Pergamon

Bioorganic & Medicinal Chemistry, Vol. 5, No. 8, pp 1621–1647, 1997

PII: S0968-0896(97)00090-4
0968-0896/97 $17.00 + 0.00

Synthesis of Structural Analogues of Leukotriene B_4 and their Receptor Binding Activity

Mitoshi Konno, Takahiko Nakae, Shigeru Sakuyama, Minoru Nishizaki, Yoshihiko Odagaki, Hisao Nakai and Nobuyuki Hamanaka*

Department of Medicinal Chemistry, Minase Research Institute, Ono Pharmaceutical Co., Ltd, Shimamoto, Mishima, Osaka 618, Japan

Abstract—Structural analogues of leukotriene B_4 (LTB_4) were designed based on the plausible conformation of LTB_4 (**1**). Joining C-7–C-9 of the conformer A or B into an aromatic ring system led to the discovery of benzene analogues **2**, **4** and **6a**. Joining C-4–C-9 of the conformer C or D into an aromatic ring system led to the discovery of analogues **3**, **5** and **7**. The compounds examined in this study were evaluated as to their inhibition of [^{3}H] LTB_4 binding to human neutrophils, and by a secondary intact human neutrophil functional assay for agonist/antagonist activity. The first analogues prepared, compounds **2–7**, demonstrated moderate potency in the LTB_4 receptor binding assay. The modification of these compounds by the introduction of another substituent into the aromatic ring produced a marked increase in receptor binding (**28c**, IC_{50} = 0.020 μM; **38c**, IC_{50} = 0.020 μM; **52a**, IC_{50} = 0.020 μM; **52b**, IC_{50} = 0.018 μM). Most of these structural analogues of LTB_4 demonstrated agonist activity. Of the analogues prepared in this study, only compound **57** demonstrated weak LTB_4 receptor antagonist activity, at 10 μM. © 1997 Elsevier Science Ltd.

Introduction

Leukotriene B_4 (LTB_4, **1**), a product of the 5-lipoxygenase-catalysed oxygenation of arachidonic acid, is thought to be a mediator of inflammation and has been implicated in a variety of human inflammatory diseases. LTB_4 is produced by mast cells, polymorphonuclear leukocytes (PMNLs), monocytes, alveolar macrophages, peritoneal macrophages, and keratinocytes. The known pathophysiological responses of LTB_4 include potent neutrophil chemotactic activity, the promotion of adhesion of PMNLs to the vascular endothelium, stimulation of the release of lysosomal enzymes and superoxide radicals by PMNLs, and an increase in vascular permeability.[1] The presence of elevated concentrations of LTB_4 in psoriatic lesional skin,[2] colonic mucosa associated with inflammatory bowel disease,[3] synovial fluid from patients with active rheumatoid arthritis,[4] and in gouty effusions[5] supports the involvement of LTB_4 in human inflammatory diseases.

The pharmacological effects of LTB_4 are mediated through its interaction with specific cell surface receptors that have been characterized on PMNLs,

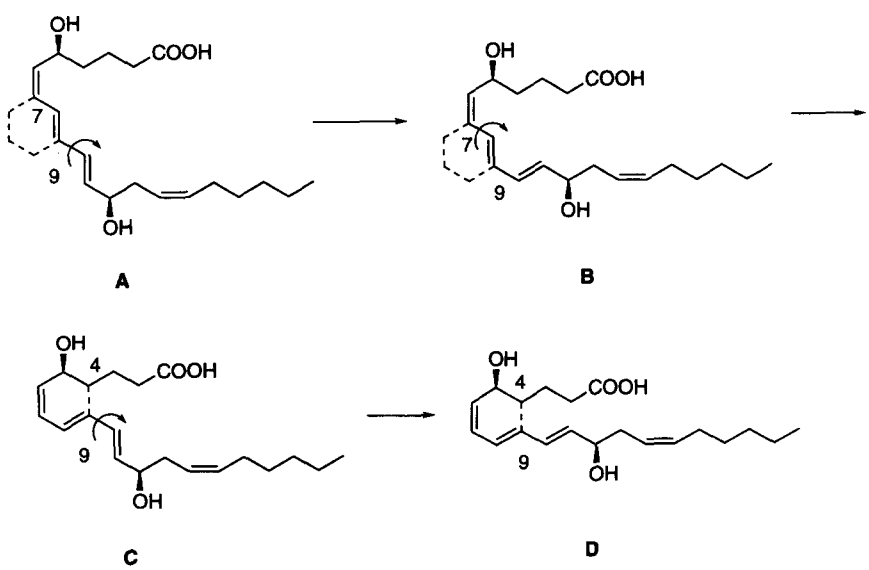


Chart 1. Possible conformers of LTB_4 (**1**).

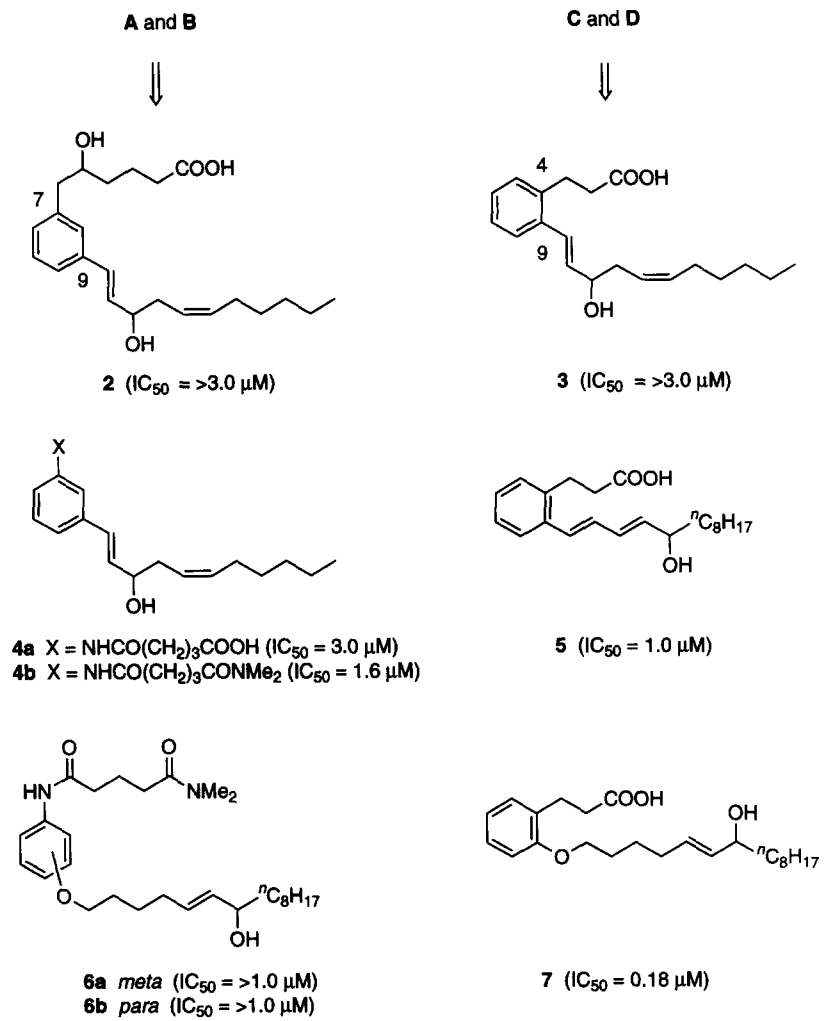


Chart 2. Partial fixation of conformers **A–D**.

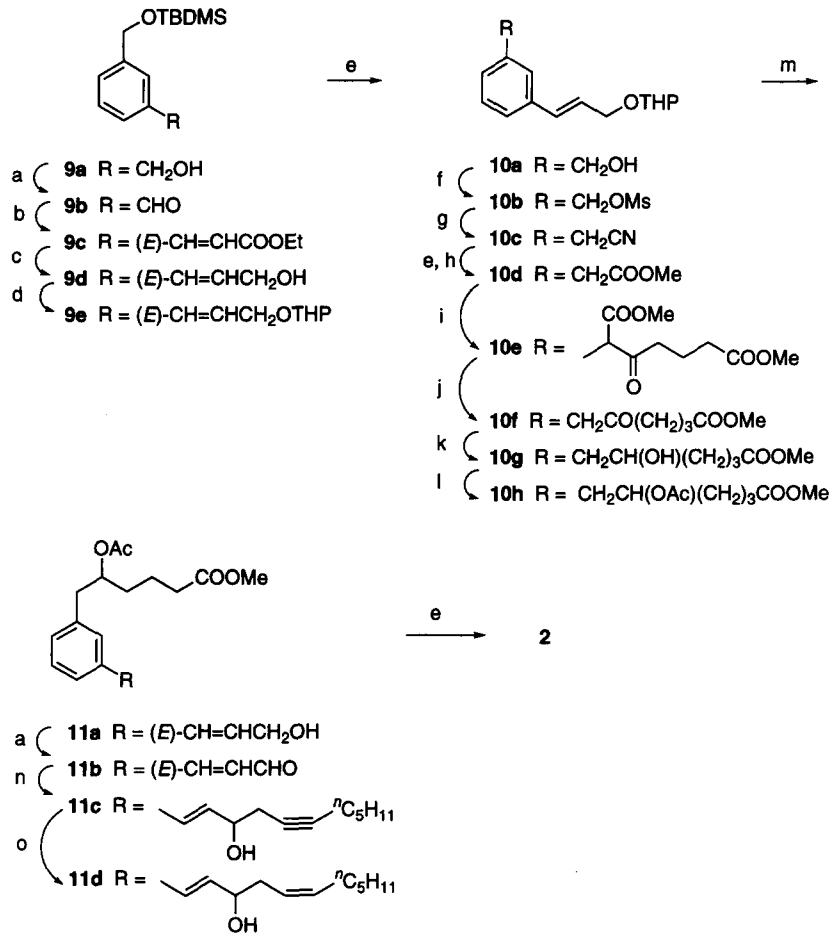
monocytes, U-937 cells, lymphocytes, mast cells, smooth muscular cells, and endothelial cells, as well as on various tissues such as spleen, lung, heart, brain, small intestine, uterus and kidney.[6] The major proinflammatory activity of LTB_4 is thought to involve a receptor-mediated induction of the aggregation and adhesion of inflammatory cells, especially PMNLs, to venular endothelial cells. Thus, the availability of potent, selective LTB_4 receptor antagonists will be useful in elucidating the role of LTB_4 in human inflammatory diseases.

In the present study, we describe the results of our efforts to identify structural leads to unique LTB_4 receptor antagonists. The strategic approach was focused on building benzene analogues of LTB_4 that would restrict the conformational freedom of the molecule. Thus, a series of disubstituted and trisubstituted benzene analogues of LTB_4 were synthesized. The receptor binding affinities as well as the functional activity of the analogues in human neutrophils were determined. Based on these results, a lead to a unique LTB_4 receptor antagonist, analogue **57**, was identified.

Chemistry

Our initial target compounds **2–7** (Chart 2) were prepared as outlined in Schemes 1–5.

Compound **2** was prepared as shown in Scheme 1. The protection of one of the hydroxyl functions of 1,3-benzenedimethanol with a *t*-butyldimethylsilyl (TBDMS) group afforded **9a**. Compound **9a** was converted to **9e** by the sequential reactions: Swern oxidation; Horner–Emmons reaction; Diisobutylaluminum hydride reduction; protection of the formed hydroxyl group with a tetrahydropyranyl group (THP). The deprotection of **9e** with aqueous NaOH provided **10a**, which was converted to **10h** by the following sequential reactions: methanesulfonylation; substitution with sodium cyanide; alkaline hydrolysis followed by esterification with diazomethane; acylation with an acid chloride; decarbomethoxylation by heating; sodium borohydride reduction; acylation of the formed alcohol with acetic anhydride. The removal of the THP group was carried out under acidic conditions to give **11a**. The Swern oxidation of **11a** followed by the coupling reaction with the allenylborane reagent generated from



Reagent: (a) $(COCl)_2$, DMSO; (b) NaH, $(EtO)_2P(O)CH_2COOEt$; (c) DIBAH; (d) dihydropyran, H^+; (e) aq. NaOH; (f) MsCl, Et_3N; (g) NaCN; (h) CH_2N_2; (i) $ClCO(CH_2)_3COOMe$, LDA; (j) heat; (k) $NaBH_4$; (l) Ac_2O, Pyridine; (m) aq. AcOH; (n) 2-octyne, BuLi, $B(OPr^i)_3$;[7] (o) H_2, Lindlar catalyst

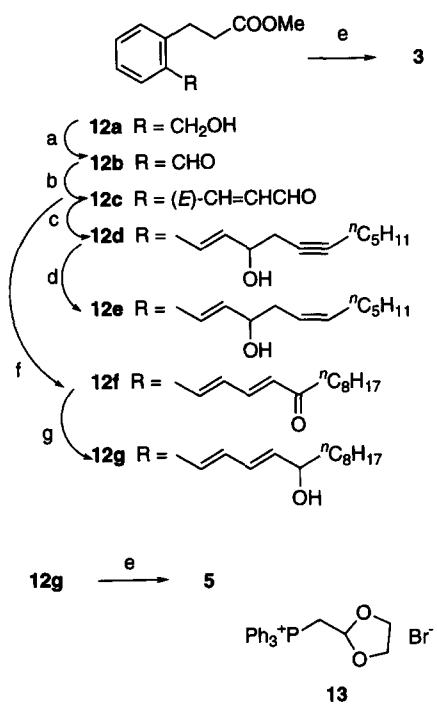
Scheme 1. Synthesis of compound **2**.

2-octyne[7] afforded **11c**. The catalytic hydrogenation of **11c** in the presence of Lindlar catalyst provided **11d**, which was converted to **2** with alkaline hydrolysis.

Compounds **3** and **5** were prepared as shown in Scheme 2. The Horner–Emmons reaction of phthalaldehyde with trimethylphosphonoacetate followed by catalytic hydrogenation afforded **12a**, which was converted to **3** by the sequential reactions: oxidation with manganese dioxide; Wittig reaction followed by acid treatment; coupling reaction with the allenylborane reagent generated from 2-octyne;[7] catalytic hydrogenation in the presence of Lindlar catalyst; alkaline hydrolysis. Compound **5** was prepared from **12c** by the following series of reactions: Horner–Emmons reaction; sodium borohydride reduction; alkaline hydrolysis.

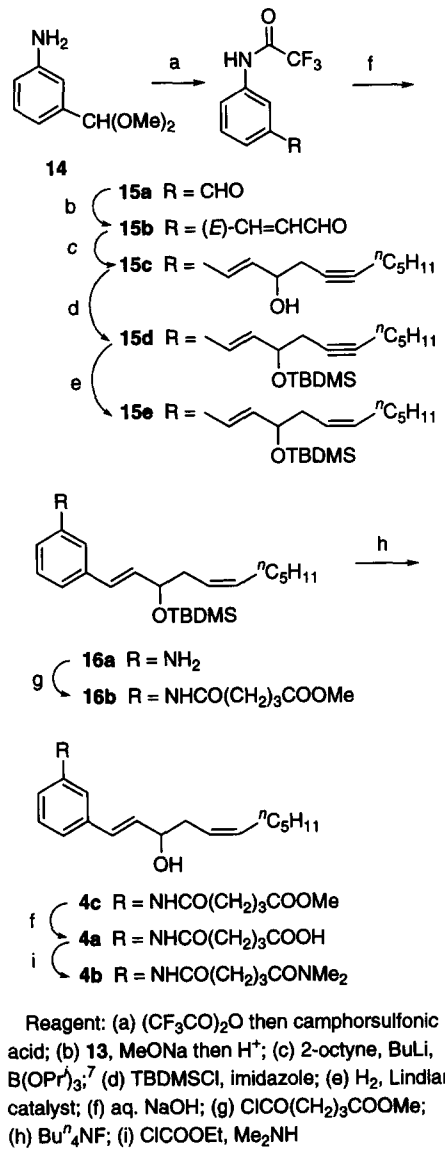
Compounds **4a–b** were prepared as shown in Scheme 3. Compound **14**, which was obtained by the catalytic hydrogenation of *m*-nitrobenzaldehyde dimethylacetal, was converted to **15e** by the sequential reactions: Acylation with trifluoroacetic anhydride followed by acidic deprotection; Wittig reaction followed by acidic deprotection; coupling reaction with the allenylborane reagent generated from 2-octyne;[7] protection of the formed hydroxyl function with TBDMS group; catalytic hydrogenation in the presence of Lindlar catalyst. The removal of the trifluoroacetyl group with alkaline hydrolysis afforded **16a**, which was acylated with 4-methoxycarbonylbutanoyl chloride to give **16b**. The deprotection of **16b** with *tetra*-butylammonium fluoride afforded **4c**, which was converted to **4a** by alkaline hydrolysis. Dimethylamide **4b** was prepared from **4a** by amide formation with dimethylamine.

The synthesis of amide analogues **6a–b** is shown in Scheme 4. Compound **17a**, which was obtained from the *N*-alkylation of *m*-aminophenol with acid chloride, was converted to **17b** by *O*-alkylation with the methanesulfonate of 5-tetrahydropyranyloxypentanol. The alkaline hydrolysis of **17b** afforded **19a**, which was converted to **19b** by amide formation with dimethylamine. The deprotection of **19b** gave an alcohol, **21a**. The Swern oxidation of **21a** followed by a Horner–Emmons



Reagent: (a) MnO_2; (b) **13**, NaOMe then H^+; (c) 2-octyne, BuLi, $B(OPr^i)_3$;[7] (d) H_2, Lindlar catalyst; (e) aq. NaOH; (f) $(MeO)_2P(O)CH_2CO$-$^nC_8H_{17}$, NaH; (g) $NaBH_4$

Scheme 2. Synthesis of compounds **3** and **5**.



Reagent: (a) $(CF_3CO)_2O$ then camphorsulfonic acid; (b) **13**, MeONa then H^+; (c) 2-octyne, BuLi, $B(OPr^i)_3$;[7] (d) TBDMSCl, imidazole; (e) H_2, Lindlar catalyst; (f) aq. NaOH; (g) $ClCO(CH_2)_3COOMe$; (h) Bu^n_4NF; (i) ClCOOEt, Me_2NH

Scheme 3. Synthesis of compounds **4b–c**.

reaction provided **21c**, which was converted to **6a**. The *O*-alkylation of **18a** provided a cyclized product, **18b**, in which the intramolecular cyclization of the amide ester chain occurred.[8] Compound **18b** was converted to **6b** with the same procedure as that applied to the conversion of **17b** to **6a**.

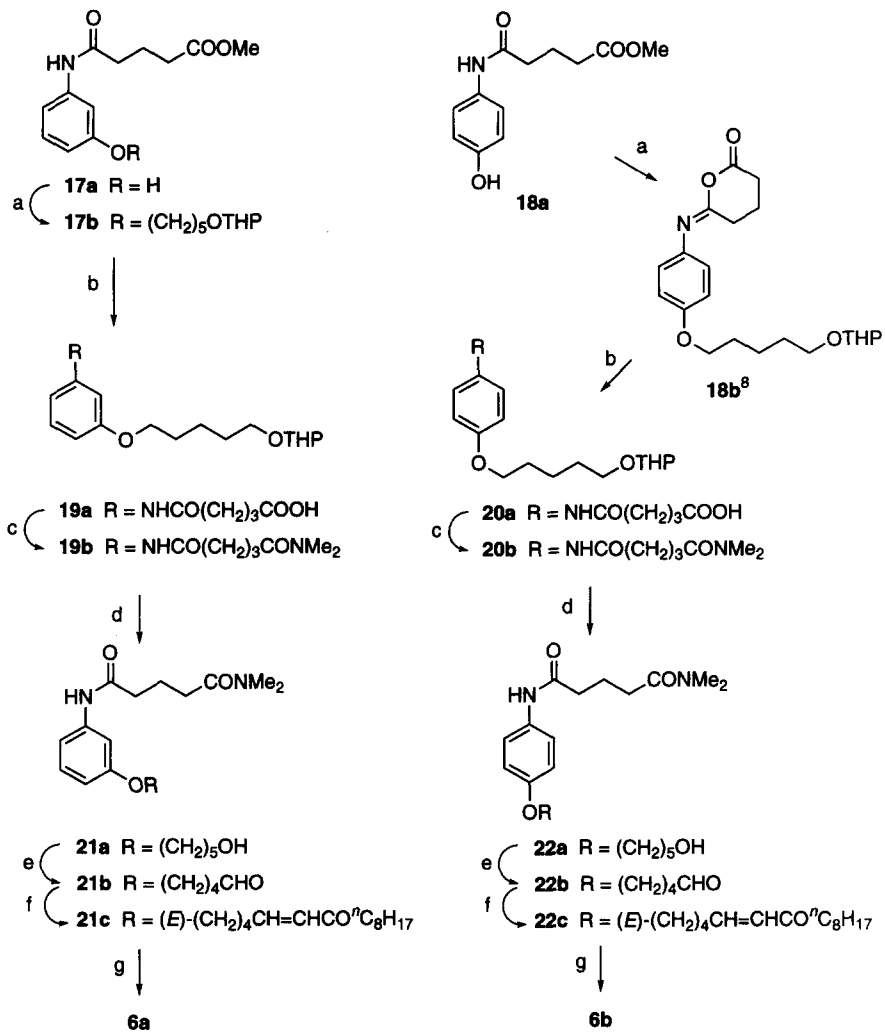
Compound **7** was prepared as shown in Scheme 5. The alkylation of ethyl-3-(2-hydroxyphenyl)propionate with 5-tetrahydropyranyloxypentyl bromide in the presence of sodium hydride followed by acidic deprotection afforded **23a**. The Swern oxidation of **23a** followed by a Horner–Emmons reaction provided **23c**, which was converted to **23d** with sodium borohydride reduction. The alkaline hydrolysis of **23d** afforded **7**.

Compounds **28a–e** were prepared as shown in Scheme 6. The catalytic hydrogenation of **24** followed by acylation gave **25**, which was converted to **28a–e** by the same reaction sequences as those described in the synthesis of **6a–b** (Scheme 4).

Compound **29a**[9] was prepared by the sequential procedures: Horner–Emmons reaction of 2-hydroxy-5-nitrobenzaldehyde with *t*-butyl-dimethylphosphonoacetate in the presence of sodium hydride; catalytic hydrogenation; *N*-acylation with methyl-4-chloroformylbutyrate; alkaline hydrolysis of methyl ester; amide formation with dimethylamine. As shown in Scheme 7, compound **29a** was converted to **29b** by treatment with HCOOH. Compound **32** was prepared from **29a** according to the same procedure as that described in the synthesis of **6a–b** (Scheme 4).

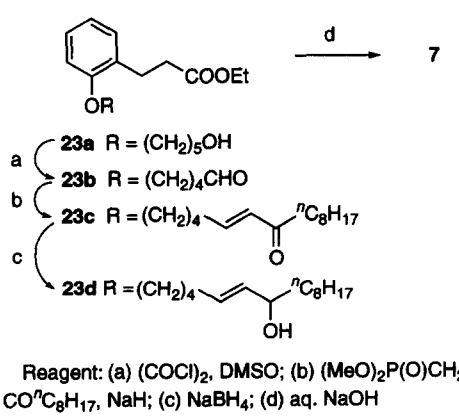
Compounds **33a–d**[10] were prepared by the alkylation of 6-hydroxy-3,4-dihydrocoumarin with the corresponding alkyl bromides followed by ethanolysis. As shown in Scheme 8, compounds **33a–d** were converted to **38a–d**, respectively, according to the same procedure as that described in the synthesis of the amide analogues **6a–b** (Scheme 4).

The synthesis of **46a–b** is shown in Scheme 9. Compound **39a**, which was prepared by the Friedel–Craft acylation of methyl-3-(2-methoxyphenyl)propionate, was converted to **40a** by the sequential reactions: sodium borohydride reduction; dehydration by heating; catalytic hydrogenation; demethylation with pyridinium hydrochloride. The esterification of **40a** with methanol



Scheme 4. Synthesis of compounds **6a–b**.

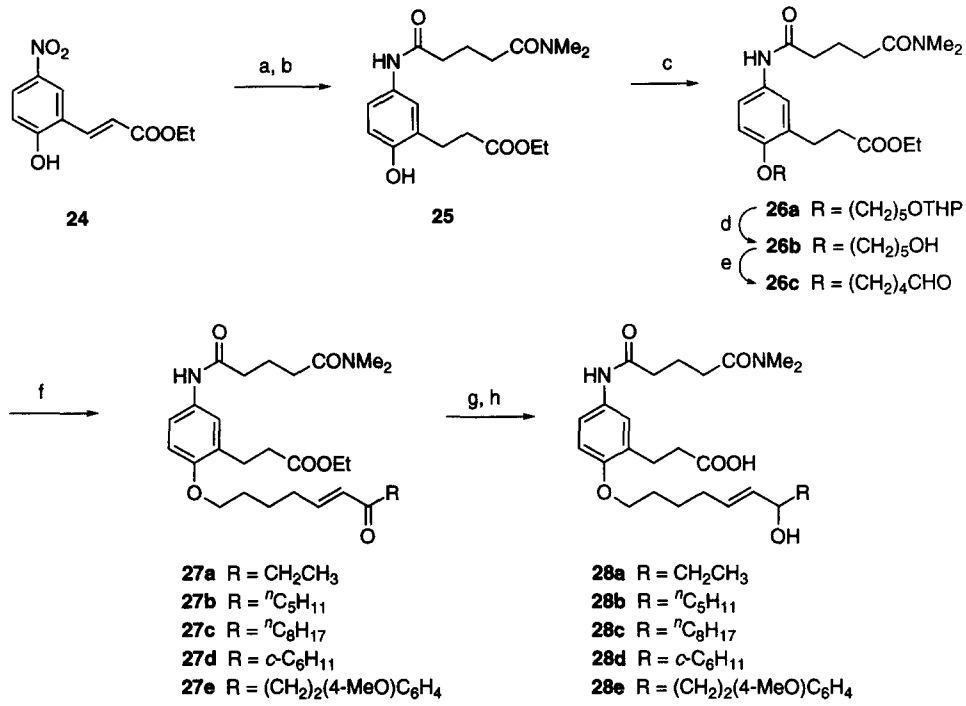
in the presence of sulfuric acid gave **40b**. Compound **40a** was converted to **40c** by the following sequential reactions: lactonization with *p*-toluenesulfonic acid; amide formation with dimethylamine; alkaline hydrolysis followed by esterification. Compounds **40b** and **40c** were converted to **46a** and **46b**, respectively, according to the same procedure as that described in the synthesis of **6a–b** (Scheme 4).



Scheme 5. Synthesis of compound **7**.

Compounds **52a–b** and **53** were prepared as shown in Scheme 10. Compounds **47a** and **b**,[11] which were obtained by the alkylation of 5-hydroxy-3,4-dihydrocoumarin with the corresponding alkyl bromides followed by ethanolysis, were converted to **52a** and **52b**, respectively, by the conventional method. The catalytic hydrogenation of **52a** in the presence of palladium carbon afforded **53**.

The synthesis of the optically active analogues (−)-**52a** and (+)-**52a** is shown in Scheme 11. The enantioselective reduction of **50a** with borane in the presence of Corey's chiral oxazaborolidine catalysts[12] afforded (*R*)-**51a** and (*S*)-**51a**, respectively. The alkaline hydrolysis of (*R*)-**51a** and (*S*)-**51a** afforded (*R*)-**52a** and (*S*)-**52a**, respectively. The enantiomeric excess of each was



Reagent: (a) H_2, Pd-C; (b) $HOOC(CH_2)_3CONMe_2$, Ph_3P, 2,2'-dipyridyl disulfide; (c) $Br(CH_2)_5OTHP$, NaH; (d) *p*-TsOH, MeOH; (e) $(COCl)_2$, DMSO; (f) $(MeO)_2POCH_2COR$, NaH; (g) $NaBH_4$; (h) aq. NaOH

Scheme 6. Synthesis of compounds **28a–e**.

judged to be about 80%, as measured by ^{19}F NMR analysis of the Mosher esters.[13] The enantiomeric assignment was based on a literature analogy[12,13] and supported by the receptor binding activity observed for this enantiomer in comparison with (DL)-**52a**.

The synthesis of compound **57** is shown in Scheme 12. The alkylation of ethyl-3-(2-hydroxyphenyl)propionate with **55**[14] in the presence of sodium hydride afforded **56**. The alkaline hydrolysis of **56** provided **57**.

Results and discussion

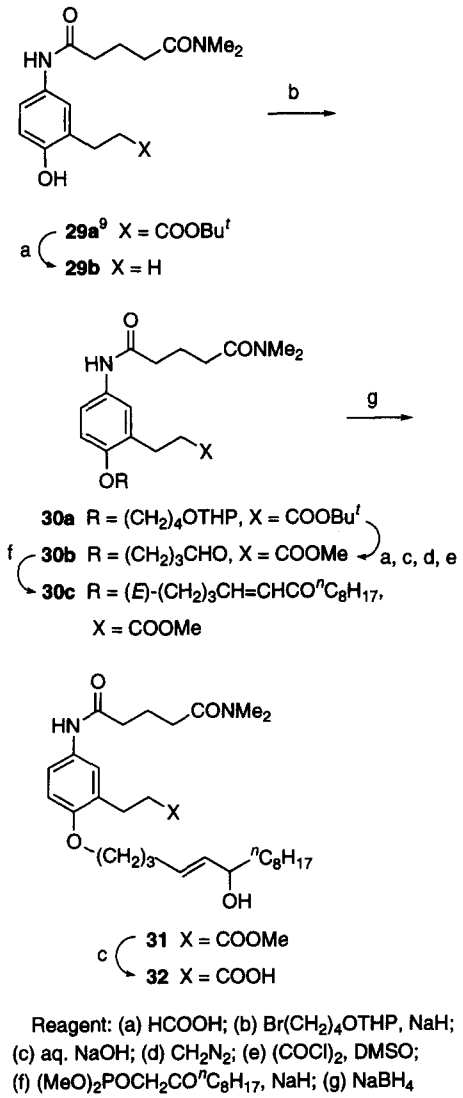
The LTB_4 receptor binding assay data for the test compounds are shown in Tables 1–3. The receptor binding studies described in this paper were done using intact human neutrophils.[15] IC_{50} values were determined by measuring the ability of the compounds to compete with [^{3}H]LTB_4 for binding to the receptor. All compounds were evaluated in a secondary intact human neutrophil functional assay for agonist/antagonist activity.[15] This assay monitors the LTB_4- or test compound-mediated aggregation, utilizing the change in light transmission. During this investigation, a number of compounds possessing agonist activity and a unique structural lead to a LTB_4 receptor antagonist (**57**) were discovered.

Our initial strategy was focused on the use of LTB_4 as a template to design structurally rigid analogues of LTB_4. This process was complicated by the lack of the conformational information related to LTB_4 at the receptor. The molecular conformation of LTB_4 is reported to be ambiguous except for the planar structure of the conjugated triene framework.[16] We selected the four conformers A, B, C and D (Chart 1) as the plausible conformers.

The partial fixation of these four conformers was efficiently accomplished by the introduction of a benzene nucleus into each conformer. Joining C-7–C-9 of A or B into an aromatic ring system led to the molecular design of a series of our initial target structures, **2**, **4a–b** and **6a–b**. Joining C-4–C-9 of the conformers C or D into a benzene nucleus produced another series of target molecules, **3**, **5** and **7**. The initial target compounds **2** and **3** showed less than 50% inhibition of [^{3}H]LTB_4 binding to the receptor at 3 μM.

However, the moderate receptor binding affinity of the initial target compounds **4a–b** and **5** provided support for our strategic approach. Compound **7**, in which the three-dimensional distance between the carboxylic acid group and the allylic alcohol group is close to that of LTB_4, demonstrated a significantly increased binding affinity, while **6a–b** showed less than 50% inhibition of [^{3}H]LTB_4 binding to the receptor at 1 μM.

These structure–activity-relationship (SAR) results can be explained by molecular modeling studies (Figure 1). The goal of this computation was to discover the



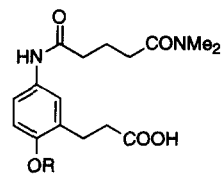
Scheme 7. Synthesis of compound **32**.

common conformation of LTB_4 and compound **7**, and to elucidate the increased activity of **7** relative to the less potent analogues **2–6**. As illustrated in Figure 1, both LTB_4 and **7** fit the alignment reasonably well. The best overlap of the oxygens and five carbons C1, C2, C10–12 (LTB_4 numbering) was obtained from one of the reasonable conformations of LTB_4 and **7**.

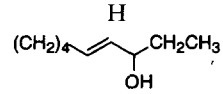
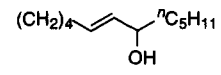
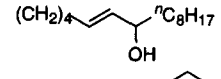
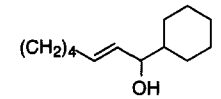
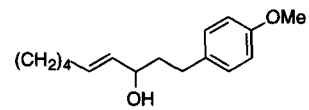
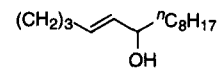
Based on these results, the distance between the carboxylic acid and the allylic alcohol group was estimated to be an essential factor for the LTB_4 receptor binding of the synthetic analogues.

We started our molecular design with a partial fixation of the triene moiety of LTB_4. As a result, **2** and **3**, designed based on the initially proposed hypothesis, were not active at 3.0 μM, while **7** demonstrated a significantly increased activity comparing to **2–6**. But the computational analysis revealed that **7** showed a good overlapping with LTB_4 in a different manner from our initial expectation. Although an acid chain and a

Table 1. 1,2,5-Trisubstituted benzene analogues: inhibition of [^{3}H]LTB_4 binding to human neutrophils



I

Compound	R	IC_{50} μM[a]
29b	H	>3.0
28a		>3.0
28b		0.30
28c		0.020[b]
28d		0.35
28e		0.70
32		0.70

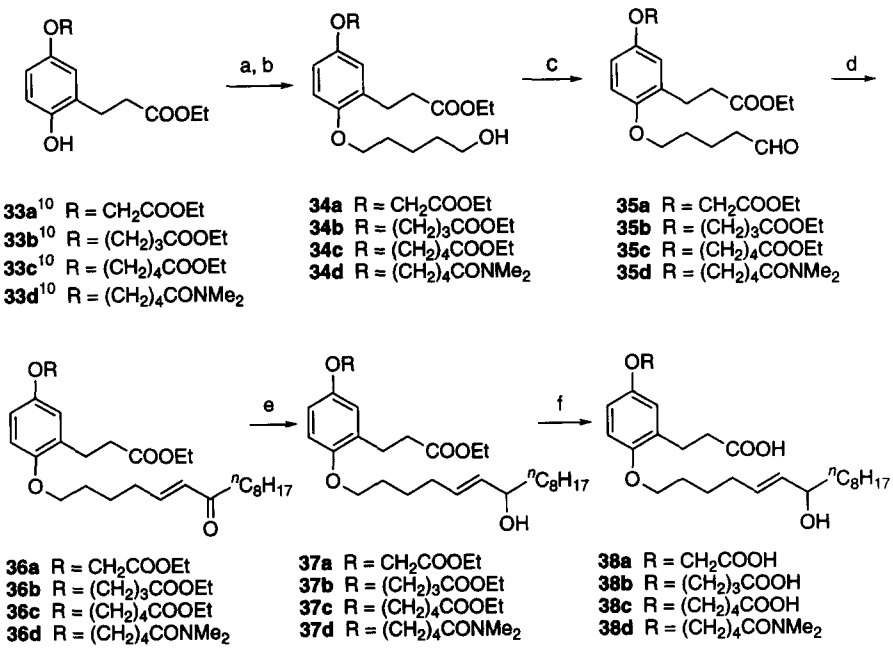
[a]The agonist activity of all of the compounds was confirmed at 10 μM.
[b]Effect on aggregation of human neutrophils: **28c** (EC_{50} = 0.013 μM).

lipid chain of **7** showed good overlapping with LTB_4, the benzene nucleus did not (Figure 1). The benzene nucleus was considered to play a role of mainly regulating a direction of both the chains. In such a meaning, our initial hypothesis of the molecular design had to be revised at this stage.

The binding affinity observed with **5** and **7** is consistent with the report that the 'C-5' deoxy analogue of LTB_4 retains high-affinity LTB_4 receptor binding;[17] the 'C-5' hydroxyl group is not a requirement for receptor binding. Compounds **4a–b**, **5** and **7** demonstrated agonist activity in the human neutrophil LTB_4 functional assay.

Since the goal of this investigation was to identify LTB_4 receptor antagonists, structural modifications of **4a–b** and **7** were made in an attempt to eliminate the LTB_4 agonist activity while maintaining or enhancing the LTB_4 receptor binding affinity.

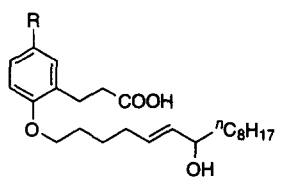
The structural hybridization of **6b** and **7** led to the discovery of a series of compounds which are 1,2,5-trisubstituted benzene derivatives. This modification produced a remarkable increase in binding affinity, as shown in Table 1. To identify the best lipophilic side chain, compounds **28a–e**, **29b** and **32** were prepared. The length of the lipid tail was found to be very sensitive



Scheme 8. Synthesis of compounds **38a–d**.

to the receptor affinity. Among the compounds synthesized, the lipid tail of **28c** was identified as the best. Based on the comparison of the binding affinities of **28c** and **32**, the tetramethylene moiety $-(CH_2)_4-$ was more tolerable to the LTB_4 receptor than trimethylene moiety $-(CH_2)_3-$ as the methylene length between the ether oxygen and the allylic alcohol moiety. Based on the result of the binding assay of **28a–e**, the '(14Z)' double bond of LTB_4 is not a requirement of the receptor affinity. As a result, the *n*-octyl group was identified as the best lipid tail among those synthesized.

Table 2. 1,2,5-Trisubstituted benzene analogues: inhibition of [^{3}H]LTB_4 binding to human neutrophils



II

Compound	R	IC_{50} μM[a]
38a	OCH_2COOH	0.15
38b	$O(CH_2)_3COOH$	0.025
38c	$O(CH_2)_4COOH$	0.020[b]
38d	$O(CH_2)_4CONMe_2$	0.040[b]
46a	$(CH_2)_4COOH$	0.022
46b	$(CH_2)_4CONMe_2$	0.070

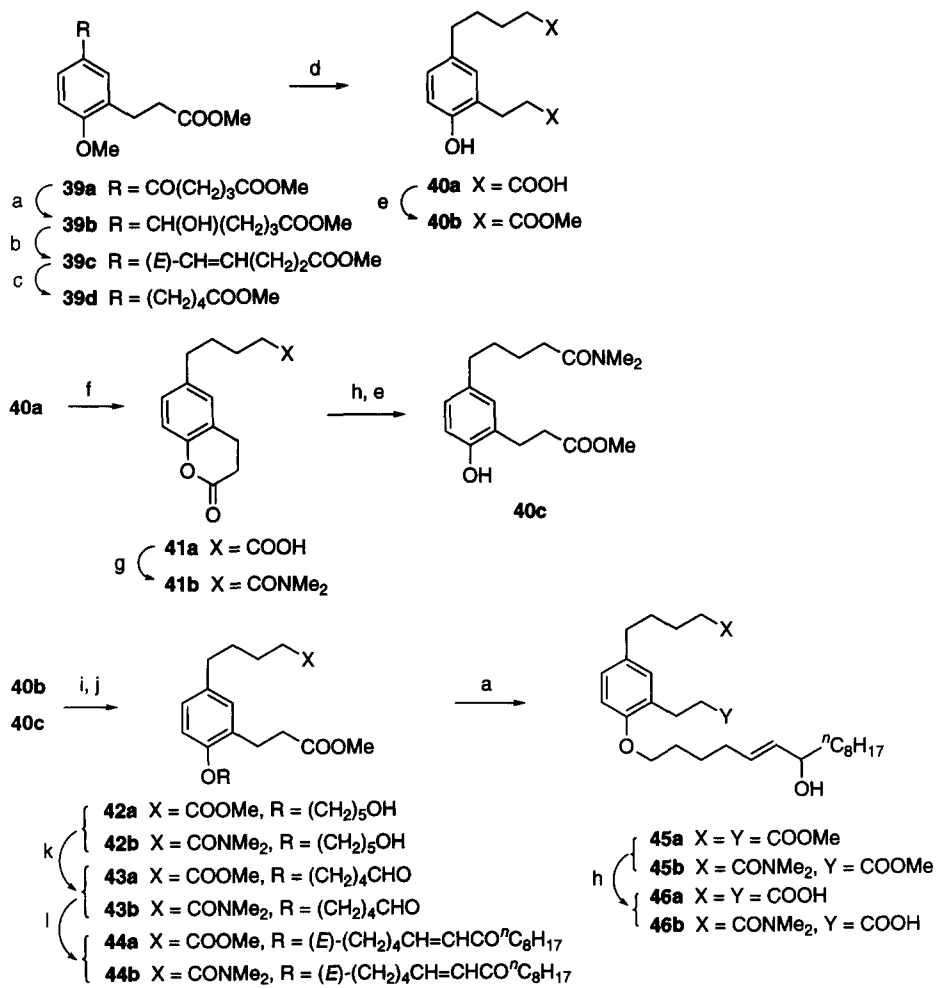
[a]The agonist activity of all of the compounds was confirmed at 10 μM.
[b] Effect on aggregation of human neutrophils: **38c** (EC_{50} = 0.66 μM), **38d** (EC_{50} = 1.2 μM).

Compound **29b**, with no lipid chain, did not show inhibitory activity at 3 μM.

The conversion of the amide chain attached to position 5 of the benzene nucleus of general formula II to ether and to the methylene moiety provided **38a–d** and **46a–b** (Table 2), respectively. Based on the result of the binding assay of **38a–c**, the chain length between the ether-oxygen and the carboxylic acid group was estimated to be $-(CH_2)_3-$ ~ $-(CH_2)_4-$ as shown in **38b–c**. The replacement of the ether-oxygen of **38b** with methylene moiety provided **46a**, with the maintenance of the potent receptor affinity. As illustrated in **38d** and **46b**, the dimethylamide derivatives demonstrated slightly less potent LTB_4 receptor affinity than the corresponding carboxylic acid derivatives **38c** and **46a**.

Shifting the ether chain on position 5 of general formula II to position 6 provided the 1,2,6-trisubstituted benzene analogues **52a–b** with maintenance of the potent binding affinity (Table 3). Saturation of the double bond of the allylic alcohol moiety of **52a** afforded **53**, giving complete loss of the receptor affinity at 3 μM.

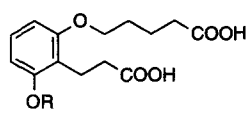
Since all of the test compounds were enantiomeric mixtures, it was of interest to determine whether the absolute configuration of the hydroxyl group would have an effect on either the potency or the agonist activity. The 12-deoxy-LTB_4 analogue is 300 times less potent than LTB_4, while the 5-deoxy analogue of LTB_4 is 10 times less potent than LTB_4.[17] Therefore, we decided to prepare (−)-**52a** with the (*R*) absolute



Reagent: (a) $NaBH_4$; (b) heat; (c) H_2, Pd-C; (d) pyridine hydrochloride; (e) MeOH, H_2SO_4; (f) *p*-TsOH; (g) ClCOOEt, Me_2NH; (h) aq. NaOH; (i) $Br(CH_2)_5OTHP$, NaH; (j) *p*-TsOH, MeOH; (k) $(COCl)_2$, DMSO; (l) $(MeO)_2P(O)CH_2CO^nC_8H_{17}$, NaH

Scheme 9. Synthesis of compounds **46a–b**.

Table 3. 1,2,6-Trisubstituted benzene analogues: inhibition of [^{3}H]LTB_4 binding to human neutrophils



III

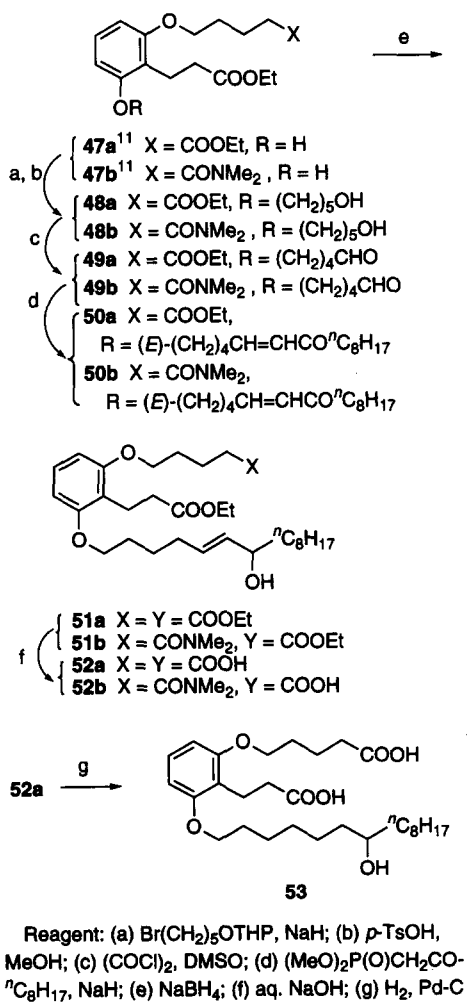
Compound	R		IC_{50} μM[a]
52a	$(CH_2)_4$ $^nC_8H_{17}$ OH		0.020
53	$(CH_2)_6$ $^nC_8H_{17}$ OH		>3.0
52b	(Chart 3)		0.018
(−)-**52a**[b]	$(CH_2)_4$ $^nC_8H_{17}$ OH	(*R*)	0.020
(+)-**52a**[b]	$(CH_2)_4$ $^nC_8H_{17}$ OH	(*S*)	0.065

[a]The agonist activity of all of the compounds was confirmed at 10 μM.
[b]Absolute configuration was tentatively assigned based on the reported information.[12, 13]

configuration, since this enantiomer would correspond to the C-12 hydroxyl configuration of natural LTB_4. Compound (−)-**52a** with the (*R*) configuration was found to have approximately 3 times more potency in receptor binding than that of (+)-**52a** with (*S*) configuration. Unfortunately, both (−)-**52a** and (+)-**52a** were found to be an agonist in the human neutrophil functional assay.

During the course of this work, Sumitomo's group reported the synthesis of the LTB_4 receptor antagonist SM-9064 (**8**, Chart 3),[18] which contained 4-methoxyphenyl moiety as a lipid tail. Variation of the lipid tail was investigated to determine whether changes in this portion of the molecule would have an effect on receptor binding or functional activity. The replacement of the lipid tail of **7** with 4-methoxyphenyl moiety afforded **57**. This change did not diminish the LTB_4 binding affinity but did result in a reduction in agonist activity. Encouragingly, it did not demonstrate significant LTB_4 agonist activity in the human neutrophil functional assay at concentrations up to 30 μM. Thus,

Figure 1. Superposition of LTB_4 and 7. One of the local minima of each molecule was superposed based on eight atoms. The RMSD value was 0.47 Å.



Scheme 10. Synthesis of compounds **52a–b** and **53**.

57 represents the first LTB_4 receptor antagonist prepared in this series. Compound **57** provided a lead for further modification.

In summary, compounds **28c**, **38b–d**, **46a–b** and **52a–b** represent examples of novel structural leads with high affinity for human LTB_4 receptors. However, all of the compounds in this study except for **57** were found to be receptor agonists.

Since our goal was to identify novel LTB_4 receptor antagonists and to determine their potential as anti-

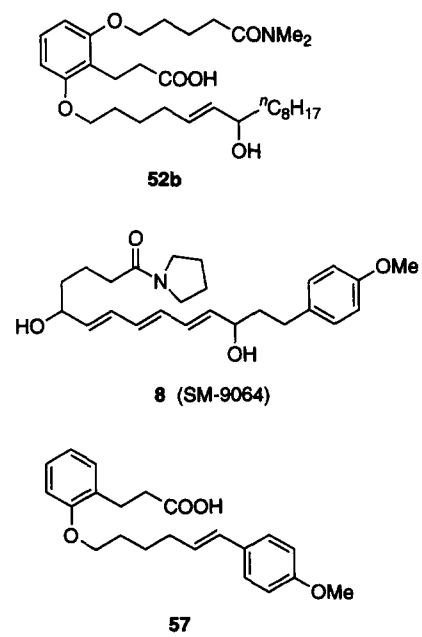
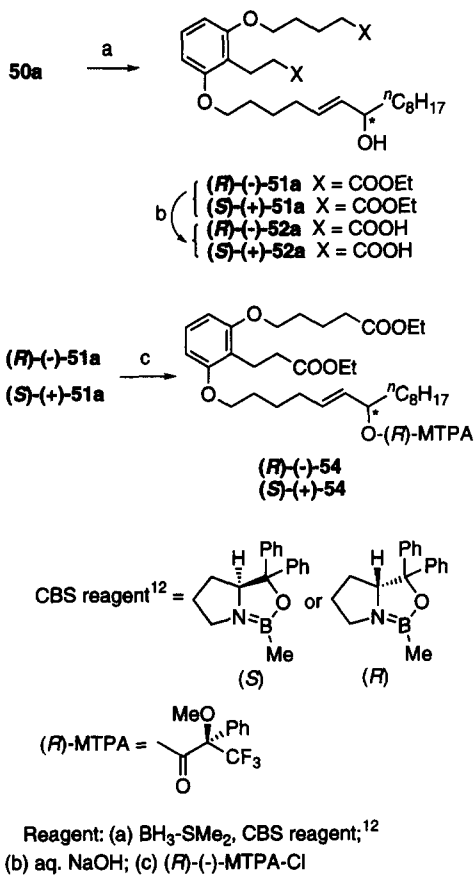
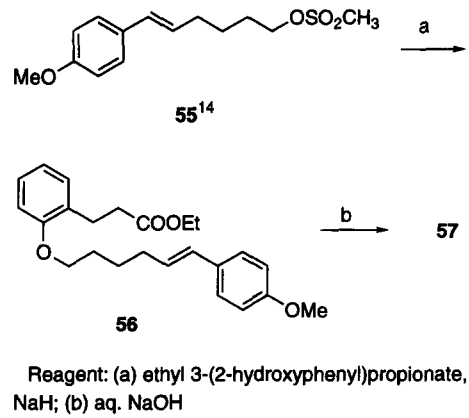


Chart 3.



Scheme 11. Synthesis of optically active allylic-alcohol derivatives (*R*)-(−)-52a and (*R*)-(+)-52a.



Scheme 12. Synthesis of compound **57**.

inflammatory agents, the agonist activity had to be deleted. As shown by compound **57**, structural modifications in the lipid tail of the molecules may be a viable starting point from which to design new synthetic targets. The results of these studies are reported in detail below.

Experimental

Chemistry

General directions. Melting points (mp) were taken on a Yanaco micro melting point apparatus and are uncorrected. All proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained with a JEOL FX-90-Q or a Varian VXR-200 spectrometer. Infrared spectra (IR) were recorded on a Perkin–Elmer 1760X FT-IR spectrometer with neat or KBr disks. Mass spectral data (MS) were determined with a JEOL JMS-DX303HF mass spectrometer. High-resolution mass spectra were within +3 μMu of the theoretical values. All solvents were freshly distilled prior to use.

Preparation of 1-*tert*-Butyldimethylsilyloxymethyl-3-(3-tetrahydropyranyloxy-(1*E*)-propenyl)benzene (9e). To a stirred suspension of sodium hydride (76 mmol) in THF (20 mL) was slowly added triethyl phosphonoacetate (18.3 g, 82 mmol) in THF (30 mL) at 0 °C under an argon atmosphere. After the initial gas evolution had subsided, the mixture was stirred at 25 °C for 30 min. A solution of **9b** (15.8 g, 63 mmol) in THF (50 mL) was added, and the mixture was allowed to warm to 40 °C. After stirring at 25 °C for 1 h, the reaction mixture was acidified with glacial acetic acid and stirring was continued for an additional 10 min. The precipitates were removed by filtration through a silica gel mat and washed with AcOEt. The combined filtrates were evaporated in vacuo. Purification of the residue by column chromatography on silica gel (hexane:AcOEt, 95:5) gave 19.2 g (95%) of ethyl-3-[3-(*tert*-butyldimethylsilyloxymethyl)phenyl]-(*E*)-propenoate **9c** as a colorless oil. R_f 0.40 (hexane:AcOEt, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.95 (s, 9H), 1.35 (t, J = 7 Hz, 3H), 4.30 (q, J = 7 Hz, 2H), 4.80 (s, 2H), 6.45 (d, J = 16 Hz, 1H), 7.30-7.60 (m, 4H), 7.75 (d, J = 16 Hz, 1H).

Diisobutylaluminium hydride (75 mL of 1.76 M toluene solution, 0.13 mol) was added dropwise to a solution of **9c** (19.2 g, 60 mmol) in toluene (100 mL) at -60 °C under argon. After stirring at −70 °C for 10 min, the mixture was warmed to 0 °C and stirred for 15 min. The reaction mixture was cooled again to −70 °C, treated with MeOH (5.0 mL), and stirred for 10 min at −70 °C. Water (30 mL) was then added dropwise to the mixture at −50 to −70 °C, and the mixture was stirred at 0 °C to 25 °C for 2 h. The precipitates were removed by filtration and washed with AcOEt (200 mL). The combined filtrates were concentrated in vacuo to give 16.1 g (97%) of 3-[3-(*tert*-butyldimethylsilyloxymethyl)-phenyl]-(2*E*)-propenol **9d** as a colorless oil. R_f 0.35 (AcOEt:hexane, 1:2); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.95 (s, 9H), 4.35 (t, J = 7 Hz, 2H), 4.80 (s, 2H), 6.40 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.20–7.50 (4H, m).

To a stirred solution of **9d** (16.1 g, 58 mmol) in CH_2Cl_2 (100 mL) was added 3,4-dihydro-2*H*-pyran (6.4 mL, 70 mmol) and DL-camphorsulfonic acid (10 mg). After stirring at 25 °C for 1h, the mixture was treated with saturated aq. $NaHCO_3$ (20 mL). The organic layer was washed with brine and dried over $MgSO_4$. Evaporation

of the solvent gave the crude **9e** as a colorless oil (21.0 g, quantitative yield), which was used for further transformations without purification. R_f 0.60 (hexane:AcOEt, 4:1); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 1.00 (s, 9H), 3.40–4.10 (m, 2H), 4.35 (m, 2H), 4.75 (s, 3H), 6.35 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.20–7.50 (m, 4H).

Preparation of methyl-3-(3-Tetrahydropyranyloxy-1*E*-propenyl)phenylacetate (10d). 2 N Sodium hydroxide (0.12 mol) was added to a solution of **9e** (21 g, 58 mmol) in EtOH (100 mL). After refluxing for 2 h, the mixture was concentrated in vacuo to remove EtOH. To the residue were added AcOEt (200 mL) and water (100 mL). The organic layer was separated and washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt:hexane, 1:1) to give 13.0 g (90%) of 3-(3-tetrahydropyranyloxy-1*E*-propenyl)benzylalcohol **10a** as a colorless oil. R_f 0.40 (AcOEt:hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 3.40–4.10 (m, 2H), 4.35 (m, 2H), 4.70 (s, 1H), 4.75 (s, 2H), 6.35 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.20–7.50 (m, 4H).

Methanesulfonyl chloride (4.4 mL, 57 mmol) was added dropwise to a solution of **10a** (12.9 g, 52 mmol) and triethylamine (11.0 mL, 78 mmol) in CH_2Cl_2 (100 mL) at −20 °C. After stirring at 0 °C for 30 min, the mixture was poured into 1 N HCl (100 mL). The resulting mixture was extracted with CH_2Cl_2 (200 mL). The CH_2Cl_2 layer was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated in vacuo to give 16.2 g (96%) of 3-(3-tetrahydropyranyloxy-1*E*-propenyl)benzylalcohol methanesulfonate **10b** as a pale yellow oil. R_f 0.20 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 2.95 (s, 3H), 3.40–4.10 (m, 2H), 4.35 (m, 2H), 4.75 (m, 1H), 5.30 (s, 2H), 6.40 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.20–7.60 (m, 4H).

Sodium cyanide (2.7 g, 55 mmol) was added to a solution of **10b** (16.2 g, 50 mmol) in dimethylsulfoxide (70 mL). After stirring at 60 °C for 1 h, the mixture was poured into cold water (200 mL). The resulting mixture was extracted with 50% Et_2O in AcOEt (200 mL × 2). The combined extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 4:1) to give 7.0 g (55%) of 3-(3-tetrahydropyranyloxy-1*E*-propenyl)phenylacetonitrile **10c** as a pale yellow oil. R_f 0.40 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 3.40–4.10 (m, 2H), 3.80 (s, 2H), 4.35 (m, 2H), 4.75 (m, 1H), 6.35 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.15–7.55 (m, 4H).

Sodium hydroxide (2 N, 80 mmol) was added to a solution of **10c** (7.0 g, 27 mmol) in EtOH (60 mL). After refluxing for 10 h, the mixture was concentrated in vacuo to remove EtOH. The residue was diluted with water (100 mL), and the resulting mixture was extracted with Et_2O (100 mL). The aqueous layer was acidified by the addition of 1 N HCl (90 mL), and the resulting mixture was extracted with AcOEt (100 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and filtrated. The filtrate was treated with the diazomethane. The resulting mixture was then evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 4:1) to give 6.28 g (79%) of **10d** as a colorless oil. R_f 0.50 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 2H), 3.40–4.10 (m, 2H), 3.70 (s, 3H), 4.35 (m, 2H), 4.75 (m, 1H), 6.35 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.10–7.40 (m, 4H); MS (EI) m/z 290 (M^+).

Preparation of methyl-6-methoxycarbonyl-5-oxo-6-[3-(3-tetrahydropyranyloxy-1*E*-propenyl)phenyl]hexanoate (10e). *n*-BuLi (21 mmol) was added dropwise to a solution of diisopropylamine (22 mmol) in THF (30 mL) at −70 °C, and the mixture was warmed to 0 °C. After stirring at 0 °C for 10 min, the mixture was cooled again to −70 °C. A solution of **10d** (2.9 g, 10 mmol) in THF (20 mL) was added dropwise to the above solution at −70 °C, and the mixture was stirred for 1 h. To the resulting mixture was added dropwise a solution of methyl-4-chloroformylbutanate (2.5 g, 15 mmol) in THF (15 mL) at −70 °C. After stirring at −70 °C for 1 h, the mixture was poured into a mixture of crushed ice (50 g) and 1 N HCl (50 mL). The resulting mixture was extracted with AcOEt (100 mL). The extract was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 3:1) to give 1.93 g (37%) of **10e** as a pale yellow oil. R_f 0.25 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 2.30 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 3.40–4.10 (m, 2H), 3.65 (s, 3H), 3.80 (s, 3H), 4.35 (m, 2H), 4.75 (m, 2H), 6.35 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.15–7.50 (m, 4H); MS (EI) m/z 386 (M^+–MeOH).

Preparation of methyl-5-oxo-6-[3-(3-tetrahydropyranyloxy-1*E*-propenyl)phenyl]hexanoate (10f). A mixture of **10e** (1.93 g, 4.6 mmol), water (0.5 mL) and hexamethylphosphoramide (9.5 mL) was heated at 190 °C for 15 min. The mixture was then poured into a mixture of crushed ice (10 g) and 1 N HCl (10 mL). The resulting mixture was extracted with 50% Et_2O in AcOEt (50 mL × 2). The combined extracts were washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 2:1) to give 1.49 g (90%) of **10f** as a colorless oil. R_f 0.25 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 2.30 (t, J = 7 Hz, 2H), 2.55 (t, J = 7 Hz, 2H), 3.40–4.10 (m, 2H), 3.70 (s, 5H), 4.35 (m, 2H), 4.75 (m, 1H), 6.35 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.00–7.50 (m, 4H); MS (EI) m/z 360 (M^+).

Preparation of methyl-5-acetoxy-6-[3-(3-hydroxy-1*E*-propenyl)phenyl]hexanoate (11a). A mixture of **10g** (1.5 g, 4.1 mmol), pyridine (10 mL) and acetic anhydride (3.9 mL, 41 mmol) was stirred at 50 °C for 1 h. The mixture was then concentrated under reduced pressure (ca. 0.1 mmHg) to give 1.66 g (quantitative yield) of 5-acetoxy-6-[3-(3-tetrahydropyranyloxy-1*E*-

propenyl)phenyl]hexanoate **10h** as a pale yellow oil. R_f 0.40 (AcOEt:hexane, 1:1); MS (EI) *m/z* 344 (M^+–AcOH).

A mixture of **10h** (1.66 g, 4.10 mmol), 65% aqueous acetic acid (10 mL) and THF (2.0 mL) was stirred at 70 °C for 1.5 h. The mixture was then concentrated in vacuo. The residue was diluted with water (20 mL), and the resulting mixture was extracted with AcOEt (100 mL). The organic layer was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated in vacuo. Purification of the residue by column chromatography on silica gel (AcOEt:hexane, 3:2) afforded 1.11 g (84% from **10g**) of **11a** as a colorless oil. R_f 0.20 (AcOEt:hexane, 1:1); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.30 (m, 2H), 2.85 (m, 2H), 3.70 (s, 3H), 4.35 (t, *J* = 7 Hz, 2H), 5.10 (m, 1H), 6.35 (dt, *J* = 16 Hz and 7 Hz, 1H), 6.70 (d, *J* = 16 Hz, 1H), 7.00–7.50 (m, 4H); MS (EI) *m/z* 320 (M^+).

General procedure A

Preparation of methyl-5-acetoxy-6-[3-(2-formyl-*E*-ethenyl)phenyl]hexanoate (11b). To a solution of oxalyl chloride (0.44 mL, 5.20 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise a solution of dimethylsulfoxide (0.76 mL, 10.8 mol) in CH_2Cl_2 (5.0 mL) at −50 °C under an argon atmosphere. The mixture was stirred at −70 °C for 20 min. To the resulting mixture was added dropwise a solution of **11a** (1.11 g, 3.47 mmol) in CH_2Cl_2 (10 mL) at −60 °C, and then the mixture was stirred at −70 °C for 30 min. Triethylamine (3.6 mL, 26 mmol) was added dropwise, and the reaction mixture was allowed to warm to 0 °C with stirring. After stirring at 0 °C for 5 min, the mixture was poured into 2 N HCl (20 mL). The resulting mixture was extracted with CH_2Cl_2 (100 mL). The extract was washed successively with saturated aq. $NaHCO_3$, brine, and dried over $MgSO_4$. Evaporation of the solvent gave 1.08 g (98%) of **11b** as a colorless oil, which was used for further transformations without purification. R_f 0.40 (AcOEt:hexane, 1:1); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.90 (d, *J* = 7 Hz, 2H), 3.70 (s, 3H), 5.10 (m, 1H), 6.75 (dd, *J* = 16 Hz and 7 Hz, 1H), 7.20–7.70 (m, 5H), 9.80 (s, 1H); MS (EI) *m/z* 258 (M^+–AcOH).

The following compounds were prepared from the indicated starting materials by using the same procedure as that described above.

3-(*tert*-Butyldimethylsilyloxymethyl)benzaldehyde (9b) from 9a. Quantitative yield; pale yellow oil; R_f 0.40 (hexane:AcOEt, 9:1); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.95 (s, 9H), 4.80 (s, 2H), 7.20–8.00 (m, 4H), 10.05 (1H, s).

***N,N*-Dimethyl-4-[4-(4-formylbutoxy)phenylaminocarbonyl]butanamide (22b) from 22a.** 61% yield; white solid (from AcOEt:hexane, 1:1); mp 86–88 °C; R_f 0.20 (AcOEt:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.05 (m, 2H), 2.50 (m, 6H), 3.00 (s, 3H), 3.05 (s, 3H), 3.95 (m, 2H), 6.80 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 8 Hz, 2H), 8.20 (s, 1H), 9.80 (t, *J* = 2 Hz, 1H); IR (KBr) 3311, 1724, 1683, 1633, 1511, 1411, 1223 cm^{-1}; MS (EI) *m/z* 334 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(4-formylbutoxy)phenyl]propanoate (26c) from 26b. Quantitative yield; pale yellow oil; R_f 0.30 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7 Hz, 3H), 1.80 (m, 4H), 2.05 (m, 2H), 2.35–2.65 (m, 8H), 2.90 (t, *J* = 7 Hz, 2H), 2.98 (s, 3H), 3.05 (s, 3H), 3.95 (m, 2H), 4.12 (q, *J* = 7 Hz, 2H), 6.75 (d, *J* = 8 Hz, 1H), 7.27 (d, *J* = 2 Hz, 1H), 7.40 (dd, *J* = 8 Hz and 2 Hz, 1H), 8.20 (s, 1H), 9.80 (t, *J* = 2 Hz, 1H); IR (neat) 3301, 2937, 1733, 1651, 1555, 1505, 1472, 1447, 1417, 1373, 1346, 1237, 1042 cm^{-1}; MS (EI) *m/z* 434 (M^+).

Ethyl-3-[5-(ethoxycarbonylmethoxy)-2-(4-formylbutoxy)-phenyl]propanoate (35a) from 34a. 69% yield; pale yellow oil; R_f 0.20 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7 Hz, 3H), 1.30 (t, *J* = 7 Hz, 3H), 1.82 (m, 4H), 2.55 (m, 4H), 2.90 (t, *J* = 7 Hz, 2H), 3.93 (m, 2H), 4.12 (q, *J* = 7 Hz, 2H), 4.27 (q, *J* = 7 Hz, 2H), 4.55 (s, 2H), 6.70 (m, 2H), 6.78 (d, *J* = 2 Hz, 1H), 9.80 (t, *J* = 2 Hz, 1H); MS (EI) *m/z* 380 (M^+).

Ethyl-4-[3-[2-(ethoxycarbonyl)ethyl]-4-(4-formylbutoxy)-phenoxy]butanoate (35b) from 34b. 84% yield; pale yellow oil; R_f 0.40 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7 Hz, 3H), 1.25 (t, *J* = 7 Hz, 3H), 1.82 (m, 4H), 2.07 (m, 2H), 2.40-2.65 (m, 6H), 2.88 (t, *J* = 7 Hz, 2H), 3.93 (m, 4H), 4.15 (m, 4H), 6.70 (m, 3H), 9.80 (t, *J* = 2 Hz, 1H); MS (EI) *m/z* 408 (M^+).

Ethyl-5-[3-[2-(ethoxycarbonyl)ethyl]-4-(4-formylbutoxy)-phenoxy]pentanoate (35c) from 34c. 66% yield; pale yellow oil; R_f 0.35 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 1.23 (m, 6H), 1.80 (m, 8H), 2.40 (m, 2H), 2.55 (m, 2H), 2.60 (t, *J* = 7 Hz, 2H), 2.90 (t, *J* = 7 Hz, 2H), 3.90 (m, 4H), 4.12 (m, 4H), 6.70 (m, 3H), 9.80 (t, *J* = 2 Hz, 1H); MS (EI) *m/z* 422 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butoxy]-2-(4-formylbutoxy)phenyl]propanoate (35d) from 34d. 79% yield; pale yellow oil; R_f 0.40 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7 Hz, 3H), 1.80 (m, 8H), 2.40 (m, 2H), 2.55 (m, 4H), 2.90 (t, *J* = 7 Hz, 2H), 2.97 (s, 3H), 3.00 (s, 3H), 3.90 (m, 4H), 4.12 (q, *J* = 7 Hz, 2H), 6.70 (m, 3H), 9.80 (t, *J* = 2 Hz, 1H); MS *m/z* 421 (M^+).

Ethyl-3-[2-[4-(dimethylaminocarbonyl)butoxy]-6-(4-formylbutoxy)phenyl]propanoate (49b) from 48b. 57% yield; pale yellow oil; R_f 0.40 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7 Hz, 3H), 1.80 (m, 8H), 2.40 (m, 4H), 2.50 (m, 2H), 2.97 (s, 3H), 3.00 (m, 2H), 3.01 (s, 3H), 3.96 (m, 4H), 4.12 (q, *J* = 7 Hz, 2H), 6.48 (d, *J* = 8 Hz, 1H), 6.50 (d, *J* = 8 Hz, 1H), 7.08 (t, *J* = 8 Hz, 1H), 9.80 (t, *J* = 2 Hz, 1H); MS (EI) *m/z* 421 (M^+).

General procedure B

Preparation of methyl-5-acetoxy-6-[3-(3-hydroxyundec-1*E*-en-5-ynly)phenyl]hexanoate (11c). To a stirred solution of 2-octyne (1.20 mL, 8.50 mmol) in THF (20 mL) was added dropwise *t*-BuLi (6.80 mmol) at −70 °C under an argon atmosphere. The mixture was stirred at −70 °C for 5 min and at 0 °C for an additional 1 h. Triisopropylborate (1.70 mL, 7.50 mmol) was then added dropwise at −70 °C. The resulting mixture was stirred at −70 °C for 30 min, and a solution of **11b** (1.08 g, 3.40 mmol) in THF (20 mL) was added dropwise. After stirring at −70 °C for 1 h, the mixture was poured into a mixture of crushed ice (10 g) and saturated aq. NH_4Cl (20 mL). The resulting mixture was extracted with AcOEt (50 mL). The extract was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (hexane:AcOEt, 2:1) gave 650 mg (45%) of **11c** as a pale yellow oil. R_f 0.20 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 2.00 (s, 3H), 2.10–2.45 (m, 4H), 2.55 (m, 2H), 2.85 (m, 2H), 3.70 (s, 3H), 4.45 (m, 1H), 5.10 (m, 1H), 6.30 (dd, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.00–7.40 (m, 4H); MS (EI) m/z 410 (M^+–H_2O).

The following compounds were prepared from the indicated starting materials by using the same procedure as that described above.

Methyl-3-[2-(3-hydroxyundec-1*E*-en-5-ynyl)phenyl]propanoate (12d) from 12c. 51% yield; pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 1.20–1.60 (m, 6H), 2.20 (m, 2H), 2.50–2.65 (m, 4H), 3.00 (t, J = 7 Hz, 2H), 3.65 (s, 3H), 4.40 (m, 1H), 6.15 (dd, J = 16 Hz and 7 Hz, 1H), 6.90 (d, J = 16 Hz, 1H), 7.20 (m, 3H), 7.45 (m, 1H); MS (EI) m/z 328 (M^+).

1-(3-Trifluoroacetylaminophenyl)undec-1*E*-en-5-yn-3-ol (15c) from 15b. 45% yield; white solid; R_f 0.30 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.20–1.60 (m, 6H), 2.17 (m, 2H), 2.25 (s, 1H), 2.52 (m, 2H), 4.40 (q, J = 7 Hz, 1H), 6.28 (dd, J = 16 Hz and 7 Hz, 1H), 6.62 (d, J = 16 Hz, 1H), 7.23 (dt, J = 8 Hz and 2 Hz, 1H), 7.33 (t, J = 8 Hz, 1H), 7.43 (dt, J = 8 Hz and 2 Hz, 1H), 7.59 (t, J = 2 Hz, 1H), 8.00 (s, 1H); MS (EI) m/z 353 (M^+).

Preparation of methyl-5-acetoxy-6-[3-(3-hydroxy-1*E*,5*Z*-undecadienyl)phenyl]hexanoate (11d). A solution of **11c** (300 mg, 0.70 mmol) in 2% quinoline containing EtOH (30 mL) was hydrogenated over 2.7% Pb-poisoned 5% Pd–$CaCO_3$ (30 mg) for 30 min at 25 °C. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was dissolved in 50% Et_2O in AcOEt (100 mL), and the solution was washed successively with 1 N HCl (10 mL × 2), saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt, 2:1) to yield 285 mg (95%) of **11d** as a pale yellow oil. R_f 0.22 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 2.00 (s, 3H), 2.05 (m, 2H), 2.30 (m, 2H), 2.40 (m, 2H), 2.65-3.00 (m, 2H), 3.65 (s, 3H), 4.32 (m, 1H), 5.05 (m, 1H), 5.30–5.70 (m, 2H), 6.25 (dd, J = 16 Hz and 7 Hz, 1H), 6.57 (d, J = 16 Hz, 1H), 6.95–7.12 (m, 1H), 7.12–7.30 (m, 3H); MS (EI) m/z 412 (M^+–H_2O).

Methyl-3-[2-(3-hydroxy-1*E*,5*Z*-undecadienyl)phenyl]propanoate (12e). This compound was prepared from **12d** using the same procedure as described above: quantitative yield; pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 1.20–1.50 (m, 6H), 1.75 (m, 2H), 2.05 (m, 2H), 2.60 (t, J = 7 Hz, 2H), 3.00 (t, J = 7 Hz, 2H), 3.65 (s, 3H), 4.35 (m, 1H), 5.30–5.70 (m, 2H), 6.10 (dd, J = 16 Hz and 7 Hz, 1H), 6.85 (d, J = 16 Hz, 1H), 7.10–7.25 (m, 3H), 7.40 (m, 1H); MS (EI) m/z 313 (M^+–H_2O).

General procedure C

Preparation of 5-hydroxy-6-[3-(3-hydroxy-1*E*,5*Z*-undecadienyl)phenyl]hexanoic acid (2). 1 N Sodium hydroxide (0.37 mmol) was added to a solution of **11d** (40 mg, 0.093 mmol) in MeOH (0.5 mL) and THF (0.5 mL). After stirring at 25 °C for 16 h, the mixture was acidified by the addition of 1 N HCl (0.40 mL), and the resulting mixture was extracted with AcOEt (50 mL). The extract was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt:MeOH, 19:1), giving 30 mg (86%) of **2** as a pale yellow oil. R_f 0.15 (AcOEt:MeOH, 19:1); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 2.03 (m, 2H), 2.40 (m, 4H), 2.65 (dd, J = 14 Hz and 8 Hz, 1H), 2.80 (dd, J = 14 Hz and 4 Hz, 1H), 3.82 (m, 1H), 4.30 (q, J = 7 Hz, 1H), 5.30–5.70 (m, 2H), 6.25 (dd, J = 16 Hz and 7 Hz, 1H), 6.57 (d, J = 16 Hz, 1H), 6.95–7.15 (m, 1H), 7.15–7.30 (m, 3H); IR (neat) 3350, 2920, 2860, 1705, 1430, 1245, 1040, 965 cm^{-1}; MS (EI) m/z 338 (M^+–$2H_2O$).

The following compounds were prepared from the indicated starting materials by using the same procedure as that described above.

3-[2-(3-Hydroxy-1*E*,5*Z*-undecadienyl)phenyl]propanoic acid (3) from 12e. 16% yield; pale yellow oil; R_f 0.40 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.20–1.40 (m, 6H), 2.00–2.15 (m, 2H), 2.35–2.50 (m, 2H), 2.95–3.10 (m, 2H), 4.30–4.40 (m, 1H), 5.35–5.70 (m, 2H), 6.10 (dd, J = 16 Hz and 7 Hz, 1H), 6.85 (d, J = 16 Hz, 1H), 7.10–7.25 (m, 3H), 7.40–7.48 (m, 1H); IR (neat) 2927, 1715, 1486, 1456, 1298, 1034, 967, 752 cm^{-1}; MS (EI) m/z 299 (M^+–OH).

4-[3-(3-Hydroxy-1*E*,5*Z*-undecadienyl)phenylaminocarbonyl]butanoic Acid (4a) from 4c. 96% yield; colorless oil; R_f 0.10 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.30 (m, 6H), 2.03 (m, 4H), 2.40 (m, 6H), 4.28 (q, J = 7 Hz, 1H), 5.48 (m, 2H), 6.22 (dd, J = 16 and 7 Hz, 1H), 6.52 (d, J = 16 Hz, 1H), 7.08 (d, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.55 (s, 1H), 7.85 (s, 1H); MS (EI) m/z 355 (M^+–H_2O).

3-[2-(5-Hydroxy-1*E*,3*E*-tridecadienyl)phenyl]propanoic acid (5) from 12g. 57% yield; colorless oil; R_f 0.40 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.40–1.50 (m, 12H), 1.50–1.65 (m, 2H), 2.50–2.65 (m, 2H), 2.95–3.10 (m, 2H), 2.95 (t, J = 7 Hz, 2H), 4.15–4.25 (m, 1H), 6.00 (dd, J = 16 Hz and 7 Hz, 1H), 6.42 (dd, J = 16 Hz and 10 Hz, 1H), 6.70–6.90 (m, 2H), 7.15–7.20 (m, 3H), 7.45–7.55 (m, 1H); IR (neat) 3367, 2926, 2855, 1714, 1566, 1483, 1455, 1402, 1295, 990, 752 cm^{-1}; MS (EI) *m/z* 344 (M^+).

4-[4-[5-(Tetrahydropyranyloxy)pentoxy]phenylaminocarbonyl]butanoic acid (20a) from 18b. 86% yield; white solid (from AcOEt:hexane, 1:1); mp 97–98.5 °C; R_f 0.10 (AcOEt:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 1.40–1.75 (m, 10H), 1.80 (m, 2H), 2.05 (m, 2H), 2.35–2.55 (m, 4H), 3.35–3.60 (m, 2H), 3.70–3.95 (m, 2H), 3.95 (t, J = 7 Hz, 2H), 4.55 (m, 1H), 6.85 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H); IR (KBr) 3328, 2945, 1704, 1660, 1525, 1252, 1027 cm^{-1}; MS (EI) *m/z* 393 (M^+).

3-[5-[4-(Dimethylaminocarbonyl)butanoylamino]-2-(6-hydroxy-4*E*-tetradecenyloxy)phenyl]propanoic acid (32) from 31. 40% yield; pale yellow oil; R_f 0.35 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.25 (m, 12H), 1.50 (m, 2H), 1.87 (m, 2H), 2.05 (m, 2H), 2.23 (m, 2H), 2.45 (m, 4H), 2.65 (t, J = 7 Hz, 2H), 2.98 (m, 5H), 3.05 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.50 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 7.20 (d, J = 2 Hz, 1H), 7.62 (dd, J = 8 Hz and 2 Hz, 1H), 8.45 (s, 1H); IR (neat) 3305, 1713, 1626, 1504, 1236 cm^{-1}; MS (EI) *m/z* 532 (M^+); EI HRMS *m/z* 532.3497 ($C_{30}H_{48}N_2O_6$ 532.3513).

3-[5-(Carboxymethoxy)-2-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]propanoic acid (38a) from 37a. 70% yield; white powder (from hexane:AcOEt, 2:1); mp 81–81.5 °C; R_f 0.10 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.25 (m, 12H), 1.55 (m, 4H), 1.78 (m, 2H), 2.10 (m, 2H), 2.62 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.93 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 4.60 (s, 2H), 5.47 (dd, J = 16 Hz and 7 Hz, 1H), 5.67 (dt, J = 16 Hz and 7 Hz, 1H), 6.75 (m, 3H); IR (KBr) 3419, 1725, 1500, 1222, 1181 cm^{-1}; MS (EI) *m/z* 446 (M^+–H_2O); FAB HRMS *m/z* 465.2841 (MH^+, $C_{26}H_{41}O_7$ 465.2852); Anal. calcd for $C_{26}H_{40}O_7$: C, 67.22; H, 8.68%. Found: C, 67.85; H, 8.13%.

4-[3-(2-Carboxyethyl)-4-(7-hydroxy-5*E*-pentadecenyloxy)phenoxy]butanoic acid (38b) from 37b. 91% yield; white solid (from hexane:AcOEt, 5:1); mp 70–71 °C; R_f 0.25 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.25 (m, 12H), 1.55 (m, 4H), 1.78 (m, 2H), 2.10 (m, 4H), 2.53 (t, J = 7 Hz, 2H), 2.62 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.90 (t, J = 7 Hz, 2H), 3.97 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.47 (dd, J = 16 Hz and 7 Hz, 1H), 5.67 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (m, 3H); IR (KBr) 3531, 1694, 1507, 1228, 1060 cm^{-1}; MS (EI) *m/z* 492 (M^+); Anal. calcd for $C_{28}H_{44}O_7$: C, 68.26; H, 9.00%. Found: C, 68.10; H, 8.95%.

5-[3-(2-Carboxyethyl)-4-(7-hydroxy-5*E*-pentadecenyloxy)phenoxy]pentanoic Acid (38c) from 37c. 94% yield; white powder (from hexane:AcOEt, 2:1); mp 66–67 °C; R_f 0.35 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.25 (m, 14H), 1.60 (m, 4H), 1.80 (m, 4H), 2.10 (m, 2H), 2.40 (m, 2H), 2.62 (t, J = 7 Hz, 2H), 2.92 (t, J = 7 Hz, 2H), 3.95 (m, 4H), 4.05 (m, 1H), 5.45 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.75 (m, 3H); IR (KBr) 1696, 1508, 1229 cm^{-1}; MS (EI) *m/z* 506 (M^+); Anal. calcd for $C_{29}H_{46}O_7$: C, 68.75; H, 9.15%. Found: C, 68.94; H, 8.92%.

3-[5-[4-(Dimethylaminocarbonyl)butoxy]-2-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]propanoic acid (38d) from 37d. 90% yield; pale yellow oil; R_f 0.40 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.25 (m, 14H), 1.60 (m, 4H), 1.75 (m, 4H), 2.10 (m, 2H), 2.40 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 2.92 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.00 (s, 3H), 3.90 (t, J = 7 Hz, 2H), 4.00 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.47 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.72 (m, 2H), 6.80 (d, J = 2 Hz, 1H); IR (neat) 3402, 1727, 1626, 1500, 1220 cm^{-1}; MS (EI) *m/z* 533 (M^+); EI HRMS *m/z* 533.3715 ($C_{31}H_{51}NO_6$ 533.3717).

5-[3-(2-Carboxyethyl)-4-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]pentanoic acid (46a) from 45a. 67% yield; white wax; R_f 0.35 (AcOEt); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.20–1.70 (m, 20H), 1.80 (m, 2H), 2.10 (m, 2H), 2.35 (m, 2H), 2.60 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.93 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.47 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 6.95 (m, 2H); IR (KBr) 3426, 1719, 1703, 1503, 1241 cm^{-1}; MS (EI) *m/z* 490 (M^+); EI HRMS *m/z* 472.3202 (M^+–H_2O, $C_{29}H_{44}O_5$ 472.3189).

3-[5-[4-(Dimethylaminocarbonyl)butyl]-2-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]propanoic acid (46b) from 45b. 59% yield; white wax; R_f 0.40 (AcOEt); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.20–1.70 (m, 20H), 1.80 (m, 2H), 2.10 (m, 2H), 2.30 (m, 2H), 2.58 (m, 4H), 2.95 (m, 5H), 3.00 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.45 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 6.93 (dd, J = 8 Hz and 2 Hz, 1H), 7.00 (d, J = 2 Hz, 1H); IR (neat) 3402, 1728, 1626, 1504, 1251 cm^{-1}; MS (FAB) *m/z* 518 (MH^+); EI HRMS *m/z* 499.3654 (M^+–H_2O, $C_{31}H_{49}NO_4$ 499.3662).

5-[2-(2-Carboxyethyl)-3-(7-hydroxy-5*E*-pentadecenyloxy)phenoxy]pentanoic acid (52a) from 51a. 98% yield; colorless oil; R_f 0.30 (AcOEt); ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.20–1.70 (m, 16H), 1.70–2.00 (m, 6H), 2.10 (m, 2H), 2.50 (m, 4H), 3.03 (t, J = 7 Hz, 2H), 3.97 (m, 4H), 4.05 (m, 1H), 5.47 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.50 (m, 2H), 7.10 (t, J = 8 Hz, 1H); IR (neat) 1708, 1595, 1463, 1104 cm^{-1}; MS (EI) *m/z* 506 (M^+); EI HRMS *m/z* 506.3224 ($C_{29}H_{46}O_7$ 506.3244).

(−)-5-[2-(2-Carboxyethyl)-3-(7*R*-hydroxy-5*E*-pentadecenyloxy)phenoxy]pentanoic acid ((*R*)-(−)-52a) from (*R*)-(−)-51a. 70% yield; white solid; mp 73–74 °C; R_f 0.35 (AcOEt); $[\alpha]_D^{23}$ -2.2 (c = 2.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7 Hz, 3H), 1.20–1.60 (m, 22H), 1.70–2.00 (m, 6H), 2.48 (m, 2H), 2.52 (m, 2H), 3.03 (m, 2H), 3.60 (m, 1H), 3.95 (m, 4H), 5.50 (s, 1H), 6.48 (d, *J* = 8 Hz, 1H), 6.50 (d, *J* = 8 Hz, 1H), 7.10 (t, *J* = 8 Hz, 1H); IR (KBr) 3440, 1709, 1595, 1461, 1243, 1100 cm^{-1}; MS (FAB) *m/z* 509 (MH^+); Anal. calcd for $C_{29}H_{48}O_7$: C, 68.47; H, 9.51%. Found: C, 68.33; H, 9.52%.

(+)-5-[2-(2-Carboxyethyl)-3-(7*S*-hydroxy-5*E*-pentadecenyloxy)phenoxy]pentanoic acid ((*S*)-(+)-52a) from (*S*)-(+)-51a. 70% yield; white solid; mp 73–74 °C; R_f 0.35 (AcOEt); $[\alpha]_D^{23}$ +2.2 (c = 1.9, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7 Hz, 3H), 1.20–1.60 (m, 22H), 1.70–2.00 (m, 6H), 2.48 (m, 2H), 2.52 (m, 2H), 3.03 (m, 2H), 3.60 (m, 1H), 3.95 (m, 4H), 5.50 (s, 1H), 6.48 (d, *J* = 8 Hz, 1H), 6.50 (d, *J* = 8 Hz, 1H), 7.10 (t, *J* = 8 Hz, 1H); IR (KBr) 3440, 1709, 1595, 1461, 1243, 1100 cm^{-1}; MS (FAB) *m/z* 509 (MH^+); Anal. calcd for $C_{29}H_{48}O_7$: C, 68.47; H, 9.51%. Found: C, 68.33; H, 9.52%.

3-[2-[6-(4-Methoxyphenyl)-5*E*-hexenyloxy]phenyl]-propanoic acid (57) from 56. 88% yield; white needles (from hexane:AcOEt, 8:1); mp 62–62.5 °C; R_f 0.45 (AcOEt:hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.85 (m, 2H), 2.25 (m, 2H), 2.67 (t, *J* = 7 Hz, 2H), 2.95 (t, *J* = 7 Hz, 2H), 3.80 (s, 3H), 4.00 (t, *J* = 7 Hz, 2H), 6.08 (dt, *J* = 16 Hz and 7 Hz, 1H), 6.35 (d, *J* = 16 Hz, 1H), 6.85 (m, 4H), 7.18 (m, 2H), 7.27 (d, *J* = 8 Hz, 2H); IR (KBr) 1716, 1676, 1510, 1497, 1250, 1236 cm^{-1}; MS *m/z* 354 (M^+); Anal. calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39%. Found: C, 74.79; H, 6.81%.

3-[2-(7-Hydroxy-5*E*-pentadecenyloxy)phenyl]propanoic acid (7). This compound was prepared from **23a** through ethyl-3-[2-(4-formylbutoxy)phenyl]propanoate **23b**, ethyl-3-[2-(7-oxo-5*E*-pentadecenyloxy)phenyl]-propanoate **23c** and ethyl-3-[2-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]propanoate **23d** by using the general procedures A, G, H and C. 64% yield; colorless oil; R_f 0.55 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7 Hz, 3H), 1.25 (m, 12H), 1.55 (m, 4H), 1.80 (m, 2H), 2.10 (m, 2H), 2.42 (t, *J* = 7 Hz, 2H), 2.95 (t, *J* = 7 Hz, 2H), 3.98 (t, *J* = 7 Hz, 2H), 4.05 (m, 1H), 5.48 (dd, *J* = 16 Hz and 7 Hz, 1H), 5.67 (dt, *J* = 16 Hz and 7 Hz, 1H), 6.82 (m, 2H), 7.17 (m, 2H); IR (neat) 1713, 1495, 1455, 1244 cm^{-1}; MS (EI) *m/z* 390 (M^+); EI HRMS *m/z* 390.2780 ($C_{24}H_{38}O_4$ 390.2770).

Preparation of methyl-3-(2-formylphenyl)propanoate (12b). Manganese dioxide (3.6 g, 42 mmol) was added to a solution of **12a** (1.35 g, 7.0 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred at 25 °C for 2 h. Manganese dioxide (1.8 g, 21 mmol) was also added, and the resulting mixture was stirred at 25 °C for 16 h. The manganese dioxide was then removed by filtration on a silica gel mat and washed with CH_2Cl_2 (100 mL). The combined filtrate was concentrated in vacuo. Purification of the residue by column chromatography on silica gel (hexane:AcOEt, 4:1) afforded 860 mg (64%) of **12b** as a pale yellow oil. R_f 0.50 (hexane: AcOEt, 3:1); ^{1}H NMR ($CDCl_3$) δ 2.65 (t, *J* = 7 Hz, 2H), 3.35 (t, *J* = 7 Hz, 2H), 3.65 (s, 3H), 7.30–7.60 (m, 3H), 7.80 (dd, *J* = 8 Hz and 2 Hz, 1H), 10.20 (s, 1H); MS (EI) *m/z* 192 (M^+).

Preparation of methyl-3-[2-(2-Formyl-*E*-ethenyl)-phenyl]propanoate (12c). To a solution of **12b** (106 mg, 0.55 mmol) and (1,3-dioxolane-2-methyl)phosphonium bromide **13** (690 mg, 1.66 mmol) in DMF (3.0 mL) was added dropwise a solution of sodium methoxide (38 mg, 1.66 mmol) in MeOH (1.0 mL) at 25 °C under argon atmosphere. After stirring at 60 °C for 30 min, the reaction mixture was poured into a mixture of 1 N HCl (2.0 mL) and crushed ice (5 g). The resulting mixture was extracted repeatedly with AcOEt (20 mL × 3). The combined extract was dried over $MgSO_4$, and evaporated in vacuo. The residue was taken up in THF (1.5 mL), and 1 N HCl (1.5 mL) was added. After stirring at 25 °C for 1 h, the mixture was diluted with water (10 mL). The resulting mixture was extracted with AcOEt (50 mL). The extract was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 3:1), giving 60 mg (50%) of **12c** as a colorless oil. R_f 0.20 (hexane:AcOEt, 3:1); ^{1}H NMR ($CDCl_3$) δ 2.65 (t, *J* = 7 Hz, 2H), 3.15 (t, *J* = 7 Hz, 2H), 3.65 (s, 3H), 6.70 (dd, *J* = 16 Hz and 7 Hz, 1H), 7.20–7.40 (m, 3H), 7.60 (m, 1H), 7.85 (d, *J* = 16 Hz, 1H), 9.75 (d, *J* = 7 Hz, 1H); MS (EI) *m/z* 218 (M^+).

3-(3-Trifluoroactetylaminophenyl)-*E*-propenal (15b). This compound was prepared from **15a** by using the same procedure as that described above: 91% yield; white needles (from AcOEt:hexane, 1:1); mp 149.5–150 °C; ^{1}H NMR ($CDCl_3$) δ 6.73 (dd, *J* = 16 Hz and 7 Hz, 1H), 7.45 (m, 2H), 7.46 (d, *J* = 16 Hz, 1H), 7.60 (m, 1H), 7.87 (s, 1H), 8.12 (s, 1H), 9.72 (d, *J* = 7 Hz, 1H); MS (EI) *m/z* 243 (M^+); Anal. calcd for $C_{11}H_8NO_2F_3$: C, 54.33; H, 3.32; N, 5.76%. Found: C, 54.60; H, 3.09; N, 5.70%.

Preparation of 3-(trifluoroacetylamino)benzaldehyde (15a). Trifluoroacetic anhydride (4.20 mL, 30.0 mmol) was added dropwise to a solution of **14** (3.34 g, 20.0 mmol) and triethylamine (5.50 mL, 40.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was poured into cooled 1 N HCl (100 mL). The resulting mixture was extracted with AcOEt (500 mL), washed with saturated aq. $NaHCO_3$, then brine, and dried over $MgSO_4$ and evaporated in vacuo. The residue was taken up in acetone (100 mL), and a catalytic amount of DL-camphorsulfonic acid was added. After stirring at 25 °C for 16 h, the mixture was concentrated in vacuo, and the residue was diluted with AcOEt (200 mL). The resulting solution was washed successively with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 4:1), giving a white solid.

Recrystallization of the solid from hexane:AcOEt (17:3) yielded 3.29 g (76%) of **15a**. R_f 0.40 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 7.58 (t, J = 8 Hz, 1H), 7.75 (dt, J = 8 Hz and 2 Hz, 1H), 7.93 (dt, J = 8 Hz and 2 Hz, 1H), 8.03 (t, J = 2 Hz, 1H), 8.15 (s, 1H), 10.00 (s, 1H); MS (EI) m/z 217 (M^+).

Preparation of 3-(3-*tert*-butyldimethylsilyoxy-1*E*,5*Z*-undecadienyl)-1-trifluoroacetylaminobenzene (15e). To a solution of **15c** (780 mg, 2.20 mmol) in DMF (3.0 mL) were added *t*-butyldimethylsilyl chloride (500 mg, 3.30 mmol) and imidazole (370 mg, 5.50 mmol). After stirring at 25 °C for 30 min, the reaction mixture was poured into a mixture of crushed ice (10 g) and 1 N HCl (10 mL). The resulting mixture was extracted with 50% Et_2O in AcOEt (50 mL × 2). The combined extract was washed with saturated aq. $NaHCO_3$ and then brine, dried over $MgSO_4$, and evaporated. Chromatography of the residual crude oil on a silica gel column (CH_2Cl_2:hexane, 3:2) afforded 980 mg (95%) of 3-(3-*tert*-butyldimethylsilyoxyundec-1*E*-en-5-ynyl)-1-trifluoroacetylaminobenzene **15d** as a colorless oil. R_f value 0.25 (CH_2Cl_2:hexane, 3:2); MS (EI) m/z 467 (M^+).

Compound **15d** was converted to **15e** using the same procedure as that described for the synthesis of **11d** in quantitative yield. Pale yellow oil; R_f 0.35 (CH_2Cl_2:hexane, 1:1); ^1H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.08 (s, 3H), 0.85 (t, J = 7 Hz, 3H), 0.93 (s, 9H), 1.10–1.45 (m, 6H), 2.00 (m, 2H), 2.33 (m, 2H), 4.28 (q, J = 7 Hz, 1H), 5.43 (m, 2H), 6.22 (dd, J = 16 Hz and 7 Hz, 1H), 6.48 (d, J = 16 Hz, 1H), 7.22 (d, J = 8 Hz, 1H), 7.30 (t, J = 8 Hz, 1H), 7.42 (d, J = 8 Hz, 1H), 7.53 (s, 1H), 7.85 (s, 1H); MS (EI) m/z 469 (M^+).

Preparation of 3-(3-*tert*-butyldimethylsilyloxy-1*E*,5*Z*-undecadienyl)phenylamine (16a). 1 N Sodium hydroxide (10.0 mmol) was added to a solution of **15e** (950 mg, 2.03 mmol) in a 4:1 mixture of THF and MeOH (25 mL). After stirring at 25 °C for 16 h, the mixture was diluted with water (50 mL). The resulting mixture was extracted with Et_2O (200 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to give 750 mg (quantitative yield) of **16a** as a pale yellow oil. R_f 0.30 (hexane:AcOEt, 9:1); ^1H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.85 (t, J = 7 Hz, 3H), 0.92 (s, 9H), 1.10–1.45 (m, 6H), 2.00 (m, 2H), 2.32 (m, 2H), 3.65 (s, 2H), 4.25 (q, J = 7 Hz, 1H), 5.40 (m, 2H), 6.12 (dd, J = 16 Hz and 7 Hz, 1H), 6.38 (d, J = 16 Hz, 1H), 6.55 (d, J = 8 Hz, 1H), 6.67 (s, 1H), 6.75 (d, J = 8 Hz, 1H), 7.07 (t, J = 8 Hz, 1H); MS (EI) m/z 373 (M^+).

Preparation of methyl-4-[3-(3-hydroxy-1*E*,5*Z*-undecadienyl)phenylaminocarbonyl]butanoate (4c). Methyl-4-chloroformylbutanoate (0.083 mL, 0.60 mmol) was added dropwise to a solution of **16a** (187 mg, 0.50 mmol) in CH_2Cl_2 (3.0 mL) and triethylamine (0.14 mL, 1.0 mmol) at 0 °C. After stirring at 0 °C for 1 h, the mixture was poured into cooled 1 N HCl (10 mL). The resulting mixture was extracted with AcOEt (50 mL). The organic layer was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated in vacuo to give 250 mg (quantitative yield) of methyl-4-[3-(3-*tert*-butyldimethylsilyloxy-1*E*,5*Z*-undecadienyl)phenylaminocarbonyl]butanoate **16b** as a pale yellow oil. Tetrabutylammonium fluoride (2.0 mmol) was added to a solution of **16b** (250 mg, 0.50 mmol) in THF (1.0 mL). After stirring at 25 °C for 2 h, the mixture was poured into 1 N HCl (10 mL). The resulting mixture was extracted with AcOEt (100 mL). The organic layer was washed with saturated aq. $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated. Column chromatography of the residual oil on silica gel (AcOEt:hexane, 1:1) afforded 180 mg (93%) of **4c** as a colorless oil. R_f 0.30 (AcOEt:hexane, 1:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.30 (m, 6H), 2.05 (m, 4H), 2.40 (m, 6H), 3.70 (s, 3H), 4.30 (q, J = 7 Hz, 1H), 5.48 (m, 2H), 6.23 (dd, J = 16 Hz and 7 Hz, 1H), 6.55 (d, J = 16 Hz, 1H), 7.10 (d, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.58 (s, 1H), 7.65 (s, 1H); MS (EI) m/z 387 (M^+).

General procedure D

Preparation of *N,N*-dimethyl-4-[3-(3-hydroxy-1*E*,5*Z*-undecadienyl)phenylaminocarbonyl]butanamide (4b). Ethyl chloroformate (0.32 mL, 3.40 mmol) was added dropwise to a solution of **4a** (850 mg, 2.27 mmol) and triethylamine (0.63 mL, 4.54 mmol) in THF (15 mL) at −15 °C under an argon atmosphere. The mixture was stirred at −15 °C for 15 min after completion of the addition. Dimethylamine (23.0 mmol) was then added dropwise at −10 °C. After stirring at −10 °C for 10 min, the mixture was allowed to warm to 25 °C, stirred for 30 min, poured into cooled 1 N HCl (50 mL), and extracted with AcOEt (200 mL). The extract was washed with saturated aq. $NaHCO_3$ and then brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt), giving 770 mg (85%) of **4b** as a pale yellow oil. R_f 0.50 (AcOEt:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.30 (m, 6H), 2.03 (m, 4H), 2.20 (s, 1H), 2.45 (m, 6H), 2.98 (s, 3H), 3.03 (s, 3H), 4.30 (m, 1H), 5.48 (m, 2H), 6.25 (dd, J = 16 Hz and 7 Hz, 1H), 6.55 (d, J = 16 Hz, 1H), 7.10 (d, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.42 (d, J = 8 Hz, 1H), 7.63 (s, 1H), 8.50 (s, 1H); IR (neat) 3306, 2955, 2929, 2857, 1667, 1627, 1590, 1556, 1489, 1264, 1050, 970, 785 cm^{-1}; MS (EI) m/z 400 (M^+); EI HRMS m/z 400.2738 ($C_{24}H_{36}N_2O_3$ 400.2726).

The following compounds were prepared from the indicated starting materials by using the same procedure as that described above.

***N,N*-Dimethyl-4-[4-[5-(tetrahydropyranyloxy)pentoxy]-phenylaminocarbonyl]butanamide (20b) from 20a.** 60% yield; white solid (from hexane:AcOEt, 2:1); mp 75–76 °C; R_f 0.20 (AcOEt:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 1.45–1.95 (m, 12H), 2.05 (m, 2H), 2.45 (m, 4H), 3.00 (s, 3H), 3.05 (s, 3H), 3.35–3.60 (m, 2H), 3.70–

3.90 (m, 2H), 3.95 (t, J = 7 Hz, 2H), 4.60 (m, 1H), 6.85 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 8.10 (s, 1H); IR (KBr) 3309, 2941, 1683, 1639, 1513, 1224 cm^{-1}; MS (EI) m/z 420 (M^+).

***N,N*-Dimethyl-5-(3,4-dihydrocoumarin-6-yl)pentanamide (41b) from 41a.** 77% yield; white solid; R_f 0.40 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.35 (m, 2H), 2.60 (m, 2H), 2.75 (m, 2H), 2.95 (s, 3H), 2.97 (m, 2H), 3.00 (s, 3H), 6.95 (d, J = 8 Hz, 1H), 7.00 (d, J = 2 Hz, 1H), 7.05 (dd, J = 8 Hz and 2 Hz, 1H); MS (EI) m/z 275 (M^+).

***N,N*-Dimethyl-4-[3-[5-(tetrahydropyranyloxy)pentoxy]-phenylaminocarbonyl]butanamide (19b).** This compound was prepared from **17b** through 4-[3-[5-(tetrahydropyranyloxy)pentoxy]phenylaminocarbonyl]butanoic acid **19a** by using general procedure C followed by general procedure D. 95% yield; white solid; mp 71–73 °C; R_f 0.50 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 2.05 (m, 2H), 2.45 (m, 4H), 3.00 (s, 3H), 3.05 (s, 3H), 3.35–3.60 (m, 2H), 3.60–3.90 (m, 2H), 3.95 (t, J = 7 Hz, 2H), 4.60 (m, 1H), 6.60 (d, J = 8 Hz, 1H), 7.00 (d, J = 8 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 7.35 (s, 1H), 8.35 (s, 1H); IR (KBr) 3274, 2940, 1691, 1632, 1620, 1603, 1550, 1483, 1447, 1424, 1233, 1037 cm^{-1}; MS (EI) m/z 420 (M^+).

General procedure E

Preparation of methyl-4-[3-[5-(tetrahydropyranyloxy)-pentoxy]phenylaminocarbonyl]butanoate (17b). A solution of **17a** (2.8 g, 12 mmol) in DMF (10 mL) was added dropwise to a suspension of sodium hydride (12 mmol) in DMF (5.0 mL) under an argon atmosphere at 0 °C. The mixture was then stirred for 10 min at 0 °C and for an additional 30 min at 25 °C. A solution of the methanesulfonate of 5-tetrahydropyranyloxypentanol (3.3 g, 13 mmol) in DMF (5.0 mL) was then added, and the mixture was stirred at 75 °C for 1 h. The reaction mixture was poured into a mixture of crushed ice (50 g) and 1N HCl (20 mL), and the resulting mixture was extracted with 50% Et_2O in AcOEt (200 mL × 2). The combined extract was washed with saturated aq. $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated. Chromatography of the crude product on a silica gel column (AcOEt:hexane, 1:1) afforded 3.2 g (66%) of **17b** as a pale yellow oil. R_f 0.40 (AcOEt:hexane, 2:1); ^1H NMR ($CDCl_3$) δ 2.05 (m, 2H), 2.40 (m, 4H), 3.35–3.60 (m, 2H), 3.70 (s, 3H), 3.70–3.90 (m, 2H), 3.95 (t, J = 8 Hz, 2H), 4.60 (m, 1H), 6.65 (d, J = 8 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H), 7.30 (s, 1H), 7.35 (s, 1H); MS (EI) m/z 407 (M^+).

The following compounds were prepared from the indicated starting materials and the corresponding bromides or methanesulfonates by using the same procedure as that described above.

2-Oxo-6-[4-[5-(tetrahydropyranyloxy)pentoxy]phenylimino]tetrahydropyran (18b) from 18a and $MsO(CH_2)_5OTHP$. **18b** was obtained in 25% yield instead of the corresponding methyl ester[8]. White powder (from hexane:AcOEt, 6:1); R_f 0.20 (AcOEt:hexane, 2:1); ^1H NMR ($CDCl_3$) δ 1.40–1.90 (m, 12H), 2.10 (m, 2H), 2.80 (m, 4H), 3.35–3.60 (m, 2H), 3.70–3.90 (m, 2H), 3.95 (t, J = 7 Hz, 2H), 4.60 (m, 1H), 6.95 (m, 4H); MS (EI) m/z 375 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-[5-(tetrahydropyranyloxy)pentoxy]phenyl]propanoate (26a) from 25 and $Br(CH_2)_5OTHP$. 89% yield; pale brown oil; R_f 0.20 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 1.40–1.75 (m, 10H), 1.80 (m, 2H), 2.05 (m, 2H), 2.45 (m, 4H), 2.57 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 2.97 (s, 3H), 3.03 (s, 3H), 3.45 (m, 2H), 3.80 (m, 2H), 3.95 (t, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 4.58 (m, 1H), 6.65 (d, J = 8 Hz, 1H), 7.27 (d, J = 2 Hz, 1H), 7.42 (dd, J = 8 Hz and 2 Hz, 1H), 8.25 (s, 1H); MS (EI) m/z 520 (M^+).

***tert*-Butyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-[4-(tetrahydropyranyloxy)butoxy]phenyl]-propanoate (30a) from 29a[9] and $Br(CH_2)_4OTHP$.** Quantitative yield; pale brown oil; R_f 0.60 ($CHCl_3$:MeOH, 19:1); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.40–1.95 (m, 10H), 2.05 (m, 2H), 2.45 (m, 6H), 2.88 (t, J = 7 Hz, 2H), 2.97 (s, 3H), 3.03 (s, 3H), 3.50 (m, 2H), 3.80 (m, 2H), 3.98 (t, J = 7 Hz, 2H), 4.58 (m, 1H), 6.75 (d, J = 8 Hz, 1H), 7.25 (d, J = 2 Hz, 1H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H), 8.00 (s, 1H); MS (EI) m/z 534 (M^+).

Ethyl-3-[2-[6-(4-methoxyphenyl)-5*E*-hexenyloxy]phenyl]-propanoate (56) from ethyl-3-(2-hydroxyphenyl)-propanoate and 55[14]. 46% yield; colorless oil; R_f 0.50 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.85 (m, 2H), 2.25 (m, 2H), 2.60 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.82 (m, 4H), 7.15 (m, 2H), 7.27 (d, J = 8 Hz, 2H).

General procedure F

Preparation of *N,N*-dimethyl-4-[3-(5-hydroxypentoxy)-phenylaminocarbonyl]butanamide (21a). *p*-Toluenesulfonic acid hydrate (5.0 mg) was added to a solution of **19b** (3.0 g, 7.1 mmol) in MeOH (30 mL). After stirring at 45 °C for 30 min, the mixture was diluted with saturated aq. $NaHCO_3$ (50 mL). The resulting mixture was extracted with AcOEt (200 mL). The extract was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (AcOEt:MeOH, 9:1), giving 2.0 g (82%) of **21a** as a white solid. Mp 88–89 °C; R_f 0.20 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 1.60 (m, 4H), 1.80 (m, 2H), 2.05 (m, 2H), 2.45 (m, 4H), 3.00 (s, 3H), 3.05 (s, 3H), 3.70 (m, 2H), 3.95 (t, J = 7 Hz, 2H), 4.60 (m, 1H), 6.60 (d, J = 8 Hz, 1H), 7.00 (d, J = 8 Hz, 1H), 7.20 (d, J = 8

Hz, 1H), 7.35 (s, 1H), 8.35 (s, 1H); IR (KBr) 3471, 3272, 2930, 1690, 1676, 1630, 1620, 1603, 1553, 1483, 1449, 1423, 1240 cm^{-1}; MS (EI) *m/z* 336 (M^+).

The following compounds were prepared from the indicated starting materials by using the same procedure as described above.

***N,N*-Dimethyl-4-[4-(5-hydroxypentoxy)phenylaminocarbonyl]butanamide (22a) from 20b.** 80% yield; white solid (from AcOEt); mp 81–82.5 °C; R_f 0.15 (AcOEt:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 1.60 (m, 4H), 1.80 (m, 2H), 2.05 (m, 2H), 2.45 (m, 4H), 3.00 (s, 3H), 3.05 (s, 3H), 3.70 (m, 2H), 3.95 (t, J = 7 Hz, 2H), 6.85 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 8.15 (s, 1H); IR (KBr) 3456, 3330, 1665, 1628, 1530, 1518, 1236, 1060, 1042 cm^{-1}; MS (EI) *m/z* 336 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(5-hydroxypentoxy)phenyl]propanoate (26b) from 26a. 43% yield; pale yellow oil; R_f 0.25 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 1.50-1.75 (m, 4H), 1.80 (m, 2H), 2.05 (m, 2H), 2.45 (m, 4H), 2.58 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 2.98 (s, 3H), 3.05 (s, 3H), 3.67 (m, 2H), 3.95 (t, J = 7 Hz, 2H), 4.13 (q, J = 7 Hz, 2H), 6.75 (d, J = 8 Hz, 1H), 7.27 (d, J = 2 Hz, 1H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H), 8.12 (s, 1H); MS (EI) *m/z* 436 (M^+).

Preparation of ethyl-3-[5-(ethoxycarbonylmethoxy)-2-(5-hydroxypentoxy)phenyl]propanoate (34a). This compound was prepared from **33a**[10] by using general procedure E followed by general procedure F. 50% yield; colorless oil; R_f 0.10 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 1.50–1.70 (m, 4H), 1.80 (m, 2H), 2.58 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.65 (m, 2H), 3.92 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 4.25 (q, J = 7 Hz, 2H), 4.55 (s, 2H), 6.70 (m, 2H), 6.78 (d, J = 2 Hz, 1H); MS *m/z* 382 (M^+).

Preparation of ethyl-4-[3-[2-(ethoxycarbonyl)ethyl]-4-(5-hydroxypentoxy)phenoxy]butanoate (34b). This compound was prepared from **33b**[10] by using general procedure E followed by general procedure F. 83% yield; colorless oil; R_f 0.25 (AcOEt:hexane, 1:1); ^1H NMR ($CDCl_3$) δ 1.25 (m, 6H), 1.60 (m, 4H), 1.80 (m, 2H), 2.05 (m, 2H), 2.50 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.65 (m, 2H), 3.92 (m, 4H), 4.13 (m, 4H), 6.70 (m, 3H); MS (EI) *m/z* 410 (M^+).

Preparation of ethyl-5-[3-[2-(ethoxycarbonyl)ethyl]-4-(5-hydroxypentoxy)phenoxy]pentanoate (34c). This compound was prepared from **33c**[10] by using general procedure E followed by general procedure F. 51% yield; colorless oil; R_f 0.25 (AcOEt/hexane, 1:1); ^1H NMR ($CDCl_3$) δ 1.23 (m, 6H), 1.60 (m, 4H), 1.80 (m, 6H), 2.40 (m, 2H), 2.60 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.70 (m, 2H), 3.90 (m, 4H), 4.12 (m, 4H), 6.70 (m, 3H); MS (EI) *m/z* 424 (M^+).

Preparation of ethyl-3-[5-[4-(dimethylaminocarbonyl)-butoxy]-2-(5-hydroxypentoxy)phenyl]propanoate (34d). This compound was prepared from **33d**[10] by using general procedure E followed by general procedure F. 56% yield; colorless oil; R_f 0.10 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.60 (m, 4H), 1.80 (m, 6H), 2.38 (m, 2H), 2.58 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz), 2H, 2.95 (s, 3H), 3.00 (s, 3H), 3.67 (m, 2H), 3.90 (m, 4H), 4.12 (q, J = 7 Hz, 2H), 6.70 (m, 3H); MS (EI) *m/z* 423 (M^+).

Preparation of methyl-5-[4-(5-hydroxypentoxy)-3-[2-(methoxycarbonyl)ethyl]phenyl]pentanoate (42a). This compound was prepared from **40b** by using general procedure E followed by general procedure F. 76% yield; colorless oil; R_f 0.15 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 1.40–2.00 (m, 10H), 2.30 (m, 2H), 2.60 (m, 4H), 2.90 (m, 2H), 3.63 (m, 2H), 3.65 (s, 6H), 3.95 (t, J = 7 Hz, 2H), 6.70 (d, J = 8 Hz, 1H), 6.90 (m, 2H); MS (EI) *m/z* 380 (M^+).

Preparation of methyl-3-[5-[4-(dimethylaminocarbonyl)-butyl]-2-(5-hydroxypentoxy)phenyl]propanoate (42b). This compound was prepared from **40c** by using general procedure E followed by general procedure F. 55% yield; colorless oil; R_f 0.20 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.40–2.00 (m, 10H), 2.30 (m, 2H), 2.60 (m, 4H), 2.90 (m, 2H), 2.95 (s, 3H), 3.00 (s, 3H), 3.65 (m, 5H), 3.93 (t, J = 7 Hz, 2H), 6.65 (d, J = 8 Hz, 1H), 6.90 (m, 2H); MS (EI) *m/z* 393 (M^+).

Preparation of ethyl-5-[3-[2-(ethoxycarbonyl)ethyl]-3-(5-hydroxypentoxy)phenoxy]pentanoate (48a). This compound was prepared from **47a**[11] by using general procedure E followed by general procedure F. 63% yield; colorless oil; R_f 0.30 (AcOEt:hexane, 1:1); ^1H NMR ($CDCl_3$) δ 1.23 (m, 6H), 1.60 (m, 4H), 1.80 (m, 6H), 2.38 (t, J = 7 Hz, 2H), 2.45 (t, J = 7 Hz, 2H), 3.00 (t, J = 7 Hz, 2H), 3.67 (t, J = 7 Hz, 2H), 3.95 (m, 4H), 4.12 (m, 4H), 6.48 (m, 2H), 7.08 (t, J = 8 Hz, 1H); MS (EI) *m/z* 424 (M^+).

Preparation of ethyl-3-[2-[4-(dimethylaminocarbonyl)-butoxy]-6-(5-hydroxypentoxy)phenyl]propanoate (48b). This compound was prepared from **47b**[11] by using general procedure E followed by general procedure F. 37% yield; colorless oil; R_f 0.15 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.60 (m, 4H), 1.82 (m, 6H), 2.40 (m, 4H), 2.97 (s, 3H), 3.00 (m, 2H), 3.02 (s, 3H), 3.67 (m, 2H), 3.98 (m, 4H), 4.12 (q, J = 7 Hz, 2H), 6.48 (m, 2H), 7.08 (t, J = 8 Hz, 1H); MS (EI) *m/z* 423 (M^+).

General procedure G

Preparation of *N,N*-dimethyl-4-[4-(7-oxo-5*E*-pentadecenyloxy)phenylaminocarbonyl]butanamide (22c). A solution of dimethyl-2-oxodecanylphosphonate (250 mg, 0.96 mmol) in THF (2.0 mL) was added dropwise to a suspension of sodium hydride (0.88 mmol) in THF (1.0 mL) at 0 °C under an argon atmosphere. The

mixture was stirred for 10 min at 0 °C and for an additional 30 min at 25 °C. A solution of **22b** (130 mg, 0.40 mmol) in THF (2.0 mL) was added to the mixture in one portion, and the temperature was allowed to rise to 40 °C. After stirring at 25 °C for 1 h, the mixture was acidified with glacial acetic acid, filtered through a silica gel mat, and washed with AcOEt. The combined filtrate was evaporated in vacuo to give a white solid. Recrystallization of the solid from hexane:AcOEt (9:1) afforded 93 mg (49%) of **22c** as a white solid. Mp 80–81 °C; R_f value 0.40 (AcOEt:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.15–1.40 (m, 10H), 1.50–1.90 (m, 6H), 2.05 (m, 2H), 2.30 (m, 2H), 2.50 (m, 6H), 3.00 (s, 3H), 3.05 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.10 (d, J = 16 Hz, 1H), 6.80 (m, 3H), 7.45 (d, J = 8 Hz, 2H), 8.20 (s, 1H); IR (KBr) 3312, 2922, 1690, 1656, 1637, 1542, 1249 cm^{-1}; MS (EI) m/z 472 (M^+).

The following compounds were prepared from the indicated starting materials and the corresponding phosphonates by using the same procedure as that described above.

Methyl-3-[2-(5-oxo-1*E*,3*E*-tridecadienyl)phenyl]propanoate (12f) from 12c and $(MeO)_2POCH_2CO^nC_8H_{17}$. 51% yield; colorless oil; R_f 0.40 (hexane:AcOEt, 5:1); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 1.20-1.40 (m, 10H), 1.30 (m, 10H), 1.65 (m, 2H), 2.60 (m, 4H), 3.05 (t, J = 7 Hz, 2H), 3.65 (s, 3H), 6.30 (d, J = 16 Hz, 1H), 6.80 (dd, J = 16 Hz and 14 Hz, 1H), 7.10–7.30 (m, 4H), 7.35 (dd, J = 16 Hz and 14 Hz, 1H), 7.55 (m, 1H); MS (EI) m/z 356 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(7-oxo-5*E*-nonenyloxy)phenyl]propanoate (27a) from 26c and $(MeO)_2POCH_2COC_2H_5$. 82 % yield; pale yellow oil; R_f 0.50 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 1.07 (t, J = 7 Hz, 3H), 1.23 (t, J = 7 Hz, 3H), 1.70 (m, 2H), 1.80 (m, 2H), 2.05 (m, 2H), 2.30 (m, 2H), 2.40–2.70 (m, 8H), 2.90 (t, J = 7 Hz, 2H), 2.97 (s, 3H), 3.03 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 6.10 (d, J = 16 Hz, 1H), 6.70–6.90 (m, 2H), 7.27 (d, J = 8 Hz, 1H), 7.43 (dd, J = 8 Hz and 2 Hz, 1H), 8.20 (s, 1H); MS (EI) m/z 488 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(7-oxo-5*E*-dodecenyloxy)phenyl]propanoate (27b) from 26c and $(MeO)_2POCH_2CO^nC_5H_{11}$. 80 % yield; pale yellow oil; R_f 0.45 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 1.30 (m, 4H), 1.50–1.70 (m, 4H), 1.80 (m, 2H), 2.05 (m, 2H), 2.30 (m, 2H), 2.40–2.65 (m, 8H), 2.90 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.05 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 6.12 (d, J = 16 Hz, 1H), 6.70–6.90 (m, 2H), 7.27 (d, J = 2 Hz, 1H), 7.42 (dd, J = 8 Hz and 2 Hz, 1H), 8.20 (s, 1H); MS (EI) m/z 530 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(7-oxo-5*E*-pentadecenyloxy)phenyl]propanoate (27c) from 26c and $(MeO)_2POCH_2CO^nC_8H_{17}$. 82 % yield; pale yellow oil; R_f 0.10 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.15–1.40 (m, 10H), 1.22 (t, J = 7 Hz, 3H), 1.50–1.75 (m, 4H), 1.80 (m, 2H), 2.05 (m, 2H), 2.30 (m, 2H), 2.37–2.65 (m, 8H), 2.92 (t, J = 7 Hz, 2H), 2.98 (s, 3H), 3.05 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 6.12 (d, J = 16 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 6.83 (dt, J = 16 Hz and 7 Hz, 1H), 7.27 (d, J = 2 Hz, 1H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H), 8.12 (s, 1H); MS (EI) m/z 572 (M^+).

Ethyl-3-[2-(7-cyclohexyl-7-oxo-5*E*-heptenyloxy)-5-[4-(dimethylaminocarbonyl)butanoylamino]phenyl]propanoate (27d) from 26c and $(MeO)_2POCH_2CO^cC_6H_{11}$. 75% yield; pale yellow oil; R_f 0.55 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 1.00–1.45 (m, 6H), 1.23 (t, J = 7 Hz, 3H), 1.60–2.00 (m, 8H), 2.05 (m, 2H), 2.30 (m, 2H), 2.40–2.65 (m, 7H), 2.90 (t, J = 7 Hz, 2H), 2.97 (s, 3H), 3.05 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 6.18 (d, J = 16 Hz, 1H), 6.70–6.90 (m, 2H), 7.27 (d, J = 2 Hz, 1H), 7.43 (dd, J = 8 Hz and 2 Hz, 1H), 8.22 (s, 1H); MS (EI) m/z 542 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-[9-(4-methoxyphenyl)-7-oxo-5*E*-nonenyloxy]phenyl]-propanoate (27e) from 26c and $(MeO)_2POCH_2COCH_2CH_2(4\text{-}MeO)C_6H_4$. 83 % yield; pale yellow oil; R_f 0.45 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.80 (m, 2H), 2.05 (m, 2H), 2.30 (m, 2H), 2.38–2.65 (m, 6H), 2.80–2.95 (m, 6H), 2.95 (s, 3H), 3.02 (s, 3H), 3.78 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 6.10 (d, J = 16 Hz, 1H), 6.72–6.90 (m, 4H), 7.10 (d, J = 8 Hz, 2H), 7.27 (d, J = 2 Hz, 1H), 7.42 (dd, J = 8 Hz and 2 Hz, 1H), 8.20 (s, 1H); MS (EI) m/z 594 (M^+).

Methyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(6-oxo-4*E*-tetradecenyloxy)phenyl]propanoate (30c) from 30b and $(MeO)_2POCH_2CO^nC_8H_{17}$. 78% yield; pale yellow oil; R_f 0.15 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.30 (m, 10H), 1.60 (m, 4H), 2.00 (m, 4H), 2.35–2.70 (m, 8H), 2.90 (t, J = 7 Hz, 2H), 2.97 (s, 3H), 3.02 (s, 3H), 3.68 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.15 (d, J = 16 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 6.85 (dt, J = 16 Hz and 7 Hz, 1H), 7.25 (d, J = 2 Hz, 1H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H), 8.13 (s, 1H); MS (EI) m/z 544 (M^+).

Ethyl-3-[5-(ethoxycarbonylmethoxy)-2-(7-oxo-5*E*-pentadecenyloxy)phenyl]propanoate (36a) from 35a and $(MeO)_2POCH_2CO^nC_8H_{17}$. 82% yield; pale yellow oil; R_f 0.50 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.15–1.75 (m, 14H), 1.22 (t, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 1.80 (m, 2H), 2.08 (m, 2H), 2.53 (t, J = 7 Hz, 2H), 2.55 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.92 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 4.27 (q, J = 7 Hz, 2H), 4.55 (s, 2H), 6.10 (d, J = 16 Hz, 1H), 6.65–6.80 (m, 3H), 6.82 (dt, J = 16 Hz and 7 Hz, 1H); MS (EI) m/z 518 (M^+).

Ethyl-4-[3-[2-(ethoxycarbonyl)ethyl]-4-(7-oxo-5*E*-pentadecenyloxy)phenoxy]butanoate (36b) from 35b and $(MeO)_2POCH_2CO^nC_8H_{17}$. 60% yield; pale yellow oil; R_f 0.50 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.10–1.40 (m, 10H), 1.22 (t, J = 7 Hz, 3H),

1.25 (t, J = 7 Hz, 3H), 1.65 (m, 4H), 1.80 (m, 2H), 2.05 (m, 2H), 2.28 (m, 2H), 2.40–2.65 (m, 6H), 2.90 (t, J = 7 Hz, 2H), 3.92 (m, 4H), 4.12 (m, 4H), 6.12 (d, J = 16 Hz, 1H), 6.70 (m, 3H), 6.82 (dt, J = 16 Hz and 7 Hz, 1H); MS (EI) m/z 546 (M^+).

Ethyl-5-[3-[2-(ethoxycarbonyl)ethyl]-4-(7-oxo-5*E*-pentadecenyloxy)phenoxy]pentanoate (36c) from 35c and $(MeO)_2POCH_2CO^nC_8H_{17}$. 92% yield; pale yellow oil; R_f 0.50 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.23 (m, 6H), 1.15–1.40 (m, 10H), 1.50–1.75 (m, 4H), 1.80 (m, 6H), 2.30 (m, 4H), 2.50 (t, J = 7 Hz, 2H), 2.58 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.90 (m, 4H), 4.12 (m, 4H), 6.12 (d, J = 16 Hz, 1H), 6.70 (m, 3H), 6.82 (dt, J = 16 Hz and 7 Hz, 1H); MS (EI) m/z 560 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butoxy]-2-(7-oxo-5*E*-pentadecenyloxy)phenyl]propanoate (36d) from 35d and $(MeO)_2POCH_2CO^nC_8H_{17}$. 92% yield; pale yellow oil; R_f 0.50 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.80 (m, 6H), 2.17 (m, 2H), 2.37 (m, 2H), 2.58 (t, J = 7 Hz, 2H), 2.90 (m, 6H), 3.80 (s, 3H), 3.90 (m, 4H), 4.12 (m, 4H), 6.10 (d, J = 16 Hz, 1H), 6.70 (m, 3H), 6.80 (d, J = 8 Hz, 2H), 6.82 (dt, J = 16 Hz and 7 Hz, 1H), 7.10 (d, J = 8 Hz, 2H); MS (EI) m/z 582 (M^+).

Ethyl-3-[2-[4-(dimethylaminocarbonyl)butoxy]-6-(7-oxo-5*E*-pentadecenyloxy)phenyl]propanoate (50b) from 49b and $(MeO)_2POCH_2CO^nC_8H_{17}$. 92% yield; pale yellow oil; R_f 0.50 (AcOEt); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 1.30 (m, 10H), 1.60 (m, 2H), 1.80 (m, 10H), 2.30 (m, 2H), 2.40 (m, 2H), 2.52 (m, 2H), 2.97 (s, 3H), 3.00 (m, 2H), 3.01 (s, 3H), 3.95 (m, 4H), 4.12 (q, J = 7 Hz, 2H), 6.10 (d, J = 16 Hz, 1H), 6.45 (d, J = 8 Hz, 1H), 6.48 (d, J = 8 Hz, 1H), 6.82 (dt, J = 16 Hz and 7 Hz, 1H), 7.08 (t, J = 8 Hz, 1H); MS (EI) m/z 559 (M^+).

Preparation of *N,N*-dimethyl-4-[3-(7-oxo-5*E*-pentadecenyloxy)phenylaminocarbonyl]butanamide (21c). This compound was prepared from **21a** through *N,N*-dimethyl-4-[3-(4-formylbutoxy)phenylaminocarbonyl]-butanamide **21b** by using general procedure A followed by general procedure G. 41 % yield; white wax; R_f 0.40 (AcOEt:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.15–1.40 (m, 10H), 1.50–1.90 (m, 6H), 2.05 (m, 2H), 2.30 (m, 2H), 2.50 (m, 6H), 3.00 (s, 3H), 3.05 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 6.10 (d, J = 16 Hz, 1H), 6.60 (d, J = 8 Hz, 1H), 6.85 (dt, J = 16 Hz and 7 Hz, 1H), 7.00 (d, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H),7.40 (s, 1H), 8.40 (s, 1H); MS (EI) m/z 472 (M^+).

Preparation of methyl-5-[3-[2-(methoxycarbonyl)-ethyl]-4-(7-oxo-5*E*-pentadecenyloxy)phenyl]pentanoate (44a). This compound was prepared from **42a** through methyl-5-[4-(4-formylbutoxy)-3-[2-(methoxycarbonyl)-ethyl]phenyl]pentanoate **43a** by using general procedure A followed by general procedure G with $(MeO)_2POCH_2CO^nC_8H_{17}$. 87% yield; pale yellow oil; R_f 0.60 (hexane:AcOEt, 3:1); ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.20–1.90 (m, 20H), 2.30 (m, 4H), 2.55 (m, 6H), 2.92 (t, J = 7 Hz, 2H), 3.65 (s, 6H), 3.95 (t, J = 7 Hz, 2H), 6.13 (d, J = 16 Hz, 1H), 6.72 (d, J = 8 Hz, 1H), 6.83 (dt, J = 16 Hz and 7 Hz, 1H), 6.95 (m, 2H); MS (EI) m/z 516 (M^+).

Preparation of methyl-3-[5-[4-(dimethylaminocarbonyl)-butyl]-2-(7-oxo-5*E*-pentadecenyloxy)phenyl]propanoate (44b). This compound was prepared from **42b** through methyl-3-[5-[4-(dimethylaminocarbonyl)butyl]-2-(4-formylpentoxy)phenyl]propanoate **43b** by using general procedure A followed by general procedure G with $(MeO)_2POCH_2CO^nC_8H_{17}$. 52% yield; pale yellow oil; R_f 0.60 (AcOEt); ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.20–1.90 (m, 20H), 2.30 (m, 4H), 2.55 (m, 6H), 2.90 (t, J = 7 Hz, 2H), 2.93 (s, 3H), 2.98 (s, 3H), 3.67 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.10 (d, J = 16 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 6.83 (dt, J = 16 Hz and 7 Hz, 1H), 6.95 (m, 2H); MS (EI) m/z 529 (M^+).

Preparation of ethyl-5-[2-[2-(ethoxycarbonyl)ethyl]-3-(7-oxo-5*E*-pentadecenyloxy)phenoxy]pentanoate (50a). This compound was prepared from **48a** through ethyl-5-[2-[2-(ethoxycarbonyl)ethyl]-3-(4-formylbutoxy)phenoxy]-pentanoate **49a** by using general procedure A followed by general procedure G with $(MeO)_2POCH_2CO^nC_8H_{17}$. 87% yield; pale yellow oil; R_f 0.30 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.23 (m, 6H), 1.30 (m, 10H), 1.45–1.90 (m, 10H), 2.20–2.60 (m, 8H), 3.00 (t, J = 7 Hz, 2H), 3.97 (m, 4H), 4.12 (m, 4H), 6.10 (d, J = 16 Hz, 1H), 6.48 (m, 2H), 6.82 (dt, J = 16 Hz and 7 Hz, 1H), 7.10 (t, J = 8 Hz, 1H); IR (neat) 2930, 1735, 1595, 1463, 1103 cm^{-1}; MS (EI) m/z 560 (M^+); EI HRMS m/z 560.3740 ($C_{33}H_{52}O_7$ 560.3713).

General procedure H

Preparation of *N,N*-dimethyl-4-[3-(7-hydroxy-5*E*-pentadecenyloxy)phenylaminocarbonyl]butanamide (6a). Sodium borohydride (110 mg, 3.0 mmol) was added to a solution of **21c** (480 mg, 1.0 mmol) in MeOH (10 mL) at 0 °C, and the mixture was stirred for 15 min. The reaction mixture was then neutralized with glacial acetic acid at 0 °C and diluted with saturated aq. $NaHCO_3$. The resulting mixture was extracted with AcOEt (100 mL). The extract was washed with brine, dried over $MgSO_4$, and evaporated. Chromatography of the residual oil on a silica gel column (AcOEt:MeOH, 49:1) afforded 360 mg (75%) of **6a** as a colorless oil. R_f 0.35 (AcOEt:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.20–1.65 (m, 16H), 1.80 (m, 2H), 2.07 (m, 4H), 2.45 (m, 4H), 2.97 (s, 3H), 3.03 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.48 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.60 (d, J = 8 Hz, 1H), 7.02 (d, J = 8 Hz, 1H), 7.17 (t, J = 8 Hz, 1H), 7.33 (s, 1H), 8.50 (s, 1H); IR (neat) 3311, 1630, 1549, 1494, 1444, 1245 cm^{-1}; MS (EI) m/z 474 (M^+); EI HRMS m/z 474.3453 ($C_{28}H_{46}N_2O_4$ 474.3458).

The following compounds were prepared from the indicated starting materials by using the same procedure as that described above.

***N,N*-Dimethyl-4-[4-(7-hydroxy-5*E*-pentadecenyloxy)-phenylaminocarbonyl]butanamide (6b) from 22c.** 85% yield; white crystals (from hexane:AcOEt, 2:1); mp 80–82 °C; R_f 0.40 (AcOEt:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.20–1.65 (m, 16H), 1.75 (m, 2H), 2.07 (m, 4H), 2.45 (m, 4H), 2.97 (s, 3H), 3.02 (s, 3H), 3.93 (t, J = 7 Hz, 2H), 4.02 (m, 1H), 5.48 (dd, J = 16 Hz and 7 Hz, 1H), 5.63 (dt, J = 16 Hz and 7 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.43 (d, J = 8 Hz, 2H), 8.20 (s, 1H); IR (KBr) 3310, 1655, 1638, 1625, 1543, 1515, 1249 cm^{-1}; MS (EI) *m/z* 474 (M^+); Anal. calcd for $C_{28}H_{46}N_2O_4$: C, 70.85; H, 9.77; N, 5.90%. Found: C, 70.59; H, 9.99; N, 5.80%.

Methyl-5-hydroxy-6-[3-(3-tetrahydropyranyloxy-1*E*-propenyl)phenyl]hexanoate (10g) from 10f. Quantitative yield; colorless oil; R_f 0.25 (AcOEt:hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.40 (m, 2H), 2.80 (m, 2H), 3.40–4.10 (m, 3H), 3.70 (s, 3H), 4.35 (m, 2H), 4.75 (m, 1H), 6.35 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (d, J = 16 Hz, 1H), 7.00–7.50 (m, 4H); MS (EI) *m/z* 344 (M^+–H_2O).

Methyl-3-[2-(5-hydroxy-1*E*,3*E*-tridecadienyl)phenyl]-propanoate (12g) from 12f. 87% yield; colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 1.20–1.65 (m, 14H), 2.55 (t, J = 7 Hz, 2H), 3.00 (t, J = 7 Hz, 2H), 3.65 (s, 3H), 4.20 (m, 1H), 5.80 (dt, J = 16 Hz and 7 Hz, 1H), 6.40 (dd J = 16 Hz and 14 Hz, 1H), 6.70 (dd, J = 16 Hz and 14 Hz, 1H), 6.80 (d, J = 16 Hz, 1H), 7.20 (3H, m), 7.50 (1H, m); MS (EI) *m/z* 358 (M^+).

Methyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(6-hydroxy-4*E*-tetradecenyloxy)phenyl]propanoate (31) from 30c. Quantitative yield; pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.20–1.70 (m, 14H), 1.87 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 2.45 (t, J = 7 Hz, 2H), 2.50 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 2.98 (s, 3H), 3.03 (s, 3H), 3.68 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.50 (dd, J = 16 H and 7 Hz, 1H), 5.68 (dt, J = 16 Hz and 7 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.25 (d, J = 2 Hz, 1H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H), 8.05 (1H, s); MS (EI) *m/z* 546 (M^+).

Ethyl-3-[5-(ethoxycarbonylmethoxy)-2-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]propanoate (37a) from 36a. Quantitative yield; pale yellow oil; R_f 0.30 (hexane: AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 1.20–1.70 (m, 16H), 1.30 (t, J = 7 Hz, 3H), 1.80 (m, 2H), 2.10 (m, 2H), 2.58 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.90 (t, J = 7 Hz, 2H), 4.02 (m, 1H), 4.12 (q, J = 7 Hz, 2H), 4.27 (q, J = 7 Hz, 2H), 4.55 (s, 2H), 5.08 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.65–6.80 (m, 3H); MS (EI) *m/z* 520 (M^+).

Ethyl-4-[3-[2-(ethoxycarbonyl)ethyl]-4-(7-hydroxy-5*E*-pentadecenyloxy)phenoxy]butanoate (37b) from 36b. Quantitative yield; pale yellow oil; R_f 0.25 (hexane: AcOEt, 3:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.15–1.70 (m, 16H), 1.80 (m, 2H), 2.10 (m, 4H), 2.50 (t, J = 7 Hz, 2H), 2.55 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.90 (m, 4H), 4.05 (m, 1H), 4.15 (m, 4H), 5.08 (dd, J = 16 Hz and 7 Hz, 1H), 5.63 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (m, 3H); MS (EI) *m/z* 548 (M^+).

Ethyl-5-[3-[2-(ethoxycarbonyl)ethyl]-4-(7-hydroxy-5*E*-pentadecenyloxy)phenoxy]pentanoate (37c) from 36c. Quantitative yield; pale yellow oil; R_f 0.30 (hexane: AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.23 (m, 6H), 1.15–1.70 (m, 16H), 1.80 (m, 6H), 2.10 (m, 2H), 2.37 (m, 2H), 2.58 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.90 (m, 4H), 4.03 (m, 1H), 4.12 (m, 4H), 5.08 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (m, 3H); MS (EI) *m/z* 562 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)butoxy]-2-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]propanoate (37d) from 36d. Quantitative yield; pale yellow oil; R_f 0.20 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 1.20–1.60 (m, 18H), 1.80 (m, 4H), 2.10 (m, 2H), 2.38 (m, 2H), 2.58 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.00 (s, 3H), 3.90 (m, 4H), 4.05 (m, 1H), 4.12 (q, J = 7 Hz, 2H), 5.10 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.70 (m, 3H); MS (EI) *m/z* 561 (M^+).

Methyl-5-hydroxy-5-[4-methoxy-3-[2-(methoxycarbonyl)-ethyl]phenyl]pentanoate (39b) from 39a. 84% yield; colorless oil; R_f 0.40 (AcOEt:hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.60–1.90 (m, 4H), 2.35 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 3.67 (s, 3H), 3.68 (s, 3H), 3.82 (s, 3H), 4.60 (m, 1H), 6.80 (d, J = 8 Hz, 1H), 7.12 (d, J = 2 Hz, 1H), 7.15 (dd, J = 8 Hz and 2 Hz, 1H); MS (EI) *m/z* 324 (M^+).

Methyl-5-[4-(7-hydroxy-5*E*-pentadecenyloxy)-3-[2-(methoxycarbonyl)ethyl]phenyl]pentanoate (45a) from 44a. 94% yield; colorless oil; R_f 0.20 (hexane:AcOEt, 4:1); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7 Hz, 3H), 1.20–1.70 (m, 20H), 1.80 (m, 2H), 2.10 (m, 2H), 2.32 (t, J = 7 Hz, 2H), 2.55 (m, 4H), 2.90 (t, J = 7 Hz, 2H), 3.65 (s, 3H), 3.67 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.48 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.72 (d, J = 8 Hz, 1H), 6.95 (m, 2H); MS (EI) *m/z* 518 (M^+).

Methyl-3-[5-[4-(dimethylaminocarbonyl)butyl]-2-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]propanoate (45b) from 44b. Quantitative yield; pale yellow oil; R_f 0.50 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7 Hz, 3H), 1.20–1.85 (m, 22H), 2.10 (m, 2H), 2.30 (t, J = 7 Hz, 2H), 2.60 (m, 4H), 2.90 (t, J = 7 Hz, 2H), 2.93 (s, 3H), 3.00 (s, 3H), 3.67 (s, 3H), 3.93 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.47 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 HZ, 1H), 6.72 (d, J = 8 Hz, 1H), 6.95 (m, 2H); MS (EI) *m/z* 531 (M^+).

Ethyl-5-[2-[2-(ethoxycarbonyl)ethyl]-3-(7-hydroxy-5*E*-pentadecenyloxy)phenoxy]pentanoate (51a) from 50a. 99% yield; colorless oil; R_f 0.40 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.23 (m, 6H), 1.20–1.70 (m, 16H), 1.82 (m, 6H), 2.10 (m, 4H), 2.40 (t, J = 7 Hz, 2H), 2.45 (t, J = 7 Hz, 2H), 3.00 (t, J = 7 Hz, 2H), 3.97 (m, 4H), 4.05 (m, 1H), 4.13 (m, 4H), 5.48 (dd, J = 16 Hz and 7 Hz, 1H), 5.63 (dt, J = 16 Hz and 7 Hz, 1H), 6.48 (m, 2H), 7.08 (t, J = 8 Hz, 1H); MS (EI) m/z 562 (M^+).

Preparation of 3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(7-oxo-5*E*-nonenyloxy)phenyl]propanoic acid (28a). This compound was prepared from **27a** by using general procedure H followed by general procedure C. 34% yield; brown oil; R_f 0.30 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 1.57 (m, 4H), 1.80 (m, 2H), 2.07 (m, 4H), 2.45 (m, 4H), 2.62 (t, J = 7 Hz, 2H), 2.93 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.02 (s, 3H), 3.95 (m, 3H), 5.47 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.20 (d, J = 2 Hz, 1H), 7.58 (dd, J = 8 Hz and 2 Hz, 1H), 8.45 (s, 1H); IR (neat) 3305, 1723, 1658, 1615, 1504, 1235 cm^{-1}; MS (EI) m/z 462 (M^+); EI HRMS m/z 462.2726 ($C_{25}H_{38}N_2O_6$ 462.2730).

Preparation of 3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(7-oxo-5*E*-dodecenyloxy)phenyl]propanoic acid (28b). This compound was prepared from **27b** by using general procedure H followed by general procedure C. 40% yield; pale brown oil; R_f 0.30 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.30 (m, 6H), 1.55 (m, 4H), 1.80 (m, 2H), 2.10 (m, 4H), 2.45 (m, 4H), 2.62 (t, J = 7 Hz, 2H), 2.92 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.03 (s, 3H), 3.93 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.45 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.20 (d, J = 2 Hz, 1H), 7.60 (dd, J = 8 Hz and 2 Hz, 1H), 8.45 (s, 1H); IR (neat) 3304, 1718, 1626, 1504, 1235 cm^{-1}; MS (EI) m/z 504 (M^+); EI HRMS m/z 504.3201 ($C_{28}H_{44}N_2O_6$ 504.3200).

Preparation of 3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-(7-oxo-5*E*-pentadecenyloxy)phenyl]propanoic acid (28c). This compound was prepared from **27c** by using general procedure H followed by general procedure C. 51% yield; colorless oil; R_f 0.30 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.25 (m, 12H), 1.60 (m, 4H), 1.80 (m, 2H), 2.10 (m, 4H), 2.45 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.03 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.05 (m, 1H), 5.47 (dd, J = 16 Hz and 7 Hz, 1H), 5.67 (dt, J = 16 Hz and 7 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.20 (d, J = 2 Hz, 1H), 7.58 (dd, J = 8 Hz and 2 Hz, 1H), 8.40 (s, 1H); IR (neat) 3304, 1724, 1626, 1504, 1236 cm^{-1}; MS (EI) m/z 546 (M^+).

Preparation of 3-[2-(7-cyclohexyl-7-oxo-5*E*-heptenyloxy)-5-[4-(dimethylaminocarbonyl)butanoylamino]phenyl]-propanoic acid (28d). This compound was prepared from **27d** by using general procedure H followed by general procedure C. 33% yield; pale yellow oil; R_f 0.30 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 1.10–1.50 (m, 6H), 1.50-1.90 (m, 9H), 2.07 (m, 4H), 2.45 (m, 4H), 2.62 (t, J = 7 Hz, 2H), 2.93 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.02 (s, 3H), 3.80 (m, 1H), 3.93 (t, J = 7 Hz, 2H), 5.47 (dd, J = 16 Hz and 7 Hz, 1H), 5.63 (dt, J = 16 Hz and 7 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 7.20 (d, J = 2 Hz, 1H), 7.58 (dd, J = 8 Hz and 2 Hz, 1H), 8.50 (s, 1H); IR (neat) 3305, 1714, 1626, 1504, 1235 cm^{-1}; MS (EI) m/z 516 (M^+); EI HRMS m/z 516.3208 ($C_{29}H_{44}N_2O_6$ 516.3200).

Preparation of 3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-[9-(4-methoxyphenyl)-7-oxo-5*E*-nonenyloxy]-phenyl]propanoic acid (28e). This compound was prepared from **27e** by using general procedure H followed by general procedure C. 32% yield; pale yellow oil; R_f 0.30 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 4H), 2.07 (m, 2H), 2.43 (m, 4H), 2.60 (m, 4H), 2.93 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.02 (s, 3H), 3.80 (s, 3H), 3.93 (t, J = 7 Hz, 2H), 4.07 (m, 1H), 5.45 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.20 (d, J = 2 Hz, 1H), 7.60 (dd, J = 8 Hz and 2 Hz, 1H), 8.45 (s, 1H); IR (neat) 3305, 1718, 1614, 1512, 1504, 1246 cm^{-1}; MS (EI) m/z 568 (M^+); EI HRMS m/z 550.3029 (M^+–H_2O), $C_{32}H_{42}N_2O_6$ 550.3043).

Preparation of 3-[2-[4-(dimethylaminocarbonyl)butoxy]-6-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]propanoic acid (52b). This compound was prepared from **50b** through ethyl-3-[2-[4-(dimethylaminocarbonyl)butoxy]-6-(7-hydroxy-5*E*-pentadecenyloxy)phenyl]propanoate **51b** by using general procedure H followed by general procedure C. 80% yield; pale yellow oil; R_f 0.45 ($CHCl_3$:MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.25 (m, 14H), 1.60 (m, 4H), 1.82 (m, 4H), 2.10 (m, 2H), 2.40 (t, J = 7 Hz, 2H), 2.50 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.02 (s, 3H), 3.05 (t, J = 7 Hz, 2H), 3.95 (m, 4H), 4.05 (m, 1H), 5.28 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.48 (m, 2H), 7.08 (t, J = 8 Hz, 1H); IR (neat) 1723, 1596, 1463, 1255, 1103 cm^{-1}; MS (EI) m/z 533 (M^+); EI HRMS m/z 533.3704 ($C_{31}H_{51}NO_6$ 533.3717), 515.3591 (M^+–H_2O, $C_{31}H_{49}NO_5$ 515.3611).

Preparation of 3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-hydroxyphenyl]propanoic acid (29b). A solution of **29a**[9] (80 mg, 0.21 mmol) in formic acid (2.0 mL) was stirred at 25°C for 16 h. The mixture was then evaporated in vacuo to remove formic acid, giving a white powder. Recrystallization of the powder from AcOEt afforded 26 mg (38%) of **37c** as a white powder. R_f 0.35 ($CHCl_3$:MeOH, 3:1); ^{1}H NMR (CD_3OD) δ 1.98 (m, 2H), 2.42 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.87 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.05 (s, 3H), 6.70 (d, J = 8 Hz, 1H), 7.20–7.25 (m, 2H); IR (KBr) 3354, 3257, 1714, 1641, 1617, 1554, 1438 cm^{-1}; MS (EI) m/z 304 (M^+–H_2O).

Preparation of methyl-3-[5-[4-(dimethylaminocarbonyl)-butanoylamino]-2-(3-formylpropoxy)phenyl]propanoate (30b). Formic acid (10 mL) was added to **30a** (800 mg, 1.5 mmol), and the mixture was stirred at 40 °C for 2 h. The mixture was then evaporated in vacuo to remove formic acid. 1 N Sodium hydroxide (7.0 mmol) was added to a solution of the residue in MeOH (5.0 mL). After stirring at 40 °C for 3 h, the mixture was acidified with 1 N HCl (8.0 mL). The resulting mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and evaporated. Chromatography of the residue on a silica gel column ($CHCl_3$:MeOH, 19:1) afforded 476 mg of oil. Diazomethane was added to a solution of the oily product in AcOEt at 0 °C, and the mixture was concentrated to give 452 mg (74%) of methyl-3-[2-(4-hydroxybutyloxy)-5-[4-(dimethylaminocarbonyl)butanoylamino]phenyl]-propanoate, which was converted to **30b** according to general procedure A. 42%; pale yellow oil; R_f 0.50 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 2.03 (m, 2H), 2.15 (m, 2H), 2.42 (t, J = 7 Hz, 2H), 2.48 (t, J = 7 Hz, 2H), 2.58 (t, J = 7 Hz, 2H), 2.68 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 2.98 (s, 3H), 3.03 (s, 3H), 3.68 (s, 3H), 3.98 (t, J = 7 Hz, 2H), 6.75 (d, J = 8 Hz, 1H), 7.25 (d, J = 2 Hz, 1H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H), 8.23 (s, 1H), 9.85 (m, 1H); MS (EI) m/z 406 (M^+).

Preparation of methyl-5-[4-methoxy-3-[2-(methoxy-carbonyl)ethyl]phenyl]-4*E*-pentenoate (39c). A solution of **39b** (1.0 g, 3.1 mmol) in DMSO (2.0 mL) was heated at 180 °C for 30 min. The mixture was then cooled to 25 °C, and diluted with Et_2O (100 mL). The resulting mixture was washed with 1 N HCl and then brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 4:1), yielding 850 mg (90%) of **39c** as a colorless oil. R_f 0.45 (hexane:AcOEt, 3:1); ^1H NMR ($CDCl_3$) δ 2.50 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.92 (t, J = 7 Hz, 2H), 3.68 (s, 3H), 3.70 (s, 3H), 3.82 (s, 3H), 6.03 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.15 (m, 2H); MS (EI) m/z 306 (M^+).

Preparation of 5-[3-(2-carboxyethyl)-4-hydroxyphenyl]-pentanoic acid (40a). A mixture of **39d** (1.66 g, 5.08 mmol) and pyridine hydrochloride (15 g) was heated at 180 °C for 4 h with stirring. After cooling to 100 °C, 1 N HCl (100 mL) was added. The resulting mixture was extracted with AcOEt (300 mL × 2). The combined extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent afforded 1.73 g (quantitative yield) of **40a** as a brown oil, which was used for further transformation without purification. ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.62 (m, 4H), 2.30 (m, 2H), 2.50 (m, 2H), 2.70 (t, J = 7 Hz, 2H), 2.85 (t, J = 7 Hz, 2H), 6.73 (d, J = 8 Hz, 1H), 6.85 (m, 2H); MS (EI) m/z 266 (M^+).

Preparation of methyl-5-[4-hydroxy-3-[2-(methoxy-carbonyl)ethyl]phenyl]pentanoate (40b). Concentrated sulfuric acid (0.50 mL) was added to a solution of **40a** (2.55 g, 8.57 mmol) in MeOH (10 mL), and the mixture was refluxed for 16 h. After cooling to 25 °C, the mixture was diluted with AcOEt (100 mL). The resulting mixture was washed successively with water, saturated aq. $NaHCO_3$ and then brine, dried over $MgSO_4$ and evaporated in vacuo. Purification of the residue by column chromatography on silica gel (hexane:AcOEt, 3:1) afforded 1.84 g (73%) of **40b** as a colorless oil. R_f 0.40 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.35 (t, J = 7 Hz, 2H), 2.53 (t, J = 7 Hz, 2H), 2.72 (t, J = 7 Hz, 2H), 2.88 (t, J = 7 Hz, 2H), 3.67 (s, 3H), 3.70 (s, 3H), 6.77–6.95 (m, 3H); IR (neat) 3421, 2951, 1737, 1714, 1510, 1438, 1264, 1206 cm^{-1}; MS (EI) m/z 294 (M^+).

Preparation of 5-(3,4-dihydrocoumarin-6-yl)pentanoic acid (41a). Resin (10 mL of Dowex 50W × 8, H^+ form) and benzene (100 mL) were added to a solution of **40a** (1.73 g, 5.08 mmol) in THF (2.0 mL). The mixture was heated at reflux under a Dean–Stark apparatus for 2 h. The resin was removed by filtration and washed with benzene. Evaporation of the combined filtrate afforded 1.28 g (quantitative yield) of **41a** as a white solid, which was used for further transformations without purification. R_f 0.50 ($CHCl_3$:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 1.60 (m, 4H), 2.40 (m, 2H), 2.60 (m, 2H), 2.80 (m, 2H), 2.95 (m, 2H), 6.95 (d, J = 8 Hz, 1H), 6.98 (d, J = 2 Hz, 1H), 7.05 (dd, J = 8 Hz and 2 Hz, 1H); MS (EI) m/z 248 (M^+).

Preparation of methyl-3-[5-[4-(dimethylamino-carbonyl)butyl]-2-hydroxyphenyl]propanoate (40c). A solution of NaOH (40 g, 1.0 mol) in H_2O (100 mL) was added to a solution of **41b** (195 g, 0.37 mol) in EtOH (300 mL) at 60 °C. After refluxing for 1 h, the mixture was evaporated to remove EtOH. The residue was partitioned between water (500 mL) and Et_2O (200 mL). The aqueous layer was acidified with concentrated HCl. The resulting mixture was extracted with AcOEt (500 mL × 2). The combined extract was washed with brine, dried over $MgSO_4$, and evaporated, giving a white solid. Recrystallization of the solid from AcOEt:hexane (1:1) afforded 166 g of solid. The solid (2.55 g) was taken up in MeOH (10 mL), and a few drops of concentrated sulfuric acid was added. After refluxing for 16 h, the mixture was diluted with AcOEt (100 mL) and water (50 mL). The organic layer was separated, washed successively with water, saturated aq. $NaHCO_3$ and then brine, dried over $MgSO_4$ and evaporated in vacuo. Purification of the residue by column chromatography on silica gel (hexane:AcOEt, 3:1) gave 1.84 g (73%) of **40c** as a pale yellow oil. R_f 0.50 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.50–1.80 (m, 4H), 2.32 (t, J = 7 Hz, 2H), 2.55 (t, J = 7 Hz, 2H), 2.70 (t, J = 7 Hz, 2H), 2.87 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.00 (s, 3H), 3.68 (s, 3H), 6.77 (d, J = 8 Hz, 1H), 6.80–6.95 (m, 2H), 7.15 (s, 1H); IR (neat) 3497, 2939, 2794, 1635, 1460, 1432, 1296, 1274, 1020, 1002 cm^{-1}; MS (EI) m/z 307 (M^+).

General procedure I

Preparation of 5-[2-(2-carboxyethyl)-3-(7-hydroxypentadecanyloxy)phenoxy]pentanoic acid (53). A solution of **52a** (320 mg, 0.63 mmol) in EtOH (20 mL) was hydrogenated over 10% palladium on carbon (30 mg) at 25 °C under atmospheric pressure. After stirring for 2 h, the catalyst was removed by filtration and the filtrate was evaporated in vacuo. Chromatography of the residue on a silica gel column (hexane:AcOEt, 3:2) afforded 174 mg (54%) of **53** as a white solid. White crystals (from hexane:AcOEt, 6:1); mp 73–74 °C; R_f 0.30 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.20–1.60 (m, 22H), 1.70–2.00 (m, 6H), 2.48 (m, 2H), 2.52 (m, 2H), 3.03 (m, 2H), 3.60 (m, 1H), 3.95 (m, 4H), 5.50 (s, 1H), 6.48 (d, J = 8 Hz, 1H), 6.50 (d, J = 8 Hz, 1H), 7.10 (t, J = 8 Hz, 1H); IR (KBr) 3440, 1709, 1595, 1461, 1243, 1100 cm^{-1}; MS (FAB) m/z 509 (MH^+); Anal. calcd for $C_{29}H_{48}O_7$: C, 68.47; H, 9.51%. Found: C, 68.33; H, 9.52%.

Methyl-5-[4-methoxy-3-[2-(methoxycarbonyl)ethyl]-phenyl]pentanoate (39d). This compound was prepared from **39c** by using general procedure I. 94% yield; colorless oil; R_f 0.50 (hexane:AcOEt, 3:1); ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 4H), 2.32 (t, J = 7 Hz, 2H), 2.55 (m, 2H), 2.60 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.67 (s, 6H), 3.80 (s, 3H), 6.75 (d, J = 8 Hz, 1H), 6.95 (d, J = 2 Hz, 1H), 6.98 (dd, J = 8 Hz and 2 Hz, 1H); MS m/z 308 (M^+).

Preparation of ethyl-3-[5-[4-(dimethylaminocarbonyl)-butanoylamino]-2-hydroxyphenyl]propanoate (25). 2,2-Dipyridyl disulfide (206 mg, 0.94 mmol) was added to a solution of 4-(dimethylaminocarbonyl)butanoic acid (142 mg, 0.90 mmol) and triphenylphosphine (246 mg, 0.94 mmol) in CH_2Cl_2 (5.0 mL) in one portion, and the mixture was stirred at 25 °C for 30 min. A solution of ethyl 3-(5-amino-2-hydroxyphenyl)propanoate (196 mg, 0.94 mmol), prepared from **24** by using general procedure I in quantitative yield, in CH_2Cl_2 (3.0 mL) was then added, and the mixture was stirred at 25 °C for 15 min. The mixture was diluted with AcOEt (100 mL) and 1 N HCl (10 mL). The organic layer was washed with saturated aq. $NaHCO_3$ and then brine, dried over $MgSO_4$ and evaporated in vacuo. Chromatography of the residue on a silica gel column (AcOEt) afforded 126 mg (44%) of **25** as a white solid. White solid (from AcOEt:hexane, 2:1); mp 124–126 °C; R_f 0.10 (AcOEt:hexane, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 2.03 (m, 2H), 2.45 (m, 4H), 2.70 (t, J = 7 Hz, 2H), 2.87 (t, J = 7 Hz, 2H), 2.97 (s, 3H), 3.05 (s, 3H), 4.12 (q, J = 7 Hz, 2H), 6.83 (d, J = 8 Hz, 1H), 7.15 (dd, J = 8 Hz and 2 Hz, 1H), 7.40 (m, 2H), 8.12 (s, 1H); IR (KBr) 3250, 1731, 1646, 1630, 1615, 1559, 1505, 1452, 1425, 1270 cm^{-1}; MS (EI) m/z 350 (M^+); Anal. calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 7.99%. Found: C, 61.76; H, 7.48; N, 7.67%.

Preparation of (−)-ethyl-5-[2-[2-(ethoxycarbonyl)ethyl]-3-(7*R*-hydroxy-5*E*-pentadecenyloxy)phenoxy]pentanoate ((*R*)-(−)-51a). A solution of borane–methyl sulfide complex (0.50 mL of 2.0 M THF solution, 1.0 mmol) was added dropwise to a solution of **50a** (560 mg, 1.0 mmol) and *boron*-methylated (*S*)-oxazaborolidine reagent[12] (277 mg, 1.0 mmol), as illustrated in Scheme 11, in THF (5.0 mL) with stirring at 25 °C under argon. After stirring for 5 min, the mixture was diluted with water (5.0 mL) with stirring and ice-bath cooling. After stirring for 30 min, the mixture was evaporated to remove THF, giving an oily residue. The residue was taken up in AcOEt (50 mL), and the resulting solution was washed successively with 1 N HCl, saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. Purification of the residue by column chromatography on silica gel (hexane:AcOEt, 3:1) afforded 404 mg (72%) of the title compound as a colorless oil. Enantiomeric purity (79.4% ee) was established by ^{19}F NMR analysis of the MTPA (Mosher) ester (*R*)-(−)-**54**. R_f 0.35 (hexane:AcOEt, 2:1); $[\alpha]_D^{23}$ −1.05 (c = 6.12, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.20–1.70 (m, 18H), 1.23 (m, 6H), 1.82 (m, 6H), 2.10 (m, 2H), 2.30–2.52 (m, 4H), 3.00 (t, J = 7 Hz, 2H), 3.97 (m, 4H), 4.05 (m, 1H), 4.15 (m, 4H), 5.48 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.48 (d, J = 8 Hz, 2H), 7.08 (t, J = 8 Hz, 1H); MS (EI) m/z 562(M^+).

(+)-Ethyl-5-[2-[2-(ethoxycarbonyl)ethyl]-3-(7*S*-hydroxy-5*E*-pentadecenyloxy)phenoxy]pentanoate ((*S*)-(+)-51a). This compound was prepared from **50a** using *boron*-methylated (*R*)-oxazaborolidine reagent[12] in place of (*S*)-oxazaborolidine reagent as a catalyst according to the procedure described above. Enantiomeric purity (80.1% ee) was established by ^{19}F NMR analysis of the MTPA (Mosher) ester (*S*)-(+)-**54**. 70% yield; colorless oil; R_f 0.35 (hexane:AcOEt, 2:1); $[\alpha]_D^{23}$ +1.14 (c = 7.64, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.20–1.70 (m, 18H), 1.23 (m, 6H), 1.82 (m, 6H), 2.10 (m, 2H), 2.30–2.52 (m, 4H), 3.00 (t, J = 7 Hz, 2H), 3.97 (m, 4H), 4.05 (m, 1H), 4.15 (m, 4H), 5.48 (dd, J = 16 Hz and 7 Hz, 1H), 5.65 (dt, J = 16 Hz and 7 Hz, 1H), 6.48 (d, J = 8 Hz, 2H), 7.08 (t, J = 8 Hz, 1H); MS (EI) m/z 562(M^+).

Preparation of (−)-ethyl-5-[2-[2-(ethoxycarbonyl)-ethyl]-3-[(7*R*)-[(*R*)-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy]-5*E*-pentadecenyloxy]phenoxy]pentanoate ((*R*)-(−)-54). (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl, 350 mg, 1.4 mmol) was added to a solution of (*R*)-(−)-**51a** (31 mg, 0.05 mmol) and pyridine (0.20 mL) in CCl_4 (1.0 mL) at 25 °C, and the mixture was stirred for 16 h at 25 °C. The mixture was diluted with AcOEt (50 mL), and the resulting solution was washed successively with 2 N HCl, saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated in vacuo. Chromatography of the residue on a silica gel column (hexane:AcOEt, 5:1) gave 41 mg (99%) of the title compound as a colorless oil. R_f 0.50 (hexane:AcOEt, 2:1); ^{1}H NMR (C_6D_6) δ 0.85–1.05 (m, 9H), 1.10–1.80 (m, 16H), 1.87 (m, 2H),

2.12 (t, J = 7 Hz, 2H), 2.75 (m, 2H), 3.30–3.55 (m, 5H), 3.60 (q, J = 7 Hz, 2H), 3.65 (q, J = 7 Hz, 2H), 3.95 (q, J = 7 Hz, 2H), 4.00 (q, J = 7 Hz, 2H), 5.40 (dd, J = 16 Hz and 7 Hz, 1H), 5.55 (m, 1H), 5.77 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 8 Hz, 1H), 6.42 (d, J = 8 Hz, 1H), 7.20–7.70 (m, 4H), 7.75 (d, J = 8 HZ, 2H); MS (EI) *m/z* 778 (M^+); ^{19}F NMR (C_6D_6) δ 80.40:80.31 = 8.7:1 (79.4% ee).

(+)-Ethyl-5-[2-[2-(ethoxycarbonyl)ethyl]-3-[(7*S*)-[(*R*)-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy]-5*E*-pentadecenyloxy]phenoxy]pentanoate ((*S*)-(+)-54). This compound was prepared from (*S*)-(+)-**51a** by using the procedure described above. 99% yield; colorless oil; R_f 0.50 (hexane:AcOEt, 2:1); ^1H NMR (C_6D_6) δ 0.85-1.05 (m, 9H), 1.10–1.88 (m, 16H), 1.85 (m, 2H), 2.12 (t, J = 7 Hz, 2H), 2.75 (m, 2H), 3.30–3.55 (m, 5H), 3.60 (q, J = 7 Hz, 2H), 3.65 (q, J = 7 Hz, 2H), 3.95 (q, J = 7 Hz, 2H), 3.98 (q, J = 7 Hz, 2H), 5.28 (dd, J = 16 Hz and 7 Hz, 1H), 5.50 (m, 1H), 5.70 (dt, J = 16 Hz and 7 Hz, 1H), 6.38 (d, J = 8 Hz, 1H), 6.40 (d, J = 8 Hz, 1H), 7.00–7.20 (m, 4H), 7.75 (d, J = 8 Hz, 2H); MS (EI) *m/z* 778 (M^+); ^{19}F NMR (C_6D_6) δ 80.40:80.31 = 1:9.1 (80.1% ee).

Computational methods

Molecular modeling was performed with the use of the modeling package Quanta/CHARMm[19] on a Silicon Graphics Indigo (R4400) workstation. Superposition was carried out using torsional flexible-fit and rigid body-fit procedures based on two carboxyl oxygens, five carbons (C1, C2, C10–12), and an allylic-alcohol oxygen. Some of the conformers obtained from torsional flexible fitting were minimized with the CHARMm force field (Adopted-Basis Newton–Raphson method) and then superposed using the rigid body-fit procedure.

Biological methods

Materials. Tritiated LTB_4 preparations with a specific activity of 32 Ci/mmol and a radiochemical purity of >95% were purchased from New England Nuclear (Boston). Non-radioactive LTB_4 was prepared according to Corey's method.[20] Ficoll-paque was purchased from Pharmacia LKB (Uppsala, Sweden). All other chemicals were commercial reagent-grade materials.

Neutrophil preparation. Human neutrophils were isolated from the citrated peripheral blood of normal volunteers by dextran sedimentation, followed by Ficoll-paque gradient centrifugation, and hypotonic lysis of erythrocytes.

Binding assay studies. The effectiveness of compounds to inhibit the binding of $[^3H]LTB_4$ to neutrophils was measured by using an adaptation of a radioligand-binding assay reported by Gorman and Lin.[21] The following were added to polypropylene tubes in a final volume of 1.0 mL: 10 μL DMSO containing different amounts of tested compounds, 100 μL of 10 nM $[^3H]LTB_4$ (final concentration of 1.0 nM), and 0.5 mL of neutrophils enriched to 95% purity suspended at a concentration of 2×10^7 cells/mL in ice-cold Hank's balanced salt solution (HBSS) pH 7.4 and 0.39 mL of HBSS. The tubes were then incubated at 0 °C for 20 min. The reaction was terminated by the addition of ice-cold HBSS (2.5 mL) followed by vacuum filtration through Whatman CF/C glass fiber filters. The radioactivity retained in the filters was measured by liquid scintillation spectrometry. Nonspecific binding was defined as $[^3H]LTB_4$ bound in the presence of 3.0 μM unlabled LTB_4. The specific binding was determined by subtracting the nonspecific binding from the total binding. The concentration of the compounds which inhibited 50% of the specific $[^3H]LTB_4$ binding was identified as the IC_{50} value.

Aggregation assay studies. Human neutrophils (10^7 cells/mL) in HBSS containing 0.5% bovine serum albumin (pH 7.4) were incubated with 10 nM LTB_4 or 10 μL DMSO containing different amounts of tested compounds at 37 °C for 1 min. Aggregation was monitored as the change in light transmission using the multichannel aggregometer (HEMA TRACER 1, Nikou Bio Science, Tokyo). The effective concentration of the compounds which induced 50% of the maximal aggregation by 10 nM LTB_4 alone was identified as the EC_{50} value.

References

1. (a) Bray, M. A. *Agents Actions* **1986**, *19*, 87. (b) Brain, S. D.; Williams, T. J. *Pharmac. ther.* **1990**, *46*, 57.

2. Thorsen, S.; Fogh, K.; Broby-Johansen, U.; Sondergaard, J. *Allergy* **1990**, *45*, 457.

3. Fretland, D. J.; Widomski, D. L.; Levin, S.; Gaginella, T. S. *Inflammation* **1990**, *14*, 143.

4. Klickstein, L. B.; Shapleigh, C.; Goetzl, E. J. *J. Clin. Invest.*. **1980**, *66*, 1166.

5. Rae, S. A.; Davidson, E. M.; Smith, M. J. H. *Lancet* **1982**, 1122.

6. Ford-Hutchinson, A. W. *Crit. Rev. Immunol.* **1990**, *10*, 1.

7. Yamamoto, H.; Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768.

8. The intramolecular cyclization of the amide ester chain of **18b** was observed in this case. This difference from other similar examples may depend on slight differences in the reaction conditions such as reaction temperature, reaction time, and equivalent of sodium hydride, among others. This reaction was not optimized.

9. Physical and spectroscopic data of *tert*-butyl-3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-hydroxyphenyl]-propanoate **29a**: white solid (from AcOEt:hexane, 2:1); mp 105–105.5 °C; R_f value (AcOEt:MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.03 (m, 2H), 2.45 (m, 4H), 2.62 (t, J = 7 Hz, 2H), 2.80 (t, J = 7 Hz, 2H), 2.98 (s, 3H), 3.05 (s, 3H), 6.80 (d, J = 8 Hz, 1H), 7.13 (dd, J = 8 Hz and 2 Hz, 1H), 7.35 (d, J = 2 Hz, 1H), 7.85 (s, 1H), 8.18 (s, 1H); IR (KBr) 3486, 3242, 1719, 1643, 1601, 1164 cm^{-1}; MS (EI) *m/z* 378 (M^+); Anal. calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40%. Found: C, 63.00; H, 7.19; N, 7.44%.

10. Physical and spectroscopic data of ethyl-3-[5-(ethoxycarbonylmethoxy)-2-hydroxyphenyl]propanoate **33a**: pale yellow oil. R_f 0.25 (hexane:AcOEt, 3:1); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 2.47 (t, J = 7 Hz, 2H), 2.85 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 4.27 (q, J = 7 Hz, 2H), 4.55 (s, 2H), 6.67 (m, 2H), 6.80 (d, J = 8 Hz, 1H), 7.00 (s, 1H); MS (EI) m/z 296 (M^+). Physical and spectroscopic data of ethyl-4-[3-[2-(ethoxycarbonyl)ethyl]-4-hydroxyphenoxy]butanoate **33b**: pale yellow oil; R_f 0.25 (hexane:AcOEt, 3:1); ^{1}H NMR ($CDCl_3$) δ 1.23 (m, 6H), 2.07 (m, 2H), 2.50 (t, J = 7 Hz, 2H), 2.70 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 3.92 (t, J = 7 Hz, 2H), 4.13 (m, 4H), 6.63 (m, 2H), 6.80 (d, J = 8 Hz, 1H), 6.88 (s, 1H); MS (EI) m/z 324 (M^+). Physical and spectroscopic data of ethyl-5-[3-[2-(ethoxycarbonyl)ethyl]-4-hydroxyphenoxy]pentanoate **33c**: pale orange oil; R_f 0.20 (hexane:AcOEt, 3:1); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.80 (m, 4H), 2.38 (m, 2H), 2.70 (t, J = 7 Hz, 2H), 2.85 (t, J = 7 Hz, 2H), 3.88 (t, J = 7 Hz, 2H), 4.12 (m, 4H), 6.65 (m, 2H), 6.80 (d, J = 8 Hz, 1H), 6.85 (s, 1H); MS (EI) m/z 338 (M^+). Physical and spectroscopic data of ethyl-3-[5-[4-(dimethylaminocarbonyl)butoxy]-2-hydroxyphenyl]propanoate **33d**: white needles (from AcOEt:hexane, 1:1); mp 76–77 °C; R_f 0.30 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.80 (m, 4H), 2.40 (m, 2H), 2.70 (t, J = 7 Hz, 2H), 2.85 (t, J = 7 Hz, 2H), 2.97 (s, 3H), 3.00 (s, 3H), 3.90 (m, 2H), 4.12 (q, J = 7 Hz, 2H), 6.65 (m, 2H), 6.80 (d, J = 8 Hz, 1H), 6.90 (s, 1H); IR (KBr) 3181, 1735, 1623, 1610, 1508, 1443, 1290, 1202 cm^{-1}; MS (EI) m/z 337 (M^+); Anal. calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15%. Found: C, 64.12; H, 7.79; N, 4.08%.

11. Physical and spectroscopic data of ethyl-5-[3-[2-(ethoxycarbonyl)ethyl]-3-hydroxyphenoxy]pentanoate **47a**: white needles (from hexane:AcOEt, 9:1); mp 41.5–42.5 °C; R_f 0.30 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.82 (m, 4H), 2.40 (m, 2H), 2.70 (m, 2H), 2.88 (m, 2H), 3.95 (m, 2H), 4.12 (m, 4H), 6.40 (d, J = 8 Hz, 1H), 6.58 (d, J = 8 Hz, 1H), 7.05 (t, J = 8 Hz, 1H), 7.90 (s, 1H); IR (KBr) 3398, 1728, 1708, 1598, 1465, 1182, 1078 cm^{-1}; MS (EI) m/z 338 (M^+); Anal. calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74%. Found: C, 63.96; H, 7.65%. Physical and spectroscopic data of ethyl-3-[2-[4-(dimethylaminocarbonyl)-butoxy]-6-hydroxyphenyl]propanoate **47b**: pale brown oil; R_f 0.20 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.85 (m, 4H), 2.40 (m, 2H), 2.70 (m, 2H), 2.88 (m, 2H), 2.98 (s, 3H), 3.02 (s, 3H), 3.97 (m, 2H), 4.12 (q, J = 7 Hz, 2H), 6.40 (d, J = 8 Hz, 1H), 6.58 (d, J = 8 Hz, 1H), 7.05 (t, J = 8 Hz, 1H), 7.85 (s, 1H); IR (neat) 3240, 2943, 1724, 1610, 1465, 1089 cm^{-1}; MS (EI) m/z 337 (M^+); EI HRMS m/z 337.1883 ($C_{18}H_{27}NO_5$ 337.18894).

12. Corey, E.J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611, and references therein.

13. Mosher, H. S.; Sullivan, G. R.; Dale, J. A. *J. Org. Chem.* **1973**, *38*, 2143, and references therein.

14. The synthetic method of compound **55** will be described in an accompanying paper. Konno, M.; Nakae, T.; Sakuyama, S.; Odagaki, Y.; Nakai, H.; Hamanaka, N. *Bioorg. Med. Chem.* **1997**, *5*, 1649.

15. (a) Kishikawa, K.; Tateishi, N.; Maruyama, R.; Seo, R.; Toda, M.; Miyamoto, T. *Prostaglangins* **1992**, *44*, 261–275. (b) Kishikawa, K.; Nakao, S.; Matsumoto, S.; Kondo, K.; Hamanaka, N. In *Advances in Prostaglandin, Thromboxane, and Leukotriene Reseach*; Samuelsson, B. et al., Eds; Raven Press: New York, 1995; Vol. 23, pp 279–281.

16. Sugiura, M.; Beierbeck, H.; Belanger, P. C.; Kotovych, G. *J. Am. Chem. Soc.* **1984**, *106*, 4021.

17. LeBlanc, Y.; Fitzsimmons, B. J.; Charleston, S.; Alexander, P.; Evans. J. F.; Rokach, J. *Prostaglandins* **1987**, *33*, 617.

18. Namiki, M.; Iganashi, Y.; Sakamoto, K.; Koga, Y. *Biochem. Biophys. Res. Commun.* **1986**, *138*, 540.

19. Quanta/CHARMm, a molecular modeling system, is supplied by Molecular Simulations, 9685 Scranton Road, San Diego, CA 92121-3752, U.S.A.

20. Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984.

21. Gorman, R. R.; Lin, A. H. In *Methods Enzymol.*; Conn, P. M.; Means, A. R., Ed.; Academic Press: London, 1987; Vol 141, pp 372–378.

(*Received in Japan* 20 *February* 1997; *accepted* 17 *April* 1997)