0.035)	0.074 (0.052–0.11)	$C_{32}H_{55}IN_2O_5 \cdot {}^1/_2H_2O$	C,H,N
128	V	$C_{14}H_{29}OCH_2$	I	0.11 (0.032–0.46)	0.20 (0.031–1.2)	$C_{30}H_{51}IN_2O_6 \cdot {}^1/_2H_2O$	C,H,N
129	V	$C_{16}H_{33}OCH_2$	I	0.019 (0.010–0.033)	0.029 (0.019–0.045)	$C_{32}H_{55}IN_2O_6$	C,H,N
130	V	$C_{16}H_{33}OCH_2$	Cl	0.015 (0.013–0.018)	0.057 (0.026–0.12)	$C_{32}H_{55}ClN_2O_6 \cdot 2H_2O$	C,H,N
131	V	$C_{18}H_{37}OCH_2$	I	0.094 (0.064–0.15)	0.017 (0.012–0.025)	$C_{34}H_{59}IN_2O_6 \cdot {}^3/_2H_2O$	C,H,N
132	V	$C_{15}H_{31}NHCO_2CH_2$	I	0.0075 (0.0052–0.011)	0.093 (0.062–0.12)	$C_{32}H_{54}IN_3O_7 \cdot {}^1/_2H_2O$	C,H,N
133	V	$C_{17}H_{35}NHCO_2CH_2$	I	0.015 (0.0066–0.035)	0.048 (0.018–0.13)	$C_{34}H_{58}IN_3O_7 \cdot H_2O$	C,H,N
3 (I^-)		–	I	0.011 (0.0078–0.015)	0.011 (0.0063–0.018)	$C_{34}H_{60}IN_3O_6 \cdot H_2O$	C,H,N
3 (Cl^-)		–	Cl	0.012 (0.010–0.014)	0.0078 (0.0056–0.011)	$C_{34}H_{60}ClN_3O_6 \cdot H_2O$	C,H,N

[a] Concentration required to inhibit PAF-induced maximum aggregation by 50%. Parentheses contain 95% confidence limits. [b] Dose required to reduce the lowering of the arterial blood pressure caused by PAF by 50%. Parentheses contain 95% confidence limits. [c] Empirical formula with amount of water of hydration. [d] Analytical results for the indicated elements are within ±0.4% of the calculated values, unless indicated otherwise. [e] H: calcd, 8.64; found, 8.04. [f] Cl: calcd, 5.76; found, 6.38.

and/or the *N*-acyl group (entries **98** and **99**). All minor alterations resulted in considerably decreased activity. Only the replacement of the *N*-acetyl group by a *N*-ethoxycarbonyl group (entry **99**) maintained the original activity. In contrast, replacement by a hydrogen atom resulted in a decrease in potency of 2 orders of magnitude (entry **98**). The corresponding compound bearing an *N*-methyl group instead of an *N*-acetyl group could not be prepared due to an unexpected reluctance of its pyridine nitrogen toward quaternization. The importance of the cationic nature of these compounds is demonstrated when comparing the activities of compounds **95** and **100**.

With these preliminary results in hand, we planned to make an overall optimization of the compounds carrying the group B_2. This would include substituent A (functionality and length) and ring pattern (class) (Table VI).

We first focused our attention on the influence of the nature of substituent A among the different classes of compounds. We found that in classes II, III, and IV there was a significant effect on the activity in the in vitro test. Thus, pure alkyl substituents showed a much lower (30–10 times) activity than radicals containing an ether or carbamate function (entries **114** vs **93** or **116**; **94** or **118** vs **95** or **122**; and **97** vs **126**). This strongly contrasts with the trends observed in the thiazolium salts, where the activities for optimal substituents A were of the same order of magnitude (Table I, entries **58** vs **65**; **69** vs **77**). On the other hand, the compounds belonging to classes I and V showed comparable potencies independent of the nature of substituent A (entries **92**, **110**, **111**, **112**, and **113**; entries **127**, **129**, and **132**). Secondly, we were most interested in assessing the effect of the precise placement of the oxygen atom(s) (i.e., the class). Thus, some differences in activity were found when the class of compound was taken as the only variable (compare the series **110**, **114**, **118**, **97**, and **127**; or **111**, **93**, **95**, **96**, and **129**; or **112**, **116**, **122**, **126**, and **132**). The most active tetrahydrofuran pattern was that of classes III and II, with similar potencies for comparable compounds (entries **93**, **116**, **122**). Tetrahydrofurans I were between 10 and 5 times less active (entries **111**, **112**). Regarding dioxolanes, class V was between 10 and 3 times more potent than class IV for comparable compounds (entries **97** vs **127**; **96** vs **129**; and **126** vs **132**). However, the compounds of class V showed some chemical unstability. In addition, the pharmacological results were not fully reproducible for this family of products. When comparing tetrahydrofurans with dioxolanes, no clear preference was observed. Thus, dioxolanes V were similar in potency to tetrahydrofurans II and III (entries **129** vs **95**; **132** vs **116** and **122**), whereas dioxolanes IV were more comparable to tetrahydrofurans I (entries **96** vs **111**; **126** vs **112**). Several compounds in Table VI were more potent than the reference compound **3** in the in vitro test, whereas none of them had a higher activity in the PAF-induced

blood pressure lowering test. Furthermore, the differences in this in vivo test were sometimes insignificant among the classes: for example, all five of the ether derivatives (entries 111, **93**, **95**, **96**, and **129**) showed a practically invariable activity. In summary and taking into account both tests, the compounds of classes II and III carrying an ether or a carbamate function in its substituent A proved to bear the best ring pattern.

The effect of the relative stereochemistry in the five-membered ring was studied in two cases. In the thiazolium series, both cis and trans stereoisomers of compound **57** were stereoselectively synthesized. The values reported in Table I for these two compounds show no significant difference in activity. In the 2-pyridinium series, the pure cis and trans forms of compound **116** were also prepared. Here, a slight difference in activity was observed in the in vitro test, whereas the trans isomer was approximately twice as active as the cis isomer (Table VI). In consequence, at least for these two pairs of substances, the relative stereochemistry of the substituents seemed not to be crucial for the activity.

In conclusion, the replacement of the PAF glycerol backbone by a disubstituted five-membered ring containing one or two oxygen atoms and the optimization of those two substituents has led to a new series of compounds showing high PAF antagonist activity. Given the above biological data, some of the most active compounds are proceeding into further development.

Experimental Section

A. Chemistry. Melting points were determined with a Mettler FP 80 central processor melting point apparatus and are uncorrected. Melting points of organic salts varied, depending on the amount of water of the sample and should be regarded as approximated. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer. ^{1}H NMR spectra (60 MHz) were recorded on a Varian 360A spectrometer and are reported in ppm on the δ scale, from the indicated reference. ^{1}H (80 MHz) and ^{13}C (20.1 MHz) NMR spectra were recorded on a Brücker AC 80 spectrometer and are also reported in ppm on the δ scale, from the indicated reference. ^{13}C NMR spectra (50.3 MHz) were recorded on a Varian XL-200 spectrometer and are also reported in ppm on the δ scale, from the indicated reference. Combustion analyses were performed with a Carlo Erba 1106 analyzer. Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on SDS Silica Gel Chromagel 60 a C.C. (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed with Magery-Nagel 0.25-mm silica gel SIL G-25 plates. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane and triethylamine were distilled from calcium hydride. Dimethyl sulfoxide and dimethylformamide were distilled under reduced pressure from calcium hydride and stored over activated 4-Å molecular sieves. Unless otherwise specified, all nonaqueous reactions were conducted under a rigorously dried argon atmosphere, with oven-dried glassware.

C18-PAF-acether was synthesized from (*S*)-batyl alcohol[23] following a published procedure.[27] Compound **3** was prepared according to the literature[15b] and was selected as the reference compound.

1-Docosen-5-ol (8e). A published procedure for the preparation of a related series of compounds was followed.[17] An oven-dried flask was charged with magnesium turnings (1.22 g, 50 mmol), an iodine crystal, and ether (100 mL). A small amount of 1-bromo-3-butene was added under vigorous stirring. Once the reaction had started (disappearance of the orange color) a solution containing the rest of the alkene (4.8 mL, 48 mmol) in ether (30 mL) was slowly added. The mixture was stirred at room temperature for 30 min. Next, a solution containing *n*-octadecanal (**6e**, 30 mmol) in ether (40 mL) was added and the reaction mixture was stirred at reflux for 1 h. The reaction was quenched by the addition of a 10% ammonium chloride aqueous solution (100 mL). The ethereal layer was decanted and dried with anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated in vacuo to a white solid. Flash-chromatography purification (1:5 ethyl acetate/hexane) afforded the title compound as a white solid (5.20 g, 53%): mp 54–55 °C; IR (KBr) ν 3401, 2919, 2848, 1638, 1463, 1347, 911 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 6.1–5.6 (**m**, 1 H, =CH), 5.2–4.9 (m, 2 H, $=CH_2$), 3.65 (m, 1 H, C*H*OH), 2.4–2.0 (m, 2 H, $=CHCH_2$), 1.7–0.8 (m, ca. 37 H). Anal. ($C_{22}H_{44}O$) C, H.

In a similar manner, compounds **8c** and **11** were prepared.

1-(Benzyloxy)-5-hexen-2-ol (11): 36% yield; oil; IR (film) ν 3442, 3061, 3027, 2913, 2855, 1637, 1449, 1362, 1096, 910 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.33 (s, 5 H, Ar), 6.1–5.6 (m, 1 H, =CH), 5.2–4.9 (m, 2 H, $=CH_2$), 4.55 (s, 2 H, $ArCH_2$), 3.8 (m, 1 H, C*H*OH), 3.6–3.2 (m, 2 H, CH_2O), 2.4–2.2 (m, 2 H, $=CHCH_2$), 1.7–1.4 (m, 2 H, $=CHCH_2CH_2$). Anal. ($C_{13}H_{18}O_2$) C, H.

5-(Heptadecyl)tetrahydrofuran-2-methanol (9e). A dried solution of *m*-chloroperbenzoic acid was prepared by dissolving the substance (55% pure, 3.35 g, 10.6 mmol) in dichloromethane (25 mL), decanting the aqueous phase, and drying the organic layer with anhydrous sodium sulfate. After filtration of the drying agent, the solution was cooled to 0 °C and 1-docosen-5-ol (**8e**, 2.67 g, 8.22 mmol) was added in one portion. The mixture was stirred at room temperature overnight and then quenched by the addition of a 10% sodium thiosulfate aqueous solution (50 mL). The aqueous phase was separated and the organic layer was washed with a 10% sodium hydroxide aqueous solution (3 × 15 mL) and dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated under reduced pressure to a white solid. ^{13}C NMR analysis of the unpurified reaction mixture indicated a roughly 2:1 mixture of diastereomers. Purification by flash chromatography (1:2 ethyl acetate/hexane) afforded the title compound as a white, waxy solid (1.54 g, 55%): IR (KBr) ν 3367, 2914, 2845, 1464, 1096, 1073, 1042 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 3.9 (m, 2 H, CHOCH), 3.7–3.4 (m, 2 H, CH_2OH), 2.1–0.8 (m, ca. 39 H). ^{13}C NMR (20 MHz, $CDCl_3$) δ (TMS) 80.19 (maj), 79.49 (min.), 79.19 (maj), 78.86 (min.), 65.28 (maj), 65.03 (min.), 35.91 (maj), 35.82 (min.), 31.89 (min.), 31.35 (maj), 31.30, 29.64, 29.31, 27.05, 26.21, 22.63, 14.03. Anal. ($C_{22}H_{44}O_2$) C, H.

In a similar manner, compound **9c** was prepared.

5-[(Benzyloxy)methyl]tetrahydrofuran-2-methanol (12). Following the above described procedure, the title product was obtained from alcohol **11**, in 75% yield, as a colorless oil. Analysis by ^{13}C NMR indicated a 1:1 mixture of diastereomers: IR (film) ν 3431, 3058, 3025, 2865, 1491, 1449, 1362, 1075, 738, 698 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.32 (s, 5 H, Ar), 4.57 (s, 2 H, $ArCH_2$), 4.15 (m, 2 H, CHOCH), 3.9–3.4 (m, 4 H, $BnOCH_2$, CH_2OH), 2.3–1.6 (m, 4 H, CH_2CH_2); ^{13}C NMR (20 MHz, $CDCl_3$) δ (TMS) 137.51 (C), 137.46 (C), 137.35 (C), 127.25 (CH), 126.54 (CH), 126.48 (CH), 79.35 (CH), 78.95 (CH), 77.42 (CH), 77.07 (CH), 72.14 (CH_2), 71.95 (CH_2), 71.78 (CH_2), 63.96 (CH_2), 63.60 (CH_2), 27.52 (CH_2), 27.07 (CH_2), 26.49 (CH_2), 26.24 (CH_2). Anal. ($C_{13}H_{18}O_3$) C, H.

5-[(Hexadecyloxy)methyl]-2-[(benzyloxy)methyl]tetrahydrofuran (13d). To a cooled (0 °C) suspension of sodium hydride (55% oil dispersion, 0.353 g, 8.09 mmol) in dimethylformamide (10 mL) was added a solution containing **12** (1.05 g, 6.75 mmol) in dimethylformamide (5 mL). The mixture was stirred for 5 min, and then a solution of *n*-hexadecyl bromide (2.26 g, 7.42 mmol) in dimethylformamide (8 mL) was added. The reaction mixture was vigorously stirred for 1 h at 70 °C, then at room temperature for 18 h. The mixture was poured into cold water, ether was added, and the ethereal phase was separated. The aqueous phase was extracted with more ether (2 × 20 mL). The combined ethereal phases were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated on a rotary evaporator to an oil. Flash-chromatography purification (1:8 ethyl acetate/hexane) gave the title compound as a colorless oil (1.74 g, 58%): IR (film) ν 3026, 2919, 2849, 1463, 1362, 1093, 1027, 733, 696 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.31 (s, 5 H, Ar), 4.56 (s, 2 H, $ArCH_2O$), 4.4–3.9

(27) Wissner, A.; Kohler, C. A.; Golstein, B. M. *J. Med. Chem.* **1986**, *29*, 1315.

(m, 2 H, CHOCH), 3.45 (t, J = 5.3 Hz, 6 H, CH_2OCH_2, $BnOCH_2$), 2.2–0.7 (m, ca. 35 H). Anal. ($C_{29}H_{50}O_3$) C, H.

5-[[(*N*-Pentadecylcarbamoyl)oxy]methyl]-2-[(benzyloxy)methyl]tetrahydrofuran (13h). A solution containing **12** (2.5 g, 11.24 mmol) in dry pyridine (9 mL) was treated with pentadecylisocyanate (nonpurified, 8.5 g) and the resulting mixture was heated to 70 °C for 4 h. Chloroform (125 mL) was added, and the resulting mixture was washed successively with a solution of concentrated HCl (8 mL) in water (40 mL), 10% aqueous sodium bicarbonate (40 mL), and brine (40 mL). The organic layer was decanted and dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated in vacuo and purified by flash chromatography (1:2 ethyl acetate/hexane) to afford the title compound as a white solid (4.09 g, 76%): mp 54–56 °C; IR (KBr) ν 3342, 3029, 2916, 2848, 1676, 1525, 1479, 1314, 1293, 1272, 1252, 1236, 1122 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.31 (s, 5 H, Ar), 4.8 (m, 1 H, NH), 4.56 (s, 2 H, $ArCH_2$), 4.4–3.9 (m, 4 H, CHOCH, O=$COCH_2$), 3.48 (d, J = 5.2 Hz, 2 H, $BnOCH_2$), 3.35 (br q, J = 6 Hz, 2 H, NCH_2), 2.2–0.7 (m, ca. 37 H). Anal. ($C_{29}H_{49}NO_4$) C, H, N.

In a similar manner, compound **13i** was prepared.

5-[(Hexadecyloxy)methyl]tetrahydrofuran-2-methanol (14d). A mixture containing **13d** (1.70 g, 3.8 mmol), dichloromethane (35 mL), ethanol (4 mL), and 5% palladium on carbon (250 mg) was hydrogenated on a Parr hydrogenator at 100 psi for 18 h. The reaction mixture was filtered and concentrated under reduced pressure to afford the title compound as a colorless oil (1.20 g, 88%): IR (film) ν 3421, 2917, 2847, 1636, 1463, 1375, 1075, 947 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 4.3–3.9 (m, 2 H, CHOCH), 3.9–3.3 (m, 6 H, CH_2OCH_2), 2.2–0.7 (m, ca. 35 H). Anal. ($C_{22}H_{44}O_3$) C, H.

In a similar manner, compounds **14h** and **14i** were prepared.

5-[[(*N*-Pentadecylcarbamoyl)oxy]methyl]tetrahydrofuran-2-methanol (14h): 99% yield; mp 60–64 °C; IR (KBr) ν 3337, 2917, 2845, 1677, 1525, 1464, 1314, 1292, 1271, 1251, 1236, 1030 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.31 (s, 5 H, Ar), 4.8 (m, 1 H, NH), 4.57 (s, 2 H, $ArCH_2$), 4.4–4.0 (m, 4 H, O=$COCH_2CHOCH$), 3.50 (d, J = 5 Hz, 2 H, $BnOCH_2$), 3.30 (br q, J = 6 Hz, 2 H, NCH_2), 2.2–0.7 (m, ca. 29 H). Anal. ($C_{22}H_{43}NO_4$) C, H, N.

Ethyl 2-(2-Propenyl)hexadecanoate (16b). To a cooled (0 °C) solution containing n-butyllithium in hexane (0.048 mol), diisopropylamine (6.8 mL, 0.048 mol), and tetrahydrofuran (120 mL) was added dropwise a solution of ethyl hexadecanoate (11.3 g, 0.04 mol) in tetrahydrofuran (15 mL). The mixture was stirred for 1 h, and then allyl bromide (4.0 mL, 0.048 mmol) was added. The resulting mixture was stirred at room temperature for 12 h, then poured into water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated in vacuo to an oil (11.9 g). Purification by flash chromatography (1:20 ethyl acetate/hexane) afforded the title product as a colorless oil (8.7 g, 67%): IR (film) ν 3075, 2921, 2851, 1731, 1638, 1462, 1176 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ (TMS) 5.8 (m, 1 H, =CH), 5.1 (m, 2 H, $=CH_2$), 4.2 (q, J = 7 Hz, 2 H, CH_2O), 2.4 (m, 4 H), 2.0–0.7 (m, ca. 29 H). Anal. ($C_{21}H_{40}O_2$) C, H.

In a similar manner, compound **16f** was prepared.

4-Tetradecyltetrahydrofuran-2-methanol (17b). To a cooled (0 °C) suspension of lithium aluminum hydride (2 g, 0.052 mol) in anhydrous tetrahydrofuran (150 mL) was added a solution containing **16b** (8.7 g, 0.026 mol) in tetrahydrofuran (20 mL), and the resulting mixture was stirred at room temperature for 2 h. Then, dichloromethane (120 mL) was added, followed by a saturated aqueous solution of potassium and sodium tartrate (8.4 mL). Anhydrous sodium sulfate was added, the mixture was filtered, and the filtrate was concentrated to an oil. Flash-chromatography purification (1:10 ethyl acetate/hexane) afforded the intermediate alcohol as a colorless oil (6.2 g, 82%).

The alcohol thus prepared was dissolved in dichloromethane (150 mL) and treated with m-chloroperbenzoic acid as described for the preparation of compound **9e**. Usual workup and product isolation afforded 6.4 g of an oil, which was purified by flash chromatography (1:3 ethyl acetate/hexane) to give the title product as a white solid (4.7 g, 71%). ^{13}C NMR analysis indicated a roughly 1:1 mixture of diastereomers: mp 27–28 °C; IR (KBr) ν 3422, 2919, 2850, 1463, 1375, 1049 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ (TMS) 3.95 (m, 2 H, CHO), 3.5 (m, 3 H, CHO), 3.0 (m, 1 H, OH), 2.2–0.6 (m, ca. 32 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ ($CDCl_3$) 80.12 (CH), 79.00 (CH), 73.88 (CH_2), 73.44 (CH_2), 65.32 (CH_2), 64.97 (CH_2), 40.17 (CH), 39.48 (CH), 34.27 (CH_2), 33.85 (CH_2), 33.19 (CH_2), 33.11 (CH_2), 31.94 (CH_2), 29.76 (CH_2), 29.68 (CH_2), 29.59 (CH_2), 29.37 (CH_2), 28.59 (CH_2), 28.48 (CH_2), 22.69 (CH_2), 14.11 (CH_3). Anal. ($C_{19}H_{38}O_2$) C, H.

In a similar manner, compound **17f** was prepared.

2-[(Hexadecyloxy)methyl]-4-penten-1-ol (20d). To a suspension of sodium hydride (1.5 g, 34 mmol) in dimethylformamide (30 mL) was added dropwise a mixture of 2-(hydroxymethyl)-4-penten-1-ol (**19**, 3 g, 26 mmol) and 1-bromohexadecane (7.8 g, 26 mmol) dissolved in dimethylformamide (30 mL). The mixture was stirred at 60 °C for 6 h and then cooled to room temperature, poured into a 1 M, pH 7 phosphate buffer aqueous solution, and extracted with hexane. The organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated in vacuo to an oil (8.6 g), which was purified by flash chromatography (1:6 ethyl acetate/hexane) to afford the title product as a colorless oil (6.2 g, 71%): IR (film) ν 3425, 3072, 2921, 2850, 1637, 1463, 1373, 1236, 1114, 1043 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ (TMS) 5.6 (m, 1 H, =CH), 5.05 (m, 2 H, $=CH_2$), 3.5 (m, 6 H, CH_2O), 2.2–0.7 (m, ca. 35 H).

In a similar manner, compounds **20b** and **20f** were prepared.

2-[[(*N*-Pentadecylcarbamoyl)oxy]methyl]-4-penten-1-ol (20h). A mixture containing 2-(hydroxymethyl)-4-penten-1-ol (**19**, 1 g, 8.6 mmol) and pentadecyl isocyanate (16 mmol) in dry pyridine (8 mL) was heated at 60 °C for 3 h. The reaction mixture was cooled to room temperature, the volatiles were removed in vacuo, and the residue was partitioned between chloroform (75 mL) and 2 N HCl aqueous solution (25 mL). The aqueous phase was reextracted with more chloroform and the combined organic layers were washed with a 5% aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated to a yellowish solid (3.8 g). Purification by flash chromatography (1:5 ethyl acetate/hexane) yielded the title product as a white solid (2.1 g, 67%): IR (KBr) ν 3328, 3074, 2916, 2846, 1681, 1531, 1465, 1269, 1253, 1236, 1041 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ (TMS) 5.5 (m, 1 H, =CH), 5.0 (m, 2 H, $=CH_2$), 4.15 (m, 2 H, CH_2OCO), 3.6 (m, 2 H, CH_2OH), 3.15 (m, 2 H, CH_2C=), 2.3–0.7 (m, ca. 34 H).

In a similar manner, compound **20i** was prepared.

4-[(Hexadecyloxy)methyl]tetrahydrofuran-2-methanol (21d). Following the procedure described for the preparation of compound **9e**, the title compound was obtained as a colorless oil. ^{13}C NMR analysis indicated a 1:1 mixture of diastereomers: 65% yield; mp 37–38 °C; IR (film) ν 3403, 2913, 1463, 1376, 1113, 1050, 721 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ (TMS) 4.3–3.2 (m, 9 H, CH_2O), 2.5 (m, 1 H), 1.8–0.7 (m, ca. 34 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ ($CDCl_3$) 79.97 (CH), 79.04 (CH), 73.00 (CH_2), 72.52 (CH_2), 71.40 (CH_2), 71.13 (CH_2), 64.86 (CH_2), 64.65 (CH_2), 39.78 (CH), 39.59 (CH), 31.96 (CH_2), 30.55 (CH_2), 30.42 (CH_2), 29.72 (CH_2), 29.65 (CH_2), 29.51 (CH_2), 29.39 (CH_2), 26.17 (CH_2), 22.71 (CH_2), 14.13 (CH_3).

In a similar manner, compounds **21b,f,h,i** were prepared.

4-[[(*N*-Pentadecylcarbamoyl)oxy]methyl]tetrahydrofuran-2-methanol (21h): 90% yield; mp 70–71 °C; IR (KBr) ν 3350, 2917, 2846, 1682, 1524, 1464, 1249, 1235 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ (TMS) 4.9 (m, 1 H, NH), 4.0 (m, 5 H, CHO), 3.6 (m, 2 H, CHO), 3.15 (m, 2 H, CH_2N), 2.7 (m, 2 H, $CHCH_2OR$), 2.1–0.7 (m, ca. 32 H). Anal. ($C_{22}H_{43}NO_4$) C, H, N.

4-[(Trityloxy)methyl]tetrahydrofuran-2-methanol (22). To a solution of 2-(hydroxymethyl)-4-penten-1-ol (**19**, 8 g, 69 mmol) in dichloromethane (60 mL), and pyridine (10 mL) was added trityl chloride (19.7 g, 70 mmol) and the mixture was stirred at room temperature for 18 h. Dichloromethane (300 mL) was added and the resulting solution was washed with 1 N aqueous HCl solution (4×). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to an oil (29 g) which was purified by flash chromatography (1:9 ethyl acetate/hexane) to afford 2-[(trityloxy)methyl]-5-penten-1-ol as a white wax (12.6 g, 51%): IR (KBr) ν 3421, 3055, 3027, 2919, 2871, 1635, 1593, 1486, 1445, 1219, 1151, 1087, 1067, 1033 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ (TMS) 7.4 (m, 15 H, Ar), 5.7 (m, 1 H, =CH), 5.0 (m, 2 H, $=CH_2$), 3.7 (m, 2 H, CH_2O), 3.25 (m, 2 H, CH_2O), 2.1 (m, 4 H).

This product (12.6 g, 35 mmol) was dissolved in dichloromethane (100 mL) and treated with MCPBA (53 mmol) in the way described for the preparation of **9e**. The title compound was obtained as a white solid in practically quantitative yield (14.8 g). ^{13}C NMR analysis indicated a roughly 1:1 mixture of diastereomers: IR (KBr) ν 3419, 3081, 3053, 3027, 2924, 2863, 1486, 1445, 1215, 1070, 1032 cm^{-1}.

***cis*- and *trans*-4-[(Trityloxy)methyl]tetrahydrofuran-2-methanol (*cis*- and *trans*-22).** To a solution of a 1:1 mixture of cis/trans-4-[(trityloxy)methyl]tetrahydrofuran-2-methanol (**22**, 14.2 g, 38 mmol) in dichloromethane (150 mL) was added triethylamine (6.34 mL, 45 mmol) and palmitoyl chloride (11.5 g, 42 mmol). The mixture was stirred at room temperature for 2 h. Water was added, the organic phase was separated and dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated to an oil (27 g). The 1:1 diastereomeric mixture of palmitates was carefully flash chromatographed (contaminated fractions were rechromatographed two more times) with a 1:10 mixture of ethyl acetate/hexane. Fractions of 4 g (6.52 mmol) containing the pure isomers were each independently treated with a 2:1 mixture of tetrahydrofuran and 1 N aqueous potassium hydroxide (100 mL, 5 equiv) at room temperature for 48 h. Concentration of the volatiles and extraction of the aqueous residue with dichloromethane afforded the pure *trans*- and *cis*-alcohols after column chromatography (1:3 EtOAc/hexane) in 98 and 95% yield, respectively. Recrystallization from hexane/ethyl acetate afforded an analytical sample of each isomer. The assignment of their relative stereochemistry was made by conversion to 2-hexyl-4-methyltetrahydrofuran[21] and comparison with the published NMR data of its isomers.[22]

Trans isomer: mp 98–99 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.6–7.0 (m, 15 H, Ar), 4.2–3.7 (m, 2 H, CH_2O), 3.7–3.3 (m, 2 H, CH_2O), 3.08 (dd, J = 2.5 Hz, J = 7 Hz, 2 H), 2.57 (m, J = 7 Hz, 1 H, $TrOCH_2CH$), 2.21 (s, 1 H, OH), 1.72 (dt, J_d = 2 Hz, J_t = 7 Hz, 2 H, $TrOCH_2CHCH_2$); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ ($CDCl_3$) 143.86, 128.42, 127.54, 126.75, 86.25, 78.92, 71.04, 64.52, 64.41, 39.52, 30.31. Anal. ($C_{25}H_{26}O_3$) C, H.

Cis isomer: mp 83–84 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.6–7.0 (m, 15 H, Ar), 4.2–3.2 (m, 4 H), 3.07 (dd, J = 2.5 Hz, J = 7 Hz, 2 H), 2.60 (m, J = 7 Hz, 1 H, $TrOCH_2CH$), 2.2–1.7 (m, 1 H, $TrOCH_2CHC(H)H$), 2.0 (s, 1 H, OH), 1.30 (dt, J_d = 12.2 Hz, J_t = 8.5 Hz, 1 H, $TrOCH_2CHC(H)H$); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ ($CDCl_3$) 143.86, 128.42, 127.54, 126.75, 86.25, 79.90, 70.80, 65.13, 64.78, 64.36, 41.74, 30.71. Anal. ($C_{25}H_{26}O_3$) C, H.

2-[(Hexadecyloxy)methyl]-4-[(trityloxy)methyl]tetrahydrofuran (23d). Following the procedure described for the preparation of **13d**, the title product was obtained from compound **22** in a similar fashion: 79% yield; IR (film) ν 3081, 3054, 2919, 2849, 1445, 1071 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.30 (m, 15 H, Ar), 4.0 (m, 3 H, CH_2O), 3.35 (m, 4 H, CH_2O), 3.15 (m, 2 H, CH_2O), 2.6 (m, 1 H), 1.26 (m, ca. 32 H), 0.87 (m, 3 H).

In a similar manner, compound **23f** was prepared.

2-[(Hexadecyloxy)methyl]tetrahydrofuran-4-methanol (24d). A solution containing compound **23d** (7.2 g, 12 mmol) in methanol (80 mL) and tetrahydrofuran (20 mL) was treated with *p*-toluenesulfonic acid (1.1 g, 5.7 mmol) at room temperature for 15 h. The volatiles were then removed and the residue was dissolved in ether and washed with a saturated aqueous sodium bicarbonate solution. The organic phase was separated and dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated in vacuo to a solid that was purified by flash chromatography (1:3 ethyl acetate/hexane) to afford the title product as a waxy solid (2.6 g, 60%): IR (KBr) ν 3357, 2916, 2846, 1464, 1377, 1257, 1117 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 3.95 (m, 3 H, CH_2O), 3.50 (m, 6 H, CH_2O), 2.50 (m, 1 H), 2.0 (m, 1 H, OH), 1.26 (m, ca. 33 H), 0.88 (m, 3 H).

In a similar manner, compounds **24f** and **24h** were prepared.

2-[[(*N*-Pentadecylcarbamoyl)oxy]methyl]tetrahydrofuran-4-methanol (24h): 43% yield; mp 77–78 °C; IR (KBr) ν 3341, 2916, 2845, 1677, 1525, 1251 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 4.70 (m, 1 H, NH), 3.95 (m, 5 H, CH_2O), 3.60 (d, J = 6.4 Hz, 2 H, CH_2O), 3.15 (m, 2 H, CH_2N), 2.42 (m, 1 H), 1.56 (m, 1 H, OH), 1.25 (m, ca. 33 H), 0.87 (m, 3 H). Anal. ($C_{22}H_{43}NO_4$) C, H, N.

Ethyl 2-(Ethoxycarbonyl)-4-oxoheneicosanoate (26e). To a suspension of sodium hydride (0.38 g, 8.4 mmol) in dimethylformamide (5 mL) was added diethyl malonate (0.84 mL, 5.5 mmol) dropwise. The mixture was stirred at room temperature for 30 min and then cooled to 0 °C. A solution containing 1-bromo-2-nonadecanone (2.77 g, 7.67 mmol) in tetrahydrofuran (8 mL) was then added carefully at 0 °C, the resulting mixture was stirred at room temperature for 1 h and finally poured into a 1 M, pH 7 phosphate buffer aqueous solution and extracted with hexane. The organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated in vacuo to an oil (3.0 g) which was purified by flash chromatography (1:20 ethyl acetate/hexane) to afford the title compound as a colorless oil (2.09 g, 70%): IR (film) ν 2915, 2845, 1733, 1702, 1462, 1393, 1367, 1331, 1268, 1173 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 4.20 (q, J = 7.2 Hz, 4 H, CH_2O), 3.86 (t, J = 6.4 Hz, 1 H, $CH(COOEt)_2$), 3.01 (d, J = 7.2 Hz, 2 H, $CH_2CH(COOEt)_2$), 2.45 (t, J = 7.1 Hz, 2 H, $CH_2C{=}O$), 1.25 (m, ca. 13 H), 0.87 (t, J = 7.2 Hz, 6 H, 2 CH_3).

2-(Heptadecyl)tetrahydrofuran-4-methanol (27e). Compound **26e** was treated with lithium aluminum hydride as described in the preparation of compound **17b**. Usual workup and product isolation afforded 2-(hydroxymethyl)heneicosane-1,4-diol as an oil. The crude triol was dissolved in dichloromethane (60 mL) and pyridine (10 mL), a solution containing *p*-toluenesulfonyl chloride (0.6 g, 3.4 mmol) in dichloromethane (10 mL) was added, and the resulting mixture was stirred at 4 °C for 48 h and then poured into a saturated sodium bicarbonate aqueous solution. The organic phase was separated, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated to a colorless oil (1.5 g). Next, a solution of this compound in methanol (10 mL) was treated with potassium carbonate (0.2 g) at room temperature for 1 h. The solution was then concentrated to dryness, and the residue was partitioned between 1 M, pH 7 buffer phosphate solution and ethyl acetate. The organic layer was decanted, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to an oil. Flash chromatography purification (1:3 ethyl acetate/hexane) gave the title compound as a colorless oil (0.3 g, 27%). ^{13}C NMR analysis indicated a roughly 1:1 mixture of diastereomers: IR (film) ν 3355, 2914, 2845, 1464, 1375, 1188, 1050 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 3.9–3.5 (m, 5 H, CHO), 2.5 (m, 2 H), 1.5–0.9 (m, ca. 36 H), 0.87 (m, 3 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ ($CDCl_3$) 80.11 (CH), 79.00 (CH), 70.20 (2 CH_2), 65.26 (CH_2), 64.57 (CH_2), 41.97 (CH), 41.61 (CH), 35.74 (2 CH_2), 35.06 (CH_2), 34.48 (CH_2), 31.97 (CH_2), 29.72 (CH_2), 29.39 (CH_2), 26.43 (CH_2), 22.70 (CH_2), 14.10 (CH_3).

2-Heptadecyl-1,3-dioxolane-4-methanol (30e). A solution of 1-benzyl-*rac*-glycerol (**29**, 1.48 g, 8.12 mmol), octadecanal (2.40 g, 8.90 mmol), and camphorsulfonic acid (189 mg, 0.8 mmol) in dry toluene (20 mL) was stirred at room temperature for 18 h. The reaction was quenched by the addition of 1 M, pH 7 aqueous phosphate buffer solution (15 mL). The aqueous phase was separated and the organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to a colorless oil (4.0 g). ^{13}C NMR analysis of the unpurified reaction mixture indicated a ca. 6:1 ratio of diastereomers. The resulting solid residue was purified by flash chromatography (1:20 ethyl acetate/hexane) to afford 2.74 g (77%) of a white solid. This substance (2.56 g, 5.91 mmol) was dissolved in a 1:10 mixture of ethanol/dichloromethane, and 5% palladium on carbon (400 mg) was added. The mixture was hydrogenated on a Parr hydrogenator at 100 psi for 18 h at room temperature. Filtration and concentration gave the title product as a white solid (2.00 g, 76% overall): mp 53–54 °C; IR (KBr) ν 3240, 2916, 2846, 1464, 1129, 1043, 958, 721 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ (TMS) 5.2–4.9 (m, 1 H, OCHO), 4.4–4.0 (m, 1 H, CH_2CHO), 4.0–3.6 (m, 4 H, $HOCH_2CHCH_2$), 2.2–2.0 (s, 1 H, OH), 1.9–0.8 (m, ca. 35 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 105.18 (maj), 104.88 (min.), 76.26 (maj), 75.41 (min.), 66.53 (min.), 66.35 (maj), 63.42 (maj), 62.73 (min.), 34.12 (min.), 33.85 (maj), 31.90, 29.66, 29.51, 29.32, 23.97, 22.64, 18.04. Anal. ($C_{21}H_{42}O_3$) C, H.

In a similar manner, compounds **30a,c,g** were prepared.

2-[(Hexadecyloxy)methyl]-1,3-dioxolane-4-methanol (33d). A solution of 1-hexadecyl-*rac*-glycerol (**31d**, 2.27 g, 7.17 mmol) in acetone (100 mL) was added to a solution of sodium metaperiodate (3.07 g, 14.34 mmol) in water (90 mL) and the resulting slurry was stirred at room temperature for 1.5 h. The mixture

was poured into cold (0 °C) water (1.5 L). The resulting white precipitate was filtered, washed with water, and dissolved in dichloromethane. The aqueous layer was discarded and the organic phase was washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated in vacuo to afford (hexadecyloxy)ethanal (**32d**) as a white solid (2.11 g, ca. 100%), pure by TLC analysis. Following the two-step procedure described for the preparation of **30e** and using freshly prepared (hexadecyloxy)ethanal and 1-benzyl-*rac*-glycerol (**29**) gave the title compound as a white solid (1.1 g, 43% overall). ^{1}H NMR analysis of both the unpurified and purified ring formation reaction mixture indicated a ca. 8:1 mixture of diastereomers: mp 34–35 °C; IR (KBr) ν 3381, 2912, 2845, 1464, 1375, 1238, 1128, 867, 721 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 5.20 (t, J = 2.5 Hz, ca. 1/9 H, OCHO), 5.09 (t, J = 2.5 Hz, ca. 8/9 H, OCHO), 4.4–3.4 (m, 9 H), 2.5 (br s, 1 H, OH), 1.7–0.8 (m, ca. 31 H). Anal. ($C_{21}H_{42}O_4$) C, H.

In a similar manner, compound **33f** was prepared.

[2-[(Benzyloxy)methyl]-1,3-dioxolan-4-yl]methyl Phenylcarbonate (34). To a cooled (0 °C) solution of 1,2-isopropylideneglycerol (**28**, 13.2 g, 0.1 mol) in pyridine (16.1 mL, 0.2 mol) and dichloromethane (250 mL) was added dropwise phenyl chlorocarbonate (14.4 mL, 0.115 mol). The reaction mixture was stirred at room temperature for 2 h and quenched by the addition of a 2 N aqueous hydrochloric acid solution (250 mL). The organic phase was washed with a 2 N aqueous hydrochloric acid solution (250 mL) and then with a 10% aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated in vacuo to a dense liquid (29.9 g). A portion (3.78 g, 15 mmol) was dissolved in toluene (30 mL) and treated with freshly prepared (benzyloxy)ethanal (2.25 g, 15 mmol) and camphorsulfonic acid (350 mg, 1.5 mmol) at room temperature for 18 h. Usual workup and isolation afforded a yellowish, thick oil (5.86 g) which was purified by flash chromatography (1:4 ethyl acetate/hexane) to give the title product as a colorless oil. ^{1}H NMR analysis indicated a ca. 4:1 mixture of diastereomers: IR (film) ν 3058, 3026, 2912, 1759, 1588, 1489, 1448, 1243, 1208, 1110 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.32 (s, 10 H, Ar), 5.26 (t, J = 3.4 Hz, 1/5 H, OCHO), 5.14 (t, J = 3.4 Hz, 1/5 H, OCHO), 4.60 (s, 3 H, $ArCH_2$, OCH), 4.30 (br s, 3 H, $O{=}COCH_2$, OCH), 4.1–3.8 (m, 2 H, OCH), 3.7–3.5 (m, 2 H, $BnOCH_2$).

[2-[[(*N*-Pentadecylcarbamoyl)oxy]methyl]-1,3-dioxolan-4-yl]methyl Phenylcarbonate (35h). A mixture containing compound **34** (2.70 g, 7.84 mmol), dichloromethane (35 mL), ethanol (6 mL), and 5% palladium on carbon was hydrogenated on a Parr hydrogenator at 80 psi for 18 h. The reaction mixture was filtered and concentrated to a colorless, thick oil (1.86, 93%), pure by TLC analysis. This product (1.61 g, 6.32 mmol) was dissolved in a mixture of pyridine (5.1 mL) and chloroform (10 mL) and *n*-pentadecyl isocyanate (2.40 g, nonpurified) was added. The reaction mixture was stirred at reflux for 6 h, cooled to room temperature, and quenched by the addition of water (25 mL). The organic phase was successively washed with a 6 N aqueous hydrochloric acid solution (20 mL), 10% sodium bicarbonate aqueous solution (20 mL), and brine (20 mL), and then dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate concentrated to a white paste (9.5 g). Purification by flash chromatography afforded the title compound as a white solid: mp 38–40 °C; IR (film) ν 3302, 2917, 2848, 1759, 1714, 1632, 1525, 1646, 1244, 1209, 1139, 1060, 775, 721 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.5–7.1 (m, 5 H, Ar), 5.28 (t, J = 3.7 Hz, 1/5 H, OCHO), 5.16 (t, J = 3.7 Hz, 4/5 H, OCHO), 4.8 (br s, 1 H, NH), 4.6–3.9 (m, 8 H, OCH), 3.2 (q, J = 6.1 Hz, 2 H, NCH_2), 1.6–0.7 (m, ca. 29 H).

In a similar manner, compound **35i** was prepared.

2-Hydroxy-1-nonadecanol (37e). A cooled (0 °C) suspension containing 1-nonadecene (**36e**, 1.5 g, 5.63 mmol) in acetone (15 mL) and water (2 mL) was treated with a 70% aqueous solution of *tert*-butyl hydroperoxide (1.16 mL, 8.44 mmol) and a 0.02 M solution of osmium tetroxide in *tert*-butyl alcohol (1.4 mL, 0.028 mmol), according to a published general procedure.[25] The mixture was stirred 1 h at 0 °C and 24 h at room temperature. An additional 1 mL of *tert*-butyl hydroperoxide and 1.2 mL of osmium tetroxide solution was added and the mixture was stirred for 24 h. Ether (25 mL) was added, followed by a 5% aqueous solution of sodium bisulfite (7 mL). After stirring for 1.5 h at room temperature, the aqueous phase was separated and extracted with ethyl acetate (2 × 25 mL). The combined organic phases were washed with brine (25 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to a pale brown solid (3 g), which was purified by flash chromatography (1:1 ethyl acetate/hexane) to afford the title compound as a white solid (1.35 g, 80%): mp 79–80 °C; IR (KBr) ν 3353, 2912, 2845, 1461, 1352, 1113, 1087, 1073 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 3.8–3.3 (m, 3 H, $CHCH_2OH$), 1.89 (s, 2 H, OH, OH), 1.7–0.7 (m, ca. 35 H). Anal. ($C_{19}H_{40}O_2$) C, H.

4-Heptadecyl-1,3-dioxolane-2-methanol (38e). Following the two-step procedure described for the preparation of **30e** and using freshly prepared (benzyloxy)ethanal gave the title product as a white solid (1.08 g, 80%). ^{1}H NMR analysis of the unpurified reaction mixture indicated a ca. 8:1 ratio of diastereomers: mp 61–62 °C; IR (KBr) ν 3447, 2913, 2844, 1464, 1381, 1346, 1246, 1162, 1139, 1110, 1078, 1066, 1051, 1038, 996 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 5.10 (t, J = 3 Hz, ca. 1/9 H, OCHO), 5.00 (t, J = 3 Hz, ca. 8/9 H, OCHO), 4.2–3.9 (m, 2 H, CH_2OCH), 3.66 (d, J = 3 Hz, 2 H, CH_2OH), 3.7–3.4 (m, 1 H, CH_2CHO), 1.7–0.7 (m, ca. 35 H). Anal. ($C_{21}H_{42}O_3$) C, H.

4-[(Hexadecyloxy)methyl]-1,3-dioxolane-2-methanol (39d). According to the procedure described for the preparation of **38e**, the title compound was obtained in a similar manner in 78% yield. ^{1}H NMR of the unpurified ring formation reaction mixture indicated a ca. 8:1 ratio of diastereomers: mp 46–47 °C; IR (KBr) ν 3323, 2913, 2847, 1464, 1423, 1154, 1118, 1061, 1032, 845 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 5.10 (t, J = 2.5 Hz, ca. 1/9 H, OCHO), 5.07 (t, J = 2.5 Hz, ca. 8/9 H, OCHO), 4.5–4.0 (m, 1 H), 3.95 (dd, J = 2 Hz, J = 6 Hz, 2 H), 3.71 (d, J = 2.5 Hz, 2 H, CH_2OH), 3.6–3.3 (m, 4 H, CH_2OCH_2), 2.0 (s, 1 H, OH), 1.7–0.7 (m, ca. 31 H). Anal. ($C_{21}H_{42}O_4$) C, H.

In a similar manner, compounds **39b** and **39f** were prepared.

4-[[(*N*-Pentadecylcarbamoyl)oxy]methyl]-1,3-dioxolane-2-methanol (39h). Following the method used for the preparation of compound **30e** the title compound was obtained in a similar way in 45% yield. ^{1}H NMR of the unpurified ring formation reaction mixture indicated a ca. 2:1 ratio of diastereomers: mp 73–75 °C; IR (KBr) ν 3329, 2916, 2846, 1675, 1633, 1529, 1464, 1372, 1313, 1291, 1271, 1253, 1237, 1148, 1044 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 5.12 (t, J = 2.5 Hz, 1/3 H, OCHO), 5.04 (t, J = 2.5 Hz, 2/3 H, OCHO), 4.7 (br s, 1 H, N H), 4.5–3.5 (m, 7 H), 3.16 (q, J = 5 Hz, 2 H, NCH_2), 1.89 (s, 1 H, OH), 1.7–0.7 (m, ca. 29 H).

In a similar manner, compound **39i** was prepared.

General Method for the Preparation of Tosylates 40. To a cooled (0 °C) solution of the corresponding alcohol (15 mmol) and dry pyridine (45 mmol) in dichloromethane (75 mL) was added a solution of the corresponding ω-tosyloxy acid chloride (21 mmol) in dichloromethane (30 mL). The mixture was then stirred for 24 h at room temperature and quenched by the addition at 0 °C of 1 N aqueous HCl solution (100 mL). The aqueous layer was separated and the organic phase was successively washed with a saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated to an oil which was purified by flash chromatography (1:3 ethyl acetate/hexane). The product was obtained generally as a solid, in 60–80% yield.

General Method for the Preparation of Tosylates 41. A solution of the corresponding alcohol (10 mmol) in dimethylformamide (25 mL) was treated with sodium hydride (12 mmol) and then with the corresponding ω-(tetrahydropyranyl-2-oxy)alkyl *p*-toluenesulfonate ester (11 mmol) at 100 °C for 4 h, as described for the preparation of **20d**. The product thus obtained was dissolved in methanol (35 mL) and treated with camphorsulfonic acid (20 mg) at room temperature for 16 h. The volatiles were removed in vacuo and the residue was partitioned between ethyl acetate and 1 M, pH 7 phosphate buffer aqueous solution. The aqueous phase was reextracted with more ethyl acetate (2×), the combined extracts were dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated to an oil. The compound thus obtained was dissolved in dichloromethane (15 mL) and treated with pyridine (5 mL) and *p*-toluenesulfonyl chloride (10 mmol) at room temperature for 12 h. The resulting mixture was then poured into a saturated sodium bicarbonate aqueous solution and the organic phase was decanted, dried over anhydrous sodium

sulfate, and filtered, and the filtrate was concentrated in vacuo to a oil which was purified by flash chromatography (1:4 ethyl acetate/hexane). The product was obtained generally as a solid, in 50–70% overall yield.

General Method for the Preparation of Salts 42 and 43. A solution of the corresponding tosylate **40** or **41** (10 mmol) in the nitrogen-containing heterocycle or amine (15–30 mL) was heated at reflux for 5–18 h, until disappearance of the starting material by TLC analysis. The volatiles were removed in vacuo and the solid residue was recrystallized from dichloromethane/ether to afford the title products as white to pale brown solids, in 90–95% yields.

General Method for the Preparation of Carbamates 45. (The following compounds, 44–48, were prepared according to a published procedure[15b].) A cooled (0 °C) solution containing the corresponding alcohol (10 mmol), pyridine (20 mmol), and dichloromethane (40 mL) was treated dropwise with phenyl chlorocarbonate (11.5 mmol). After 1 h, the reaction was quenched by the addition of a 1 N HCl aqueous solution (50 mL), and the organic phase was washed with a 10% sodium bicarbonate aqueous solution (30 mL) and with brine (30 mL). Anhydrous sodium sulfate was added, the mixture was filtered, and the filtrate was concentrated in vacuo. The substance thus obtained (**44**) was diluted in chloroform (30 mL) and treated with 2-pycolylamine (12 mmol) at reflux for 20 h. The solution was cooled to room temperature and washed successively with a 1 N sodium hydroxide aqueous solution (2 × 20 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to an oil that was purified by flash chromatography (1:3 ethyl acetate/hexane) to afford the title product in 90–100% yield.

General Method for the Preparation of *N*-Acetylcarbamates 46. The following procedure has consistently given better yields than the reported method for the synthesis of CV-6209.[15b] To a cooled (0 °C) solution of compound **45** (5 mmol) in dichloromethane (10 mL) was slowly added acetyl chloride (6.5 mmol). The resulting reddish solution was stirred for 0.5 h at 0 °C and 20 h at room temperature. The solution was then cooled (0 °C) and treated with triethylamine (6.5 mmol) and additional acetyl chloride (6.5 mmol). After stirring for 20 h at room temperature, triethylamine was added (10 mmol) and the mixture was washed with water (2 × 20 mL) and brine (20 mL). The solution was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated in vacuo to a red-brown residue. Flash chromatography (1:1 ethyl acetate/hexane) afforded the title product in 90–100% yield.

General Method for the Preparation of Iodides 47. A solution of compound **46** (10 mmol) and ethyl iodide (10 mmol) in acetonitrile (10 mL) was heated at 80 °C for 1–3 days (monitored by TLC). The volatiles were then removed in vacuo and the residue was recrystallized from dichloromethane/ether to afford the title product as a yellow, low-melting powder in 85–95% yield containing variable amounts of water. Recrystallization from acetone/ether tended to give the compounds as higher melting point, white polymorphs.

General Method for the Preparation of Chlorides 48. A solution of iodide **47** in 30% methanol/water was passed through a column of Amberlite IRA-410 ion-exchange resin previously washed with brine and water. The fractions containing the product were mixed, extracted with dichloromethane (2×), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated to a white powder. Recrystallization from acetone/ether afforded the chloride salts containing variable amounts of water, in 70–100% yield, as white powders.

2-[[*N*-Acetyl-*N*-[[[4-[[(pentadecylcarbamoyl)oxy]methyl]-2-tetrahydrofuranyl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (122). The corresponding carbamate **45** was obtained as a white solid in 99% yield from a 1:1 diastereomeric mixture of alcohol **21h** following the general procedure described above: mp 77–78 °C; IR (KBr) ν 3320, 3051, 2915, 2847, 1681, 1532, 1262 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.50 (d, J = 4.6 Hz, 1 H, pyr), 7.60 (dt, J_d = 1.6 Hz, J_t = 7.4 Hz, 1 H, pyr), 7.4–7.1 (m, 2 H, pyr), 6.2 (br s, 1 H, NH), 5.1 (br s, 1 H, NH), 4.48 (d, J = 5.6 Hz, 2 H, pyr-CH_2), 4.4–3.4 (m, 7 H), 3.14 (q, J = 6.3 Hz, 2 H, CH_2NH), 2.60 (quint, J = 7 Hz, 1 H), 2.4–1.9 (m, 1 H), 1.71 (t, J = 6.4 Hz, 1 H), 1.6–0.7 (m, ca. 29 H). Anal. ($C_{29}H_{49}N_3O_5$) C, H, N.

This compound was acetylated according to the general procedure described above to afford the corresponding *N*-acetylcarbamate **46** as a white wax in 95% yield: IR (KBr) ν 3363, 3054, 2919, 2846, 1739, 1692, 1591, 1518, 1464, 1376, 1333, 1287, 1266, 1246, 1232, 1216, 1155, 1097, 1052, 1006, 994 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.50 (br d, J = 4.0 Hz, 1 H, pyr), 7.63 (br t, J = 8.6 Hz, 1 H, pyr), 7.16 (m, 2 H, pyr), 5.10 (s, 2 H, pyr-CH_2), 4.77 (m, 1 H, NH), 4.3–3.3 (m, 7 H, CH_2O), 3.15 (q, J = 5.7 Hz, 2 H, CH_2NH), 2.7–2.2 (m, 1 H), 2.63 (s, 3 H, O=CCH_3), 2.2–1.9 (m, 1 H), 1.8–0.7 (m, ca. 30 H).

Next, this compound was treated with ethyl iodide in acetonitrile at reflux for 3 days, according to the general procedure described above, to give a 1:1 diastereomeric mixture of iodide **122** in 83% yield, as a yellowish powder: mp 32–35 °C; IR (KBr) ν 3333, 2920, 2849, 1750, 1696, 1624, 1518, 1446, 1367, 1209 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.67 (br d, J = 5.8 Hz, 1 H, pyr), 8.52 (br t, J = 8 Hz, 1 H, pyr), 8.08 (br t, J = 6.2 Hz, 1 H, pyr), 7.82 (br d, J = 8 Hz, 1 H, pyr), 5.85 (s, 2 H, pyr-CH_2), 5.08 (q, J = 7.4 Hz, 2 H, NEt), 4.8 (br s, 1 H, NH), 4.4–3.4 (m, 7 H, CH_2O), 3.15 (q, J = 5.7 Hz, 2 H, CH_2NH), 2.7–2.2 (m, 1 H), 2.67 (s, 3 H, O=CCH_3), 2.2–1.9 (m, 1 H), 1.74 (t, J = 7.4 Hz, 3 H, NEt), 1.8–0.7 (m, ca. 30 H). Anal. ($C_{33}H_{56}IN_3O_6 \cdot H_2O$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[4-[[(pentadecylcarbamoyl)oxy]methyl]-2-tetrahydrofuranyl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Chloride (123). The 1:1 diastereomeric mixture of iodides **122** was converted into their chloride salt, according to the previously described general procedure, to afford compound **123**. Recrystallization from acetone/ether gave the title product as a white powder in 99% yield, as a ca. 1:1 diastereomeric mixture: mp 30–34 °C; IR (KBr) ν 3415, 2921, 2849, 1740, 1692, 1624, 1579, 1448, 1367, 1225, 1163 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 10.01 (br d, J = 6 Hz, 1 H, pyr), 8.52 (br t, J = 8 Hz, 1 H, pyr), 8.08 (br t, J = 6.5 Hz, 1 H, pyr), 7.74 (br d, J = 8 Hz, 1 H, pyr), 5.46 (s, 2 H, pyr-CH_2), 5.17 (m, 3 H, NH, NEt), 4.4–3.4 (m, 7 H), 3.15 (q, J = 5.7 Hz, 2 H, CH_2NH), 2.7–2.2 (m, 1 H), 2.65 (s, 3 H, O=CCH_3), 2.2–1.9 (m, 1 H), 1.71 (t, J = 7.4 Hz, 3 H, NEt), 1.8–0.7 (m, ca. 30 H). Anal. ($C_{33}H_{56}ClN_3O_6 \cdot H_2O$) C, H, Cl, N.

2-[[*N*-Acetyl-*N*-[[[2-[[(hexadecyl)oxy]methyl]-4-tetrahydrofuranyl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Chloride (115). Following the sequence of reactions described above, the title compound was obtained from alcohol **24d** as a white powder, as a ca. 1:1 diastereomeric mixture: mp 34–39 °C; IR (KBr) ν 3417, 2913, 2846, 1744, 1679, 1624, 1579, 1462, 1367, 1212 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.93 (br d, J = 6 Hz, 1 H, pyr), 8.50 (br t, J = 8 Hz, 1 H, pyr), 8.07 (br t, J = 6.5 Hz, 1 H, pyr), 7.70 (br d, J = 8 Hz, 1 H, pyr), 5.47 (s, 2 H, pyr-CH_2), 5.17 (q, J = 7.2 Hz, 2 H, NEt), 4.4–3.3 (m, 9 H, CH_2O), 2.83 (s, 3 H, O=CCH_3), 1.70 (t, J = 7 Hz, 3 H, NEt), 1.7–0.7 (m, ca. 32 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ ($CDCl_3$) 172.44 (C), 153.22 (C), 147.53 (CH), 145.52 (CH), 127.26 (CH), 125.25 (CH), 78.40 (CH), 77.46 (CH), 73.03 (CH_2), 72.67 (CH_2), 71.78 (CH_2), 70.26 (CH_2), 69.83 (CH_2), 54.13 (CH_2), 44.66 (CH_2), 38.14 (CH), 31.85 (CH_2), 31.0 (CH_2), 29.62 (CH_2), 29.29 (CH_2), 26.41 (CH_3), 26.05 (CH_2), 22.61 (CH_2), 16.09 (CH_3), 14.03 (CH_3). Anal. ($C_{33}H_{57}ClN_2O_5 \cdot H_2O$) C, H, N; Cl: calcd, 5.80; found, 6.40.

2-[[*N*-Acetyl-*N*-[[[2-[[(pentadecylcarbamoyl)oxy]methyl]-4-tetrahydrofuranyl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (116). The title compound was prepared from a 1:1 mixture of alcohols **24h** and obtained as a yellow powder: mp 35–37 °C; IR (KBr) ν 3399, 2918, 2849, 1745, 1692, 1624, 1525, 1367, 1224 cm^{-1}. Anal. ($C_{33}H_{56}IN_3O_6 \cdot {}^1/_2H_2O$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[2-[[(pentadecylcarbamoyl)oxy]methyl]-4-tetrahydrofuranyl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Chloride (117). The title compound was prepared from a 1:1 mixture of iodides **116** and obtained as a white powder: mp 61–73 °C; IR (KBr) ν 3399, 2918, 2849, 1745, 1692, 1624, 1525, 1367, 1224 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.90 (br d, J = 6 Hz, 1 H, pyr), 8.54 (br t, J = 8 Hz, 1 H, pyr), 8.06 (br t, J = 6.5 Hz, 1 H, pyr), 7.73 (br d, J = 8 Hz, 1 H, pyr), 5.51 (s, 2 H, pyr-CH_2), 5.18 (m, 3 H, NH, NEt), 4.4–3.9 (m, 7 H), 3.0 (m, 4 H), 2.64 (s, 3 H, O=CCH_3), 1.79 (t, J = 7 Hz, 3 H, NEt), 1.7–0.7 (m, ca. 31 H). Anal. ($C_{33}H_{56}ClN_3O_6 \cdot {}^1/_2H_2O$) C, H, Cl, N.

***trans*- and *cis*-2-[[*N*-Acetyl-*N*-[[[2-[[(pentadecylcarbamoyl)oxy]methyl]-4-tetrahydrofuranyl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (*cis*- and *trans*-116).** Using diastereomerically pure *trans*- and *cis*-alcohols **24h** and following the same procedure as above gave pure *trans*- and *cis*-iodides **116**.

trans-**116**: mp 64–78 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.50 (br d, J = 6 Hz, 1 H, pyr), 8.56 (br t, J = 8 Hz, 1 H, pyr), 8.06 (br t, J = 6.5 Hz, 1 H, pyr), 7.73 (br d, J = 8 Hz, 1 H, pyr), 5.48 (s, 2 H, pyr-CH_2), 5.05 (m, 3 H, NH, NEt), 4.4–3.8 (m, 7 H), 3.52 (dd, J = 5.3 Hz, J = 9 Hz, 1 H), 3.0 (m), 3.15 (q, J = 5.7 Hz, 2 H, CH_2NH), 2.65 (s, 3 H, O=CCH_3), 1.72 (t, J = 7 Hz, 3 H, NEt), 1.7–0.7 (m, ca. 31 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ ($CDCl_3$) 172.47 (C), 156.34 (C), 153.34 (C), 153.17 (C), 147.35 (CH), 145.56 (CH), 127.12 (CH), 125.25 (CH), 76.61 (CH), 70.23 (CH_2), 69.72 (CH_2), 66.07 (CH_2), 54.12 (CH_2), 44.68 (CH_2), 41.14 (CH_2), 37.93 (CH), 31.80 (CH_2), 30.91 (CH_2), 29.91 (CH_2), 29.54 (CH_2), 29.22 (CH_2), 26.74 (CH_2), 26.27 (CH_3), 22.54 (CH_2), 16.00 (CH_3), 13.96 (CH_3). Anal. ($C_{33}H_{56}IN_3O_6$) C, H, N.

cis-**116**: mp 67–70 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.50 (br d, J = 6 Hz, 1 H, pyr), 8.54 (br t, J = 8 Hz, 1 H, pyr), 8.06 (br t, J = 6.5 Hz, 1 H, pyr), 7.73 (br d, J = 8 Hz, 1 H, pyr), 5.48 (s, 2 H, pyr-CH_2), 5.05 (m, 3 H, NH, NEt), 4.4–3.5 (m, 8 H), 3.15 (q, J = 5.7 Hz, 2 H, CH_2NH), 2.9 (m), 2.65 (s, 3 H, O=CCH_3), 2.5–1.9 (m, 2 H), 1.79 (t, J = 7 Hz, 3 H, NEt), 1.7–0.7 (m, ca. 31 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ ($CDCl_3$) 172.47 (C), 156.25 (C), 153.34 (C), 153.17 (C), 147.35 (CH), 145.56 (CH), 127.12 (CH), 125.25 (CH), 77.37 (CH), 70.23 (CH_2), 69.72 (CH_2), 65.86 (CH_2), 54.12 (CH_2), 44.68 (CH_2), 41.14 (CH_2), 38.08 (CH), 31.80 (CH_2), 30.91 (CH_2), 29.91 (CH_2), 29.54 (CH_2), 29.22 (CH_2), 26.74 (CH_2), 26.27 (CH_3), 22.54 (CH_2), 16.00 (CH_3), 13.96 (CH_3). Anal. ($C_{33}H_{56}IN_3O_6$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[4-[[(hexadecyl)oxy]methyl]-1,3-dioxolan-2-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Chloride (130). The title compound was similarly prepared from alcohol **39d**. Recrystallization from acetone afforded a white powder, as a ca. 8:1 mixture of diastereomers: mp 39–42 °C; IR (KBr) ν 3441 (H_2O), 2918, 2848, 1752, 1685, 1624, 1579, 1508, 1445, 1367, 1294, 1213, 1144, 1089, 986 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.91 (br d, J = 6 Hz, 1 H, pyr), 8.49 (br t, J = 8 Hz, 1 H, pyr), 8.11 (br t, J = 6.5 Hz, 1 H, pyr), 7.75 (br d, J = 8 Hz, 1 H, pyr), 5.43 (s, 2 H, pyr-CH_2), 5.1–4.8 (m, 3 H, OCHO, NEt), 4.30 (d, J = 4.5 Hz, 2 H, O=$COCH_2$), 4.2–3.5 (m, 3 H), 3.5–3.3 (m, 4 H), 2.66 (s, 3 H, O=CCH_3), 1.72 (t, J = 7 Hz, 3 H, NEt), 1.7–0.7 (m, ca. 31 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ ($CDCl_3$) 172.51 (C), 152.85 (C), 152.75 (C), 147.88 (CH), 145.49 (CH), 127.38 (CH), 125.65 (CH), 100.54 (CH, maj), 100.24 (CH, min), 75.70 (CH), 71.90 (CH_2), 70.70 (CH_2), 67.21 (CH_2), 67.07 (CH_2), 54.05 (CH_2), 44.19 (CH_2), 31.84 (CH_2), 29.59 (CH_2), 29.28 (CH_2), 26.28 (CH_3), 25.99 (CH_2), 22.59 (CH_2), 16.18 (CH_3), 13.99 (CH_3). Anal. ($C_{32}H_{55}ClN_2O_8 \cdot 2H_2O$) C, H, N.

B. Biological Methods: Inhibition of Platelet Aggregation in Vitro. Platelet-aggregation studies were done by the method of Born.[28] Blood was collected in 3.16% sodium citrate (1 volume for 9 volumes of blood) by cardiac puncture from male New Zealand rabbits (2–2.5 kg of body weight). Platelet rich plasma (PRP) was prepared by centrifugation of the blood at 250 g for 10 min at 4 °C. The PRP was diluted with platelet-poor plasma obtained by further centrifugation at 3000 g for 10 min. The platelet number was adjusted to 3.5×10^5 cells/mm^3. Platelet aggregation was induced by C18-PAF (1.5×10^{-8} M) and measured by using a dual-channel aggregometer Chrono-log 500. Activity of the inhibitors was expressed as the IC_{50} value, i.e. the concentrations required to inhibit platelet-aggregatory response by 50%. The values shown in the tables were calculated by linear regression from a single experimental curve with no less than four data points, each point being the mean of the percent inhibition at a given concentration obtained from one to three independent experiences.

Inhibition of PAF-Induced Hypotension in Normotensive Rats. Hypotension studies were performed as described by Baranes.[29] Male Sprague–Dawley rats, weighing 180–220 g, were anesthetized with sodium pentobarbital (50 mg/kg ip). Blood pressure was recorded from the left carotid artery with a Beckman pressure transducer coupled to a Beckman R611 polygraph. Right and left femoral veins were catheterized to inject PAF (0.5 μg/kg) or the test compound. Test compounds were administered by intravenous injection (1 mL/kg, dissolved in saline) 3 min before PAF injection. Control animals received only the vehicle. Blood pressure was monitored and percent inhibition of PAF-induced hypotension with respect to controls was calculated. The results were expressed as ID_{50} values, i.e. the doses of the test compound required to inhibit the PAF-induced hypotension by 50%. The results were calculated by linear regression from a single experimental curve with not less than four points, each point being the mean of the percent inhibition at a given dose obtained from two or more independent experiences.

Statistics. Statistical analyses of pharmacological data (i.e. IC_{50} and ID_{50} values with their 95% confidence limits) were made by using standard pharmacology programs implemented on an IBM PC.[30]

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