Eur J Med Chem (1996) 31, 347–358

Synthesis and PAF antagonist activity of some 2,5-diaryltetrahydrofurans incorporating PAF-like functional groups

S Smith[1]*, GJ Blackwell[2], DA Demaine[1], LG Garland[2], HF Hodson[1], RM Hyde[3], AJ Parke[2], VS Rose[3], DA Sawyer[1], L Tilling[2]

[1]*Department of Medicinal Chemistry, Wellcome Research Laboratories;*
[2]*Department of Biochemical Sciences, Wellcome Research Laboratories;*
[3]*Department of Physical Sciences, Wellcome Research Laboratories, Langley Court, South Eden Park Road, Beckenham, Kent, BR3 3BS, UK*

(Received 1 August 1995; accepted 27 November 1995)

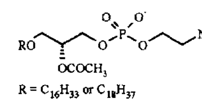
Summary — This paper describes the synthesis and structure–activity relationships of a series of 2,5-diaryltetrahydrofurans, as specific and potent antagonists at the rabbit washed platelet activating factor (PAF) receptor. The methoxyl groups in the known PAF antagonist L-652,731 were replaced with functional groups present in PAF and in the 'PAF-like' antagonists. Activity was generally retained or enhanced when one aryl ring in L-652,731 was elaborated; however incorporation of these functional groups into both of the aryl rings greatly reduced or abolished activity. These results are discussed in relation to a putative model for the PAF receptor.

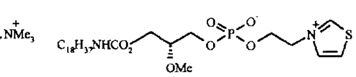
PAF antagonist / diaryltetrahydrofuran / PAF receptor modelling

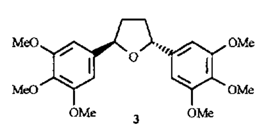
Introduction

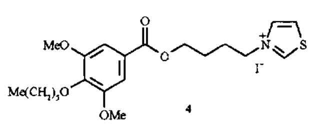
Platelet activating factor (PAF) **1** is a phospholipid derivative which acts as a potent mediator of numerous physiological responses [1]. PAF is believed to act via specific high affinity receptors, and antagonists of PAF are currently under investigation as potential therapies for such conditions as asthma and septic shock [2]. To date, a large number of PAF antagonists have been described in the literature, and are of many, widely varying, structural types. One series of antagonists bears a structural resemblance to PAF, eg, CV3988 **2** [3]. Other, 'non-PAF-like', antagonists include the natural products Ginkgolide B [4] and kadsurenone [5] and the synthetic compounds WEB 2086 (Apafant) [6] and L-652,731 **3** [7]. More recently a highly potent series of antagonists has been described by workers at British Biotechnology [8].

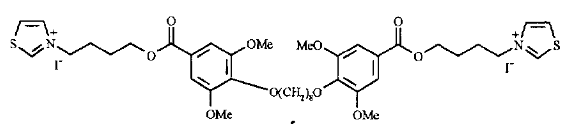
Much effort has been directed towards attempts to find a common pharmacophore amongst these apparently diverse chemical entities, and to develop a model for the binding of PAF and its antagonists to the receptor. A simple hypothesis, first put forward by Braquet et al [9] for the binding of Ginkgolide B, has been successively modified and refined in the light of


1


2


3


4


5

new results [10–15]. A model was developed which consisted of a pair of negative electrostatic potential regions likened to 'cache-oreilles' or 'ear-muffs'. The receptor was postulated to be a multipolarized cylinder, with a set of 'cache-oreilles' 10–12 Å apart, at 180° to each other, and a hydrophobic pocket inside the cylinder [10, 14].

We have developed a series of potent trialkoxyphenyl PAF antagonists, eg, **4** [16], and have found that symmetrical molecules, eg **5** (Sawyer et al, unpublished results), incorporating two of these moieties

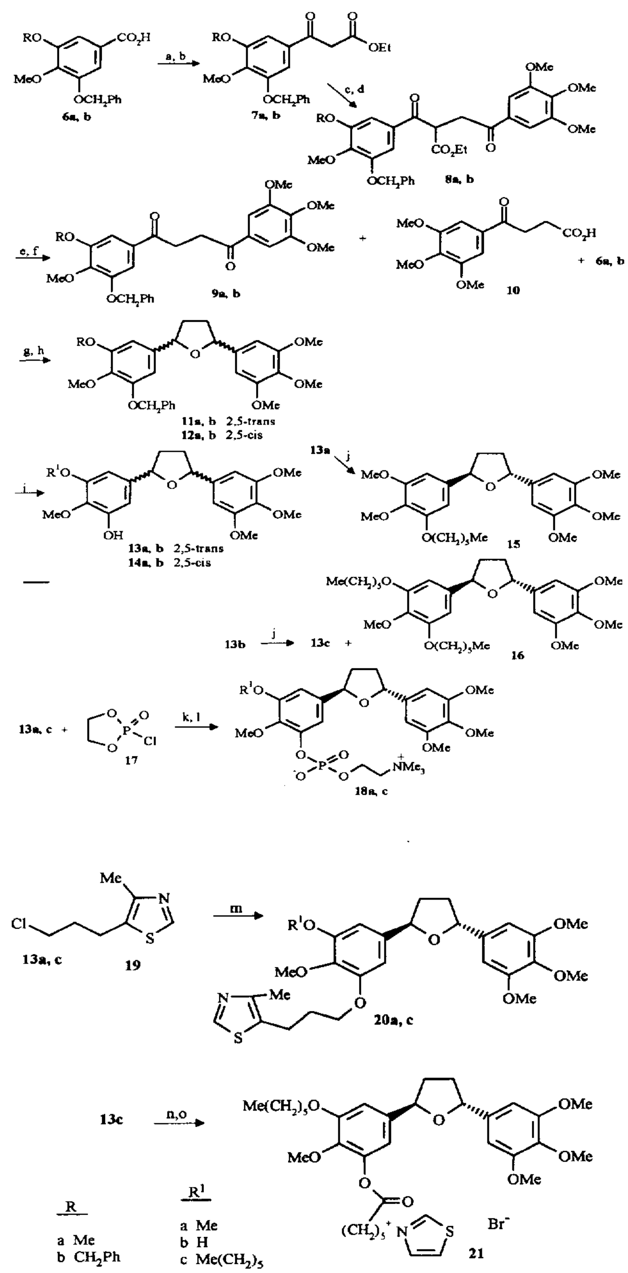
*Current address: Department of Enzyme Medicinal Chemistry I, GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, UK joined 'tail to tail', show enhanced PAF antagonism in rabbit washed platelets (pK_B values of 6.16 and 7.30 for **4** and **5** respectively). These results led us to speculate that two PAF receptors may be closely associated in the membrane, or that two PAF molecules act together on the sàme receptor complex. This hypothesis appeared reasonable considering the tendency of phosphatide molecules such as PAF to associate into micelles or other aggregates in solution.

A structural feature common to PAF and to the antagonists **2** and **4** is a chain terminating in a quaternary nitrogen atom, which is absent in L-652,731 **3**. Hence we postulated that two nitrogen terminated chains incorporated into the structure of L-652,731 **3** may have increased affinity by locating the quaternary N^+ binding sites for the putative two PAF molecules, as may be the case with **5**. The suggestion that L-652,731 may be a 'loose fit' on the receptor and that tighter binding may be achieved by incorporating an appropriate charged substituent has also been made by Corey [17]. In this paper we describe the synthesis and antagonistic activity at the rabbit washed platelet PAF receptor, of a series of analogues of L-652,731 **3** which incorporate polar N-terminated chains and also lipophilic alkyl chains to mimic those present in PAF. Results obtained with our series of antagonists, eg, **4** [16], suggested that it would be wise to limit the lipophilic chain length to six carbon atoms, since longer alkyl chains may lead to problems of non-specificity (characterized by a general inhibition of cellular functions in our bio-assay).

Analogues **11a–21**, which could be regarded as analogous to the 'mono' series, eg **4**, in which the substituents on one of the trimethoxyphenyl rings of **3** were extended, were synthesized first and then both trimethoxyphenyl rings were elaborated to provide **27a–29b**, analogues of the 'bis' series, eg, **5**. The intermediates in the syntheses were also assayed for PAF antagonism, so as to provide further structure–activity (SAR) information.

Chemistry

The unsymmetrically substituted diaryltetrahydrofurans **11a–21**, ie, compounds retaining one 3,4,5-trimethoxyphenyl ring, were synthesized as shown in scheme 1, starting from 3-benzyloxy-4,5-dimethoxybenzoic acid [18] and 3,5-dibenzyloxy-4-methoxybenzoic acid [19]. Thus the acids **6** were converted in high yield, via the acid chlorides, to the β-ketoesters **7**, which were alkylated with 3,4,5-trimethoxyphenacyl bromide. Subsequent hydrolysis and decarboxylation afforded the required 1,4-diketones **9** in modest yield, together with **6** and **10**. Reduction to the 1,4-diol followed by cyclization with TFA as reported in



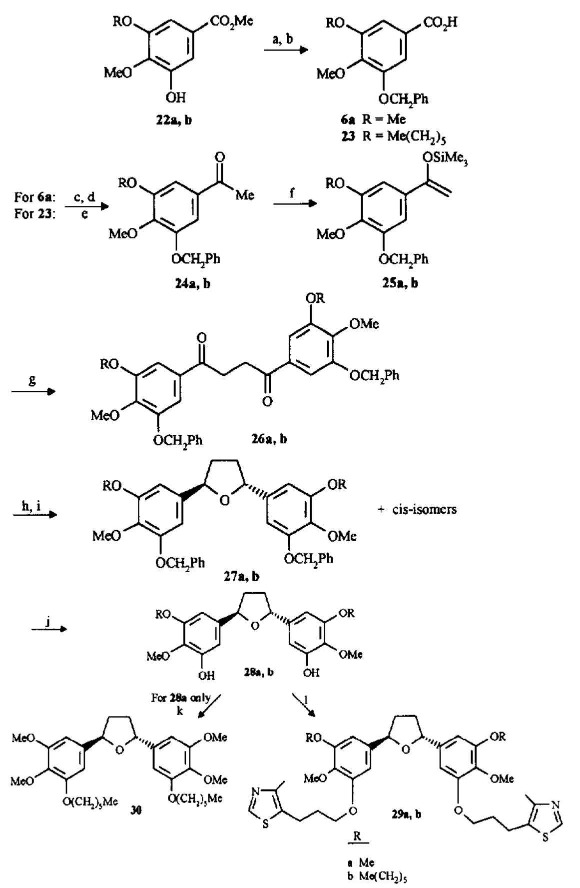
All asymmetric compounds are racemic mixtures

Reagents: a) $(COCl)_2$, C_6H_6; b) EtOAc, $LiNPr^i_2$, -60°C; c) NaH, Et_2O; d) 3,4,5-trimethoxyphenacyl bromide; e) NaOH, H_2O, EtOH; f) HCl; g) $NaBH_4$, EtOH; h) CF_3CO_2H; i) H_2, Pd/C; j) $Me(CH_2)_5Br$, K_2CO_3, DMF; k) NEt_3, C_6H_6; l) NMe_3, MeCN; m) K_2CO_3, DMF; n) 6-bromohexanoyl chloride, C_6H_6, pyridine; o) thiazole, 100°C.

Scheme 1.

the literature [20], gave a mixture of *cis* and *trans* 2,5-diaryltetrahydrofurans **11** and **12**. In the case of **11a** and **12a** (R = Me), separation was accomplished by means of preparative HPLC, the yields being 51% of the *trans* isomer **11a** and 9% of the *cis* isomer **12a**. In the case of **11b** and **12b** however, the major *trans* isomer crystallized from the mixture. Hydrogenolysis afforded the phenols **13** and **14**. Hexylation of **13a** gave **15**, whereas hexylation of **13b** afforded a mixture of **13c** (42%) and the 1,3-dihexyloxy-compound **16** (17%). The phosphocholine moiety was introduced into **13a** and **13c** by means of the cyclic reagent **17** [21, 22]. The phenols **13a** and **13c** were also alkylated using the chloride **19** [23], since a 4-methylthiazolyl-terminated chain appeared to be an acceptable replacement for a quaternary nitrogen in the series exemplified by **4** [16]. An example of a quaternary thiazolium salt **21** was provided by acylation of **13c** with 6-bromohexanoyl chloride, followed by quaternization using thiazole.

For the synthesis of the symmetrically substituted analogues (scheme 2) a different approach was adopted, namely the oxidative coupling of two molecules of an appropriately substituted acetophenone. The coupling methodology described [20] for the synthesis of **3** gave poor results with compounds **24**, but after some experimentation, successful coupling was achieved via the trimethylsilyl enol ethers **25a** and **25b**, which furnished the 1,4-diketones **26a** and **26b** in moderate to good yield upon treatment with methyllithium and copper(II) triflate [24]. The diketones **26a,b** were reduced and cyclized to the tetrahydrofurans **27a,b**, as for compounds **9**. The major *trans* isomers were separated from the minor *cis* congeners by means of preparative HPLC. After deprotection, the dihydroxy compounds **28a** and **28b** were alkylated by means of 5-(3-chloropropyl)-4-methylthiazole **19** to afford the symmetrical 'bis-PAF' analogues **29a** and **29b**. The dihexyloxy compound **30** was prepared by hexylation of **28a**. All compounds were synthesized as racemic mixtures. The acetophenone coupling methodology was also employed for synthesis of the parent compound L-652,731, **3**. Two simple model compounds, **31a** and **31b**, devoid of the tetrahydrofuran ring, were also prepared (scheme 3), starting from 2-methoxyresorcinol.

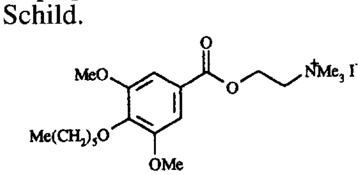


Reagents: a) $PhCH_2Br$, K_2CO_3, DMF; b) NaOH, H_2O, MeOH; c) $(COCl)_2$; d) $LiCH(CO_2SiMe_3)_2$, then H^+, Δ; e) MeLi, Me_3SiCl, then HCl; f) Me_3SiCl, NEt_3, MeCN; g) MeLi, THF, then $Cu(OSO_2CF_3)_2$; h) $NaBH_4$; i) CF_3CO_2H; j) H_2, Pd/C; k) $Me(CH_2)_5Br$, K_2CO_3, DMF; l) **19**, K_2CO_3, DMF

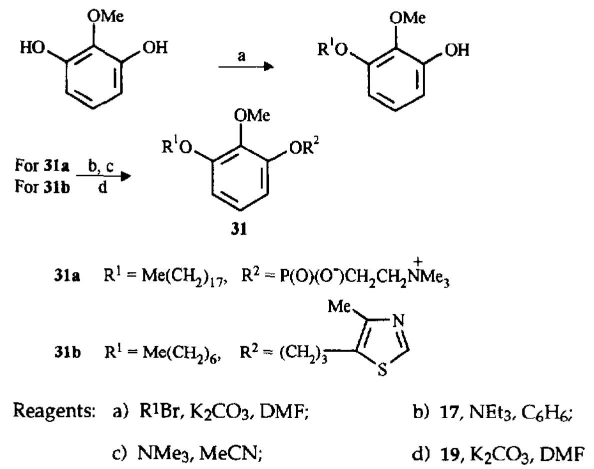
Scheme 2.

Pharmacology

The methods used to evaluate compounds at the rabbit platelet receptor have been detailed in a previous paper [16]. Briefly, the ability of the test compounds to antagonize PAF-induced aggregation of rabbit washed platelets was determined. In a primary assay, an IC_{50} value was obtained, by measuring the aggregations produced by an ED_{50} dose of PAF at a range of antagonist concentrations. The IC_{50} value of an internal reference antagonist **32** [16] was also determined each time, so as to give an IC_{50} ratio value for each compound. Full dose-response curves were then obtained and pK_B values determined, according to the method of Schild.



32



Scheme 3.

Results and discussion

Considering the unsymmetrical analogues (table I), the replacement of one methoxyl group of **3** with a benzyl group (**11a**) or a hexyl chain (**15**) results in an increase in potency, albeit small. However, if both R^1 and R^2 are hexyl (**16**), no enhancement is seen. The two phosphocholine analogues **18a** and **18c** both show significant loss of potency relative to their methoxy analogues **3** and **15**. This is in keeping with previous studies on phosphocholine compounds in which modifications elsewhere have generally led to loss of affinity [25]. The thiazole-containing phosphocholine replacements which had been successfully employed in **4**, here led to enhancements in potency of 0.4 log units (**20a** and **20c**) relative to their methoxyl counterparts **3** and **15** respectively. Thiazolium salt **21** is also a potent compound. Thus the incorporation of one lipophilic chain and one N-terminated chain into L-652,731 **3** (ie, **20c**) has led to an increase of 1 log unit in potency. Whilst this increase is modest, and it should be borne in mind that these compounds are racemic mixtures, these results lend some support to the hypothesis that the affinity of **3** may be increased by incorporating 'PAF-like' moieties.

The primary IC_{50} assay indicated that the *cis* analogues **12a** and **14a** were significantly less potent than their *trans* counterparts, consistent with previous reports [17] and so full pK_B values were not determined for these compounds.

The symmetrically substituted analogues (table II), in contrast to the above, showed a striking loss of activity. The 'bis' analogue **29b** of the potent 'mono' compound **20c** was essentially inactive. Only **29a** which contains two thiazolyl chains and no hexyl chains, showed modest activity. The compound **31b** (table III), devoid of the tetrahydrofuran and second trialkoxyphenyl rings, was inactive, clearly indicating the necessity of one or more of the latter.

Independently of Braquet et al [10–15], we had attempted to develop a simple working model for the rabbit platelet PAF receptor, which is obviously difficult in view of the flexibility of both PAF and our series of antagonists, eg, **5**. Indeed, the receptor itself may be a rather flexible structure with multiple conformations [26]. However, the symmetrical appearance of the more rigid antagonist L-652,731 **3**, which contains a pair of 'cache-oreilles', led us to suggest a model incorporating both this structure and two PAF molecules (fig 1) and accommodating our antagonist **5**, which may be regarded as containing both 'cache-oreille' and 'PAF-like' moieties (fig 2). (This makes the assumption that PAF and these antagonists bind at the same site.) The L-652,731 molecule was proposed to bridge across the two putative PAF binding sites, with the oxygen 'cache-oreilles' of the two trimethoxyphenyl groups corresponding to the glyceryl oxygen atoms in the PAF molecules. Between the two regions of negative potential there is a deep hydrophobic cleft, which can accommodate the long alkyl chains in the PAF molecules. The linking chain in **5** is also accommodated within this region, provided the molecule adopts the conformation depicted in figure 2. This view is supported by the reported [27] high affinity of an analogue of **3** in which the central tetrahydrofuran ring is replaced by a lipophilic cyclopentane ring with a pendant propynyl chain. The two N-terminated chains are proposed to extend onto the same face of the putative membrane-bound receptor complex. It is emphasized that these modes of overlay represent only one of several possibilities; however they appeared to form a plausible basis for the design of the extended L-652,731 molecules reported herein.

The results obtained (table II) therefore cast doubt upon the validity of this approach, appearing to suggest the non-equivalence of the two aryl rings in **3**, a finding supported by more recent papers from the Merck group, describing potent non-symmetrical analogues of **3** [28, 29]. Both rings appear to be necessary however (activity of **20c** compared to **31b**). Any model will however, need to explain the enhanced affinity of **5** over **4**. Compound **5** could adopt different conformations from that depicted in figure 2, in particular, a fully extended, linear conformation is probable. This would also be compatible with the 'cache-oreilles' model, the distance between the central oxygen atoms forming the 'cache-oreilles'

Table I. Activity of unsymmetrically substituted (±)-trans-2,5-diaryltetrahydrofurans.

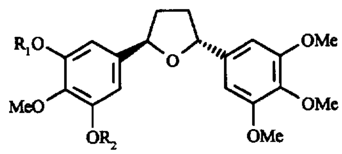
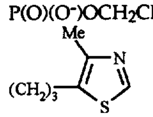


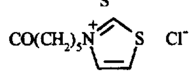
Figure indicates relative stereochemistry. All compounds are racemic.

Compound	R_1	R_2	*Mp (°C)*	*Formula*	pK_B
3(L652,731)	Me	Me	138–140[a]	$C_{22}H_{28}O_7$	6.8
11a	Me	$PhCH_2$	Oil	$C_{28}H_{32}O_7$	7.2
11b	$PhCH_2$	$PhCH_2$	141–142	$C_{34}H_{36}O_7$	7.2
13a	Me	H	Oil	$C_{21}H_{26}O_7$	6.3
13b	H	H	129–132	$C_{20}H_{24}O_7$	6.2
15	$Me(CH_2)_5$	Me	Oil	$C_{27}H_{38}O_7$	7.4
13c	$Me(CH_2)_5$	H	70–73	$C_{26}H_{36}O_7$	8.1
16	$Me(CH_2)_5$	$Me(CH_2)_5$	Oil	$C_{32}H_{48}O_7$	6.8[b]
18a	Me	PC	138–141	$C_{26}H_{38}NO_{10}P{\cdot}1.2H_2O$	4.3
18c	$Me(CH_2)_5$	PC	[c]	$C_{31}H_{48}NO_{10}P{\cdot}H_2O$	5.7
20a	Me	A	Oil	$C_{28}H_{35}NO_7S{\cdot}1.5H_2O$	7.2
20c	$Me(CH_2)_5$	A	Oil	$C_{33}H_{45}NO_7S{\cdot}0.5H_2O$	7.8
21	$Me(CH_2)_5$	B	[c]	$C_{35}H_{48}ClNO_8S{\cdot}0.5H_2O$	7.5

[a]Lit [20] 140–141 °C; [b]pA_2 value; [c]hygroscopic lyophilisate, no sharp mp.

PC = $P(O)(O^-)OCH_2CH_2N^+Me_3$

A = 

B = 

being ca 11.2 Å in an extended conformation of **5**. Further studies are in progress in order to elucidate the precise manner in which either one or two PAF molecules are related to the 'cache-oreilles' model and to compound **5**.

Experimental protocols

Biological assays

The detailed experimental protocols have been fully described previously [16].

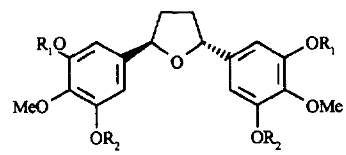
Chemistry

Melting points were determined on an Electrothermal apparatus and are uncorrected. ^{1}H-NMR spectra were recorded at 200 MHz using a Bruker AM200 instrument. Mass spectra were obtained at 70 eV on a Kratos MS-25 spectrometer and IR spectra were recorded on a Perkin-Elmer 580 instrument. Chemical shifts are quoted in ppm relative to tetramethylsilane. TLC was performed using Merck pre-coated silica gel plates. Column chromatography was performed using 'flash' technique on Merck silica gel 60 (230-400 mesh). High performance liquid chromatography (HPLC) was carried out using silica columns (analytical or preparative as appropriate) on a Waters instrument, compounds being detected by their UV absorbance at 254 nm.

Compound **3** has been described in the literature [7]. All other analogues are novel.

*Ethyl-(3-benzyloxy-4,5-dimethoxy)benzoylacetate **7a***
To a suspension of 3-benzyloxy-4,5-dimethoxybenzoic acid **6a** [18] (26.3 g, 0.091 mol) in dry benzene (100 mL) was added oxalyl chloride (17 mL, 0.195 mol) and DMF (0.3 mL). The mixture was stirred for 45 min at room temperature, then

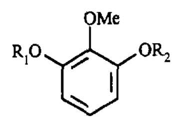
Table II. Activity of symmetrically substituted (±)-trans-2,5-diaryltetrahydrofurans.



Compound	R_1	R_2	*Mp (°C)*	*Formula*	pK_B
27a	Me	$PhCH_2$	118–120	$C_{34}H_{36}O_7$	a
27b	$Me(CH_2)_5$	$PhCH_2$	Oil	$C_{44}H_{56}O_7$	I[b]
28a	Me	H	156–158	$C_{20}H_{24}O_7$	6.4[c]
28b	$Me(CH_2)_5$	H	Oil	$C_{30}H_{44}O_7{\cdot}0.25H_2O$	I
30	$Me(CH_2)_5$	Me	Oil	$C_{32}H_{48}O_7$	I
29a	Me	A	Oil	$C_{34}H_{42}N_2O_7S_2$	6.2
29b	$Me(CH_2)_5$	A	Oil	$C_{44}H_{62}N_2O_7S_2{\cdot}H_2O$	I

[a]Insoluble in assay medium; [b]I = inactive at 10^{-5} M; [c]pA_2 value.

Table III. Activity of 1,2,3-trisubstituted benzenes.



Compound	R_1	R_2	*Mp (°C)*	*Formula*	pK_B
31a	$Me(CH_2)_{17}$	PC	262–265	$C_{30}H_{56}NO_6P$	NS[a]
31b	$Me(CH_2)_5$	A	Oil	$C_{20}H_{29}NO_3S$	I[b]

[a]Non-specific inhibition of platelet aggregation; [b]inactive at 10^{-5} M.

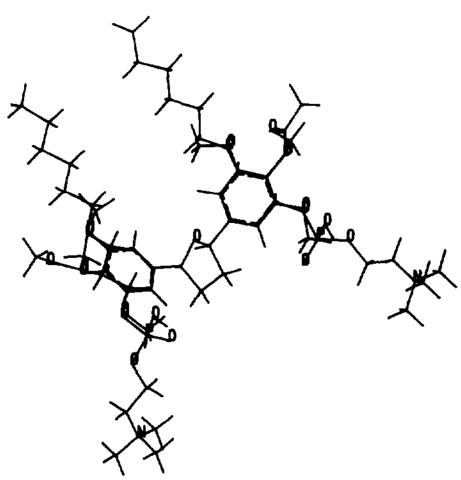


Fig 1. Putative overlay of L-652,731 **3** and two PAF molecules (shown with alkyl chains truncated to six carbons).

30 min at 60 °C. After cooling, the solution was decanted from a small oily phase and the solvent evaporated, giving acid chloride [18] as a yellow solid which was directly converted to the β-ketoester **7a** as follows: lithium diisopropylamide was generated by the slow addition of *n*-butyllithium (114 mL of 1.6 M solution in hexane, 0.182 mol) to diisopropylamine (25.5 mL, 0.182 mol) in dry THF (150 mL) at –70 °C. This solution was stirred for 10 min, then dry ethyl acetate (8.94 mL, 0.091 mol) was added, maintaining the temperature below –60 °C. After a further 10 min, a solution of the acid chloride in dry THF (150 mL) was added over 10 min. After 30 min at –60 °C, 6M HCl (55 mL) was added and the mixture allowed to warm to room temperature. The product was extracted with Et_2O, the extracts washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent removed. Purification by chromatography (EtOAc/hexane, 2:5) gave **7a** as a colourless oil (30.4 g, 93%); ^{1}H-NMR ($CDCl_3$), 1.20 (3H, t, J = 7 Hz, CH_2CH_3), 3.82 (6H, s, 2 x OMe), 3.86 (2H, s, $COCH_2$), 4.10 (2H, q, J = 7 Hz, CH_2CH_3), 5.10 (2H, s, $PhCH_2$), 7.2–7.4 (7H, m, aromatic); IR (film) 1740, 1680 cm^{-1}; m/z 358 (M^+); anal $C_{20}H_{22}O_6$ (C, H).

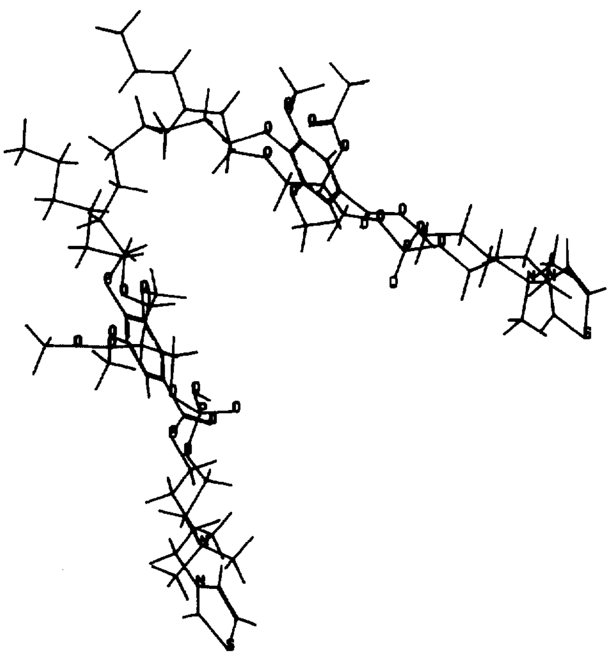


Fig 2. Putative overlay of **5** with two truncated PAF molecules.

(±)-Ethyl-2-(3-benzyloxy-4,5-dimethoxybenzoyl)-4-(3,4,5-trimethoxyphenyl)-4-oxobutanoate ***8a***

Sodium hydride (60% dispersion, 3.5 g, 87.5 mmol) was washed free of oil using dry Et_2O, under N_2, and suspended in fresh Et_2O (50 mL). To this suspension was added a solution of **7a** (30.4 g, 85 mmol) in dry Et_2O (150 mL). When initial effervescence had subsided, the mixture was refluxed gently for 2.5 h, then cooled to room temperature. A solution of 3,4,5-trimethoxyphenacyl bromide (24.6 g, 85 mmol) in dry Et_2O (150 mL) was added and heating continued at reflux for 4 h. After cooling, the mixture was washed with water, dried (Na_2SO_4) and the solvent removed. Chromatography (EtOAc/hexane, 2:3) afforded **8a** (40.0 g, 83%) as a viscous gum; ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J = 7 Hz, CH_2CH_3), 3.67–3.73 (2H, m, $COCH_2$), 3.90–3.98 (15H, 5s, 5 x OMe), 4.17 (2H, q, J = 7 Hz, CH_2CH_3), 5.03 (1H, t, J = 7 Hz, COCH), 5.18 (2H, s, $PhCH_2$), 7.2–7.5 (9H, m, aromatics); IR ($CHCl_3$) 1730, 1675 cm^{-1}.

1-(3-Benzyloxy-4,5-dimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)butan-1,4-dione ***9a***

The ester **8a** (39.5 g, 69.8 mmol) in EtOH (100 mL) was stirred vigorously with 5% aqueous NaOH (112 mL, 140 mmol), at room temperature for 7 h. The resulting yellow suspension was acidified to pH 3 using 2M HCl, and heated to reflux for 15 min. Water (100 mL) was added and the solution refrigerated for crystallization. The first crop was filtered off, dissolved in $CHCl_3$ and washed with 5% $NaHCO_3$. The solution was dried over Na_2SO_4 and the solvent removed. Recrystallization from aqueous EtOH afforded **9a** (9.1 g, 26%), mp 156–158 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.40 (4H, s, 2 x CH_2CO), 3.9–4.0 (15H, m, 5 x OMe), 5.19 (2H, s, $PhCH_2$), 7.25–7.55 (9H, m, aromatics); m/z 494 (M^+); anal $C_{28}H_{30}O_8$ (C, H).

On standing, the mother liquor from the first crystallization slowly deposited a second crystalline solid, which was identified as 4-(3,4,5-trimethoxyphenyl)-4-oxobutanoic acid **10** (5.5 g, 29%), mp 113–115 °C (lit [30] 117–118 °C). The mother liquors also contained 3-benzyloxy-4,5-dimethoxybenzoic acid **6a**.

(±)-cis-2-(3-Benzyloxy-4,5-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran ***12a*** *and (±)-trans-2-(3-benzyloxy-4,5-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran* ***11a***

The diketone **9a** (9.0 g, 18.2 mmol) was suspended in dry EtOH (150 mL) and sodium borohydride (1.60 g, 42 mmol) was added. The mixture was heated at 70 °C for 80 min, cooled and quenched by adding saturated aqueous ammonium chloride, and extracted three times with Et_2O. The extracts were washed with saturated NaCl solution, dried (Na_2SO_4) and the solvent evaporated to give the diastereomeric mixture of (±)-1-(3-benzyloxy-4,5-dimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)butan-1,4-diols as a viscous gum, used directly in the next step. ^{1}H-NMR ($CDCl_3$) δ: 1.70–1.95 (4H, m, CH_2CH_2), 3.80–3.85 (15H, m, 5 x OMe), 4.58–4.68 (2H, m, 2 x $CHOH$), 5.10 (2H, s, $PhCH_2$), 6.50–6.60 (4H, m, aryl), 7.25–7.50 (5H, m, Ph); m/z 498 (M^+). To a solution of this diol (8.8 g, 17.7 mmol) in $CHCl_3$ (70 mL) was added a mixture of trifluoroacetic acid (7 mL) and $CHCl_3$ (70 mL). After stirring at room temperature for 80 min, solid sodium carbonate (18 g) was added and the mixture stirred for a further 30 min. The solids were filtered off and the solvent evaporated. This residue showed two spots on TLC, Rfs 0.33 and 0.37 (EtOAc/hexane, 1:1). The mixture was chromatographed on a column of silica (200 g), eluting with EtOAc/hexane (1:2). This failed to separate the two components effectively, however. The recovered mixture (6.8 g) was then subjected to preparative HPLC (silica column, 25 mm diameter) using EtOAc/hexane (1:3), injecting the mixture in batches of 200 mg. The first eluted component was the pure *trans* isomer **11a** (4.32 g, 51%), obtained as a viscous gum. ^{1}H-NMR ($CDCl_3$) δ: 1.86–2.06 (2H, m, ring CH_2), 2.34–2.52 (2H, m, ring, CH_2), 3.85–3.92 (15H, m, 5 x OMe), 5.10–5.22 (4H, m, $PhCH_2$ + 2 x CHO), 6.6–6.7 (4H, m, aryl), 7.25–7.50 (5H, m, Ph); m/z 480 (M^+); anal $C_{28}H_{32}O_7$ (C, H).

The second eluted component (0.80 g) was contaminated with a small quantity of **11a** and so the preparative HPLC was repeated on this material to give essentially pure *cis* isomer **12a** (0.76 g, 9%) as a gum; ^{1}H-NMR ($CDCl_3$) δ 1.88–2.05 (2H, m, ring CH_2), 2.30–2.50 (2H, m, ring CH_2), 3.83–3.88 (15H, m, 5 x OMe), 5.00 (2H, m, 2 x CHO), 5.10 (2H, s, $PhCH_2$), 6.62–6.72 (4H, m, aryl), 7.25–7.50 (5H, m, Ph); m/z 480 (M^+); anal $C_{28}H_{32}O_7$ (C, H).

(±)-trans-2-(5-Hydroxy-3,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran ***13a***

The *trans* benzyl compound **11a** (1.56 g, 3.25 mmol) in EtOH (60 mL) was hydrogenated at atmospheric pressure and ambient temperature, using 5% palladium on carbon (300 mg) as catalyst. When H_2 uptake had ceased, the mixture was filtered through Celite and the solvent evaporated, giving **13a** as a gum (1.20 g, 94%) which showed a single component on TLC and HPLC (EtOAc/hexane, 2:5). ^{1}H-NMR ($CDCl_3$) δ: 1.90–2.06 (2H, m, ring CH_2), 2.36–2.52 (2H, m, ring CH_2), 3.80–3.90 (15H, m, 5 x OMe), 5.17 (2H, m, 2 x CHO), 6.54–6.66 (4H, m, aryl); m/z 390 (M^+); anal $C_{21}H_{26}O_7$ (C, H).

*(±)-cis-2-(5-Hydroxy-3,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran **14a***

This compound was obtained by hydrogenolysis of **12a** as described above. The product **14a** crystallized from EtOAc/hexane (75% yield); mp 102–104 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.88–2.05 (2H, m, ring CH_2), 2.30–2.48 (2H, m, ring CH_2), 3.80–3.90 (15H, m, 5 x OMe), 4.98 (2H, m, 2 x C*H*O), 6.56–6.72 (4H, m, aryl); *m/z* 390 (M^+); anal $C_{21}H_{26}O_7$ (C, H).

*(±)-trans-2,3-Dimethoxy-5-[5-(3,4,5-trimethoxyphenyl)-2-tetrahydrofuranyl]phenyl 2-(trimethylammonio)ethyl phosphate **18a***

To (±)-*trans*-2-(5-hydroxy-3,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran **13a** (585 mg, 1.5 mmol) in dry benzene (4 mL) was added triethylamine (0.21 mL, 1.5 mmol), and the mixture stirred, under N_2, at 0 °C as a solution of 2-chloro-2-oxo-1,3,2-dioxaphospholane **17** [22] (214 mg, 1.5 mmol) in dry benzene (0.5 mL) was added, dropwise. The mixture was stirred at room temperature for 3 h, the precipitated triethylamine hydrochloride filtered off, and the solvent evaporated. The residual gum was dissolved in dry MeCN (2 mL) and treated with a solution of trimethylamine (0.5 g) in MeCN (2 mL). The mixture was heated at 65 °C in an autoclave for 20 h. After cooling, the solvent was removed and the gummy residue chromatographed on silica (25 g) eluting with $CHCl_3$/MeOH/H_2O (60:35:5). The purified product was taken up in acetone, and on standing, crystallization occurred. The white solid, hydrated **18a**, was rapidly filtered off, washed with acetone and dried in vacuo over P_2O_5 (324 mg, 37%); mp 138–141 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.75–1.97 (2H, m, ring CH_2), 2.30–2.48 (2H, m, ring CH_2), 3.12 (9H, s, N^+Me_3), 3.50–3.59 (2H, m, CH_2N), 3.66 (3H, s, OMe), 3.71 (3H, s, OMe), 3.79 (9H, s, 3 x OMe), 4.10–4.23 (2H, m, CH_2O), 5.10 (2H, m, 2 x C*H*O), 6.69 (3H, s, aryl), 7.14 (1H, s, aryl); *m/z* 556 (M^+ + 1); anal $C_{26}H_{38}NO_{10}P{\cdot}1.2H_2O$ (C, H, N).

*(±)-trans-2-(3-Hexyloxy-4,5-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran **15***

To the phenol **13a** (280 mg, 0.72 mmol) in dry DMF (15 mL) was added K_2CO_3 (0.39 g, 2.83 mmol) followed by a solution of 1-bromohexane (0.12 g, 0.72 mmol) in dry DMF (5 mL). The mixture was heated at 80 °C for 5 h, then cooled, poured into water and extracted with Et_2O. The extracts were washed with water, dried over Na_2SO_4 and the solvent evaporated. Chromatography on a column of silica (EtOAc/hexane, 1:3) afforded the pure **15** as a gum (160 mg, 47%); ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7.0 Hz, CH_3), 1.38–1.55 (6H, m, $(CH_2)_3$), 1.73–1.90 (2H, m, $OCCH_2$-), 1.92–2.10 (2H, m, ring CH_2), 2.38–2.55 (2H, m, ring CH_2), 3.83–3.88 (15H, 2s, 5 x OMe), 4.02 (2H, t, J = 6.7 Hz, OCH_2), 5.20 (2H, m, CHO), 6.61–6.65 (4H, 2s, aryl); anal $C_{27}H_{38}O_7$ (C, H).

*(±)-trans-2-{4,5-Dimethoxy-3-[3-(4-methylthiazol-5-yl)propoxy]-phenyl}-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran **20a***

The phenol **13a** (0.28 g, 0.72 mmol) in dry DMF (4 mL) was treated with K_2CO_3 (0.30 g, 2.17 mmol) followed by a solution in DMF (1 mL) of 5-(3-chloropropyl)-4-methylthiazole **19** (0.13 g, 0.72 mmol). The mixture was heated at 80 °C for 6 h, then cooled and poured into water. Extraction with Et_2O (x 3) followed by washing with water, drying (Na_2SO_4) and evaporation of the solvent gave a residue which was purified by chromatography (EtOAc/hexane, 2:1). This afforded pure **20a** (160 mg, 42%) as a gum; ^{1}H-NMR ($CDCl_3$) δ: 1.89–2.01 (2H, m, ring CH_2), 2.04–2.20 (2H, m, CCH_2C), 2.35–2.54 (5H, m and s, MeC and ring CH_2), 3.03 (2H, t, J = 7.5 Hz, $OCCCH_2$), 3.82, 3.85, 3.88 (15H, 3s, 5 x OMe), 4.15 (2H, t, J = 6 Hz, OCH_2), 5.18 (2H, m, CHO); 6.55 (4H, s and d, J < 1 Hz, aryl); 8.55 (1H, s, S-CH); anal $C_{28}H_{35}NO_7S{\cdot}1.5H_2O$ (C, H, N).

Compounds **7b–9b** were synthesized as described for **7a–9a**.

*Ethyl-(3,5-dibenzyloxy-4-methoxy)benzoylacetate **7b**.* Yield 94%, oil; ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7 Hz, CH_2CH_3), 3.85 (2H, s, CH_2CO), 3.96 (3H, s, OMe), 4.18 (2H, q, J = 7 Hz, CH_2CH_3), 5.15 (4H, s, 2 x $PhCH_2$), 7.25–7.50 (12H, m, aromatic); *m/z* 434 (M^+).

*(±)-Ethyl-2-(3,5-dibenzyloxy-4-methoxybenzoyl)-4-(3,4,5-trimethoxyphenyl)4-oxobutanoate **8b**.* Yield 66%, mp 132–134 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J = 7 Hz, CH_2CH_3), 3.62 (2H, d, J = 7 Hz, CH_2CO), 3.88–3.94 (9H, m, 3 x OMe), 3.96 (3H, s, OMe), 4.15 (2H, q, J = 7 Hz, CH_2CH_3), 4.97 (1H, t, J = 7 Hz, CHCO), 5.18 (4H, s, 2 x $PhCH_2$), 7.2–7.5 (14H, m, aromatics); *m/z* 642 (M^+); anal $C_{37}H_{38}O_{10}$ (C, H).

*1-(3,5-Dibenzyloxy-4-methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-butan-1,4-dione **9b**.* Yield 35%, mp 129–131 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.28–3.42 (4H, m, 2 x CH_2CO), 3.91 (9H, s, 3 x OMe), 3.95 (3H, s, OMe), 5.18 (4H, s, 2 x $PhCH_2$), 7.25–7.50 (14H, m, aromatics); *m/z* 570 (M^+); anal $C_{34}H_{34}O_8$ (C, H).

*(±)-trans-2-(3,5-Dibenzyloxy-4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran **11b***

The diketone **9b** was reduced using $NaBH_4$ as described for **9a**, yielding (±)-1-(3,5-dibenzyloxy-4-methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)butan-1,4-diol, 97%, gum; ^{1}H-NMR ($CDCl_3$) δ: 1.77 (4H, br s, CH_2CH_2), 3.8–3.9 (12H, m, 4 x OMe), 4.60 (2H, br s, 2 x C*H*OH), 5.10 (4H, s, 2 x $PhCH_2$), 6.53 (2H, s, aryl), 6.61 (2H, s, aryl), 7.25–7.50 (10H, m, 2 x Ph); *m/z* 574 (M^+). To a solution of the diol (13.88 g, 24.18 mmol) in $CHCl_3$ (100 mL) was added a mixture of trifluoroacetic acid (10 mL) and $CHCl_3$ (100 mL). After 1 h 45 min stirring, the mixture was worked up as for **11a**. The *trans* isomer **11b** crystallized directly from an EtOAc/hexane solution of the crude reaction product. Two further recrystallizations gave pure **11b** shown by HPLC to be free of the *cis* isomer. Yield 5.58 g (41%), mp 141–142 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.79–2.02 (2H, m, ring CH_2), 2.30–2.47 (2H, m, ring CH_2), 3.84 (3H, s, OMe), 3.87–3.91 (9H, m, 3 x OMe), 5.10 (2H, m, 2 x CHO), 5.15 (4H, s, 2 x $PhCH_2$), 6.60 (2H, s, aryl), 6.70 (2H, s, aryl), 7.25–7.50 (10H, m, 2 x Ph); *m/z* 556 (M^+); anal $C_{34}H_{36}O_7$ (C, H).

*(±)-trans-2-(3,5-Dihydroxy-4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran **13b***

Compound **11b** (5.25 g, 9.45 mmol) was hydrogenated in EtOH (200 mL), using 5% palladium on carbon (1 g) at atmospheric pressure and ambient temperature. Workup as for **13a** gave initially a gum, which was found to crystallize from EtOAc/hexane. Recrystallization afforded pure **13b** (2.75 g, 77%), mp 129–132 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.85–2.03 (2H, m, ring CH_2), 2.32–2.50 (2H, m, ring CH_2), 3.85–3.90 (12H, m, 4 x OMe), 5.12 (2H, m, 2 x CHO), 5.50 (2H, s, 2 x OH), 6.55 (2H, s, aryl), 6.62 (2H, s, aryl); *m/z* 376 (M^+); anal $C_{20}H_{24}O_7$ (C, H).

*(±)-trans-2-(3,5-Dihexyloxy-4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran **16** and (±)-trans-2-(3-hexyloxy-5-hydroxy-4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran **13c***

The dihydroxy compound **13b** (2.50 g, 6.65 mmol) in dry DMF (30 mL) was stirred as K_2CO_3 (2.75 g, 19.9 mmol) was added, followed by a solution of 1-bromohexane (1.10 g, 6.67 mmol) in dry DMF (15 mL). The mixture was heated at 80 °C under N_2, for 4 h. After cooling, aqueous ammonium chloride was added, and the mixture extracted with EtOAc. The extracts were washed with water (x 3), then with saturated NaCl, dried over Na_2SO_4 and the solvent evaporated. The residue contained two new compounds which were separated by chromatography (EtOAc/hexane, 1:2). The first eluted component was the dihexyl derivative **16** (0.60 g, 17%), a colourless oil; ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, t, J = 7 Hz, 2 x CH_3), 1.25–1.57 (12H, m, 2 x $(CH_2)_3$), 1.69–1.89 (4H, m, 2 x $OCCH_2C$), 1.90–2.08 (2H, m, ring CH_2), 2.35–2.52 (2H, m, ring CH_2), 3.83, 3.85, 3.88 (12H, 3s, 4 x OMe), 4.03 (4H, t, J = 7 Hz, 2 x OCH_2), 5.15 (2H, m, CHO), 6.60, 6.62 (4H, 2s, aryl); anal $C_{32}H_{48}O_7$ (C, H). The second eluted compound was the mono-hexyl derivative **13c** (1.30 g, 42%), obtained as an oil which crystallized on prolonged standing, mp 70–73 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7 Hz, CH_3C), 1.30–1.85 (8H, m, 4 x CH_2), 1.90–2.05 (2H, m, ring CH_2), 2.34–2.52 (2H, m, ring CH_2), 3.83–3.90 (12H, m, 4 x OMe), 4.02 (2H, t, CH_2O), 5.16 (2H, m, 2 x CHO), 5.75 (1H, s, OH), 6.55 (1H, d, aryl), 6.62 (3H, m, aryl); m/z 460 (M^+); anal $C_{26}H_{36}O_7$ (C, H).

*(±)-trans-3-Hexyloxy-2-methoxy-5-[5-(3,4,5-trimethoxyphenyl)-2-tetrahydrofuranyl]phenyl 2-(trimethylammonio)ethyl phosphate **18c***

The phenol **13c** (460 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in dry benzene (3 mL) were stirred at 0 °C under N_2 as 2-chloro-2-oxo-1,3,2-dioxaphospholane **17** (143 mg, 1 mmol) in dry benzene (1 mL) was added. Following 3 h stirring at room temperature, the mixture was filtered and the filtrate evaporated to dryness. This residue was dissolved in MeCN (3 mL) containing trimethylamine (0.6 mL) and heated in an autoclave at 65 °C for 21 h. After solvent removal, this material was subjected to column chromatography on silica ($CHCl_3$/MeOH/H_2O, 60:35:5). The non-crystalline material thus obtained was further purified by passage through a column of Amberlite MB-3 mixed-bed ion-exchange resin (10 mL), eluting with water. The appropriate fractions were combined and lyophilized to give **18c** as a white hygroscopic solid (270 mg, 42%); ^{1}H-NMR (D_2O) δ: 0.85 (3H, t, CH_3C), 1.15–1.75 (8H, m, 4 x CH_2), 1.75–1.95 (2H, m, ring CH_2), 2.20–2.48 (2H, m, ring CH_2), 3.20 (9H, s, NMe_3), 3.60–3.70 (2H, m, CH_2N), 3.70–3.85 (12H, m, 4 x OMe), 3.85–4.02 (2H, m, CH_2O), 4.41 (2H, br s, CH_2OP), 5.12 (2H, m, 2 x CHO), 6.70 (2H, s, aryl), 6.78 (1H, s, aryl), 7.08 (1H, s, aryl); m/z 626 (M^+ + 1); anal $C_{31}H_{48}NO_{10}P{\cdot}H_2O$ (C, H, N).

*(±)-trans-N-{5-[3-Hexyloxy-2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)-2-tetrahydrofuranyl)phenoxycarbonyl]pentyl}thiazolium chloride **21***

The phenol **13c** (420 mg, 0.91 mmol) was dissolved in a mixture of dry benzene (4 mL) and dry pyridine (0.15 mL). The solution was stirred and cooled to 0 °C, then 6-bromohexanoyl chloride (300 mg, 1.41 mmol) in dry benzene (1 mL) was added dropwise. The mixture was then stirred at room temperature for 20 h, washed with water, 5% aqueous $NaHCO_3$ and saturated aqueous NaCl, dried (Na_2SO_4), filtered and the solvent evaporated. Purification by chromatography on silica (EtOAc/hexane, 2:5) gave (±)-*trans*-2-[3-(6-bromohexanoyloxy)-5-hexyloxy-4-methoxyphenyl]-5-(3,4,5-trimethoxyphenyl)-tetrahydrofuran as a colourless oil (430 mg, 74%); ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7 Hz, CH_3C), 1.3–1.9 (14H, m, 7 x CH_2), 1.88–2.07 (2H, m, ring CH_2), 2.38–2.52 (2H, m, ring CH_2), 2.60 (2H, t, J = 7 Hz, CH_2CO), 3.44 (2H, t, J = 7 Hz, CH_2Br), 3.83 (3H, s, OMe), 3.85 (3H, s, OMe), 3.89 (6H, s, 2 x OMe), 4.03 (2H, t, J = 7 Hz, CH_2O), 5.18 (2H, m, 2 x CHO), 6.61 (2H, s, aryl), 6.68 (1H, d, J = 2 Hz, aryl), 6.89 (1H, d, J = 2 Hz, aryl); IR (film) 1755 cm^{-1}. This material (400 mg, 0.63 mmol) was dissolved in thiazole (2.5 mL) and heated, under N_2, at 100 °C for 4 h. After cooling, the excess thiazole was evaporated under reduced pressure. The residual gum was taken up in water and applied to a column of Amberlite CG400 (Cl^- form). The product was eluted with water; the aqueous eluates were lyophilized to give a product which still contained some impurities, by TLC analysis. Further purification was effected by column chromatography on silica, eluting with $CHCl_3$/MeOH/H_2O (60:35:5). This afforded a gum which was dissolved in water and lyophilized, to give pure **21** as a hygroscopic white solid (390 mg, 57%); ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7 Hz, CH_3C), 1.25–2.15 (14H, m, 7 x CH_2), 1.98–2.15 (2H, m, ring CH_2), 2.37–2.50 (2H, m, ring CH_2), 2.60 (2H, t, J = 7 Hz, CH_2CO), 3.78 (3H, s, OMe), 3.83 (3H, s, OMe), 3.88 (6H, s, 2 x OMe), 4.02 (2H, t, J = 7 Hz, CH_2O), 4.90 (2H, t, J = 7 Hz, CH_2N), 5.16 (2H, m, 2 x CHO), 6.61 (2H, s, phenyl), 6.68 (1H, d, J = 2 Hz, phenyl), 6.85 (1H, d, J = 2 Hz, phenyl), 8.11 (1H, m, thiazolyl), 8.48 (1H, m, thiazolyl); IR ($CHCl_3$), 1757 cm^{-1}; m/z 642 (M^+-Cl); anal $C_{35}H_{48}ClNO_8S{\cdot}0.5H_2O$ (C, H, N).

*(±)-trans-2-{5-Hexyloxy-4-methoxy-3-[3-(4-methylthiazol-5-yl)propoxy]phenyl}-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran **20c***

To a solution of the phenol **13c** (0.50 g, 1.09 mmol) in dry DMF (6 mL) was added K_2CO_3 (0.45 g, 3.26 mmol) and 5-(3-chloropropyl)-4-methylthiazole (0.19 g, 1.09 mmol) in dry DMF (1 mL). The mixture was heated at 80 °C for 5 h, then cooled and poured into water. The mixture was extracted with EtOAc (x 3), the extracts washed with water, dried (Na_2SO_4) and the solvent evaporated. The product was isolated by column chromatography (EtOAc/hexane, 2:1). Further purification on a second column (EtOAc/hexane, 1:1) gave pure product **20c** (20 mg, 3%) as a colourless viscous gum, together with a significant quantity of slightly impure material; ^{1}NMR ($CDCl_3$) δ: 0.92 (3H, t, J = 7.3 Hz, CH_3), 1.25–1.58 (6H, m, $(CH_2)_3$), 1.71–1.88 (2H, m, $OCCH_2C_4$), 1.90–2.00 (2H, m, ring CH_2); 2.02–2.18 (2H, m, CH_2CCS), 2.35–2.50 (5H, m and s, ring CH_2 and MeC), 3.01 (2H, t, J = 7.5 Hz CH_2CS), 3.85, 3.83, 3.88 (12H, 3s, 4 x OMe), 4.05 (4H, 2t, J = 6.7 Hz and 6.0 Hz, 2 x $ArOCH_2$), 5.16 (2H, m, CHO), 6.60 (4H, s and d, J < 1 Hz, aryl), 8.54 (1H, s, SCH); m/z 599 (M^+); anal $C_{33}H_{45}NO_7S{\cdot}0.5H_2O$ (C, H, N).

*2-Methoxy-3-octadecyloxyphenyl 2-(trimethylammonio)ethyl phosphate **31a***

To a solution of 2-methoxyresorcinol (0.98 g, 7 mmol) in dry DMF (25 mL) was added K_2CO_3 (2.90 g, 21 mmol) followed by 1-bromooctadecane (2.33 g, 7 mmol). The mixture was heated at 80 °C for 5 h, then cooled and poured into 1M HCl (100 mL). The product was extracted with Et_2O, the extracts washed with NaCl, dried (Na_2SO_4) and the solvent evaporated. The mixture of mono- and bis-alkylated products was separated by column chromatography (EtOAc/hexane, 1:6), the second eluted component being the required 2-methoxy-3-octadecyloxyphenol (1.24 g, 45%); mp 43–45 °C; anal $C_{25}H_{44}O_3$ (C, H). To the phenol (430 mg, 1.1 mmol) in dry benzene (2 mL) was added at 0 °C, under N_2, triethylamine (112 mg, 1.1 mmol) followed by 2-chloro-2-oxo-1,3,2-dioxaphospholane **17** (158 mg, 1.1 mmol). The mixture was then stirred at room temperature for 2 h, after which the triethylamine hydrochloride was rapidly filtered off and washed with benzene. Evaporation of the filtrate gave the intermediate cyclic phosphate as a white solid

(500 mg). This was suspended in dry MeCN (2.5 mL) and a solution containing trimethylamine (0.3 g) in MeCN (1.5 mL) was added. The mixture was heated in an autoclave at 60–65 °C overnight. After cooling, the white solid product was filtered off, washed with MeCN and dried over P_2O_5. This material was chromatographed on a small silica column, eluting with $CHCl_3$/MeOH/H_2O (60:35:5) to yield pure **31a** (190 mg, 31%) as a white waxy solid, mp 262–265 °C (dec); ^{1}H-NMR (D_2O) δ: 1.00 (3H, br t, CH_3C), 1.2–1.9 (32H, br m, 16 x CH_2), 3.15 (9H, s, NMe_3), 3.53–3.67 (2H, br m, CH_2N), 3.80–4.00 (5H, br m, OMe and OCH_2), 4.28–4.42 (2H, br m, CH_2OP), 6.60 (1H, m, aryl), 7.03 (2H, m, aryl); *m/z* 557 (M^+); anal $C_{30}H_{56}NO_6P$ (C, H, N).

*5-[3-(3-Hexyloxy-2-methoxyphenoxy)propyl]-4-methylthiazole **31b***

2-Methoxyresorcinol (280 mg, 2 mmol) was alkylated successively with 1-bromohexane and with chloride **19** under the conditions described for **13c** and **20c** respectively, giving **31b** (200 mg, 28% overall) as a colourless gum; ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, CH_3), 1.30–1.55 (6H, m, $(CH_2)_3$), 1.80 (2H, quintet, J = 7 Hz, $OCCH_2$), 2.12 (2H, quintet, J = 7 Hz, $OCCH_2$), 2.40 (3H, s, CH_3CN), 3.00 (2H, t, J = 7 Hz, CH_2CS), 3.88 (3H, s, OMe), 4.02 (4H, m, 2 x OCH_2), 6.49–6.60 (2H, m, aryl), 6.93 (1H, t, J = 8 Hz, aryl), 8.56 (1H, s, thiazolyl); *m/z* 363 (M^+); anal $C_{20}H_{29}NO_3S$ (C, H, N).

*Methyl 3-hexyloxy-5-hydroxy-4-methoxybenzoate **22b***

A mixture of methyl 3,5-dihydroxy-4-methoxybenzoate (174 g, 0.88 mol), K_2CO_3 (60.9 g, 0.44 mol), DMF (700 mL) and 1-bromohexane (146.1 g, 0.88 mol) was heated at 80 °C for 5 h then cooled and poured into water. The aqueous mixture was extracted with Et_2O (2 x 1000 mL) and the combined ethereal solutions were extracted with ice-cold 1 M NaOH solution (2 x 500 mL). The basic extracts were acidified with 2M HCl and the crude product was extracted into Et_2O (2 x 500 mL). Evaporation of the dried extracts gave an orange oil (162 g). Flash chromatography using CH_2Cl_2/MeOH (50:1) gave 71. 4 g (29%) of **22b** as a colourless oil which crystallized on standing: mp 46–48 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7 Hz, CH_3), 1.20–1.55 (6H, m, $(CH_2)_3$) 1.68–1.87 (2H, m, $OCCH_2$), 3.85 (3H, s, COOMe), 3.93 (3H, s, OMe), 3.98 (2H, t, J = 7 Hz, OCH_2C), 6.95 (1H, br s, OH), 7.20 (1H, d, J < 1 Hz, aryl), 7.28 (1H, d, J < 1 Hz, aryl); IR (KBr) 3400, 1707 cm^{-1}; *m/z* 282; anal $C_{15}H_{22}O_5$ (C, H).

*3-Benzyloxy-5-hexyloxy-4-methoxybenzoic acid **23***

A mixture of methyl 3-hexyloxy-5-hydroxy-4-methoxybenzoate **22b** (50.8 g, 0.18 mol), K_2CO_3 (24.8 g, 0.18 mol), dry DMF (170 mL) and benzyl bromide (45 g, 0.27 mol) was heated at 80 °C for 5 h then cooled and poured into water. The aqueous mixture was extracted with Et_2O (2 x 250 mL) and the combined extracts were washed with water (2 x 150 mL), dried (Na_2SO_4) and evaporated in vacuo to an orange oil (65.9 g). Flash chromatography using CH_2Cl_2/hexane (3:1) gave 50.3 g (75%) of methyl 3-benzyloxy-5-hexyloxy-4-methoxybenzoate as a pale yellow oil which crystallized on standing: mp 46–49 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J = 7 Hz, CH_3), 1.22–1.58 (6H, m, $(CH_2)_3$), 1.72–1.91 (2H, m, $OCCH_2$), 3.90 (3H, s, COOMe), 3.95 (3H, s, ArOMe), 4.05 (2H, t, J = 7 Hz, OCH_2), 5.14 (2H, s, $PhCH_2$), 7.35 (7H, m, aryl); IR (KBr) 1713 cm^{-1}; *m/z* 372 (M^+); anal $C_{22}H_{28}O_5$ (C, H). The methyl ester (47.4 g, 0.127 mol) was dissolved in MeOH (700 mL) at 50 °C. To this was added 1M NaOH solution (210 mL) and the mixture was refluxed for 2 h then cooled and evaporated in vacuo to 250 mL. The residue was acidified with acetic acid and the product extracted into EtOAc (2 x 250 mL). The combined extracts were washed with water (2 x 100 mL), dried (Na_2SO_4) and evaporated in vacuo to a white solid. Recrystallization from EtOAc/hexane (1:1) gave 33 g (73%) of **23** as white crystals; mp 103–105 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J = 7 Hz, CH_3), 1.24–1.60 (6H, m, $(CH_2)_3$), 1.75–1.85 (2H, m, $OCCH_2$), 3.95 (3H, s, OMe), 4.08 (2H, t, J = 7 Hz, OCH_2), 5.20 (2H, s, $PhCH_2$), 7.22–7.55 (7H, m, aryl), 10.45 (1H, br, COOH); IR (KBr) 1686 cm^{-1}; *m/z* 358 (M^+); anal $C_{21}H_{26}O_5$ (C, H).

*3'-Benzyloxy-5'-hexyloxy-4'-methoxyacetophenone **24b***

3-Benzyloxy-5-hexyloxy-4-methoxybenzoic acid **23** (33 g, 92 mmol) was stirred with dry THF (600 mL) under nitrogen at 0 °C. To this was added 1.4 M MeLi solution (260 mL, 364 mmol) and stirring at 0 °C continued for 2 h after which time chlorotrimethylsilane (230 mL) was added at 0 °C. The mixture was allowed to come to room temperature and 1M HCl (600 mL) was added. The resulting 2-phase system was stirred at room temperature for 30 min then the organic layer was separated and the aqueous phase extracted with Et_2O (2 x 200 mL). The combined organic solutions were washed with water (2 x 200 mL), dried (Na_2SO_4) and evaporated in vacuo to a red oil (33 g). Flash chromatography using EtOAc/hexane (1:5) gave 23 g (71%) of **24b** as a colourless oil; ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J = 7 Hz, CH_3), 1.24–1.60 (6H, m, $(CH_2)_3$), 1.77–1.90 (2H, m, $OCCH_2$), 2.49 (3H, s $COCH_3$), 3.90 (3H, s, OMe), 4.04 (2H, t, J = 7 Hz, OCH_2), 5.13 (2H, s, $PhCH_2$), 7.20–7.50 (7H, m, aryl); IR (KBr) 1660 cm^{-1}; *m/z* 356 (M^+); anal $C_{22}H_{28}O_4$ (C, H).

*1-(3-Benzyloxy-5-hexyloxy-4-methoxyphenyl)-1-trimethylsilyloxyethene **25b***

The acetophenone **24b** (23 g, 64.6 mmol) was dissolved in dry MeCN (90 mL). Triethylamine (7.8 g, 77.4 mmol) was added followed by chlorotrimethylsilane (8.4 g, 77.4 mmol). A solution of sodium iodide (11.6 g, 77.4 mmol) in dry MeCN (100 mL) was added dropwise and the mixture was then stirred at room temperature for 15 min. The solvent was removed in vacuo to give an orange oil (31 g). Flash chromatography using EtOAc/hexane (1:10) gave 13.3 g (48%) of **25b** as a colourless oil; ^{1}H-NMR ($CDCl_3$) δ: 0.27 (9H, s, $SiMe_3$), 0.91 (3H, t, J = 7 Hz, CH_3), 1.22–1.58 (6H, m, $(CH_2)_3$), 1.73–1.90 (2H, m, $OCCH_2$), 3.88 (3H, s, OMe), 4.02 (2H, t, J = 7 Hz, OCH_2), 4.38 (1H, d, J = 2 Hz, C=CH), 4.75 (1H, d, J = 2 Hz, C=CH), 5.15 (2H, s, $PhCH_2$), 6.82 (2H, 2s, aryl), 7.20–7.45 (5H, m, aryl).

*1,4-Bis(3-benzyloxy-5-hexyloxy-4-methoxyphenyl)butan-1,4-dione **26b***

A 1.4M MeLi solution (22.1 mL, 30.9 mmol) was added to dry THF (180 mL) under N_2 at –70 °C. A solution of **25b** (13.3 g, 30.9 mmol) in dry THF (50 mL) was added dropwise and stirring continued for 10 min. A solution of copper(II)trifluoromethanesulphonate (18.6 g, 51.4 mmol) in dry isobutyronitrile (290 mL) was added dropwise keeping the temperature below –60 °C. The mixture was stirred for 0.5 h at –70 °C, kept at room temperature for 2 h, evaporated in vacuo to one third volume then poured onto water and extracted with EtOAc (2 x 100 mL). The combined extracts were dried (Na_2SO_4) then evaporated in vacuo to a purple solid (22 g). Flash chromatography using EtOAc/hexane (1:4) gave 6.5 g (59%) of **26b** as a white solid, mp 94–96 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, t, J = 7 Hz, 2 x CH_3), 1.22–1.58 (12H, m, 2 x $(CH_2)_3$), 1.72–1.92 (4H, m, 2 x $OCCH_2$), 3.31 (4H, s, CH_2CH_2), 3.90 (6H, s, 2 x OMe), 4.05 (4H, t, J = 7 Hz, 2 x OCH_2), 5.15 (4H, s, 2 x $PhCH_2$), 7.22–7.52 (14H, m, aryl); IR (KBr) 1674 cm^{-1}; *m/z* (FAB) 711 (M^+ + 1); anal $C_{44}H_{54}O_8$ (C, H).

(±)-trans-2,5-Bis(3-benzyloxy-5-hexyloxy-4-methoxyphenyl)-tetrahydrofuran **27b**
To a suspension of **26b** (6.4 g, 9 mmol) in absolute EtOH (100 mL) under N_2 was added $NaBH_4$ (1.1 g, 29.2 mmol). The mixture was heated at 70 °C until the solid dissolved and for 80 min thereafter, then cooled and evaporated in vacuo. The residue was treated with excess NH_4Cl solution then extracted with Et_2O (2 x 50 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated in vacuo to give 6.2 g (97%) of 1,4-bis(3-benzyloxy-5-hexyloxy-4-methoxyphenyl)butan-1,4-diol as a yellow oil. This was used without further purification; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, t, J = 7 Hz, 2 x CH_3), 1.25–1.55 (12H, m, 2 x $(CH_2)_3$), 1.63–1.88 (8H, m, 2 x $OCCH_2$ and CH_2CH_2), 3.85 (6H, s, 2 x OMe), 3.95 (4H, t, J = 7 Hz, 2 x OCH_2), 4.55 (2H, m, 2 x C*H*OH), 5.11 (4H, s, 2 x PhC*H*$_2$), 6.53 (4H, s, aryl), 7.29–7.48 (10H, m, aryl); IR (KBr) 3400 cm^{-1}. The diol (6 g, 8.6 mmol) was dissolved in $CHCl_3$ (35 mL) and stirred at room temperature as a solution of trifluoroacetic acid (10% v/v in $CHCl_3$, 35 mL) was added. After stirring at room temperature for 1.5 h, solid Na_2CO_3 (8.5 g) was added and stirring was continued for a further 0.5 h. Solids were removed by decanting and the solution was evaporated in vacuo to a brown gum (6.1 g). Flash chromatography gave 4.3 g (72%) of *cis/trans* mixture. HPLC on a silica column using hexane/EtOAc (15:1) gave 1.9 g of pure *trans* isomer **27b** as a colourless gum; ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, t, J = 7 Hz, 2 x CH_3); 1.35–1.58 (12H, m, 2 x $(CH_2)_3$), 1.72–1.95 (6H, m, ring CH_2 and 2 x $OCCH_2$), 2.25–2.44 (2H, m, ring CH_2), 3.85 (6H, s, 2 x OMe), 4.04 (4H, t, J = 7 Hz, 2 x OCH_2), 5.13 (6H, m, 2 x PhC*H*$_2$ and 2 x ring CHO), 6.62 (4H, 2s, aryl), 7.25–7.52 (10H, m, aryl); m/z 696 (M^+); anal $C_{44}H_{56}O_7$ (C, H).

(±)-trans-2,5-Bis(3-hexyloxy-5-hydroxy-4-methoxyphenyl)-tetrahydrofuran **28b**
A mixture of **27b** (0.45 g, 0.65 mmol), EtOH (20 mL) and 5% Pd/C (25 mg) was hydrogenated at 760 mmHg and ambient temperature. Filtration of the catalyst and evaporation of the filtrate gave a colourless gum. Flash chromatography using EtOAc/hexane (1:5) gave 0.24 g (72%) of **28b** as a colourless gum; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, t, J = 7 Hz, 2 x CH_3), 1.22–1.58 (12H, m, 2 x $(CH_2)_3$), 1.72–2.03 (6H, m, ring CH_2 and 2 x $OCCH_2$), 2.30–2.50 (2H, m, ring CH_2), 3.92 (6H, s, 2 x OMe), 4.04 (4H, t, J = 7 Hz, 2 x OCH_2), 5.12 (2H, m, 2 x ring CHO), 5.86 (2H, s, 2 x OH), 6.55 (2H, d, J < 1 Hz, aryl), 6.60 (2H, d, J < 1 Hz, aryl); anal $C_{30}H_{44}O_7 \cdot 0.25H_2O$ (C, H).

(±)-trans-2,5-Bis{5-hexyloxy-4-methoxy-3-[3-(4-methylthiazol-5-yl)propoxy]phenyl}tetrahydrofuran **29b**
A mixture of **28b** (103 mg, 0.2 mmol), 5-(3-chloropropyl)-4-methylthiazole **19** (70 mg, 0.4 mmol), K_2CO_3 (0.16 g, 1.16 mmol) and dry DMF (3 mL) was heated at 80 °C for 5 h then poured onto water and extracted with EtOAc (2 x 10 mL). The combined extracts were washed with water (3 x 10 mL), dried and evaporated in vacuo to a brown gum (120 mg). Flash chromatography using EtOAc/hexane (1:2) gave 64 mg (40%) of **29b** as a colourless gum; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, t, J = 7 Hz, 2 x CH_3), 1.25–1.58 (12H, m, 2 x $(CH_2)_3$); 1.72–2.0 (6H, m, 2 x $OCCH_2$ and ring CH_2), 2.02–2.23 (4H, m, 2 x $OCCH_2$), 2.38 (8H, m and s, 2 x Me-thiazolyl and ring CH_2), 3.03 (4H, t, J = 7.5 Hz, 2 x CH_2CS), 3.83 (6H, s, 2 x OMe), 3.95–4.08 (8H, m, 4 x OCH_2), 5.15 (2H, m, 2 x CHO), 6.57 (2H, s, aryl), 6.62 (2H, s, aryl), 8.55 (2H, s, 2 x SCH); m/z 794 (M^+); anal $C_{44}H_{62}N_2O_7S_2 \cdot H_2O$ (C, H, N).

3'-Benzyloxy-4',5'-dimethoxyacetophenone **24a**
To a mixture of bis(trimethylsilyl)malonate (3.95 g, 15.9 mmol) and dry Et_2O (40 mL) at –65 °C was added *n*-butyllithium (1.6 M, 9.6 mL, 15.4 mmol), dropwise, over 10 min. The mixture was allowed to come to 0 °C and a solution of 3-benzyloxy-4,5-dimethoxybenzoyl chloride [18] (2.2 g, 7.18 mmol) in dry Et_2O (30 mL) was added. After stirring for a further 2 h at room temperature, aqueous $NaHCO_3$ was added and the layers separated. The aqueous layer was acidified, extracted with Et_2O and the extracts combined with the original organic layer. The solvent was evaporated and the residue heated in dioxan (30 mL) at reflux for 2 h. Evaporation of solvent followed by flash chromatography afforded **24a** (1.1 g, 54%) as a white solid, mp 88–91 °C; ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s, MeCO), 3.92 (3H, s, OMe), 3.95 (3H, s, OMe), 5.10 (2H, s, PhC*H*$_2$), 7.10–7.50 (7H, m, aryl); IR (KBr) 1676 cm^{-1}; anal $C_{17}H_{18}O_4$ (C, H).

Compounds **25a–29a** were synthesized analogously to their hexyl counterparts **25b–29b**.

1-(3-Benzyloxy-4,5-dimethoxyphenyl)-1-trimethylsilyloxy-ethene **25a**. 47% yield; ^{1}H-NMR ($CDCl_3$) δ: 0.22 (9H, s, Me_3Si), 3.95 (6H, 2s, 2 x OMe), 4.38 (1H, d, J = 1.5 Hz, CH=C), 4.78 (1H, d, J = 1.5 Hz, CH=C), 5.12 (2H, s, PhC*H*$_2$), 6.81 (1H, d, J = 2 Hz, aryl), 6.85 (1H, d, J = 2 Hz, aryl), 7.22–7.45 (5H, m, Ph).

1,4-Bis(3-benzyloxy-4,5-dimethoxyphenyl)butan-1,4-dione **26a**. 54% yield; mp 155–156 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.41 (4H, s, CH_2CH_2), 3.92 (6H, s, 2 x OMe), 3.93 (6H, s, 2 x OMe), 5.17 (4H, s, PhC*H*$_2$), 7.23–7.50 (14H, m, aryl); IR (KBr) 1688 cm^{-1}; m/z 570 (M^+); anal $C_{34}H_{34}O_8$ (C, H).

(±)-trans-2,5-Bis(3-benzyloxy-4,5-dimethoxyphenyl)tetrahydrofuran **27a**. *Cis/trans* isomers were separated by recrystallization of the less soluble *trans* isomer twice from EtOAc/hexane (1:2). HPLC confirmed no *cis* present. 22% yield; mp 118–120 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.90 (2H, m, ring CH_2), 2.38 (2H, m, ring CH_2), 3.88 (12H, s, 4 x OMe), 5.22 (6H, m and s, 2 x PhC*H*$_2$ and 2 x CHO), 6.62 (2H, d, J < 1 Hz , aryl), 6.67 (2H, d, J < 1 Hz, aryl), 7.22–7.49 (10H, m, 2 x Ph); anal $C_{34}H_{36}O_7$ (C, H).

(±)-trans-Bis(5-hydroxy-3,4-dimethoxyphenyl)tetrahydrofuran **28a**. 66% yield; mp 156–158 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.85–2.03 (2H, m, ring CH_2), 2.41–2.48 (2H, m, ring CH_2), 3.38 (12H, s, 4 x OMe), 5.13 (2H, m, 2 x CHO), 5.80 (2H, s, 2 x OH), 6.55 (2H, d, J < 1 Hz, aryl), 6.63 (2H, d, J < 1 Hz, aryl); IR (KBr) 3439 cm^{-1}; m/z 376 (M^+); anal $C_{20}H_{24}O_7$ (C, H).

(±)-trans-2,5-Bis{4,5-dimethoxy-3-[3-(4-methylthiazol-5-yl)propoxy]phenyl}tetrahydrofuran **29a**. ^{1}H-NMR ($CDCl_3$) δ: 1.87–2.02 (2H, m, ring CH_2); 2.05–2.20 (4H, m, $OCCH_2$), 2.32–2.51 (8H, m and s, 2 x Me-thiazolyl and ring CH_2), 3.03 (4H, t, J = 7.5 Hz, $OCCCH_2$), 3.85 (6H, s, 2 x OMe), 3.87 (6H, s, 2 x OMe), 4.06 (4H, t, J = 6.7 Hz, OCH_2), 5.16 (2H, m, 2 x CHO), 6.57 (2H, d, J < 1 Hz, aryl), 6.62 (2H, d, J < 1 Hz, aryl), 8.55 (2H, s, SCH); m/z 654.2434 (M^+), calc for $C_{34}H_{42}N_2O_7S_2$ 654.2437.

(±)-trans-2,5-Bis(3-hexyloxy-4,5-dimethoxyphenyl)tetrahydrofuran **30**
This compound was synthesized from **28a** as described for **15**, using two equivalents of 1-bromohexane. 39% yield; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, t, J = 7 Hz, 2 x CH_3), 1.25–1.52 (12H, m,

2 x $(CH_2)_3$), 1.73–1.89 (4H, m, 2 x $OCCH_2$), 1.91–2.08 (2H, m, ring CH_2), 2.35–2.52 (2H, m, ring CH_2), 3.84 (6H, s, 2 x OMe), 3.88 (6H, s, 2 x OMe), 4.02 (4H, t, J = 7 Hz, 2 x OCH_2), 5.19 (2H, m, 2 x CHO), 6.61 (4H, s, aryl); m/z 544 (M^+); anal $C_{32}H_{48}O_7$ (C, H).

References

1 Benveniste J, Henson PM, Cochrane CG (1972) *J Exp Med* 136, 1356–1377
2 Koltai M, Hosford D, Guinot P, Esanu A, Braquet P (1991) *Drugs* 42, 9–29
3 Terashita Z, Tsushima S, Yoshioka Y, Nomura H, Inada Y, Nishikawa N (1983) *Life Sci* 32, 1975–1982
4 Braquet P (1987) *Drugs Future* 12, 643–699
5 Doebber TW, Wu MS, Robbins JC, Choy BM, Chang MN, Shen TY (1985) *Biochem Biophys Res Commun* 127, 799–808
6 Casals-Stenzel J (1987) *Eur J Pharmacol* 135, 117–122
7 Hwang SB, Lam MH, Biftu T, Beattie TR, Shen TY (1985) *J Biol Chem* 260, 15639–15645
8 Hodgkin EE, Miller A, Whittaker M (1992) *Bioorg Med Chem Lett* 2, 597–602
9 Braquet P, Godfroid JJ (1986) *Trends Pharm Sci* 397–403
10 Dive G, Godfroid JJ, Lamotte-Brasseur J et al (1989) *J Lipid Mediators* 1, 201–215
11 Lamotte-Brasseur J, Dive G, Lamouri A, Heymans F, Godfroid JJ (1991) *Biochem Biophys Acta* 1085, 91–105
12 Godfroid JJ, Dive G, Lamotte-Brasseur J, Batt JP, Heymans F (1991) *Lipids* 26, 1162–1166
13 Lamotte-Brasseur J, Heymans F, Dive G et al (1991) *Lipids* 26, 1167–1171
14 Batt JP, Lamouri A, Tavet F, Heymans F, Dive G, Godfroid JJ (1991) *J Lipid Mediators* 4, 343–346
15 Lamouri A, Heymans F, Tavet F et al (1993) *J Med Chem* 36, 990–1000
16 Sawyer DA, Beams RM, Blackwell GJ et al (1995) *J Med Chem* 38, 2130–2137
17 Corey EJ, Chen CP, Parry MJ (1988) *Tetrahedron Lett* 29, 2899–2902
18 Farkas L, Nogradi M, Strelisky J (1966) *Magy Kem Foly* 72, 485
19 Haslam E, Uddin M (1968) *Tetrahedron* 24, 4015–4020
20 Biftu T, Gamble NF, Doebber T et al (1986) *J Med Chem* 29, 1917–1921
21 Lucas HJ, Mitchell Jr FW, Scully CN (1950) *J Amer Chem Soc* 72, 5491–5497
22 Edmundson RS (1962) *Chem Ind* 1828–1829
23 *Netherlands Patent* 6 510 389 (*Chem Abs* (1966) 65, 2268)
24 Kobayashi Y, Taguchi T, Tokuno E (1977) *Tetrahedron Lett* 3741–3742
25 Venuti MC (1990) Platelet activating factor receptors In: *Comprehensive Medicinal Chemistry* (Hansch C, ed) Pergamon, Vol 3, 715–761
26 Hwang SB, Lam MH (1991) *Lipids* 26, 1148–1153
27 Chiang YCP, Yang SS, Chang MN, Thomson FL (1987) *European Patent* 307, 133
28 Sahoo SP, Graham DW, Acton J et al (1991) *Bioorg Med Chem Lett* 1, 327–332
29 Bugianesi RL, Ponpipom MM, Parsons WH et al (1992) *Bioorg Med Chem Lett* 2, 181–184
30 Natori S, Kumada Y (1965) *Chem Pharm Bull* 13, 1472