Pergamon

Bioorganic & Medicinal Chemistry 8 (2000) 1087–1109

BIOORGANIC & MEDICINAL CHEMISTRY

Biaryl Diacid Inhibitors of Human s-PLA_2 with Anti-Inflammatory Activity

Dane M. Springer,[a,*] Bing-Yu Luh,[a] Joanne J. Bronson,[a] Katharine E. McElhone,[a] Muzammil M. Mansuri,[a] Kurt R. Gregor,[b] David O. Nettleton,[b] Paul L. Stanley[b] and Kenneth M. Tramposch[b]

[a]*Central Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, PO Box 5100, Wallingford, CT 06492, USA*

[b]*Dermatology Discovery Research, Bristol-Myers Squibb Pharmaceutical Research Institute, 100 Forest Avenue, Buffalo, NY 14213, USA*

Received 9 August 1999; accepted 13 January 2000

Abstract—Twenty-four hydrophobic dicarboxylic acids are described which were evaluated as inhibitors of 14 kDa human platelet phospholipase A_2 (HP-PLA_2). In general, biarylacetic acid derivatives were found to be more active than biaryl acids or biarylpropanoic acids. More potent inhibitors were obtained when hydrophobic groups were attached to the biaryl acid nucleus using an olefin linkage as compared to an ether linkage. Compounds with larger hydrophobic groups were usually more potent inhibitors of HP-PLA_2. Five of the compounds disclosed in this report (**2**, **4**, **28**, **36b** and **36i**) were found to possess significant anti-inflammatory activity in a phorbol ester induced mouse ear edema model of chronic inflammation.

Introduction

Phospholipases A_2 have been implicated as the causal or aggravating agent in the pathogenesis of various inflammatory diseases. These enzymes cleave fatty acids from the sn-2 position of glycerophospholipids. The resultant lysophospholipid products of this hydrolysis can be converted to platelet-activating factor (PAF), a potent mediator of inflammation. Arachidonic acid release from phospholipids by the action of PLA_2 is proinflammatory by virtue of the subsequent enzymatic transformations of this fatty acid into prostaglandins and leukotrienes.[1] PLA_2 activity has been linked to a variety of errant processes such as asthma, arthritis, psoriasis, pancreatitis, demyelinating diseases, hypotension during septic shock, and tissue injury during myocardial ischemia.[2–8] The normal physiological functions of PLA_2s are equally diverse, and are likely to include roles in membrane homeostasis, signal transduction, cell proliferation, differentiation, fertilization, bacterial defense, and aging.[9–16]

There are four predominant PLA_2s that are isolable from human sources; a cytosolic 85 kDa protein, a calcium-independent 40 kDa protein isolated from myocardium, a 14 kDa pancreatic enzyme, and a non-pancreatic 14 kDa PLA_2 isolated from platelets and rheumatoid synovial fluid.[17–20] Two groups have successfully crystallized the human non-pancreatic PLA_2 found in synovial fluid and determined its X-ray structure.[21,22] The interfacial mechanism of action of PLA_2 presents a challenge for kinetic analysis in this class of enzymes, and has sparked interest in the conformational changes which take place when these soluble enzymes bind to an organized phospholipid surface.[21,23]

By virtue of the occurrence of the non-pancreatic 14 kDa enzyme in inflammatory lesions, we decided to target this enzyme in a program to develop inhibitors of PLA_2 as anti-inflammatory agents. Our initial clinical goal was to develop a PLA_2 inhibitor as a topical agent for treatment of psoriasis.

Strategy

Many classes of compounds have been recently described as inhibitors of human non-pancreatic PLA_2.[24] During a broad screen of proprietary compounds, we found the diacid BMS-181162 to be a good inhibitor of

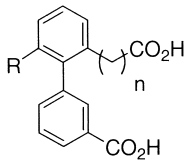
*Corresponding author.

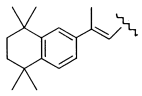
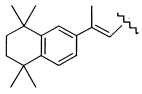
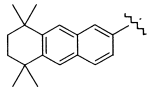
0968-0896/00/$ - see front matter
PII: S0968-0896(00)00047-X

14 kDa human platelet PLA_2 (HP-PLA_2).[24d] BMS-181162 displayed an $IC_{50} = 40\,\mu M$ against HP-PLA_2, and an $ED_{50} = 160\,\mu g$/ear for reduction of mouse ear edema in a phorbol ester induced acute inflammation assay. BMS-181162 was found to not significantly inhibit many other enzymes involved in the inflammatory response such as: PLA_1, PI-PLC, PLD, sphingomyelinase, acetyl-CoA synthetase, cyclooxygenase-1, elastase, LTA_4 hydrolase, LTC_4 synthetase, lipid peroxidase, 5-LPO, 15-LPO, and protein kinase C. BMS-181162 has also exhibited active-site directed competitive inhibition of HP-PLA_2 in a 'scooting-mode' assay.[25]

We wished to develop an anti-inflammatory program around BMS-181162, and defined its pharmacophore to be a hydrophobic tail linked to a polar, diacid head group. The chemical and photostability of the polyene unit of 181162 was a concern to us at the outset of our synthetic program. Therefore we decided to replace the β-ionone type tail with a group of similar size, yet one that is inherently more chemically stable. The tetramethyl-tetrahydronaphthalene group, well known in the retinoid literature, was chosen for this purpose. We also decided to incorporate additional atoms of the polyene chain of 181162 into an extra aryl ring to further improve the stability of our analogues. The inclusion of the extra aryl ring into the general structure would also simplify the synthesis of this class of molecules, as well as provide an opportunity to optionally substitute this ring. With these simplifications in mind, we decided to target biaryl diacids **1** and **2** as synthetic analogues of BMS-181162.

Table 1. Biological activity of diacids **1**–**4**, and BMS-181162



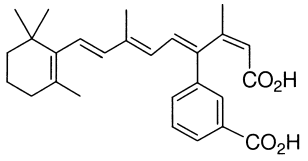
Compd	R	*n*	% Inhibition of human platelet PLA_2[a] 100 μM	10 μM	IC_{50} (μM)[b]	ED_{50}[c] (μg/per dose)
1		0	80	22	26	—
2		1	96	46	10	116
3	t-styryl	1	28	16	—	—
4		1	93	38	18	79
BMS-181162			77[d]	12[d]	45	180

[a]Values reported are the mean of two samples at each concentration.
[b]HP-PLA_2: values reported are the mean of three separate experiments.
[c]Phorbol ester induced mouse ear chronic inflammation assay. For details see ref 30.
[d]Extrapolated from the dose–response curve used in the IC_{50} determination.

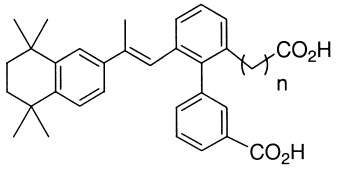
Chemistry

Our general synthetic approach[26] to molecules of type **1**–**4** (Table 1) is summarized by eq (1). Palladium-catalyzed coupling of a vinyl stannane and a biaryl triflate affords a product that can be hydrolyzed to deliver the desired biaryl diacid targets.

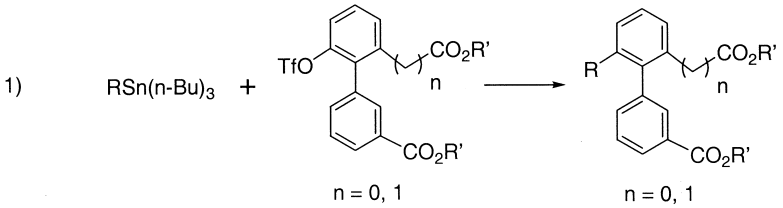
The syntheses of the required triflates are illustrated in Schemes 1 and 2. For the case where $n = 0$ in eq (1), *o*-vanillin (**5**) was converted to aryl triflate **6**. This triflate was then coupled to (3-carboethoxy)phenyltributylstannane (**7**) to provide biaryl aldehyde **8**. The aldehyde was oxidized to the acid, which was esterified to produce diester **9**. Demethylation of **9** to alcohol **10** was followed by the conversion of **10** to biaryl triflate **11**. For the $n = 1$ series (Scheme 2), intermediate biaryl aldehyde **8** was homologated via Wittig chemistry to aldehyde **12**, which was converted as above to diester



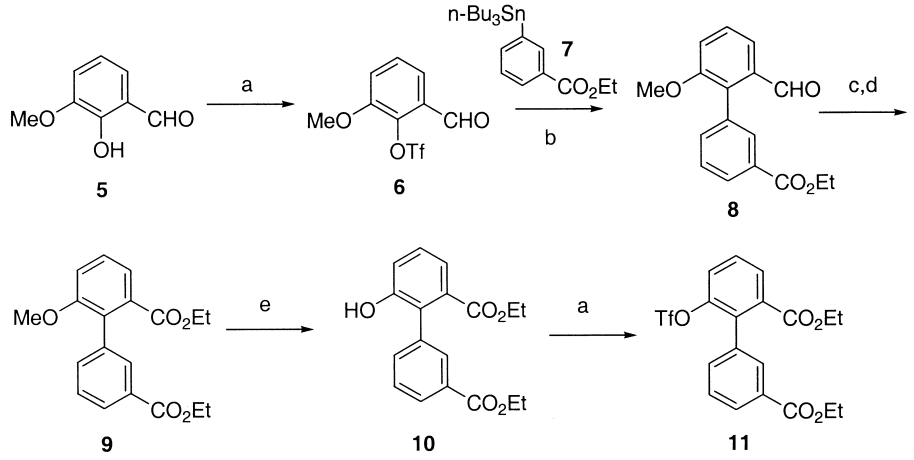
BMS-181162



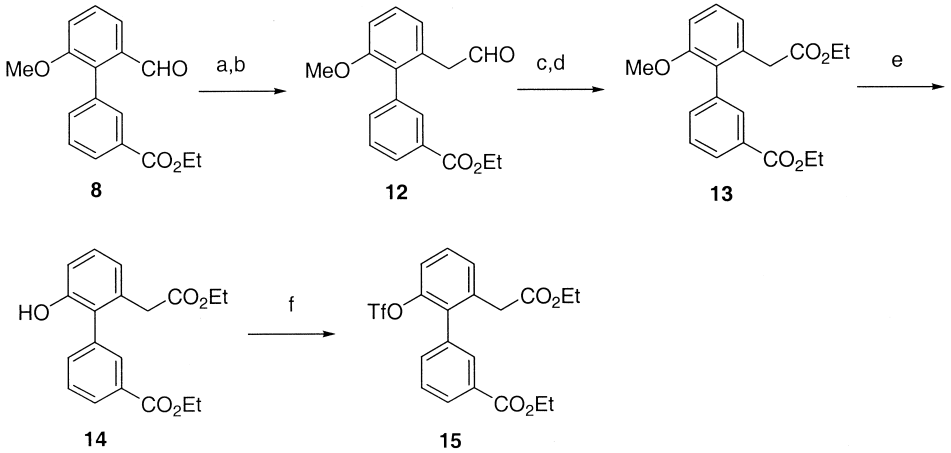
1 n = 0
2 n = 1



n = 0, 1 n = 0, 1



Scheme 1. Reaction conditions: (a) Tf_2O, DMAP, CH_2Cl_2; (b) $PdCl_2(PPh_3)_2$, LiCl, DMF, 150 °C; (c) $NaClO_2$, H_2NSO_3H, THF, H_2O; (d) HCl, EtOH, reflux; (e) Me_2BBr, $ClCH_2CH_2Cl$.



Scheme 2. Reaction conditions: (a) $Ph_3PCH_2OCH_3 + Cl^-$, *t*-BuOK, toluene, THF; (b) 1 N HCl, THF, reflux; (c) $NaClO_2$, H_2NSO_3H, THF, H_2O; (d) HCl, EtOH, reflux; (e) $(CH_3)_2BBr$, $ClCH_2CH_2Cl$; (f) Tf_2O, DMAP, CH_2Cl_2.

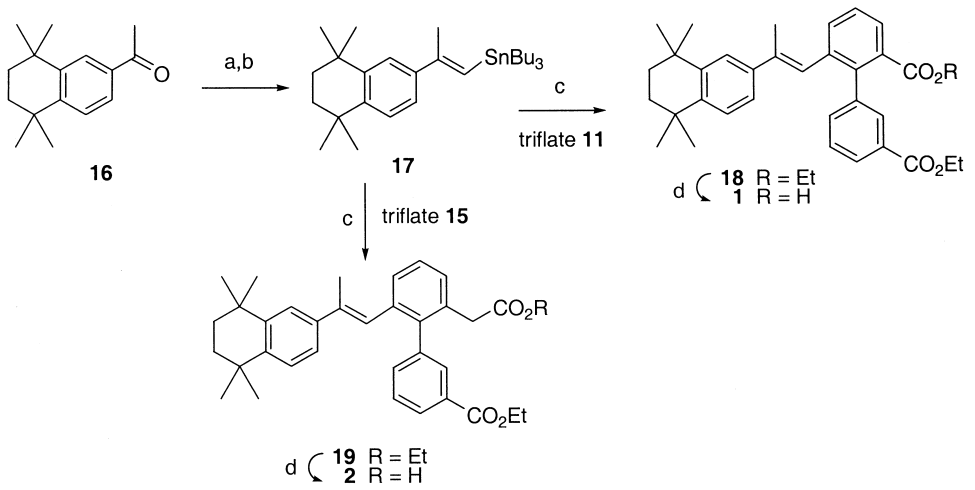
13. Demethylation of **13**, and triflation of the resultant alcohol **14** yielded aryl triflate **15**.

The syntheses of targets **1** and **2** are depicted in Scheme 3. Commercially available ketone **16** was converted to stannane **17** by a two-step sequence involving Wittig reaction to a bromo olefin, followed by metal–halogen exchange and trapping of the intermediate vinyl anion with tributyltin chloride. Palladium catalyzed cross coupling of stannane **17** with triflate **11** then afforded diester **18**, which was hydrolyzed to diacid **1**. The same sequence when applied to triflate **15** provided diacid **2**.

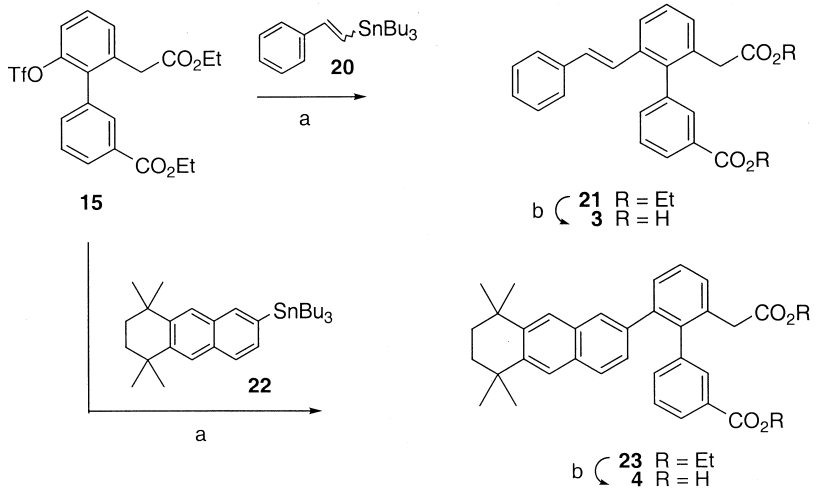
Two additional targets, **3** and **4**, containing a smaller and larger hydrophobic tail respectively, were synthesized by this general approach (Scheme 4). Commercially available stannane **20**, when coupled to triflate **15**, yielded diester **21**. Hydrolysis of **21** then afforded diacid **3**. The same process utilizing stannane **22** gave rise to diacid **4**.

We next synthesized analogues bearing an ether linkage between the biaryl portion of the molecule and the hydrophobic tail. This approach obviates the successful yet cumbersome stannane/triflate coupling of these two components, allowing more facile synthesis of analogues. The ether-linked compounds prepared in the biaryl carboxylic acid ($n=0$), and biaryl acetic acid ($n=1$) series are illustrated in Table 2. The synthetic routes that were utilized for these ethers are summarized in Schemes 5 and 6.

Ether-linked compounds that contain a tetramethyltetrahydronaphthalene as the hydrophobic tail were synthesized starting from 2,3-dihydroxybenzaldehyde **24** (Scheme 5). The dianion of 2,3-dihydroxybenzaldehyde reacted regioselectively at C-3[27] with commercially available 2-chloromethyl-5,5,8,8-tetramethyl-tetrahydronaphthalene to yield salicylaldehyde **25**. Following conversion to triflate **26**, reaction with stannane **7** provided biaryl ether **27**. Oxidation of **27** to the acid, followed by hydrolysis of the ester, afforded diacid **28**. Intermediate aldehyde **27** was additionally homologated to **29**, which was converted to diacid **30**. Triflate **26** was coupled to stannane **31** to yield aldehyde **32**, which was then transformed to diacid **33**.



Scheme 3. Reaction conditions: (a) $Ph_3PCH_2Br + Br^-$, *t*-BuOK, THF, 0 °C; (b) *t*-BuLi, THF, −78 °C, then *n*-Bu_3SnCl; (c) $PdCl_2(PPh_3)_2$, LiCl, DMF, 125 °C; (d) 2 N NaOH, CH_3OH, THF, reflux, then 1 N HCl.



Scheme 4. Reaction conditions: (a) $PdCl_2(PPh_3)_2$, LiCl, DMF, 110 °C; (b) 2 N NaOH, CH_3OH, THF, reflux, then 1 N HCl.

The remaining members of Table 2 were synthesized by the two general approaches outlined in Scheme 6. Suitably functionalized benzyl alcohols of type **34** were linked to biaryl phenols **10** or **14** using diisopropylazodicarboxylate to produce ethers **35**. Hydrolysis of the ester groups yielded acids **36**. Alternatively, benzyl iodides **37** could be used to alkylate the phenoxide derived from **10** or **14** to yield the desired ether intermediates **35**.

We additionally synthesized some biaryl diacid derivatives which incorporated a two carbon link between the biaryl nucleus and one of the carboxyl substituents. The compounds synthesized in this class are shown in Table 3. These derivatives were synthesized according to the methods illustrated in Schemes 7 and 8.

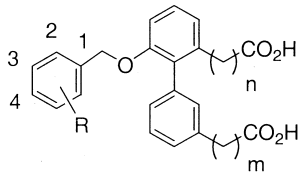
The synthesis of saturated compounds of type **40** begins with the olefination of biaryl aldehyde **8** using methyl diethylphosphonoacetate and sodium methoxide. The resulting unsaturated diester is hydrogenated, and then demethylated to afford phenol **38**. Etherification as described in Scheme 6 with appropriate benzyl alcohols and DIAD yielded diesters of type **39**. Hydrolysis of these diesters then gave the target diacids **40**. Unsaturated diacids **43** were also synthesized from biaryl aldehyde **8**. Demethylation of **8**, followed by etherification, delivered aldehydes **41**. Wadsworth–Emmons olefination of **41**, followed by hydrolysis, yielded the target diacids **43**.[28]

The synthesis of the ethyl- and ethylene-linked diacids **45** and **46**, containing the tetramethyl tetrahydronaphthalene hydrophobic group, began with the Wittig olefination of aldehyde **27** to mixed diester **44**. Hydrogenation of **44**, followed by hydrolysis, delivered the saturated diacid **45**. Direct hydrolysis of **44** yielded the unsaturated diacid **46**.

Biology

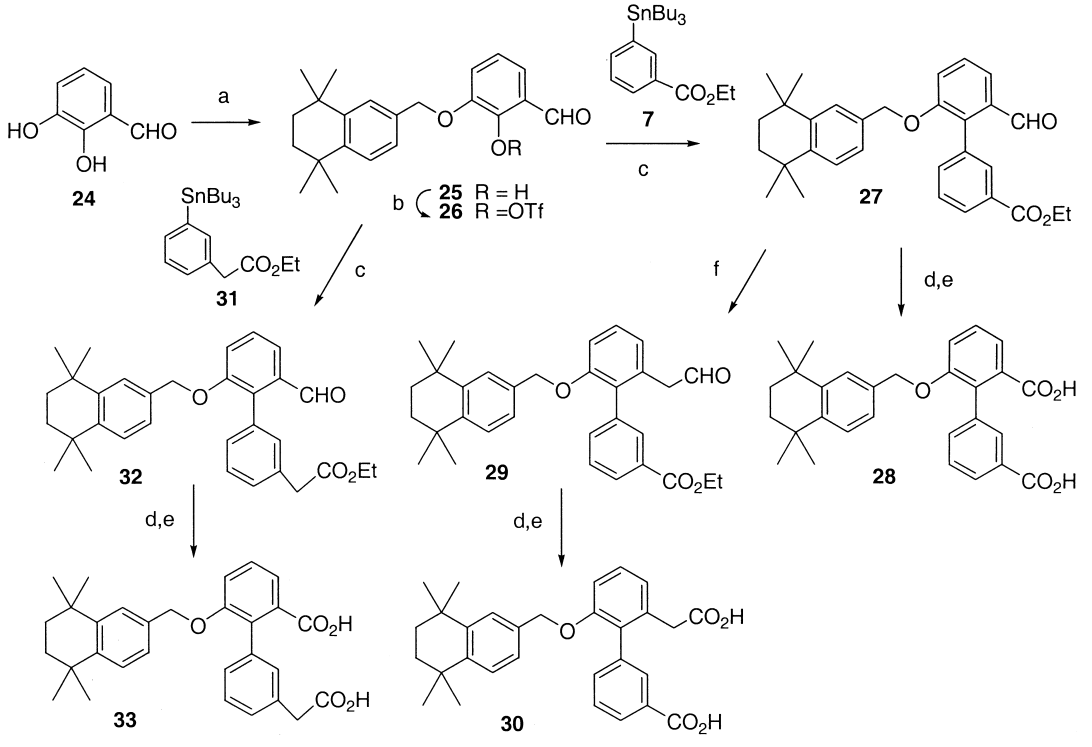
The in vitro activity of new compounds was determined as previously described.[24d] Phospholipase A_2 from human platelets (purified 3000-fold) was pre-incubated at 37 °C with test compound for 7 min. [1-^{14}C] oleic acid

Table 2. Biological activity of ether-linked diacids



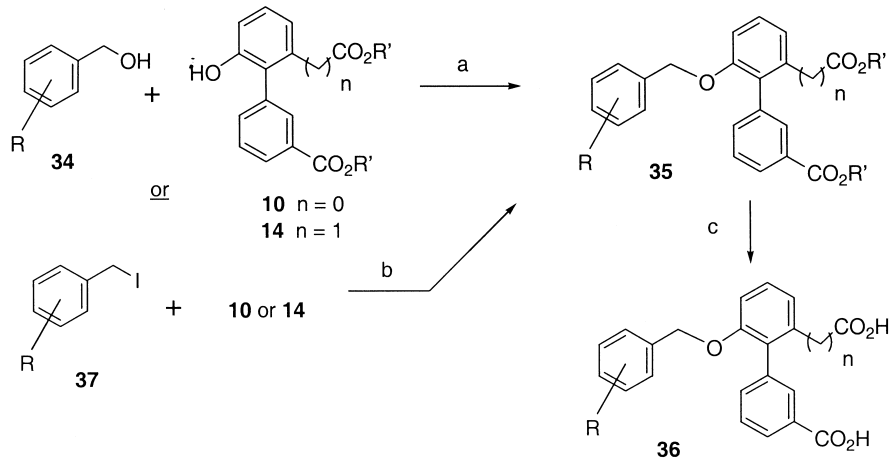
Compd	R	*n*	*m*	% Inhibition of human platelet PLA_2[a] 100 μM	% Inhibition of human platelet PLA_2[a] 10 μM	IC_{50} (μM)[b]	ED_{50}[c] (μg/ear per dose)
28	3,4-C$(CH_3)_2CH_2CH_2(CH_3)_2$C-	0	0	54	22	>100	147
30	3,4-C$(CH_3)_2CH_2CH_2(CH_3)_2$C-	1	0	80	32	24	—
33	3,4-C$(CH_3)_2CH_2CH_2(CH_3)_2$C-	0	1	72	9	—	—
36a	3,4-bis(*n*-C_5H_{11}O-)	0	0	53	27	>100	—
36b	3,4-bis(*n*-C_5H_{11}O-)	1	0	96	35	8	32
36c	3,4-bis($(CH_3)_2$C=$CHCH_2$O-)	0	0	20	7	—	—
36d	3,4-bis(c-C_5H_9O-)	0	0	73	29	—	—
36e	3,4-bis(c-C_5H_9O-)	1	0	79	14	80	—
36f	3-CH_3O-;4-(1-adamantyl)	0	0	62	24	—	—
36g	3-CH_3O-;4-(1-adamantyl)	1	0	97	52	15	—
36h	3,4-bis(*n*-$C_{10}H_{21}$O-)	0	0	99	84	2	—
36i	4-(*n*-$C_{10}H_{21}$O-)	1	0	99	77	4	73

[a]Values reported are the mean of two samples at each concentration.
[b]HP-PLA_2: values reported are the mean of three separate experiments.
[c]Phorbol ester induced mouse ear chronic inflammation assay. For details see ref 30.



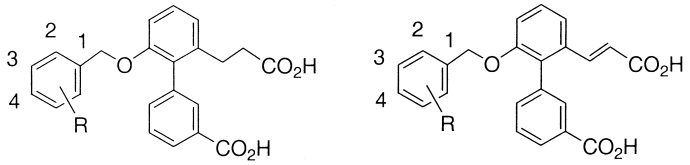
Scheme 5. Reaction conditions: (a) NaH (2.5 equiv), DMSO, 2-chloromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene; (b) Tf_2O, DMAP, CH_2Cl_2; (c) $PdCl_2(PPh_3)_2$, LiCl, DMF, 125 °C; (d) $NaClO_2$, H_2NSO_3H, THF, H_2O; (e) 2 N NaOH, CH_3OH, THF, reflux, then 1 N HCl; (f) $Ph_3PCH_2OCH_3 + Cl^-$, *t*-BuOK, toluene, THF; (g) 1 N HCl, THF, reflux.

labeled, autoclaved *Escherichia coli* membrane substrate was then added, and the reaction quenched after 30 min. The released, labeled oleic acid was quantitated by liquid scintillation counting and reported as percent inhibition relative to a vehicle control. Enzyme inhibition data determined at inhibitor concentrations of 100 and 10 μM were obtained in a high throughput screen and are the mean of two samples at each concentration. Reported IC_{50} values were determined by regression analysis of a dose response curve and are the mean of three separate experiments. For reference purposes, the IC_{50} of manoalide (a potent PLA_2 inhibitor) against



Scheme 6. Reaction conditions: (a) DlAD, PPh_3, THF, 0 °C; (b) K_2CO_3, MlBK, reflux; (c) 2 N NaOH, CH_3OH, THF, reflux, then 1 N HCl.

Table 3. Biological activity of biaryl propionic and propenoic acids



Compd	R	Type	% Inhibition of human platelet PLA_2[a]		IC_{50} (μM)[b]
			100 μM	10 μM	
40a	3,4-bis(*n*-$C_5H_{11}O$-)	Saturated	59	6	57
43a	3,4-bis(*n*-$C_5H_{11}O$-)	Unsaturated	59	22	40
40b	3,4-bis($(CH_3)_2C{=}CHCH_2O$-)	Saturated	55	6	—
43b	3,4-bis($(CH_3)_2C{=}CHCH_2O$-)	Unsaturated	73	16	—
40c	3,4-bis(c-C_5H_9O-)	Saturated	51	4	>100
43c	3,4-bis(c-C_5H_9O-)	Unsaturated	86	24	88
45	3,4-$C(CH_3)_2CH_2CH_2(CH_3)_2C$-	Saturated	54	7	—
46	3,4-$C(CH_3)_2CH_2CH_2(CH_3)_2C$-	Unsaturated	72	20	—

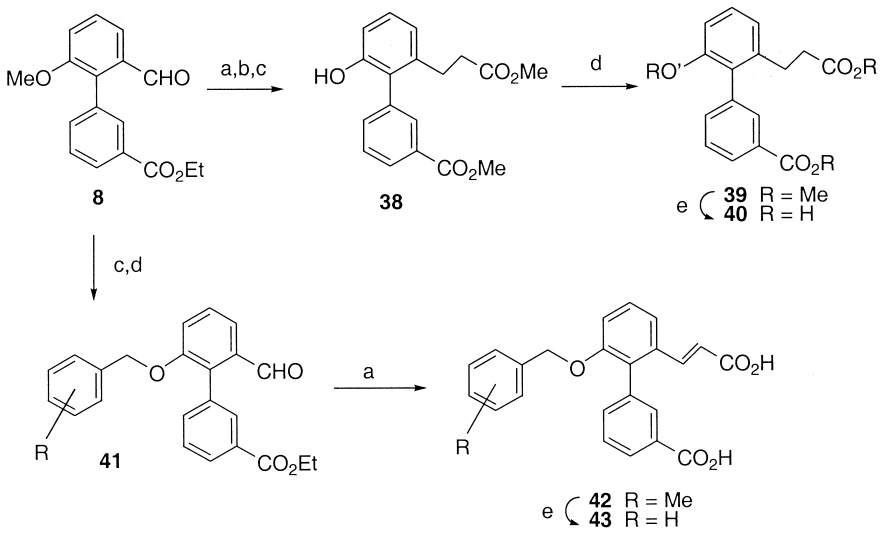
[a]Values reported are the mean of two samples at each concentration.
[b]HP-PLA_2: values reported are the mean of three separate experiments.

HP-PLA_2 was found to be 6 μM under our assay conditions.[29]

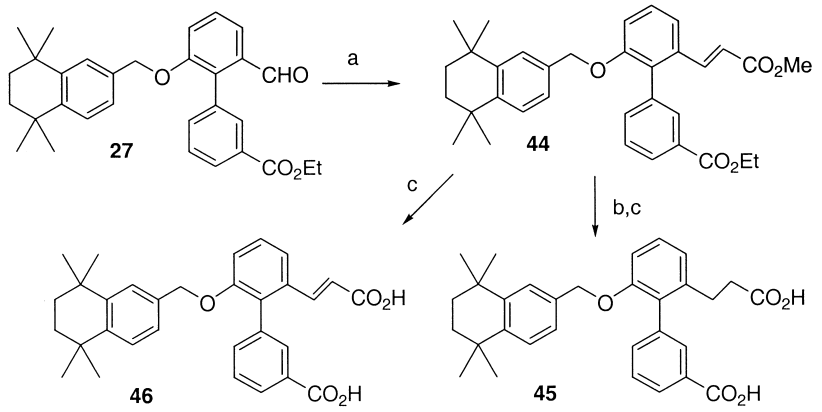
The ED_{50} values obtained in the phorbol ester induced mouse ear chronic inflammation assay (reported in Tables 1 and 2) were determined as previously reported.[30] The application of irritant alone to the mouse ear over the first 7 days of this 10-day assay invokes a chronic state of inflammation. During the final 3 days of the assay the test compound is dosed with continued application of the phorbol ester. On day 10, inflammation can be assayed by measuring epidermal thickness, or myeloperoxidase content (MPO activity is a marker for polymorphonuclear (PMN) leukocyte infiltration[31]), relative to vehicle control samples. The reported ED_{50} values in the tables are the dose concentration of test compound necessary to inhibit half the MPO activity relative to control samples.[32] This stringent assay is a measure of a compound's ability to reduce edema in an established inflammatory condition. For comparison purposes, the ED_{50} of lonapalene (a known 5-lipoxygenase inhibitor and antipsoriasis agent) in this chronic assay is 1000 μg/ear.[30a]

Discussion

Some structure–activity relationships (SAR) pertaining to the diacid portion of these molecules can be deduced from the data presented in the tables. In general, compounds in the $n=1$ series are more active than the corresponding derivatives from the $n=0$ or $n=2$ series. This effect is first observed by comparing the data for diacids **1** and **2**. Subsequent derivatives in the ether-linked series, as exemplified by the data in Tables 2 and 3, further support the general trend that $n=1$ derivatives are the more potent inhibitors of HP-PLA_2. Another generality is that in the $n=2$ series, the unsaturated compounds are more active than the corresponding saturated diacids (Table 3). A trend can be



Scheme 7. Reaction conditions: (a) $(EtO)_2P(O)CH_2CO_2Me$ (1.33 equiv), $NaOCH_3$ (2.5 equiv) in CH_3OH, toluene; (b) 10% Pd/C, H_2 (50 psi), EtOH; (c) Me_2BBr, $ClCH_2CH_2Cl$; (d) $ArCH_2OH$, DlAD, PPh_3, THF, 0 °C; (e) 2 N NaOH, CH_3OH, THF, reflux, then 1 N HCl.



Scheme 8. Reaction conditions: (a) $Ph_3P{=}CHCO_2CH_3$ (4.4 equiv), CH_2Cl_2; (b) 10% Pd/C, H_2 (1 atm), EtOAc; (c) 2 N NaOH, CH_3OH, THF, reflux, then 1 N HCl.

observed concerning SAR in the middle section of these molecules. The olefin-linked molecules **1** and **2** are both more potent than their analogous ether-linked derivatives **28** and **30**.

SARs in the hydrophobic portion of the molecule are more difficult to discern. PLA_2 enzymes have a large active site, capable of hosting geometrically diverse structures. However, it can be observed that the enzyme displays a very clear preference for molecules with larger hydrophobic groups. For example, the small styryl diacid **3** is less active than either the tetrahydronaphthalene **2** or the tetrahydroanthracene **4**. The bis-pentyloxy compound **36a** shows diminished potency relative to the bis-decyloxy molecule **36h**. The data obtained for compounds **36h** and **36i** indicates that the enzyme may prefer hydrophobic groups which resemble the large, and flexible alkyl chains of the fatty esters present in the natural substrate. These compounds were found to be the most active biaryl inhibitors of HP-PLA_2.

However, an analysis of the effect of molecular shape of certain variants of the hydrophobic group on inhibitory activity yields mixed conclusions. In one class of compounds, the $n=2$ unsaturated series of Table 3, we observed an increase in potency by molecules containing the more entropically constrained (rigid) unsaturated pentyl derivatives relative to the *n*-pentyl analogues. In contrast, the data obtained from these pentyl derivatives in the $n=0$, $n=1$, and $n=2$ saturated series indicates that there is little or no effect of rigidity on activity. Thus, subtle changes in the structure of the hydrophobic group may have a profound effect on activity in some series of compounds but not in others.

Five of these biaryl diacid compounds (**2**, **4**, **28**, **36b** and **36i**) were evaluated in a phorbol ester induced mouse ear chronic edema assay (see Tables 1 and 2).[33] All five compounds were found to reduce mouse ear edema in this in vivo model. These derivatives displayed ED_{50} values ranging between 32 and 147 μg/ear per dose. Thus, these compounds were found to be up to five times more effective as anti-inflammatory agents in this model than the lead compound BMS-181162 (ED_{50} = 180 μg/ear per dose) and up to thirty times more effective than lonapalene (ED_{50} = 1000 μg/ear per dose).

A comparison of the in vitro (human enzyme) and in vivo (mouse ear) data for diacids **2**, **4**, **28**, **36b** and **36i**, indicates there is no direct correlation between these parameters. There are many possible explanations for this discrepancy. These compounds may display differential inhibitory activity between human platelet PLA_2 and the corresponding mouse PLA_2. Pharmacological factors, such as bioavailability and metabolism, may also be affecting the in vivo efficacy of these compounds. Additionally, these compounds may affect the activity of other enzymes (such as cyclooxygenases, lipoxygenases, etc.) involved in mediating inflammatory processes. However, we believe this latter explanation to be less likely since these compounds are so closely related in structure to BMS-181162, a compound determined to be an insignificant inhibitor of many enzymes involved in the inflammatory response.[30a]

Conclusions

A number of biaryl dicarboxylic acids were synthesized which inhibit human platelet PLA_2. In general, for this collection of biaryl inhibitors, three trends in SAR were observed. Derivatives in the $n=1$ series were more active than the corresponding analogues in the $n=0$ or $n=2$ series. There was a slight increase in potency for compounds bearing olefin-linked hydrophobic groups when compared with the relevant ether-linked derivatives. It was clear that compounds with larger hydrophobic groups were better inhibitors of HP-PLA_2.

The most active compound in vitro, **36h**, was greater than 20 times more active than the lead compound BMS-181162 ($IC_{50}=2\,\mu M$ versus $45\,\mu M$). Five of the compounds reported here (**2**, **4**, **28**, **36b** and **36i**) demonstrated anti-inflammatory effects in a phorbol ester induced mouse model of chronic ear edema. The most active compound in vivo, **36b**, was found to be more than five times as effective as BMS-181162, and more than thirty times more effective than lonapalene in reducing inflammation. These compounds remain interesting leads for the development of novel, anti-inflammatory PLA_2 inhibitors.

Experimental

General

Unless otherwise indicated all reactions were performed under a nitrogen atmosphere and all solvents were of reagent grade. Analytical thin-layer chromatography (TLC) was carried out on silica gel plates (60F-254) and visualized using UV light, iodine vapors, and/or staining by heating with ethanolic phosphomolybdic acid. 'Chromatography' or 'Chromatography on silica gel' refers to flash column chromatography using E-Merck silica gel 60 (230–400 mesh) unless otherwise noted.

Proton and carbon-13 nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker AM-300 or a Varian Gemini 300 spectrometer. Chemical shifts are reported in δ (ppm) units relative to tetramethylsilane (TMS) and interproton coupling constants are reported in Hertz (Hz). Infrared spectra were determined on a Perkin–Elmer 1800 FT-IR spectrometer from 4000 to $400\,cm^{-1}$, calibrated to the $1601\,cm^{-1}$ absorption of a polystyrene film, and are reported in reciprocal centimeters (cm^{-1}). Mass spectra were recorded on a Kratos MS-50 or a Finnegan 4500 instrument utilizing direct chemical ionization (DCI, isobutene) or fast atom bombardment (FAB). Ultraviolet spectra were determined on a Hewlett Packard 8452 diode array spectrophometer in the solvent indicated.

General procedure A. Synthesis of aryl triflates: 2-trifluoromethylsulphonyloxy-3-methoxybenzaldehyde (6). *o*-Vanillin (4.00 g, 26.3 mmol) was dissolved in 115 mL of dry methylene chloride. 4-Dimethylaminopyridine (11.7 g, 95.8 mmol) was added, and the flask cooled to 0 °C. Trifluoromethanesulfonylanhydride (5.09 mL, 30.3 mmol) was added dropwise via syringe over 5 min. The mixture was stirred for 30 min at 0 °C, and then poured into 1 N HCl. The organic layer was washed twice with 1 N HCl, once with water, and then brine. The organic phase was dried ($MgSO_4$), and then concentrated in vacuo, yielding a crude solid. Chromatography on silica gel using 25 then 50% methylene chloride:hexane afforded **6** (5.52 g, 19.4 mmol, 74% yield) as a white crystalline solid, analytically identical to the known material:[34] mp = 29.5–31.5 °C; UV_{max} ($CHCl_3$) 244 nM (ε = 8641), 314 nM (ε = 3139); ^1H NMR (300 MHz, $CDCl_3$) δ 10.23 (s, 1H, CHO), 7.51 (dd, $J=2$, 8 Hz, 1H, ArH), 7.44 (dd, $J=8$, 8 Hz, 1H, ArH), 7.28 (dd, $J=2$, 8 Hz, 1H, ArH), 3.95 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.69 (C=O), 151.68, 129.53, 129.08, 121.13, 120.79, 118.59, 116.54, 56.58, (OCH_3); IR (KBr) 1706, 1608, 1580, 1482, 1422, 1294, 1230, 1210, 1132, 946, 888 cm^{-1}; MS (DCI) *m*/*e* 285 (MH^+). Anal. ($C_9H_7F_3O_5S$) C, H.

Synthesis of 3-carboethoxyphenyltributylstannane (7). Ethyl 3-bromobenzoate (13.8 mL, 86.2 mmol) and bis-(tributyl)tin (100 g, 172 mmol) were dissolved under argon in 380 mL of toluene. Tetrakis(triphenylphosphine)-palladium(0) (5.00 g, 4.33 mmol) was added, and the mixture heated to reflux overnight (ca. 16 h). The reaction was allowed to cool to room temperature, and was then filtered through Celite. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel using hexane, then 10% methylene chloride:hexane as the eluent. Stannane **7** was obtained as a clear oil (21.1 g, 48.1 mmol, 56%, 95% purity): ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H, ArH), 7.97 (ddd, $J=2$, 2, 8 Hz, 1H, ArH), 7.62 (ddd, $J=2$, 2, 8 Hz, 1H, ArH), 7.39 (dd, $J=8$, 8 Hz, 1H, ArH), 4.37 (q, $J=8$ Hz, 2H, CO_2CH_2), 1.54 (m, 6H, $3\times SnCH_2$), 1.37 (m, 9H, $3\times SnCH_2CH_2$ and $CO_2CH_2CH_3$), 1.10 (m, 6H, $3\times SnCH_2CH_2CH_2$), 0.94 (t, $J=8$ Hz, 9H, $3\times CH_3$).

General procedure B. Coupling of aryl triflates with stannanes: synthesis of 2-methoxy-3′-carboethoxy-[1,1′-biphenyl]-6-carboxaldehyde (8). Stannane **7** (4.25 g, 9.68 mmol) and triflate **6** (1.80 g, 6.44 mmol) were suspended in 17 mL of DMF. Bis(triphenylphosphine)palladium

dichloride (0.68 g, 0.969 mmol) and LiCl (0.82 g, 19.3 mmol) were added and the mixture was heated to 150 °C. After 45 min, more bis(triphenylphosphine)-palladium dichloride (0.2 g, 0.285 mmol), more LiCl (0.4 g, 9.42 mmol), and more stannane **7** (0.8 g, 1.82 mmol) were added, and heating was continued for 2 h. (The reaction generally turned from yellow–brown to black when complete.) The mixture was allowed to cool to room temperature, and 15 mL of aqueous saturated KF and 10 mL of ether were added. The mixture was stirred for 30 min, and then filtered through Celite to remove the tin salts. The filter cake was washed with EtOAc and ether, and the combined filtrates were washed with water, followed by 3% aqueous ammonia solution and then brine. The organic phase was dried ($MgSO_4$) and then concentrated in vacuo. Chromatography on silica gel using 25, 50 then 75% methylene chloride:hexane afforded aldehyde **8** (1.72 g, 6.06 mmol, 94%) as a slightly yellow oil which crystallized on standing: mp = 67–69 °C; UV_{max} ($CHCl_3$) 242 nM ($\epsilon = 15{,}819$), 324 nM ($\epsilon = 3953$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H, CHO), 8.09 (ddd, $J = 2$, 2, 7 Hz, 1H, ArH), 7.99 (s, 1H, ArH), 7.62 (dd, $J = 2$, 8 Hz, 1H, ArH), 7.49 (m, 3H, ArH), 7.19 (dd, $J = 2$, 8 Hz, 1H, ArH), 4.37 (q, $J = 7$ Hz, 2H, CO_2CH_2), 3.76 (s, 3H, OCH_3), 1.34 (t, $J = 7$ Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.93 (C=O), 166.31 (C=O), 156.98, 135.27, 133.73, 133.57, 131.92, 130.42, 129.17, 129.09, 128.09, 119.30, 115.95, 61.14, 56.06, 14.32; IR (film) 2980, 2940, 2838, 1718, 1694, 1468, 1294, 1260, 1234, 1110, 794 cm^{-1}; MS (DCI) *m/e* 285 (MH^+), 239 ($M-C_2H_5O$). Anal. ($C_{17}H_{16}O_4 \cdot 0.25\ H_2O$) C, H.

General procedure C. Conversion of aldehydes to esters: synthesis of 2-methoxy-3′-carboethoxy-[1,1′-biphenyl]-6-carboxylic acid, ethyl ester (9). Aldehyde **8** (0.512 g, 1.80 mmol) was dissolved in 17 mL of THF and 13 mL of H_2O. The solution was cooled to 0 °C. Sulfamic acid (0.525 g, 5.41 mmol) was then added, followed by a solution of sodium chlorite (80% tech, 0.612 g, 5.41 mmol) in 4 mL of H_2O. The mixture was stirred for 15 min at 0 °C, and then poured into EtOAc and water. The aqueous layer was extracted thrice with EtOAc, and the combined organic phase was washed with brine. The organic phase was dried ($MgSO_4$) and then concentrated in vacuo to afford 2-methoxy-3′-carboethoxy-[1,1′-biphenyl]-6-carboxylic acid as a pale yellow oil (0.583 g, 1.80 mmol, 100%): ^1H NMR (300 MHz, $CDCl_3$) δ 10.17 (br, 1H, CO_2H), 8.02 (ddd, $J = 2$, 2, 8 Hz, 1H, ArH), 7.94 (s, 1H, ArH), 7.56 (d, $J = 8$ Hz, 1H, ArH), 7.41 (m, 3H, ArH), 7.15 (d, $J = 8$ Hz, 1H, ArH), 4.19 (q, $J = 7$ Hz, 2H, CO_2CH_2), 3.73 (s, 3H, OCH_3), 1.39 (t, $J = 7$ Hz, 3H, $CH_2C\underline{H}_3$).

The above acid (0.583 g, 1.90 mmol) was dissolved in 12 mL of absolute EtOH. Concentrated HCl (0.6 mL) was added, and the mixture heated to reflux for 24 h. The mixture was then partitioned between EtOAc and water. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography on silica gel using 5%, then 10% EtOAc:hexane yielded **9** (0.432 g, 1.32 mmol, 73%) as a clear oil: UV_{max} ($CHCl_3$) 242 nM ($\epsilon = 12{,}036$), 296 nM ($\epsilon = 4724$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (m, 1H, ArH), 7.92 (m, 1H, ArH), 7.47–7.40 (m, 3H, ArH), 7.39 (dd, $J = 8$, 8 Hz, 1H, ArH), 7.09 (dd, $J = 2$, 8 Hz, 1H, ArH), 4.34 (q, $J = 7$ Hz, 2H, CO_2CH_2), 3.98 (q, $J = 7$ Hz, 2H, CO_2CH_2), 3.73 (s, 3H, OCH_3), 1.35 (t, $J = 7$ Hz, 3H, $CH_2C\underline{H}_3$), 0.91 (t, $J = 7$ Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.04 (C=O), 166.65 (C=O), 156.92, 137.28, 134.11, 133.22, 130.73, 130.07, 129.98, 128.78, 128.22, 127.63, 121.63, 113.87, 60.88, 56.02, 14.34, 13.65; IR (film) 2982, 1718, 1466, 1366, 1298, 1260, 1234, 1110, 1060 cm^{-1}; MS (DCI) *m/e* 329 (MH^+), 283 ($M-C_2H_5O$). Anal. ($C_{19}H_{20}O_5$) C, H.

General procedure D. Demethylation of aryl methyl ethers: synthesis of 2-hydroxy-3′-carboethoxy-(1,1′-biphenyl)-6-carboxylic acid, ethyl ester (10). Diester **9** (0.968 g, 2.95 mmol) was dissolved under argon in 9.8 mL of 1,2-dichloroethane. Dimethylboron bromide (1.16 mL, 11.9 mmol) was added, the flask was sealed and the mixture allowed to stir for 21 h at ambient temperature. Another 1.16 mL of dimethylboron bromide was added, and the mixture stirred, sealed under argon, for 3 days. The flask was cooled to 0 °C, and 20 mL of saturated $NaHCO_3$ was added with caution. The mixture was poured into 1 N HCl, and extracted thrice with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. Chromatography using 10% EtOAc:hexane yielded **10** (0.659 g, 2.10 mmol, 71%) as a yellow oil: UV_{max} ($CHCl_3$) 242 nM ($\epsilon = 10{,}155$), 296 nM ($\epsilon = 4591$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, $J = 2$, 8 Hz, 1H, ArH), 7.96 (dd, $J = 2$, 2 Hz, 1H, ArH), 7.57–7.45 (m, 3H, ArH), 7.33 (dd, $J = 8$, 8 Hz, 1H, ArH), 7.14 (dd, $J = 2$, 8 Hz, 1H, ArH), 4.98 (br, 1H, OH), 4.35 (q, $J = 7$ Hz, 2H, CO_2CH_2), 3.99 (q, $J = 7$ Hz, 2H, CO_2CH_2), 1.36 (t, $J = 7$ Hz, 3H, $CH_2C\underline{H}_3$), 0.95 (t, $J = 7$ Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.18 (C=O), 166.13 (C=O), 153.18, 135.46, 134.13, 131.76, 131.25, 130.67, 129.42, 129.16, 129.03, 127.32, 122.42, 119.19, 61.21, 60.85, 14.30, 13.70; IR (film) 3406, 2982, 1718, 1296, 1236, 758 cm^{-1}; MS (DCI) *m/e* 315 (MH^+), 269 ($M-C_2H_5O$). HRMS (FAB) *m/e* 337.1044 [$(M+Na)^+$ calcd for $C_{18}H_{18}O_5Na$: 337.1052].

Synthesis of 3′-carboethoxy-6-carboethoxy [1,1′-biphenyl] 2-trifluoromethanesulphonate (11). General procedure A was applied to phenol **10** (0.375 g, 1.19 mmol) to afford **11** (0.438 g, 0.982 mmol, 83%): chromatographed on silica using CH_2Cl_2:hexane; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (ddd, $J = 2$, 2, 7 Hz, 1H, ArH), 7.92 (m, 2H, ArH), 7.57–7.43 (m, 4H, ArH), 4.35 (q, $J = 7$ Hz, 2H, CO_2CH_2), 4.03 (q, $J = 7$ Hz, 2H, CO_2CH_2), 1.03 (t, $J = 7$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.94 (t, $J = 7$ Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.18 (C=O), 166.09 (C=O), 147.21, 135.05, 134.36, 134.05, 133.82, 130.54, 130.37, 129.77, 129.52, 129.40, 128.07, 124.67, 120.29, 61.51, 61.13, 14.27, 13.61; IR (film) 3074, 2986, 1722, 1426, 1368, 1296, 1240, 1214, 1140, 950, 850 cm^{-1}; MS (DCI) *m/e* 447 (MH^+), 401 ($M-C_2H_5O$). Anal. ($C_{19}H_{17}F_3O_7S$) C, H.

General procedure E. Wittig homologation of aldehydes: synthesis of 3′-carboethoxy-2-methoxy-1,1′-biphenyl-6-acetaldehyde (12). A solution of (methoxymethyl)-

triphenylphosphonium chloride (3.88 g, 11.3 mmol) in 15 mL of toluene and 50 mL of THF was cooled to 0 °C. Potassium *t*-butoxide (95%, 1.53 g, 12.9 mmol) was then added, and the mixture allowed to stir at 0 °C for 30 min. A solution of **8** (3.05 g, 10.7 mmol) in 15 mL of THF was then added rapidly dropwise, and the mixture allowed to stir for 5 min at 0 °C. The ice-bath was removed, and stirring continued for another 2 h at room temperature. The reaction mixture was partitioned between ether and water, and the organic phase washed with brine, dried ($MgSO_4$), and concentrated. Pentane was added to precipitate Ph_3PO, which was removed by filtration. The filtrate was concentrated to afford an oil. The crude material was chromatographed on silica gel using methylene chloride:hexane as the eluent to afford a mixture of (*E*) and (*Z*) 3′-carboethoxy-2-methoxy-6-[(1-methoxy)-2-ethenyl]-1,1′-biphenyl (3.27 g, 10.5 mmol, 98%) as a clear oil (~2:1 mixture of *E*:*Z* isomers): data for *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 7.50–7.27 (m, 3H, ArH), 7.19 (d, J = 8 Hz, 1H, ArH), 6.90 (d, J = 12 Hz, 1H, C=CH), 6.81 (d, J = 8 Hz, 1H, ArH), 5.41 (d, J = 12 Hz, 1H, C=CH), 4.38 (q, J = 7 Hz, 2H, CO_2CH_2), 3.71 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 1.36 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$).

The above mixture of *Z* and *E* enol ether isomers was dissolved in 31 mL of THF and 31 mL of 1 N HCl. The mixture was heated to reflux for 24 h, and then partitioned between ethyl acetate and water. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Crude **12** was obtained as a yellow oil (3.30 g), which was of suitable purity for use in subsequent reactions: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H, CHO), 8.03 (d, J = 8 Hz, 1H, ArH), 7.49–7.34 (m, 4H, ArH), 6.93 (d, J = 8 Hz, 1H, ArH), 6.88 (d, J = 8 Hz, 1H, ArH), 4.36 (q, J = 7 Hz, 2H, CO_2CH_2), 3.72 (s, 3H, OCH_3), 3.49 (s, 2H, $ArC\underline{H}_2CHO$), 1.38 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.08 (C=O), 166.45 (C=O), 157.34, 136.86, 134.60, 132.03, 131.09, 130.71, 130.63, 129.11, 128.54, 128.38, 122.61, 109.99, 61.02, 55.74, 48.32, 14.32.

Synthesis of 3′-carboethoxy-2-methoxy-1,1′-biphenyl-6-acetic acid, ethyl ester (13). Aldehyde **12** (3.30 g crude) was oxidized following general procedure C to afford crude 3′-carboethoxy-2-methoxy-1,1′-biphenyl-6-acetic acid (3.78 g), which was of suitable purity for use in subsequent reactions: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7 Hz, 1H, ArH), 7.90 (s, 1H, ArH), 7.55–7.31 (m, 3H, ArH), 6.95 (d, J = 7 Hz, 1H, ArH), 6.85 (d, J = 7 Hz, 1H, ArH), 4.35 (q, J = 7 Hz, 2H, CO_2CH_2), 3.70 (s, 3H, OCH_3), 3.40 (s, 2H, $ArCH_2CO_2$), 1.33 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.40 (C=O), 166.72 (C=O), 157.08, 136.89, 134.81, 133.36, 131.26, 130.50, 130.41, 128.87, 128.50, 128.31, 122.49, 109.91, 61.07, 55.73, 38.72, 14.28.

The acid from above (3.78 g crude) was then converted to the diethyl ester to afford **13** (2.77 g, 8.10 mmol, 77% overall yield from (*E*) and (*Z*) 3′-carboethoxy-2-methoxy-6-[(1-methoxy)-2-ethenyl]-1,1′-biphenyl): chromatographed on silica gel using EtOAc:hexane; UV_{max} (EtOH) 206 nM (ε = 28,222), 282 nM (ε = 817); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, J = 2, 8 Hz, 1H, ArH), 7.91 (s, 1H, ArH), 7.56–7.31 (m, 3H, ArH), 6.98 (d, J = 8 Hz, 1H, ArH), 6.90 (d, J = 8 Hz, 1H, ArH), 4.67 (s, 1H, OH), 4.37 (q, J = 7 Hz, 2H, CO_2CH_2), 4.02 (q, J = 7 Hz, 2H, CO_2CH_2), 3.68 (s, 3H, OCH_3), 3.35 (s, 2H, $ArCH_2CO_2$), 1.37 (t, J = 7 Hz, 3H, $CO2CH_2C\underline{H}_3$), 1.13 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.52 (C=O), 166.60 (C=O), 157.05, 137.03, 134.76, 134.07, 131.22, 130.42, 128.74, 128.38, 128.12, 122.44, 109.69, 60.92, 60.74, 55.75, 39.17, 14.33, 14.06; IR (KBr) 2990, 1735, 1718, 1580, 1470, 1300, 1255, 1235 cm^{-1}; MS (DCI) m/e 343 (MH^+). Anal. ($C_{20}H_{22}O_5 \cdot 0.10$ hexane) C, H.

Synthesis of 3′-carboethoxy-2-hydroxy-1,1′-biphenyl-6-acetic acid, ethyl ester (14). Diester **13** (2.77 g, 8.10 mmol) was converted via general procedure D to phenol **14** (2.40 g, 7.32 mmol, 90%): chromatographed on silica gel using EtOAc:hexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8 Hz, 1H, ArH), 7.96 (s, 1H, ArH), 7.56 (dd, J = 8, 8 Hz, 1H, ArH), 7.50 (d, J = 8 Hz, 1H, ArH), 7.24 (d, J = 8 Hz, 1H, ArH), 6.92 (d, J = 8 Hz, 1H, ArH), 6.90 (d, J = 8 Hz, 1H, ArH), 4.67 (s, 1H, OH), 4.37 (q, J = 7 Hz, 2H, CO_2CH_2), 4.02 (q, J = 7 Hz, 2H, CO_2CH_2), 3.35 (s, 2H, $ArCH_2CO_2$), 1.37 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.13 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.35 (C=O), 152.99, 135.00, 134.87, 133.74, 131.49, 129.66, 129.40, 129.24, 122.39, 114.44, 61.24, 60.81, 39.27, 14.30, 14.05; MS (DCI) m/e 329 (MH^+).

Synthesis of 3′-carboethoxy-2-trifluoromethylsulphonyloxy-1,1′-biphenyl-6-acetic acid, ethyl ester (15). Phenol **14** (1.13 g, 3.45 mmol) was converted by general procedure A to triflate **15** (1.21 g, 2.63 mmol, 76%): chromatographed on silica gel using CH_2Cl_2:hexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (ddd, J = 2, 2, 8 Hz, 1H, ArH), 7.94 (dd, J = 2, 2 Hz, 1H, ArH), 7.54 (dd, J = 8, 8 Hz, 1H, ArH), 7.44 (m, 3H, ArH), 7.33 (dd, J = 2, 8 Hz, 1H, ArH), 4.39 (q, J = 7 Hz, 2H, CO_2CH_2), 4.05 (q, J = 7 Hz, 2H, CO_2CH_2), 3.48 (s, 2H, $ArCH_2$), 1.39 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.15 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$).

Synthesis of (*E*)-2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]-1-propenyltributylstannane (17). Bromomethyltriphenylphosphonium bromide (6.07 g, 13.9 mmol) was suspended in 28 mL of dry toluene. The suspension was cooled to −40 °C. Potassium *tert*-butoxide (95%, 1.57 g, 13.3 mmol) was added and the flask allowed to warm to −20 °C over 30 min. The mixture was re-cooled to −40 °C, and 2-acetyl (5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene) **16** (3.05 g, 13.3 mmol) dissolved in 10 mL of toluene was added dropwise. The flask was allowed to warm to −30 °C and stir for 2 h. The mixture was poured into half-saturated ammonium chloride solution, and extracted with EtOAc and ether. The organic phase was washed with brine, dried ($MgSO_4$) and then concentrated in vacuo. Chromatography on silica gel using hexane as the eluent afforded (*E*)-2-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalenyl]-1-bromopropene (1.70 g, 5.54 mmol, 42%) as a 17:1 mixture of *E*:*Z* olefin isomers: Data for *E* isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8 Hz, 1H, ArH), 7.27 (d, J = 2 Hz, 1H, ArH), 7.11 (dd, J = 2, 8 Hz, 1H, ArH), 6.40 (q, J = 1 Hz, 1H, C=CHBr), 2.23 (d, J = 1 Hz, 3H, C=CCH_3), 1.70 (s, 4H, CH_2CH_2), 1.31 (s, 6H, 2×CH_3), 1.29 (s, 6H, 2×CH_3).

(*E*)-2-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl)-2-naphthalenyl]-1-bromopropene (0.680 g, 2.20 mmol) was dissolved in 6.8 mL of dry THF. The solution was cooled to −78 °C and *t*-BuLi (1.7 M in hexane, 2.74 mL, 4.62 mmol) was added dropwise. After stirring for 30 min at −78 °C, tri(*n*-butyl)tin chloride (0.60 mL, 2.2 mmol) was added. The mixture was stirred at −78 °C for 15 min and the cooling bath was removed. After 15 min, the solution was poured into water, and extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$) and then concentrated in vacuo. The yield of crude stannane **17** was 1.50 g. This material was suitable for use in subsequent reactions without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (bs, 1H, ArH), 7.28 (m, 2H, ArH), 6.23 (m, 1H, C=CH), 2.21 (s, 3H, C=CCH_3), 1.69 (s, 4H, CH_2CH_2), 1.60 (m, 6H, 3×$SnCH_2$), 1.35 (m, 12H, 3×$SnCH_2C\underline{H_2}C\underline{H_2}$), 1.32 (s, 6H, 2×$CH_3$), 1.30 (s, 6H, 2×$CH_3$), 0.95 (m, 9H, 3×$CH_3$).

Synthesis of 6-carboethoxy-2-[(*E*)-2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]-1-propenyl]-3′-carboethoxy-[1,1′-biphenyl] (18). Stannane **17** (0.840 g, 1.62 mmol) and triflate **11** (0.238 g, 0.530 mmol) were coupled at 130 °C using general procedure B to afford diester **18** (0.233 g, 0.445 mmol, 84%): chromatographed on silica gel using EtOAc:hexane; UV_{max} (EtOH) 212 nm (ε = 30,865), 278 nM (ε = 11,586); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (ddd, J = 2, 2, 8 Hz, 1H, ArH), 7.90 (s, 1H, ArH), 7.78 (dd, J = 2, 8 Hz, 1H, ArH), 7.52 (dd, J = 2, 8 Hz, 1H, ArH), 7.44 (dd, J = 8, 8 Hz, 1H, ArH), 7.39 (m, 2H, ArH), 7.16 (d, J = 8 Hz, 1H, ArH), 7.00 (d, J = 2 Hz, 1H, ArH), 6.95 (dd, J = 2, 8 Hz, 1H, ArH), 6.28 (s, 1H, C=CH), 4.31 (q, J = 7 Hz, 2H, CO_2CH_2), 4.01 (q, J = 7 Hz, 2H, CO_2CH_2), 2.08 (s, 3H, C=CCH_3), 1.62 (s, 4H, CH_2CH_2), 1.32 (t, J = 7 Hz, 3H, $CH_2C\underline{H_3}$), 1.22 (s, 6H, 2×CH_3), 1.16 (s, 6H, 2×CH_3), 0.94 (t, J = 7 Hz, 3H, $CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.20 (C=O), 166.47 (C=O), 144.46, 144.06, 140.44, 140.37, 140.26, 138.53, 137.53, 133.82, 132.92, 131.82, 130.32, 130.02, 128.24, 128.04, 127.75, 127.21, 126.30, 125.73, 123.91, 123.11, 60.91, 60.85, 35.11, 34.99, 34.20, 34.04, 31.73, 17.23, 14.27, 13.70; IR (film) 2960, 2926, 1722, 1292, 1234, 1136 cm^{-1}; MS (DCI) m/e 525 (MH^+), 479 ($M-C_2H_5O$).

General procedure F. Hydrolysis of esters: synthesis of (*E*)-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]-[1,1′-biphenyl]-6,3′-dicarboxylic acid (1). Diester **18** (0.189 g, 0.361 mmol) was dissolved in 3.1 mL of MeOH, 3.1 mL of 2 N NaOH, and 4 mL of THF. The mixture was heated to reflux for 2 h. The solution was allowed to cool to room temperature, and then acidified to pH 2 with 1 N HCl. The material was extracted thrice with chloroform, and the extracts were washed with brine, dried ($MgSO_4$), and evaporated. Reverse-phase chromatography on C-18 silica gel with 90% MeOH:H_2O as eluent afforded diacid **1** (0.149 g, 0.318 mmol, 88%) as a white solid: UV_{max} (EtOH) 212 nM (ε = 29,622), 276 nM (ε = 12,314); ^{1}H NMR (300 MHz, CD_3OD) δ 8.02 (ddd, J = 2, 2, 8 Hz, 1H, ArH), 7.89 (s, 1H, ArH), 7.79 (d, J = 8 Hz, 1H, ArH), 7.59 (d, J = 8 Hz, 1H, ArH), 7.49 (m, 2H, ArH), 7.42 (ddd, J = 2, 2, 8 Hz, 1H, ArH), 7.18 (d, J = 8 Hz, 1H, ArH), 6.95 (m, 2H, ArH), 6.20 (s, 1H, C=CH), 2.08 (s, 3H, CH_3), 1.64 (s, 4H, CH_2CH_2), 1.22 (s, 6H, 2×CH_3), 1.14 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 169.78 (C=O), 145.57, 144.93, 141.99, 141.88, 141.78, 139.76, 139.23, 135.11, 133.84, 131.96, 131.50, 129.42, 128.98, 128.36, 127.33, 126.82, 124.90, 124.33, 36.28, 36.18, 35.13, 34.95, 32.25, 32.16, 17.56; IR (KBr) 3510, 2956, 2924, 1694, 1408, 1300, 1250, 758 cm^{-1}; MS (DCI) m/e 469 (MH^+), 451 (M−OH). Anal. ($C_{31}H_{32}O_4$) C, H.

Synthesis of 3′-carboethoxy-(*E*)-2-[(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthalenyl)-1-propenyl]-[1,1′-biphenyl]-6-acetic acid, ethyl ester (19). Stannane **17** (0.860 g, 1.66 mmol) and triflate **15** (0.302 g, 0.657 mmol) were coupled using general procedure B. After heating at 110 °C for 15 min the reaction was incomplete as judged by thin-layer chromatography. The bath temperature was raised to 130 °C, and heating was continued for another 10 min to complete the reaction. Diester **19** (0.309 g, 0.574 mmol, 87%) was obtained as a clear oil: chromatographed on silica gel using EtOAc: hexane; UV_{max} (EtOH) 208 nM (ε = 30,099), 276 nM (ε = 13,855); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (ddd, J = 2, 2, 8 Hz, 1H, ArH), 7.87 (dd, J = 2, 2 Hz, 1H, ArH), 7.46 (dd, J = 8, 8 Hz, 1H, ArH), 7.37 (m, 3H, ArH), 7.26 (dd, J = 2, 8 Hz, 1H, ArH), 7.15 (d, J = 8 Hz, 1H, ArH), 6.96 (d, J = 2 Hz, 1H, ArH), 6.92 (dd, J = 2, 8 Hz, 1H, ArH), 6.26 (s, 1H, C=CH), 4.33 (q, J = 7 Hz, 2H, CO_2CH_2), 4.02 (q, J = 7 Hz, 2H, CO_2CH_2), 3.43 (s, 2H, $ArCH_2$), 2.11 (s, 3H, CH_3), 1.61 (s, 4H, CH_2CH_2), 1.34 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H_3}$), 1.22 (s, 6H, 2×CH_3), 1.15 (m, 9H, $CO_2CH_2C\underline{H_3}$ and 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.68 (C=O), 166.44 (C=O), 144.46, 143.85, 140.83, 140.57, 139.90, 137.92, 136.78, 134.47, 132.50, 130.78, 130.45, 128.62, 128.49, 128.44, 128.26, 127.41, 126.51, 126.24, 123.94, 123.12, 60.97, 60.76, 39.49, 35.10, 34.99, 34.18, 34.01, 31.74, 17.24, 14.29, 14.09; IR (film) 2960, 2928, 1722, 1462, 1366, 1298, 1240, 1158, 1110, 1034, 752 cm^{-1}; MS (DCI) m/e 539 (MH^+), 493 ($M-C_2H_5O$). Anal. ($C_{36}H_{42}O_4 \cdot 1.25\ H_2O$) C, H.

Synthesis of 3′-carboxy-(*E*)-2-[(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthalenyl)-1-propenyl]-[1,1′-biphenyl]-6-acetic acid (2). Diester **19** (0.476 g, 0.885 mmol) was hydrolyzed according to general procedure F to yield diacid **2** (0.380 g, 0.788 mmol, 89%): crystallized from CH_2Cl_2:pentane; mp = 253.5–255.5 °C; UV_{max} (EtOH) 210 nM (ε = 38,336), 276 nM (ε = 15,928); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (d, J = 8 Hz, 1H, ArH), 7.70 (s, 1H, ArH), 7.56 (dd, J = 8, 8 Hz, 1H, ArH), 7.43–7.29 (m, 4H, ArH), 7.17 (d, J = 8 Hz, 1H, ArH), 6.91 (d, J = 8 Hz, 1H, ArH), 6.85 (d, J = 2 Hz, 1H, ArH), 6.15 (s, 1H, C=CH), 3.36 (s, 2H, $ArCH_2$), 2.06 (s, 3H, CH_3), 1.56 (s, 4H, CH_2CH_2), 1.16 (s, 6H, 2×CH_3), 1.08 (s, 6H, 2×CH_3); ^{3}C NMR (75 MHz, DMSO-d_6) δ

172.46 (C=O), 167.09 (C=O), 144.01, 143.48, 140.57, 140.23, 139.53, 136.69, 136.30, 133.92, 133.15, 130.66, 130.52, 129.13, 128.56, 128.14, 127.87, 127.25, 126.22, 125.98, 123.32, 122.95, 34.58, 34.48, 33.74, 33.67, 31.47, 17.00; IR (KBr) 3422, 2964, 2926, 1698, 1460, 1432, 1406, 1292, 1258, 748 cm^{-1}; MS (DCI) *m/e* 483 (MH^+), 465 (M−OH). Anal. ($C_{34}H_{34}O_4 \cdot 0.25\ H_2O$) C,H.

Synthesis of (*E*) and (*Z*)-3′-carboethoxy-2-styryl-[1,1′-biphenyl]-6-acetic acid, ethyl ester (21). Tributyl(styryl)-stannane **20** (0.332 g, 0.845 mmol; ca. 10:1 mixture of *E*:*Z*) was coupled with triflate **15** (0.259 g, 0.563 mmol) via heating at 110 °C for 20 minutes following General procedure B to afford (after chromatography on silica gel using 20% EtOAc:hexane) a 10:1 mixture of (*E*) and (*Z*) **21** (0.221 g, 0.534 mmol, 95%). A second chromatographic purification utilizing a gradient elution of EtOAc: hexane was necessary to separate the isomers: Data for ***E*-27a**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.91 (dd, *J* = 2, 2 Hz, 1H, ArH), 7.72 (d, *J* = 8 Hz, 1H, ArH), 7.52 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.40 (m, 2H, ArH), 7.29 (dd, *J* = 2, 8 Hz, 1H, ArH), 7.23 (m, 5H, ArH), 6.99 (d, *J* = 17 Hz, 1H, CH=C), 6.66 (d, *J* = 17 Hz, 1H, CH=C), 4.39 (q, *J* = 7 Hz, 2H, CO_2CH_2), 4.04 (q, *J* = 7 Hz, 2H, CO_2CH_2), 3.40 (s, 2H, $ArCH_2$), 1.37 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.15 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$). Data for ***Z*-27a**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.86 (dd, *J* = 2, 2 Hz, 1H, ArH), 7.43 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.37 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.24–7.15 (m, 8H, ArH), 6.34 (d, *J* = 12 Hz, 1H, CH=C), 6.16 (d, *J* = 12 Hz, 1H, CH=C), 4.37 (q, *J* = 7 Hz, 2H, CO_2CH_2), 4.04 (q, *J* = 7 Hz, 2H, CO_2CH_2), 3.42 (s, 2H, $ArCH_2$), 1.35 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.16 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$).

Synthesis of (*E*)-3′-carboxy-2-styryl-[1,1′-biphenyl]-6-acetic acid (3). Diester **21** (0.123 g, 0.297 mmol) was hydrolyzed according to general procedure F to yield diacid **3** (0.091 g, 0.254 mmol, 86%): chromatographed on reverse-phase C-18 silica gel using water:methanol as eluent, then crystallized from CH_2Cl_2:pentane; UV_{max} (EtOH) 206 nM (ε = 27,755), 228 nM (ε = 26,398), 302 nM (ε = 22,153); ^1H NMR (300 MHz, CD_3OD) δ 8.09 (d, *J* = 8 Hz, 1H, ArH), 7.87 (s, 1H, ArH), 7.74 (d, *J* = 8 Hz, 1H, ArH), 7.58 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.39 (m, 2H, ArH), 7.29 (d, *J* = 8 Hz, 1H, ArH), 7.17 (m, 5H, ArH), 7.00 (d, *J* = 16 Hz, 1H, C = CH), 6.65 (d, *J* = 16 Hz, 1H, C=CH), 3.39 (s, 2H, $ArCH_2$); ^{13}C NMR (75 MHz, CD_3OD) δ 175.39 (C=O), 169.62 (C=O), 141.62, 140.87, 138.73, 137.68, 135.89, 134.75, 132.35, 130.99, 130.93, 129.89, 129.70, 129.64, 129.15, 128.64, 128.05, 127.36, 125.19, 40.13; IR (KBr) 3422, 2922, 1700, 1410, 1306, 1258, 744 cm^{-1}; MS (DCI) *m/e* 359 (MH^+), 358 (M^+), 341 (M−OH). Anal. ($C_{23}H_{18}O_4 \cdot 0.25\ H_2O$) C, H.

Synthesis of 2-tributylstannyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylanthracene (22). 2-Bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethylanthracene (2.03 g, 6.42 mmol) (for a synthesis of this bromide see ref 35) was dissolved in 20 mL THF. The solution was cooled to −78 °C, and *tert*-butyl lithium (1.7 M in hexane, 7.93 mL, 13.5 mmol) was added. The mixture was allowed to stir 30 min at −78 °C, and then tri(*n*-butyl)tin chloride (1.74 mL, 6.42 mmol) was added. The mixture was stirred at −78 °C for 15 min, and then the cooling bath was removed. After another 15 min, the solution was poured into water, and extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$) and then concentrated in vacuo. Chromatography on silica gel using hexane, then CH_2Cl_2:hexane as solvent yielded stannane **22** (3.28 g, 6.22 mmol, 97%) as a clear oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H, ArH), 7.74 (s, 2H, ArH), 7.67 (d, *J* = 8 Hz, 1H, ArH), 7.41 (d, *J* = 8 Hz, 1H, ArH), 1.76 (s, 4H, CH_2CH_2), 1.57 (m, 6H, butyl), 1.35 (m, 18H, 4×CH_3 and butyl), 1.09 (m, 6H, butyl), 0.88 (m, 9H, butyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.18, 144.10, 138.24, 135.81, 132.28, 131.77, 131.63, 125.99, 124.79, 124.54, 35.15, 34.60, 34.57, 32.57, 30.83, 29.45, 29.03, 27.73, 27.43, 13.74, 9.60, 7.88; IR (film) 2956, 2926, 2870, 2854, 1462, 1376, 1362 cm^{-1}; MS (DCI) *m/e* 529 (MH^+).

Synthesis of 3′-carboethoxy-2-[(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl)-7-anthracenyl]-[1,1′-biphenyl]-6-acetic acid, ethyl ester (23). Stannane **22** (0.775 g, 1.47 mmol) was coupled to triflate **15** (0.451 g, 0.980 mmol) using general procedure B to afford diester **23** (0.355 g, 0.650 mmol, 66%) as a clear oil: chromatographed on silica gel using EtOAc:hexane; UV_{max} ($CHCl_3$) 244 nM (ε = 37,190); ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2 Hz, 1H, ArH), 7.84 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.65 (s, 1H, ArH), 7.62 (s, 1H, ArH), 7.57 (s, 1H, ArH), 7.38 (m, 4H, ArH), 7.22 (m, 2H, ArH), 6.88 (dd, *J* = 2, 8 Hz, 1H, ArH), 4.28 (m, 2H, CO_2CH_2), 4.03 (q, *J* = 7 Hz, 2H, CO_2CH_2), 3.51 (d, *J* = 16 Hz, 1H, $ArCH_2CO_2$), 3.43 (d, *J* = 16 Hz, 1H, $ArCH_2CO_2$), 1.73 (s, 4H, CH_2CH_2), 1.36 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.33 (s, 6H, 2×CH_3), 1.29 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.15 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.72 (C=O), 166.48 (C=O), 144.36, 144.29, 142.22, 139.81, 139.64, 138.24, 135.12, 133.06, 131.49, 130.26, 129.99, 129.73, 129.48, 128.01, 127.88, 127.82, 127.36, 126.00, 124.95, 124.53, 60.89, 60.81, 39.73, 35.06, 34.54, 32.49, 14.24, 14.10; IR (film) 2960, 2926, 2860, 1734, 1720, 1462, 1298, 1232, 1110 cm^{-1}; MS (DCI) *m/e* 549 (MH^+), 503 (M−C_2H_5O).

Synthesis of 3′-carboxy-2-[(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl)-7-anthracenyl]-[1,1′-biphenyl]-6-acetic acid (4). Diester **23** was hydrolyzed using general procedure F to afford diacid **4** (0.113 g, 0.230 mmol, 57%) as a white solid: crystallized from CH_2Cl_2:pentane; mp = 235–240 °C; UV_{max} ($CHCl_3$) 242 nM (ε = 39,630); ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 7.64 (s, 1H, ArH), 7.63 (s, 1H, ArH), 7.56 (s, 1H, ArH), 7.46–7.33 (m, 6H, ArH), 7.02 (dd, *J* = 2, 8 Hz, 1H, ArH), 3.54 (d, *J* = 16 Hz, 1H, $ArCH_2CO_2$), 3.47 (d, *J* = 16 Hz, 1H, $ArCH_2CO_2$), 1.73 (s, 4H, CH_2CH_2), 1.36 (s, 3H, CH_3), 1.34 (s, 6H, 2×CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.87 (C=O), 172.12 (C=O), 144.46, 144.38, 142.18, 140.04, 139.58, 137.66, 135.03, 132.95, 132.67, 131.39, 130.31, 130.00, 128.90, 128.35, 128.12, 127.23, 126.15, 124.98, 124.51, 40.90, 35.04, 34.53, 32.49, 29.71; IR (KBr) 3420, 2960, 2926, 1704, 1298, 1248, 750 cm^{-1}; MS (DCI) *m/e* 493 (MH^+), 475 (M−OH). Anal. ($C_{33}H_{32}O_4 \cdot 0.75\ H_2O$) C, H.

Synthesis of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methoxy-salicylaldehyde (25). Sodium hydride (2.54 g, 0.106 mol; 80% dispersion, unwashed) was suspended in 75 mL of DMSO. A solution of 2,3-dihydroxybenzaldehyde (5.84 g, 42.3 mmol) in 30 mL of DMSO was added dropwise with water bath cooling, and the mixture allowed to stir 1 h at room temperature. A solution of 2-chloromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene (10 g, 42.3 mmol) in 30 mL of DMSO was added and the mixture was allowed to stir overnight at room temperature. The mixture was then poured into half-saturated ammonium chloride solution, and extracted with EtOAc. The aqueous phase was saturated with sodium chloride, and then extracted twice with EtOAc. The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated. Chromatography on silica gel using 50% CH_2Cl_2:hexane afforded aldehyde **25** as a yellow oil (6.02 g, 17.8 mmol, 44%) which occasionally crystallizes upon standing: UV_{max} ($CHCl_3$) 268 nM ($\epsilon = 9894$), 240 nM ($\epsilon = 6181$), 350 nM ($\epsilon = 2513$); ^1H NMR (300 MHz, $CDCl_3$) δ 11.01 (s, 1H, OH), 9.91 (s, 1H, CHO), 7.33 (d, $J = 2$ Hz, 1H, ArH), 7.29 (d, $J = 8$ Hz, 1H, ArH), 7.21–7.13 (m, 3H, ArH), 6.90 (dd, $J = 8$, 8 Hz, 1H, ArH), 5.10 (s, 2H, $ArCH_2O$), 1.66 (s, 4H, CH_2CH_2), 1.25 (s, 12H, $4\times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.45 (C=O), 152.31, 147.46, 145.07, 144.86, 133.33, 126.93, 125.90, 125.12, 125.01, 121.06, 120.97, 119.46, 71.78, 35.03, 35.00, 34.26, 34.16, 31.83; IR (film) 2960, 2926, 2860, 1658, 1456, 1388, 1364, 1276, 1252, 1216, 750, 736 cm^{-1}; MS (DCI) *m/e* 339 (MH^+), 201 ($C_{15}H_{21}^+$). Anal. ($C_{22}H_{26}O_3 \cdot 0.4\ H_2O$) C,H.

Synthesis of 2-trifluoromethylsulphonyloxy-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methoxy-benzaldehyde (26). General procedure A was used to convert aldehyde **25** (2.316 g, 6.85 mmol) to triflate **26** (1.47 g., 3.13 mmol, 47%): chromatographed on silica gel using CH_2Cl_2:hexane, clear oil; UV_{max} ($CHCl_3$) 250 nM ($\epsilon = 8852$), 314 nM ($\epsilon = 3184$); ^1H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H, CHO), 7.51 (dd, $J = 2$, 8 Hz, 1H, ArH), 7.40 (dd, $J = 8$, 8 Hz, 1H, ArH), 7.38–7.30 (m, 3H, ArH), 7.16 (dd, $J = 2$, 8 Hz, 1H, ArH), 5.15 (s, 2H, $ArCH_2O$), 1.67 (s, 4H, CH_2CH_2), 1.27 (s, 6H, $2\times CH_3$), 1.25 (s, 6H, $2\times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.68 (C=O), 151.07, 145.41, 145.29, 139.61, 131.81, 129.55, 128.97, 126.90, 125.79, 124.70, 121.09, 120.73, 120.13, 72.00, 35.03, 34.97, 34.31, 34.21, 31.83, 31.71; IR (film) 3028, 2962, 2930, 2866, 1704, 1580, 1478, 1460, 1426, 1282, 1250, 1208, 1140, 880, 782 cm^{-1}; MS (DCI) *m/e* 471 (MH^+), 401 ($M-CF_3$), 201 ($C_{15}H_{21}^+$). Anal. ($C_{23}H_{25}F_3O_5S$) C, H.

Synthesis of 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methoxy-[1,1′-biphenyl]-3′-carboethoxy-6-carboxaldehyde (27). General procedure B was used to couple stannane **7** (1.96 g, 4.47 mmol) with triflate **26** (1.47 g, 3.13 mmol) to afford aldehyde **27** (1.13 g, 2.40 mmol, 77%): chromatographed on silica gel using CH_2Cl_2:hexane; UV_{max} ($CHCl_3$) 242 nm ($\epsilon = 13{,}370$), 322 nM ($\epsilon = 2203$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H, CHO), 8.10 (ddd, $J = 2$, 2, 8 Hz, 1H, ArH), 8.06 (dd, $J = 2$, 2 Hz, 1H, ArH), 7.64 (dd, $J = 2$, 8 Hz, 1H, ArH), 7.53 (m, 2H, ArH), 7.47 (ddd, $J = 2$, 8, 8 Hz, 1H, ArH), 7.27 (dd, $J = 2$, 8 Hz, 1H, ArH), 7.19 (d, $J = 8$ Hz, 1H, ArH), 7.04 (d, $J = 2$ Hz, 1H, ArH), 6.92 (dd, $J = 2$, 8 Hz, 1H, ArH), 5.00 (s, 2H, $ArCH_2O$), 4.36 (q, $J = 7$ Hz, 2H, CO_2CH_2), 1.62 (s, 4H, CH_2CH_2), 1.36 (t, $J = 7$ Hz, 3H, $CO_2CH_2CH_3$), 1.22 (s, 6H, $2\times CH_3$), 1.12 (s, 6H, $2\times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.91 (C=O), 166.26 (C=O), 156.18, 144.99, 144.44, 135.36, 135.30, 134.43, 133.74, 133.25, 131.94, 130.40, 129.15, 128.77, 128.13, 126.57, 124.59, 123.79, 119.61, 117.86, 70.57, 61.12, 34.96, 34.18, 34.07, 31.80, 31.70, 14.33; IR (film) 2960, 2928, 2860, 1720, 1692, 1458, 1294, 1260, 1234, 1110, 756 cm^{-1}; MS (DCI) *m/e* 471 (MH^+), 425 ($M-C_2H_5O$), 201 ($C_{15}H_{21}^+$). HRMS (FAB) *m/e* 493.2349 [$(M+Na)^+$ calcd for $C_{31}H_{34}O_4Na$: 493.2355].

Synthesis of 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid (28). General procedure C was used to convert aldehyde **27** (1.80 g, 3.83 mmol) to the corresponding monocarboxylic acid (1.44 g, 2.97 mmol, 78%): recrystallized from CH_2Cl_2:pentane; UV_{max} ($CHCl_3$) 242 nM ($\epsilon = 11{,}785$), 298 nM ($\epsilon = 3885$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (ddd, $J = 2$, 2, 8 Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.56 (dd, $J = 1$, 8 Hz, 1H, ArH), 7.44 (m, 2H, ArH), 7.38 (t, $J = 8$ Hz, 1H, ArH), 7.20 (dd, $J = 1$, 8 Hz, 1H, ArH), 7.16 (d, $J = 8$ Hz, 1H, ArH), 6.98 (d, $J = 2$ Hz, 1H, ArH), 6.88 (dd, $J = 2$, 8 Hz, 1H, ArH), 4.94 (s, 2H, $ArCH_2O$), 4.33 (q, $J = 7$ Hz, 2H, CO_2CH_2), 1.60 (s, 4H, CH_2CH_2), 1.34 (t, $J = 7$ Hz, 3H, CH_2CH_3), 1.21 (s, 6H, $2\times CH_3$), 1.10 (s, 6H, $2\times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.22 (C=O), 166.63 (C=O), 156.32, 144.94, 144.29, 136.94, 134.06, 133.34, 131.93, 130.96, 130.63, 129.98, 128.74, 128.44, 127.75, 126.45, 124.52, 123.72, 122.84, 116.84, 70.52, 60.86, 34.96, 34.15, 34.06, 31.79, 31.67, 14.33, 11.17; IR (KBr) 3260, 3100, 2960, 2926, 1718, 1698, 1576, 1456, 1298, 1262, 1234, 758 cm^{-1}; MS (DCI) *m/e* 487 (MH^+), 469 ($M-OH$), 201 ($C_{15}H_{21}^+$). Anal. ($C_{31}H_{34}O_5 \cdot 0.5\ H_2O$) C,H.

The above acid (0.139 g, 0.286 mmol) was then hydrolyzed using general procedure F to afford diacid **28** (0.097 g, 0.212 mmol, 74%): chromatographed on C-18 silica gel using MeOH:water, then recrystallized from $CHCl_3$:pentane; mp = 239–242 °C; UV_{max} (EtOH) 214 nM ($\epsilon = 44{,}121$), 290 nM ($\epsilon = 3263$); ^1H NMR (300 MHz, CD_3OD) δ 7.98 (ddd, $J = 2$, 2, 8 Hz, 1H, ArH), 7.96 (dd, $J = 2$, 2 Hz, 1H, ArH), 7.49–7.38 (m, 4H, ArH), 7.31 (dd, $J = 2$, 8 Hz, 1H, ArH), 7.18 (d, $J = 8$ Hz, 1H, ArH), 7.04 (d, $J = 2$ Hz, 1H, ArH), 6.92 (dd, $J = 2$, 8 Hz, 1H, ArH), 4.98 (s, 2H, $ArCH_2O$), 1.63 (s, 4H, CH_2CH_2), 1.21 (s, 6H, $2\times CH_3$), 1.11 (s, 6H, $2\times CH_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 171.48 (C=O), 169.98 (C=O), 157.45, 145.88, 145.17, 139.00, 135.59, 135.09, 132.35, 131.96, 131.34, 129.92, 129.34, 128.77, 127.45, 125.83, 125.15, 122.77, 117.09, 71.49, 36.20, 36.17, 35.12, 34.98, 32.24; IR (KBr) 3422, 2956, 2922, 1690, 1598, 1576, 1452, 1412, 1312, 1284, 1262, 1064 cm^{-1}; MS (DCI) *m/e* 459 (MH^+), 441 (M-OH), 201 ($C_{15}H_{21}^+$). Anal. ($C_{29}H_{30}O_5 \cdot 0.75\ H_2O$) C, H.

Synthesis of 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methoxy-3′-carboethoxy-1,1′-biphenyl-6-acetaldehyde (29). General procedure E was used to convert aldehyde **27** (0.521 g, 1.11 mmol) to a mixture of

enol ethers (0.506 g, 1.02 mmol, 91%): chromatographed on silica gel using 20% EtOAc:hexane to afford a white solid (~2:1 mixture of *E*:*Z* isomers); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH from *Z* isomer), 8.08 (m, ArH from *E* and *Z*), 7.82 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH from *E* isomer), 7.59–7.49 (m, ArH from *E* and *Z*), 7.37–7.20 (m, ArH from *E* and *Z*), 7.11 (d, *J* = 8 Hz, 1H, ArH from *E* isomer), 7.07 (m, ArH, from *E* and *Z*), 6.94 (m, ArH, from *E* and *Z*), 6.03 (d, *J* = 8 Hz, CH=C from *Z* isomer), 5.49 (d, *J* = 14 Hz, CH=C from *E* isomer), 4.99 (s, 2H, $ArCH_2O$ from *E* isomer), 4.98 (s, 2H, $ArCH_2O$ from *Z* isomer), 4.89 (d, *J* = 8 Hz, CH=C from *Z* isomer), 4.41 (m, 2H, CO_2CH_2 from *E* and *Z*), 3.75 (s, 3H, OCH_3 from *Z* isomer), 3.49 (s, 3H, OCH_3 from *E* isomer), 1.45 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$ from *Z* isomer), 1.41 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$ from *E* isomer), 1.25 (s, 6H, 2×CH_3), 1.15 (s, 6H, 2×CH_3).

The above mixture of enol ethers was hydrolyzed to afford aldehyde **29** (0.458 g, 0.945 mmol, 93%) of suitable purity for use in subsequent reactions: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (bs, 1H, CHO), 8.10 (m, 2H, ArH), 7.60–7.49 (m, 2H, ArH), 7.39 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.22 (d, *J* = 8 Hz, 1H, ArH), 7.08 (m, 2H, ArH), 6.96 (m, 2H, ArH), 5.01 (s, 2H, $ArCH_2O$), 4.43 (q, *J* = 7 Hz, 2H, CO_2CH_2), 3.56 (bs, 2H, $ArCH_2CHO$), 1.58 (s, 4H, CH_2CH_2), 1.39 (t, *J* = 7 Hz, $CO_2CH_2C\underline{H}_3$), 1.29 (s, 6H, 2×CH_3), 1.17 (s, 6H, 2×CH_3).

Synthesis of 3′-carboxy-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methoxy-[1,1′-biphenyl]-6-acetic acid (30). General procedure C was used to oxidize aldehyde **29** (0.458 g, 0.945 mmol) to the corresponding monocarboxylic acid (0.244 g, 0.490 mmol, 48% from the mixture of enol ethers obtained in the synthesis of **29**): chromatographed on silica gel using 35% EtOAc: hexane; UV_{max} ($CHCl_3$) 242 nM (ε = 8586), 278 nM (ε = 3144); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 1H, ArH), 7.96 (s, 1H, ArH), 7.46 (m, 2H, ArH), 7.32 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.16 (d, *J* = 8 Hz, 1H, ArH), 6.98 (m, 3H, ArH), 6.87 (dd, *J* = 2, 8 Hz, 1H, ArH), 4.92 (s, 2H, $ArCH_2O$), 4.31 (q, *J* = 7 Hz, 2H, CO_2CH_2), 3.44 (s, 2H, $ArCH_2CO_2$), 1.60 (s, 4H, CH_2CH_2), 1.32 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.20 (s, 6H, 2×CH_3), 1.08 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.98 (C=O), 166.53 (C=O), 156.30, 144.83, 144.09, 136.92, 134.77, 133.81, 133.26, 131.20, 130.45, 128.83, 128.56, 128.27, 126.39, 124.47, 123.65, 122.63, 111.62, 70.02, 60.93, 38.54, 34.99, 34.14, 34.04, 31.80, 31.66, 14.27; IR (film) 3240, 2960, 2926, 1716, 1456, 1298, 1258, 1232, 758 cm^{-1}; MS (DCI) *m*/*e* 501 (MH^+), 483 (M−OH), 455 (M−C_2H_5O), 201 ($C_{15}H_{21}^+$).

The acid obtained above (0.207 g, 0.414 mmol) was hydrolyzed via general procedure F to yield diacid **30** (0.167 g, 0.354 mmol, 85%) as a white foam: chromatographed on reverse-phase C-18 silica gel using methanol; UV_{max} ($CHCl_3$) 242 nM (ε = 9965), 278 nM (ε = 3435); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 2H, ArH), 7.51 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.46 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.33 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.14 (d, *J* = 8 Hz, 1H, ArH), 7.02 (d, *J* = 8 Hz, 1H, ArH), 6.96 (d, *J* = 8 Hz, 1H, ArH), 6.93 (s, 1H, ArH), 6.85 (dd, *J* = 2, 8 Hz, 1H, ArH), 4.94 (m, 2H, $ArCH_2O$), 3.47 (s, 2H, $ArCH_2CO_2$), 1.57 (s, 4H, CH_2CH_2), 1.18 (s, 6H, 2×CH_3), 1.05 (s, 3H, CH_3), 1.03 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.77 (C=O), 172.37 (C=O), 156.30, 144.88, 144.13, 137.24, 134.77, 133.91, 133.76, 132.76, 131.08, 129.19, 129.11, 128.66, 126.38, 124.56, 123.65, 123.21, 69.94, 40.22, 34.95, 34.11, 34.02, 31.77, 31.60; IR (KBr) 3422, 2960, 2926, 1702, 1456, 1412, 1300, 1258 cm^{-1}; MS (DCI) *m*/*e* 473 (MH^+), 455 (M−OH), 201 ($C_{15}H_{21}^+$). Anal. ($C_{30}H_{32}O_5 \cdot 0.33\ H_2O$) C, H.

Synthesis of (3-carboethoxymethyl)phenyl-tributylstannane (31). *tert*-Butyllithium (1.77 M in pentane, 9.08 mL, 15.8 mmol) was added dropwise to a cooled (−5 °C) solution of diisopropylamine (1.60 g, 15.8 mmol) in 60 mL of THF. The mixture was stirred 5 min, and then cooled to −78 °C. A solution of 3-bromophenylacetic acid, ethyl ester (3.49 g, 14.4 mmol) dissolved in 12 mL THF was added dropwise, and the solution was allowed to stir for 20 min at −78 °C. *tert*-Butyllithium (1.77 M in pentane, 16.5 mL, 28.7 mmol) was added, and the bright yellow solution was stirred for 55 min at −78 °C. Tri(*n*-butyl)tin chloride (5.14 g, 15.8 mmol) was added, and the mixture allowed to warm to −10 °C over 1.5 h. The solution was partitioned between saturated $NH_4^+Cl^-$, and ether. The aqueous layer was extracted with ether, and the combined organic phase was washed with brine, dried (MgSO4), and evaporated. The residue was chromatographed on silica using EtOAc:hexane to afford stannane **31** (2.89 g, 6.38 mmol, 44%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 1H, ArH), 7.31–7.20 (m, 3H, ArH), 4.16 (q, *J* = 7 Hz, 2H, CO_2CH_2), 3.59 (s, 2H, $ArCH_2CO_2$), 1.72–1.44 (m, 6H, 3×$SnCH_2$), 1.42–1.22 (m, 15H, 3×$SnCH_2C\underline{H}_2C\underline{H}_2$ and $CO_2CH_2C\underline{H}_3$), 0.94 (m, 9H, 3×CH_3).

Synthesis of 6-carboxy-2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]methoxy-[1,1′-biphenyl]-3′-acetic acid (33). Triflate **26** (0.826 g, 1.76 mmol) was coupled to stannane **31** (1.19 g, 2.63 mmol) via the method of general procedure B to yield ester **32** (0.410 g): chromatographed on silica gel using 5% EtOAc:hexane to afford a yellow oil as a 3:1 mixture of **32** and triflate **26**.

The mixture obtained above was oxidized via the method of general procedure C to yield the corresponding carboxylic acid (0.210 g, 0.43 mmol, 25% overall from triflate **26**): chromatographed on silica gel using methanol:CH_2Cl_2 to afford a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8 Hz, 1H, ArH), 7.33 (m, 2H, ArH), 7.26–7.15 (m, 5H, ArH), 7.05 (d, *J* = 2 Hz, 1H, ArH), 6.89 (dd, *J* = 2, 8 Hz, 1H, ArH), 4.94 (s, 2H, $ArCH_2O$), 4.05 (q, *J* = 7 Hz, 2H, CO_2CH_2), 3.59 (s, 2H, $ArCH_2CO_2$), 1.63 (s, 4H, CH_2CH_2), 1.22 (s, 6H, 2×CH_3), 1.15 (s, 6H, 2×CH_3), 1.15 (t, *J* = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.68 (C=O), 171.64 (C=O), 156.21, 144.87, 144.23, 136.72, 133.58, 133.44, 132.16, 130.56, 128.42, 128.37, 128.01, 127.89, 126.55, 124.67, 123.89, 122.57, 116.76, 70.69, 60.80, 41.43, 35.03, 34.19, 34.07, 31.82, 31.74, 14.12; IR (film) 2960, 2926, 1734, 1700, 1456, 1364, 1300, 1260, 1152, 758 cm^{-1}; MS (DCI) *m*/*e* 501 (MH^+), 483 (M−OH), 201 ($C_{15}H_{21}^+$).

The acid obtained above (0.199 g, 0.41 mmol) was hydrolyzed via the method of general procedure F to afford diacid **33** (0.169 g, 0.37 mmol, 90%) as a yellow solid: UV_{max} (MeOH) 208 nM (ε = 42,683), 292 nM (ε = 3412); ^1H NMR (300 MHz, CD_3OD) δ 7.39–7.17 (m, 8H, ArH), 7.10 (d, J = 2 Hz, 1H, ArH), 6.93 (dd, J = 2, 8 Hz, 1H, ArH), 4.96 (s, 2H, $ArCH_2O$), 3.59 (s, 2H, $ArCH_2CO_2$), 1.65 (s, 4H, CH_2CH_2), 1.22 (s, 6H, 2×CH_3), 1.15 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 175.49 (C=O), 172.19 (C=O), 157.42, 145.81, 145.16, 138.56, 135.60, 135.25, 135.19, 132.46, 131.86, 129.65, 129.50, 128.92, 128.73, 127.54, 126.02, 125.32, 122.37, 117.06, 71.56, 42.09, 36.21, 35.17, 35.00, 32.29, 32.25; IR (KBr) 3430, 2960, 2926, 1706, 1456, 1298, 1260 cm^{-1}; MS (DCI) m/e 473 (MH^+), 472 (M^+), 455 (M-OH), 201 ($C_{15}H_{21}^+$). Anal. ($C_{30}H_{32}O_5 \cdot 0.5\ H_2O$) C, H.

General procedure G. Mitsunobu etherification of phenols with benzyl alcohols: synthesis of 2-[(3,4-bispentyloxy)phenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid, diethyl ester (35a). Phenol **10** (0.200 g, 0.637 mmol) was dissolved in 3.2 mL dry THF. Triphenylphosphine (0.200 g, 0.764 mmol) was added and the solution was cooled to 0 °C. Diisopropylazodicarboxylate (0.15 mL, 0.764 mmol) was added, and then a solution of (3,4-bispentyloxy)benzyl alcohol (0.178 g, 0.637 mmol; for a synthesis of this and all other benzyl alcohols used in the Mitsunobu coupling see ref 26) in 1.5 mL dry THF was added dropwise. The mixture was stirred at 0 °C for 4 h, and then poured into water and EtOAc. The aqueous layer was extracted with EtOAc, and the organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel using EtOAc:hexane afforded as a clear oil diester **35a** (0.200 g, 0.350 mmol, 55%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (ddd, J = 2, 2, 8 Hz, 1H, ArH), 8.01 (s, 1H, ArH), 7.51–7.40 (m, 3H, ArH), 7.38 (dd, J = 8, 8 Hz, 1H, ArH), 7.17 (d, J = 8 Hz, 1H, ArH), 6.76 (d, J = 8 Hz, 1H, ArH), 6.67 (dd, J = 2, 8 Hz, 1H, ArH), 6.61 (d, J = 2 Hz, 1H, ArH), 4.94 (s, 2H, $ArCH_2O$), 4.36 (q, J = 7 Hz, 2H, CO_2CH_2), 4.01 (q, J = 7 Hz, 2H, CO_2CH_2), 3.95 (t, J = 7 Hz, 2H, RCH_2O), 3.76 (t, J = 7 Hz, 2H, RCH_2O), 1.79 (m, 4H, $RC\underline{H}_2CH_2O$), 1.40 (m, 8H, pentyl), 1.39 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.91 (m, 9H, 2xRCH_3 and $CO_2CH_2C\underline{H}_3$).

Also obtained in this fashion were the following:

2-[(3,4-Bispentyloxy)phenyl]-methoxy-3′-carboethoxy-[1,1′-biphenyl]-6-acetic acid, ethyl ester (35b). Isolated as a clear oil (46% yield): chromatographed on silica gel using CH_2Cl_2:hexane; UV_{max} (EtOH) 208 nM (ε = 53,224), 280 nM (ε = 6773); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 2, 8 Hz, 1H, ArH), 7.97 (s, 1H, ArH), 7.46 (m, 2H, ArH), 7.32 (dd, J = 8, 8 Hz, 1H, ArH), 7.03 (d, J = 8 Hz, 1H, ArH), 6.97 (d, J = 8 Hz, 1H, ArH), 6.75 (d, J = 8 Hz, 1H, ArH), 6.68 (dd, J = 2, 8 Hz, 1H, ArH), 6.60 (s, 1H, ArH), 4.93 (s, 2H, $ArCH_2O$), 4.37 (q, J = 7 Hz, 2H, CO_2CH_2), 4.06 (q, J = 7 Hz, 2H, CO_2CH_2), 3.93 (t, J = 6 Hz, 2H, OCH_2R), 3.76 (t, J = 6 Hz, 2H, OCH_2R), 3.42 (s, 2H, $ArCH_2CO_2$), 1.82–0.93 (m, 24 H, pentyl and 2×$CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.45 (C=O), 166.45 (C=O), 156.11, 149.19, 148.37, 137.26, 134.90, 134.14, 131.32, 131.12, 130.36, 129.71, 128.76, 128.28, 128.03, 122.85, 118.82, 113.55, 111.93, 111.75, 70.80, 69.31, 68.83, 60.92, 60.73, 39.21, 29.01, 28.96, 28.31, 22.53, 14.33, 14.08; IR (KBr) 2930, 2955, 1720 (C=O), 1585, 1510, 1465, 1260, 1230 cm^{-1}; MS (DCI) m/e 591 (MH^+), 525, 263. Anal. ($C_{36}H_{46}O_7 \cdot 0.1\ CH_2Cl_2$) C; H: calcd, 7.80; found, 8.25.

2-[3,4-Bis(3-methyl-2-butenyloxy)phenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid, diethyl ester (35c). Isolated as a white solid (68% yield): chromatographed on silica gel using EtOAc:hexane; mp = 85.5–87.5 °C; UV_{max} ($CHCl_3$) 242 nM (ε = 19,498), 286 nM (ε = 6685); ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, J = 2, 2, 8 Hz, 1H, ArH), 7.96 (dd, J = 2, 2 Hz, 1H, ArH), 7.49–7.39 (m, 3H, ArH), 7.35 (dd, J = 8, 8 Hz, 1H, ArH), 7.13 (dd, J = 2, 8 Hz, 1H, ArH), 6.74 (d, J = 8 Hz, 1H, ArH), 6.67 (dd, J = 2, 8 Hz, 1H, ArH), 6.63 (d, J = 2 Hz, 1H, ArH), 5.44 (m, 2H, C=CH), 4.92 (s, 2H, $ArCH_2O$), 4.51 (d, J = 6 Hz, 2H, RCH_2O), 4.36 (d, J = 6 Hz, 2H, RCH_2O), 4.32 (q, J = 7 Hz, 2H, CO_2CH_2), 3.98 (q, J = 7 Hz, 2H, CO_2CH_2), 1.73 (s, 6H, 2×CH_3), 1.67 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.34 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.91 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.01 (C=O), 166.54 (C=O), 155.98, 148.89, 148.31, 137.52, 137.44, 137.07, 134.18, 133.22, 130.93, 130.78, 129.94, 129.17, 128.71, 128.16, 127.53, 122.15, 120.26, 119.92, 119.14, 116.29, 113.73, 112.40, 70.65, 66.05, 65.72, 60.88, 25.80, 25.77, 18.20, 14.30, 13.66; IR (KBr) 2982, 2930, 1714, 1574, 1512, 1290, 1252, 1232, 1038, 852, 766 cm^{-1}; MS (DCI) m/e 573 (MH^+). Anal. ($C_{35}H_{40}O_7$) C, H.

2-[(3,4-Biscyclopentyloxy)phenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid, 3′-ethyl ester, 6-methyl ester (35d). From 2-(3′-carboethoxyphenyl)-3-carbomethoxyphenol and (3,4-biscyclopentyloxy)benzyl alcohol (69% yield): chromatographed on silica gel using EtOAc:hexane; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, J = 2, 2, 8 Hz, 1H, ArH), 7.96 (dd, J = 2, 2 Hz, 1H, ArH), 7.45 (m, 3H, ArH), 7.35 (dd, J = 7, 7 Hz, 1H, ArH), 7.15 (dd, J = 2, 8 Hz, 1H, ArH), 6.74 (d, J = 8 Hz, 1H, ArH), 6.65 (dd, J = 2, 8 Hz, 1H, ArH), 6.60 (d, J = 2 Hz, 1H, ArH), 4.91 (s, 2H, $ArCH_2O$), 4.66 (m, 1H, R_2CHOR), 4.50 (m, 1H, R_2CHOR), 4.33 (q, J = 7 Hz, 2H, CO_2CH_2), 3.54 (s, 3H, CO_2CH_3), 1.85–1.63 (m, 10H, cycloalkyl), 1.54 (m, 6H, cycloalkyl), 1.36 (t, J = 7 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.19 (C=O), 166.40 (C=O), 159.04, 148.93, 137.28, 134.12, 132.71, 130.65, 129.94, 129.34, 128.71, 128.18, 127.55, 122.10, 119.32, 116.58, 116.31, 115.24, 81.13, 80.84, 70.54, 60.87, 51.94, 32.76, 32.71, 23.87, 23.83, 14.32; IR (film) 2958, 1720, 1508, 1296, 1262, 1234, 1166, 758 cm^{-1}; MS (DCI) m/e 559 (MH^+).

2-[(3,4-Biscyclopentyloxy)phenyl]methoxy-3′-carboethoxy-[1,1′-biphenyl]-6-acetic acid, ethyl ester (35e). 57% yield: chromatographed on silica gel using CH_2Cl_2:hexane; UV_{max} (EtOH) 208 nM (ε = 56,239), 282 nM (ε = 6164); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, J = 2, 5 Hz, 1H, ArH), 7.96 (s, 1H, ArH), 7.48 (d, J = 5 Hz, 2H, ArH), 7.31 (dd, J = 8, 8 Hz, 1H, ArH), 7.02 (d, J = 8 Hz, 1H, ArH), 6.96 (d, J = 8 Hz, 1H, ArH), 6.78 (d, J = 8 Hz, 1H,

ArH), 6.67 (d, $J=8$ Hz, 1H, ArH), 6.60 (s, 1H, ArH), 4.91 (s, 2H, $ArCH_2O$), 4.69–4.40 (m, 2H, $2\times R_2CHOR$), 4.35 (q, $J=7$ Hz, 2H, CO_2CH_2), 4.05 (q, $J=7$ Hz, 2H, CO_2CH_2), 3.41 (s, 2H, $ArCH_2CO_2$), 1.96–1.52 (m, 16H, cyclopentyl), 1.35 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$); 1.15 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.51 (C=O), 166.51 (C=O), 156.10, 148.88, 148.20, 137.18, 134.92, 134.12, 131.23, 131.06, 130.31, 129.87, 128.71, 128.27, 128.01, 122.78, 119.13, 116.61, 115.07, 111.71, 81.14, 81.08, 70.08, 60.91, 60.74, 39.20, 32.76, 32.71, 23.89, 23.83, 14.31, 14.06; IR (KBr) 2960, 1730 (C=O), 1720 (C=O), 1580, 1505, 1425, 1260, 1230 cm^{-1}; MS (DCI) *m/e* 587 (MH^+), 586 (M), 519, 259. Anal. ($C_{36}H_{42}O_7\cdot 0.1\ H_2O$) C; H: calcd, 7.10; found, 6.69.

2-[4-(1-Adamantyl)-3-methoxyphenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid, diethyl ester (35f). 62% yield: chromatographed on silica gel using CH_2Cl_2:hexane; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J=8$ Hz, 1H, ArH), 8.02 (s, 1H, ArH), 7.49–7.39 (m, 4H, ArH), 7.26 (d, $J=8$ Hz, 1H, ArH), 7.09 (d, $J=8$ Hz, 1H, ArH), 6.74 (d, $J=8$ Hz, 1H, ArH), 6.59 (s, 1H, ArH), 5.00 (s, 2H, $ArCH_2O$), 4.38 (q, $J=7$ Hz, 2H, CO_2CH_2), 4.02 (q, $J=7$ Hz, 2H, CO_2CH_2), 3.62 (s, 3H, CH_3O), 2.04 (s, 9H, adamantyl), 1.75 (s, 6H, adamantyl), 1.40 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$), 0.97 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.89 (C=O), 166.60 (C=O), 158.89, 156.02, 137.81, 137.64, 135.27, 134.25, 133.16, 130.81, 129.99, 128.85, 127.66, 126.36, 122.12, 118.21, 115.88, 109.57, 70.16, 60.94, 54.86, 40.53, 37.12, 36.82, 29.07, 14.38, 13.71.

2-[(3,4-Bisdecyloxy)phenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid, diethyl ester (35h). Isolated as a clear oil which crystallized on standing (44% yield): chromatographed using 25–50–75% CH_2Cl_2:hexane; mp = 59.5–60.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (ddd, $J=2$, 2, 8 Hz, 1H, ArH), 7.99 (d, $J=2$ Hz, 1H, ArH), 7.50–7.40 (m, 3H, ArH), 7.37 (dd, $J=8$, 8 Hz, 1H, ArH), 7.17 (d, $J=8$ Hz, 1H, ArH), 6.77 (d, $J=8$ Hz, 1H, ArH), 6.67 (dd, $J=2$, 8 Hz, 1H, ArH), 6.61 (d, $J=2$ Hz, 1H, ArH), 4.94 (s, 2H, $ArCH_2O$), 4.36 (q, $J=7$ Hz, 2H, CO_2CH_2), 4.02 (q, $J=7$ Hz, 2H, CO_2CH_2), 3.94 (t, $J=7$ Hz, 2H, RCH_2O), 3.77 (t, $J=7$ Hz, 2H, RCH_2O), 1.78 (m, 4H, RCH_2CH_2O), 1.43 (m, 4H, decyl), 1.36 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$), 1.29 (m, 24H, decyl), 0.95 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$), 0.89 (t, 6H, $2\times CH_3$).

3′-Carboethoxy-2-[4-decyloxyphenyl]methoxy-[1,1′-biphenyl]-6-acetic acid, ethyl ester (35i). 44% yield: chromatographed on silica gel using CH_2Cl_2:hexane; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, $J=2$, 8 Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.49–7.47 (m, 2H, ArH), 7.31 (dd, $J=8$, 8 Hz, 1H, ArH), 7.08–6.80 (m, 4H, ArH), 6.77 (d, $J=8$ Hz, 2H, ArH), 4.94 (s, 2H, $ArCH_2O$), 4.38 (q, $J=7$ Hz, 2H, CO_2CH_2), 4.07 (q, $J=7$ Hz, 2H, CO_2CH_2), 3.94 (t, $J=$ Hz, 2H, OCH_2R), 3.43 (s, 2H, $ArCH_2CO_2$), 1.76 (m, 2H, OCH_2CH_2R), 1.38 (t, $J=7$ Hz, 2H, $CO_2CH_2CH_3$), 1.28 (s, 14 H, $R(CH_2)_7CH_3$), 1.20 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$), 0.90 (t, $J=7$ Hz, 3H, RCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.54 (C=O), 158.61, 156.12, 137.03, 134.87, 134.08, 131.39, 130.25, 128.81, 128.70, 128.35, 128.18, 128.06, 122.82, 114.25, 111.90, 70.12, 67.93, 60.76, 39.22, 31.92, 29.59, 29.42, 29.36, 29.28, 22.72, 14.38, 14.18, 14.10.

Synthesis of 3′-carboethoxy-2-[4-(1-adamantyl)-3-methoxyphenyl]-methoxy-[1,1′-biphenyl]-6-acetic acid, ethyl ester (35g). Phenol **14** (0.656 g, 2.00 mmol) was dissolved in 15 mL of methyl isobutyl ketone. 4-[1-Adamantyl]-3-methoxybenzyl iodide (0.766 g, 2.00 mmol; for a synthesis of this iodide see ref 26) and potassium carbonate (1.00 g, 7.2 mmol) were added and the mixture was heated to reflux for 5 h. The solvents were evaporated and the residue was dissolved in methylene chloride. This solution was washed with water and brine, then dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica gel using 50% CH_2Cl_2:hexane to afford diester **35g** (0.725 g, 1.24 mmol, 62%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, $J=2$, 8 Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.50–7.47 (m, 2H, ArH), 7.33–6.97 (m, 4H, ArH), 6.69 (dd, $J=2$, 8 Hz, 1H, ArH), 6.57 (d, $J=2$ Hz, 1H, ArH), 4.97 (s, 2H, $ArCH_2O$), 4.38 (q, $J=7$ Hz, 2H, CO_2CH_2), 4.03 (q, $J=7$ Hz, 2H, CO_2CH_2), 3.59 (s, 3H, CH_3O), 3.41 (s, 2H, $ArCH_2CO_2$), 2.03 (s, 9H, adamantyl), 1.75 (s, 6H, adamantyl), 1.40 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$), 1.16 (t, $J=7$ Hz, 3Hz, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.48 (C=O), 166.54 (C=O), 158.84, 156.13, 137.62, 137.33, 135.74, 134.91, 134.21, 131.31, 131.05, 130.44, 128.82, 128.33, 128.14, 126.27, 122.82, 118.09, 111.49, 109.54, 69.75, 60.97, 60.77, 54.82, 40.55, 39.23, 37.13, 36.80, 29.09, 14.38, 14.12.

Synthesis of 2-[(3,4-bispentyloxy)phenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid (36a). Diester **35a** (0.200 g, 0.35 mmol) was hydrolyzed using general procedure F to afford diacid **36a** (0.105 g, 0.200 mmol, 57%): recrystallized from CH_2Cl_2:pentane; mp = 202–203 °C (dec.); UV_{max} (EtOH) 208 nM (ε = 35722), 284 nm (ε = 5099); ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, $J=8$ Hz, 1H, ArH), 7.90 (s, 1H, ArH), 7.59 (m, 2H, ArH), 7.43 (dd, $J=8$, 8 Hz, 1H, ArH), 7.37 (dd, $J=8$, 8 Hz, 1H, ArH), 7.17 (d, $J=8$ Hz, 1H, ArH), 6.73 (d, $J=8$ Hz, 1H, ArH), 6.62 (dd, $J=2$, 8 Hz, 1H, ArH), 6.56 (d, $J=2$ Hz, 1H, ArH), 4.90 (s, 2H, $ArCH_2O$), 3.91 (t, $J=7$ Hz, 2H, RCH_2O), 3.74 (t, $J=7$ Hz, 2H, RCH_2O), 1.74 (m, 4H, RCH_2CH_2O), 1.48–1.28 (m, 8H, pentyl), 0.89 (m, 6H, $2\times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.47 (C=O), 172.40 (C=O), 156.20, 149.35, 148.70, 137.35, 135.55, 131.77, 131.07, 129.14, 128.93, 127.76, 123.15, 119.16, 117.33, 113.63, 112.17, 70.77, 69.42, 69.08, 29.07, 29.03, 28.35, 28.30, 22.58, 14.15; IR (KBr) 3400, 2956, 2932, 2870, 1692, 1516, 1468, 1432, 1302, 1262, 1170, 1136, 1108, 1080, 758, 694 cm^{-1}; MS (DCI) *m/e* 521 (MH^+), 503 (M−OH). Anal. ($C_{31}H_{36}O_7\cdot 0.4\ H_2O$) C, H.

Also obtained in this fashion were the following:

2-[(3,4-Bispentyloxy)phenyl]methoxy-3′-carboxy-[1,1′-biphenyl]-6-acetic acid (36b). Isolated as a white solid (49% yield): chromatographed on reverse-phase C-18 silica gel using methanol; mp = 105–106 °C; UV_{max} (EtOH) 208 nM (ε = 52,348), 280 nM (ε = 6237); ^1H

NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J=2$ Hz, 1H, ArH), 8.01 (s, 1H, ArH), 7.52–7.46 (m, 2H, ArH), 7.34 (dd, $J=8$, 8 Hz, 1H, ArH), 7.04 (d, $J=8$ Hz, 1H, ArH), 6.98 (d, $J=8$ Hz, 1H, ArH), 6.70 (d, $J=8$ Hz, 1H, ArH), 6.63 (dd, $J=2$, 8 Hz, 1H, ArH), 6.59 (s, 1H, ArH), 4.94 (s, 2H, $ArCH_2O$), 3.95–3.69 (m, 4H, $2\times RCH_2O$), 3.48 (s, 2H, $ArCH_2CO_2H$), 1.79–0.88 (m, 18H, pentyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.72 (C=O), 172.28 (C=O), 156.11, 149.22, 148.36, 137.28, 134.84, 133.90, 132.71, 131.07, 129.54, 129.10, 128.61, 123.34, 118.84, 113.54, 112.30, 111.82, 70.05, 69.33, 68.77, 40.24, 28.89, 28.18, 22.46, 14.03; IR (KBr) 3550 (OH), 2950, 2925, 1700 (C=0), 1570, 1530, 1250 cm^{-1}; MS (DCI) *m/e* 535 (MH^+), 517 (M−OH), 273, 263, 255. Anal. ($C_{32}H_{38}O_7\cdot 0.75\ H_20$) C, H.

2-[3,4-Bis(3-methyl-2-butenyloxy)phenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid (36c). Isolated as a white solid (76% yield): chromatographed on C-18 silica gel using MeOH:water; mp = 145 °C (dec.); UV_{max} ($CHCl_3$) 242 nM (ε = 20,264), 286 nM (ε = 6689); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (ddd, $J=2$, 2, 8 Hz, 1H, ArH), 7.89 (dd, $J=2$, 2 Hz, 1H, ArH), 7.59 (m, 2H, ArH), 7.44 (dd, $J=8$, 8 Hz, 1H, ArH), 7.37 (dd, $J=8$, 8 Hz, 1H, ArH), 7.18 (dd, $J=2$, 8 Hz, 1H, ArH), 6.74 (d, $J=8$ Hz, 1H, ArH), 6.43 (dd, $J=2$, 8 Hz, 1H, ArH), 6.00 (bs, 1H, ArH), 5.44 (m, 2H, C=CH), 4.91 (s, 2H, $ArCH_2O$), 4.50 (d, $J=7$ Hz, 2H, $C=CHC\underline{H}_2O$), 4.34 (d, $J=7$ Hz, 2H, $C=CHC\underline{H}_2O$), 1.72 (s, 6H, $\overline{2}\times CH_3$), 1.66 (s, 3H, CH_3), 1.65 (s, $\overline{3}$H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.41 (C=O), 172.29 (C=O), 156.09, 148.90, 148.32, 137.61, 132.19, 137.09, 134.44, 131.62, 131.42, 130.94, 129.00, 128.92, 128.82, 127.66, 123.06, 120.25, 119.79, 119.09, 117.26, 113.67, 112.24, 70.71, 66.03, 65.70, 25.80, 18.20, 18.17; IR (KBr) 3400, 1690, 1510, 1430, 1300, 1255, 1220, 1130, 1000, 755 cm^{-1}; MS (DCI) *m/e* 517 (MH^+), 431 ($M-C_5H_9O$). Anal. ($C_{31}H_{32}O_7\cdot 0.8\ H_2O$) C, H.

2-[(3,4-Biscyclopentyloxy)phenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid (36d). Isolated as a white solid (48% yield): recrystallized from CH_2Cl_2:pentane; mp = 178–180 °C; UV_{max} ($CHCl_3$) 242 nM (ε = 48,261), 284 nM (ε = 16,536); ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (ddd, $J=2$, 2, 8 Hz, 1H, ArH), 7.90 (dd, $J=2$, 2 Hz, 1H, ArH), 7.59 (m, 2H, ArH), 7.44 (dd, $J=8$, 8 Hz, 1H, ArH), 7.38 (dd, $J=8$, 8 Hz, 1H, ArH), 7.18 (d, $J=8$ Hz, 1H, ArH), 6.74 (d, $J=8$ Hz, 1H, ArH), 6.63 (dd, $J=2$, 8 Hz, 1H, ArH), 6.58 (d, $J=2$ Hz, 1H, ArH), 4.90 (s, 2H, $ArCH_2O$), 4.66 (m, 1H, R_2CHOR), 4.50 (m, 1H, R_2CHOR), 1.80–1.50 (m, 16H, cycloalkyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.37 (C=O), 172.25 (C=O), 156.08, 148.96, 148.45, 137.20, 135.46, 131.48, 131.44, 130.94, 129.18, 128.98, 128.87, 126.68, 122.95, 119.37, 117.13, 116.52, 115.18, 81.12, 80.86, 70.62, 32.76, 32.71, 23.89, 23.84; IR (KBr) 3422, 2962, 2872, 1690, 1508, 1304, 1262 cm^{-1}; MS (DCI) *m/e* 517 (MH^+), 499 (M−OH). Anal. ($C_{31}H_{32}O_7$) C, H.

2-[(3,4-Biscyclopentyloxy)phenyl]methoxy-3′-carboxy-[1,1′-biphenyl]-6-acetic acid (36e). Isolated as a white solid (65% yield): chromatographed on reverse-phase C-18 silica gel using methanol; mp = 146–148 °C; UV_{max} (EtOH) 206 nM (ε = 61,550), 282 nM (ε = 5781); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J=8$ Hz, 1H, ArH), 8.01 (s, 1H, ArH), 7.54–7.45 (m, 2H, ArH), 7.34 (dd, $J=8$, 8 Hz, 1H, ArH), 7.03 (d, $J=8$ Hz, 1H, ArH), 6.98 (d, $J=8$ Hz, 1H, ArH), 6.76 (d, $J=8$ Hz, 1H, ArH), 6.66 (d, $J=8$ Hz, 1H, ArH), 6.61 (s, 1H, ArH), 4.94 (s, 2H, $ArCH_2O$), 4.67–4.48 (m, 2H, $2\times R_2C\underline{H}OR$), 3.47 (s, $ArCH_2CO_2$), 1.80–1.54 (m, 16H, cyclopentyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.71 (C=O), 172.26 (C=O), 156.11, 148.88, 148.23, 137.26, 134.85, 130.90, 132.64, 131.04, 129.71, 129.12, 129.10, 128.60, 123.31, 119.16, 116.57, 114.97, 112.27, 111.47, 81.13, 80.56, 70.02, 40.21, 32.69, 23.87; IR (KBr) 3400 (OH), 2950, 2840, 1690 (C=O), 1580, 1510, 1260 cm^{-1}; MS (DCI) *m/e* 531 (MH^+), 530 (M^+), 509, 445 ($M-C_5H_9O$), 395, 273, 255. Anal. ($C_{32}H_{34}O_7\cdot 1.5\ H_2O$) C, H.

2-[4-(1-Adamantyl)-3-methoxyphenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid (36f). Isolated as a white solid (51% yield): recrystallized from ether:CH_2Cl_2; mp = 245–250 °C; UV_{max} (EtOH) 206 nM (ε = 49,943), 282 nM (ε = 5808); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, $J=8$ Hz, 1H, ArH), 7.38–7.27 (m, 5H, ArH), 7.16 (d, $J=8$ Hz, 1H, ArH), 7.07 (d, $J=8$ Hz, 1H, ArH), 6.67 (d, $J=8$ Hz, 1H, ArH), 6.58 (s, 1H, ArH), 4.96 (s, 2H, $ArCH_2O$), 3.91 (s, 3H, CH_3O), 2.02 (s, 9H, adamantyl), 1.73 (s, 6H, adamantyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.90 (C=O), 156.15 (C=O), 137.79, 136.58, 135.34, 132.61, 129.58, 128.41, 127.71, 127.07, 126.30, 122.66, 118.11, 116.77, 109.64, 70.28, 54.95, 40.51, 37.09, 36.70, 29.04; IR (KBr) 3420 (OH), 2905, 1690 (C=O), 1585, 1410, 1268 cm^{-1}; MS (DCI) *m/e* 513 (MH^+), 512 (M^+), 495 (M−OH), 255. Anal. ($C_{32}H_{32}O_6$) C, H.

3′-Carboxy-2-[4-(1-adamantyl)-3-methoxyphenyl]methoxy-[1,1′-biphenyl]-6-acetic acid (36g). Isolated as a white solid (81% yield): chromatographed on silica gel using 10% MeOH:CH_2Cl_2; mp = 240–242 °C; UV_{max} (EtOH) 206 nM (ε = 47,130), 280 nM (ε = 3760); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J=8$ Hz, 1H, ArH), 8.01 (s, 1H, ArH), 7.55–7.45 (m, 2H, ArH), 7.34 (dd, $J=8$, 8 Hz, 1H, ArH), 7.05 (d, $J=8$ Hz, 1H, ArH), 7.00 (d, $J=8$ Hz, 1H, ArH), 6.94 (d, $J=8$ Hz, 1H, ArH), 6.65 (d, $J=8$ Hz, 1H, ArH), 6.56 (s, 1H, ArH), 4.99 (s, 2H, $ArCH_2O$), 3.55 (s, 3H, CH_3O), 3.47 (s, 2H, $ArCH_2CO_2$), 1.99 (s, 9H, adamantyl), 1.71 (s, 6H, adamantyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.73 (C=O), 168.55 (C=O), 158.76, 155.95, 137.44, 137.20, 135.73, 134.69, 134.46, 131.57, 130.66, 128.61, 128.43, 127.99, 126.14, 122.88, 118.01, 111.25, 109.48, 69.62, 54.83, 40.45, 40.23, 39.95, 39.67, 38.88, 37.03, 36.68, 28.96; IR (KBr) 3400 (OH), 2920, 1720 (C=O), 1680 (C=O), 1560, 1523, 1250 cm^{-1}; MS (DCI) *m/e* 527 (M^+), 255. Anal. ($C_{33}H_{34}O_6\cdot 1.33\ H_2O$) C; H: calcd, 6.70; found, 6.29.

2-[(3,4-Bisdecyloxy)phenyl]methoxy-[1,1′-biphenyl]-6,3′-dicarboxylic acid (36h). Isolated as a white solid (54% yield): recrystallized from $CHCl_3$:pentane; mp = 102–104 °C; UV_{max} ($CHCl_3$) 242 nM (ε = 19060), 286 nM (ε = 6543); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (ddd, $J=2$, 2, 8 Hz, 1H, ArH), 7.90 (dd, $J=2$, 2 Hz, 1H, ArH), 7.60 (m, 2H, ArH), 7.44 (dd, $J=8$, 8 Hz, 1H, ArH), 7.38 (dd, $J=8$, 8 Hz, 1H, ArH), 7.18 (d, $J=8$ Hz,

1H, ArH), 6.73 (d, $J=8$ Hz, 1H, ArH), 6.62 (dd, $J=2$, 8 Hz, 1H, ArH), 6.56 (d, $J=2$ Hz, 1H, ArH), 4.90 (s, 2H, $ArCH_2O$), 3.91 (t, $J=7$ Hz, 2H, RCH_2O), 3.74 (t, $J=7$ Hz, 2H, RCH_2O), 1.74 (m, 4H, RCH_2CH_2O), 1.41 (m, 4H, decyl), 1.24 (m, 20H, decyl), 0.85 (m, 6H, $2\times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.40 (C=O), 172.29 (C=O), 156.09, 149.23, 148.59, 139.40, 137.23, 135.90, 131.47, 131.37, 130.92, 129.01, 128.98, 128.00, 123.50, 119.01, 117.21, 113.53, 112.05, 70.65, 69.33, 68.97, 31.91, 29.62, 29.47, 29.43, 29.37, 29.28, 26.08, 26.01, 22.69, 14.11; IR (film) 2924, 2854, 1694, 1514, 1468, 1262 cm^{-1}; MS (FAB) *m/e* 683 (MNa^+). Anal. ($C_{41}H_{56}O_7$) C, H.

3′-Carboxy-2-[4-decyloxyphenyl]methoxy-[1,1′-biphenyl]-6-acetic acid (36i). Isolated as a white solid (69% yield): chromatographed on silica gel using CH_2Cl_2, then 10% methanol:CH_2Cl_2; mp = 130–131 °C; UV_{max} (EtOH) 204 nM (ε = 39,538), 224 nM (ε = 31,401), 280 nm (ε = 4138); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J=8$ Hz, 1H, ArH), 8.00 (s, 1H, ArH), 7.55–7.45 (m, 2H, ArH), 7.34 (dd, $J=8$, 8 Hz, 1H, ArH), 7.05 (d, $J=8$ Hz, 1H, ArH), 7.02–6.94 (m, 3H, ArH), 6.67 (d, $J=8$ Hz, 1H, ArH), 6.57 (s, 1H, ArH), 4.98 (s, 2H, $ArCH_2O$), 3.90 (t, $J=7$ Hz, 2H, $ArOCH_2R$), 3.36 (s, 2H, $ArCH_2CO_2$), 1.80-1.67 (m, 2H, OCH_2CH_2R), 1.51–1.20 (m, 14H, $R(CH_2)_7CH_3$), 0.90 (t, $J=7$ Hz, 3H, CH_3C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.20 (C=O), 172.19 (C=O), 158.66, 156.21, 137.10, 134.80, 133.90, 132.72, 131.26, 129.20, 129.06, 128.98, 128.84, 128.71, 128.59, 128.19, 123.32, 114.55, 114.33, 112.51, 70.20, 65.09, 40.09, 31.88, 29.55, 29.39, 29.31, 29.24, 26.16, 22.67, 14.11; IR (KBr) 3400 (OH), 2950, 2850, 1710 (C=O), 1690 (C=O), 1580, 1510, 1250 cm^{-1}; MS (DCI) *m/e* 510 (M^+), 273, 255, 247. Anal. ($C_{32}H_{38}O_6\cdot H_2O$) C, H.

General procedure H. Wadsworth–Emmons olefination of aldehydes: synthesis of 2-hydroxy-6-[methyl(3-propanoate)]-1,1′-biphenyl-3′-carboxylic acid, methyl ester (38). Aldehyde **8** (0.852 g, 3.00 mmol) was dissolved in 10 mL of toluene, and methyl diethylphosphonoacetate (0.840 g, 4.00 mmol) was added. A solution of 25% by weight sodium methoxide in methanol (1.62 g, 7.50 mmol) was added and the mixture stirred at room temperature for 18 h. The mixture was partitioned between saturated aqueous ammonium chloride solution and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate, and the combined extracts were washed with water and brine. The organic phase was dried ($MgSO_4$), and evaporated. The crude material was chromatographed on silica gel using CH_2Cl_2:hexane to afford (*E*) and (*Z*) 2-methoxy-6-[methyl(3-propenoate)]-1,1′-biphenyl-3′-carboxylic acid, methyl ester (0.650 g, 2.01 mmol, 67%) as a >10:1 mixture of *E*:*Z* isomers: Data for *E* isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 1H, ArH), 7.93 (s, 1H, ArH), 7.51–7.32 (m, 5H, ArH and C=CH), 7.00 (d, $J=8$ Hz, 1H, ArH), 6.31 (d, $J=16$ Hz, 1H, C=CH), 3.90 (s, 3H, OCH_3), 3.71 (s, 3H, CO_2CH_3), 3.68 (s, 3H, CO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.01 (C=O), 157.04, 143.06, 135.81, 135.23, 134.53, 131.83, 130.81, 129.99, 128.92, 128.71, 128.16, 119.46, 118.66, 112.06, 55.86, 52.05, 51.59.

A mixture of the above diester (2.40 g, 7.06 mmol; >10:1 mixture of *E*:*Z* isomers) was dissolved in 50 mL of ethanol, and 10% palladium on carbon (0.360 g, 0.338 mmol) was added. The suspension was hydrogenated at 50 psi for 4 h. An aliquot was taken, and the reaction judged to be only 30% complete by NMR analysis. More catalyst (0.180 g, 0.169 mmol) was added, and hydrogenation continued for another 18 h. The analysis of an aliquot at this time indicated the reaction was only 75% complete, and another portion of catalyst (0.200 g, 0.188 mmol) was added. After a further 5 h of hydrogenation, the reduction was complete. The suspension was filtered through Celite, and the filter cake washed with ethanol. The filtrate was evaporated to dryness, and the residue filtered through a pad of silica gel using CH_2Cl_2 to afford the saturated diester (2.10 g, 6.14 mmol, 87%): UV_{max} (EtOH) 206 nm (ε = 32,090), 280 nM (ε = 3164); ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, $J=8$ Hz, 1H, ArH), 7.97 (s, 1H, ArH), 7.57–7.50 (m, 2H, ArH), 7.18 (d, $J=8$ Hz, 1H, ArH), 6.80 (m, 2H, ArH), 3.95 (s, 3H, CO_2CH_3), 3.70 (s, 3H, CO_2CH_3), 3.60 (s, 3H, OCH_3), 2.91 (t, $J=7$ Hz, 2H, $ArCH_2CH_2$), 2.37 (t, $J=7$ Hz, 2H, $CH_2CH_2CO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.12 (C=O), 167.13 (C=O), 156.97, 139.94, 137.30, 131.22, 131.13, 130.13, 129.73, 128.79, 128.27, 121.14, 108.87, 55.71, 52.09, 51.54, 34.94, 28.37; IR (KBr) 2950, 1740, 1720, 1589, 1470, 1300, 1260, 1235 cm^{-1}; MS (DCI) *m/e* 329 (MH^+), 311 (M−OH). Anal. ($C_{19}H_{20}O_5$) C, H.

The above saturated diester (2.90 g, 8.48 mmol) was demethylated using general procedure D to afford phenolic diester 38 as a white solid (2.10 g, 6.40 mmol, 76%): chromatographed on silica gel using CH_2Cl_2:hexane, then CH_2Cl_2, then 10% EtOAc:CH_2Cl_2; mp = 98–99 °C; UV_{max} (EtOH) 206 nM (ε = 30,901), 284 nM (ε = 3178); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10–6.80 (m, 7H, ArH), 4.77 (s, 1H, OH), 3.90 (s, 3H, CO_2CH_3), 3.56 (s, 3H, CO_2CH_3), 2.67 (t, $J=8$ Hz, 2H, $ArCH_2CH_2$), 2.36 (t, $J=8$ Hz, 2H, $CH_2CH_2CO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.08 (C=O), 166.62 (C=O), 152.95, 139.61, 135.31, 134.94, 131.45, 131.26, 129.51, 129.25, 127.04, 120.86, 113.60, 52.31, 51.58, 34.84, 28.43; IR (KBr) 3410, 1750, 1700, 1580, 1465, 1320, 1280, 1270 cm^{-1}; MS (DCI) *m/e* 329 (MH^+), 315, 283. Anal. ($C_{18}H_{18}O_5$) C, H.

Synthesis of 2-[3,4-bis(pentyloxy)phenyl]methoxy-3′-carbomethoxy-[1,1′-biphenyl]-6-propanoic acid, methyl ester (39a). General procedure G was used to couple phenol **38** with (3,4-bispentyloxy)benzyl alcohol to afford diester **39a** (66% yield): chromatographed on silica gel using CH_2Cl_2:hexane to afford a clear oil; UV_{max} (EtOH) 206 nm (ε = 52,865), 280 nM (ε = 4838); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (ddd, $J=2$, 2, 8 Hz, 1H, ArH), 7.94 (d, $J=2$ Hz, 1H, ArH), 7.45–6.90 (m, 5H, ArH), 6.70 (dd, $J=2$, 8 Hz, 1H, ArH), 6.62 (dd, $J=2$, 8 Hz, 1H, ArH), 6.55 (d, $J=2$ Hz, 1H, ArH), 4.87 (s, 2H, $ArCH_2O$), 3.95 (t, $J=7$ Hz, 2H, $ArOCH_2R$), 3.70 (t, $J=7$ Hz, 2H, $ArOCH_2R$), 3.90 (s, 3H, CO_2CH_3), 3.57 (s, 3H, CO_2CH_3), 2.72 (t, $J=7$ Hz, 2H, $ArCH_2CH_2$), 2.34 (t, $J=7$ Hz, 2H, $CH_2CO_2CH_3$), 1.80–0.87 (m, 18H, pentyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.09 (C=O), 166.99 (C=O), 155.98, 149.13, 148.32, 139.98, 137.51, 134.80, 131.25, 130.49, 130.05, 129.71, 128.77, 128.17,

121.51, 118.79, 113.50, 111.91, 110.96, 70.04, 69.31, 68.84, 52.06, 51.55, 34.92, 28.98, 28.93, 28.39, 28.28, 22.51, 14.08; IR (KBr) 2950, 1740 (C=O), 1730 (C=O), 1580, 1530, 1425, 1250, 1235 cm^{-1}; MS (DCI) *m/e* 577 (MH^+), 576 (M), 575, 263. Anal. ($C_{35}H_{44}O_7$) C, H.

Also obtained in this fashion were the following:

2-[3,4-Bis(3-methyl-2-butenyloxy)phenyl]methoxy-3′-carbomethoxy-[1,1′-biphenyl]-6-propanoic acid, methyl ester (39b). 51% yield: chromatographed on silica gel using CH_2Cl_2:hexane, then CH_2Cl_2 to afford a clear oil; UV_{max} (EtOH) 208 nM (ε = 59,871), 280 nM (ε = 4832); ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.93 (d, *J* = 2 Hz, 1H, ArH), 7.49 (d, *J* = 8 Hz, 1H, ArH), 7.44 (s, 1H, ArH), 7.24 (d, *J* = 8 Hz, 1H, ArH), 6.95 (d, *J* = 8 Hz, 1H, ArH), 6.86 (d, *J* = 8 Hz, 1H, ArH), 6.70 (d, *J* = 8 Hz, 1H, ArH), 6.60 (m, 2H, ArH), 5.44 (m, 2H, 2×C=CH), 4.87 (s, 2H, $ArCH_2O$), 4.51 (d, 2H, *J* = 7 Hz, OCH_2R), 4.33 (d, 2H, *J* = 7 Hz, OCH_2R), 3.87 (s, 3H, CO_2CH_3), 3.56 (s, 3H, CO_2CH_3), 2.72 (t, 2H, $ArCH_2CH_2$), 2.36 (t, 2H, $CH_2CO_2CH_3$), 1.74 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.64 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.07 (C=O), 166.98 (C=O), 156.00, 148.83, 148.10, 139.98, 137.54, 137.46, 136.99, 134.78, 131.25, 130.50, 130.06, 129.70, 128.76, 128.16, 121.54, 120.33, 119.94, 118.95, 113.67, 112.20, 111.04, 96.10, 70.15, 66.02, 65.67, 52.04, 51.53, 34.92, 28.40, 25.78, 18.20; IR (KBr) 2920, 1740 (C=O), 1725 (C=O), 1580, 1510, 1440, 1260, 1230 cm^{-1}; MS (DCI) *m/e* 573 (MH^+), 572 (M), 315, 259. Anal. ($C_{35}H_{40}O_7$) C, H.

2-[3,4-Bis(cyclopentyloxy)phenyl]methoxy-3′-carbomethoxy-[1,1′-biphenyl]-6-propanoic acid, methyl ester (39c). 53% yield: chromatographed on silica gel using CH_2Cl_2:hexane, then CH_2Cl_2 to afford a clear oil; UV_{max} (EtOH) 208 nm (ε = 55,184), 282 nM (ε = 4919); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 1H, *J* = 8 Hz, ArH), 7.98 (s, 1H, ArH), 7.51 (d, *J* = 8 Hz, 1H, ArH), 7.46 (s, 1H, ArH), 7.27 (d, *J* = 8 Hz, 1H, ArH), 6.89 (d, *J* = 8 Hz, 1H, ArH), 6.86 (d, *J* = 8 Hz, 1H, ArH), 6.77 (d, *J* = 8 Hz, 1H, ArH), 6.64 (d, *J* = 8 Hz, 1H, ArH), 6.60 (s, 1H, ArH), 4.90 (s, 2H, $ArCH_2O$), 4.69 (m, 1H, R_2CHOR), 4.45 (m, 1H, R_2CHOR), 3.91 (s, 3H, CO_2CH_3), 3.59 (s, 3H, CO_2CH_3), 1.81–1.58 (m, 16H, cyclopentyl), 2.75 (t, *J* = 8 Hz, 2H, $ArCH_2CH_2$), 2.39 (t, *J* = 8 Hz, 2H, $CH_2CO_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.03 (C=O), 166.96 (C=O), 155.99, 148.86, 148.20, 139.98, 137.53, 134.85, 131.23, 130.42, 129.90, 128.78, 128.18, 121.47, 119.14, 116.2, 115.03, 110.88, 81.06, 80.67, 69.98, 52.04, 51.50, 34.92, 32.89, 28.41, 24.06; IR (KBr) 2960, 1740 (C=O), 1725 (C=O), 1580, 1508, 1435, 1260, 1220 cm^{-1}; MS (DCI) *m/e* 573 (MH^+), 572 (M), 517, 505, 259. Anal. ($C_{35}H_{40}O_7$) C, H.

Synthesis of 2-[3,4-bis(pentyloxy)phenyl]methoxy-3′-carboxy-[1,1′-biphenyl]-6-propanoic acid (40a). Diester **39a** was hydrolyzed using general procedure F to afford diacid **40a** (66% yield): chromatographed on reverse-phase C-18 silica gel using methanol to afford a white solid; mp = 145–146 °C; UV_{max} (EtOH) 206 nM (ε = 59,315), 280 nM (ε = 4818); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 2H, ArH), 7.50 (m, 2H, ArH), 7.27 (m, 1H, ArH), 6.95–6.55 (m, 5H, ArH), 4.88 (s, 2H, $ArCH_2O$), 3.90 (t, *J* = 6 Hz, 2H, $ArOCH_2$), 3.72, (t, *J* = 6 Hz, 2H, $ArOCH_2$), 2.71 (m, 2H, $ArCH_2CH_2$), 2.49 (m, 2H, $ArCH_2CH_2CO_2$), 1.80–0.86 (m, 18H, pentyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.33 (C=0), 172.33 (C=0), 155.98, 149.18, 148.35, 139.75, 137.53, 135.81, 132.07, 130.45, 129.68, 129.14, 128.91, 128.77, 128.19, 121.31, 118.84, 113.57, 111.93, 110.94, 70.05, 69.34, 68.86, 35.15, 28.97, 28.91, 28.25, 28.18, 27.85, 22.46, 14.03; IR (KBr) 3450 (OH), 2950, 2860, 1700 (C=0), 1270 cm^{-1}; MS (DCI) *m/e* (M^+-17), 531, 269, 263. Anal. ($C_{33}H_{40}O_7 \cdot 0.25\ H_2O$) C, H.

Also obtained in this fashion were the following:

2-[3,4-Bis(3-methyl-2-butenyloxy)phenyl]methoxy-3′-carboxy-[1,1′-biphenyl]-6-propanoic acid (37a). 83% yield: chromatographed on reverse-phase C-18 silica gel using methanol to afford a white solid; mp = 142–143 °C; UV_{max} (EtOH) 208 nM (ε = 58,708), 280 nM (ε = 4999); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 2H, ArH), 7.48 (m, 2H, ArH), 7.28 (d, *J* = 8 Hz, 1H, ArH), 6.95 (d, *J* = 8 Hz, 1H, ArH), 6.92 (d, *J* = 8 Hz, 1H, ArH), 6.75 (d, *J* = 8 Hz, 1H, ArH), 6.65 (m, 2H, ArH), 5.41 (m, 2H, OCH_2CH=C), 4.88 (s, 2H, $ArCH_2O$), 4.51 (d, *J* = 6 Hz, 2H, O-CH_2C=C), 4.33 (d, *J* = 6 Hz, 2H, O-CH_2C=C), 2.71 (m, 2H, $ArCH_2CH_2$) 2.45 (m, 2H, $ArCH_2CO_2$), 1.71 (s, 6H, 2×CH_3), 1.66 (s, 6H, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.29 (C=O), 172.29 (C=O), 156.02, 148.86, 148.12, 139.75, 137.64, 137.49, 137.03, 135.79, 131.97, 130.45, 129.67, 129.19, 128.91, 128.83, 128.21, 121.36, 120.31, 119.83, 118.97, 113.75, 112.22, 111.06, 70.18, 66.06, 65.61, 35.12, 27.92, 25.79, 25.75, 18.18; IR (KBr) 3430 (OH), 3540 (OH), 2900, 1680, (C=O), 1580, 1510, 1260 cm^{-1}; MS (DCI) *m/e* 545 (MH^+), 537, 527, 289, 269, 259. Anal. ($C_{33}H_{36}O_7 \cdot H_2O$) C, H.

2-[3,4-Bis(cyclopentyloxy)phenyl]methoxy-3′-carboxy-[1,1′-biphenyl]-6-propanoic acid (40c). 90% yield: chromatographed on reverse-phase C-18 silica gel using methanol to afford a white solid; mp = 148–150 °C; UV_{max} (EtOH) 208 nM (ε = 55,091), 280 nM (ε = 4755); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2H, ArH), 7.46–7.27 (m, 3H, ArH), 6.90 (d, *J* = 8 Hz, 1H, ArH), 6.87 (d, *J* = 8 Hz, 1H, ArH), 6.74 (d, *J* = 6 Hz, 1H, ArH), 6.25 (dd, *J* = 2, 8 Hz, 1H, ArH), 6.57 (d, *J* = 2 Hz, 1H, ArH), 4.87 (s, 2H, $ArCH_2O$), 4.65–4.48 (m, 2H, 2×R_2CHOAr), 2.75 (m, 2H, $ArCH_2CH_2$), 2.46 (m, 2H, $ArCH_2CH_2CO_2$), 1.78–1.54 (m, 16H, cyclopentyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.44 (C=O), 172.46 (C=O), 156.13, 149.02, 148.35, 139.88, 137.65, 135.96, 132.13, 130.51, 129.99, 129.27, 129.03, 128.91, 128.35, 121.40, 119.32, 116.72, 115.20, 111.03, 81.28, 80.89, 70.17, 35.23, 32.89, 28.02, 24.02, 23.96; IR (KBr) 3450 (OH), 2960, 1700 (C=O), 1430, 1265 cm^{-1}; MS (DCI) *m/e* 545 (MH^+), 544 (M^+), 527 ($M-H_2O$), 269, 259. Anal. ($C_{33}H_{36}O_7 \cdot 0.10\ H_2O$) C, H.

Synthesis of 2-[(3,4-bispentyloxy)phenyl]methoxy-3′-carboethoxy-[1,1′-biphenyl]-6-carboxaldehyde (41a). Aldehyde **8** was demethylated using general procedure D to afford the corresponding phenol (75% yield): chromatographed on silica gel using EtOAc:CH_2Cl_2; mp = 185–192 °C; UV_{max} (EtOH) 222 nM (ε = 22,861), 328 nM (ε = 2822); ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H,

CHO), 8.20 (dd, $J=2$, 8 Hz, 1H, ArH), 8.06 (d, $J=2$ Hz, 1H, ArH), 7.67–7.25 (m, 5H, ArH), 5.04 (s, 1H, OH), 4.41 (q, $J=7$ Hz, 2H, CO_2CH_2), 1.38 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.43 (C=O), 165.86 (C=O), 153.24, 135.06, 134.89, 132.15, 131.62, 130.01, 129.58, 129.42, 121.25, 120.57, 61.45, 14.29; IR (KBr) 3200, 1720, 1670, 1580, 1290, 1240 cm^{-1}; MS (DCI) *m/e* 271 (MH^+), 253, 225.

The above phenolic aldehyde was coupled to (3,4-bispentyloxy)benzyl alcohol using general procedure G to afford aldehyde **41a** (49% yield): chromatographed on silica gel using CH_2Cl_2:hexane to afford an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 8.13-8.10 (m, 1H, ArH), 8.09 (s, 1H, ArH), 7.65 (dd, $J=2$, 8 Hz, 1H, ArH), 7.55–7.40 (m, 3H, ArH), 7.27 (dd, $J=2$, 8 Hz, 1H, ArH), 6.80–6.65 (m, 3H, ArH), 4.98 (s, 2H, $ArCH_2O$), 4.39 (q, $J=7$ Hz, 2H, CO_2CH_2), 3.92 (t, $J=6$ Hz, 2H, OCH_2CH_2R), 3.79 (t, $J=6$ Hz, 2H, OCH_2CH_2R), 1.82–1.75 (m, 4H, OCH_2CH_2R), 1.45–1.36 (m, 11H, $2\times RCH_2CH_2CH_3$ and $CO_2CH_2CH_3$), 0.94 (m, 6H, $2\times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.83 (C=O), 166.19 (C=O), 149.22, 148.50, 135.31, 134.44, 133.76, 132.01, 130.36, 129.13, 129.08, 129.00, 128.92, 127.99, 119.79, 119.18, 118.23, 113.56, 112.27, 70.66, 69.30, 69.01, 61.14, 28.98, 28.19, 22.47, 14.30, 14.03.

Also obtained in this fashion were the following:

2-[3,4-Bis(3-methyl-2-butenyloxy)phenyl]methoxy-3′-carboethoxy-[1,1′-biphenyl]-6-carboxaldehyde (41b). 49% yield: chromatographed on silica gel using CH_2Cl_2:hexane to afford an oil; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 8.15–8.05 (m, 2H, ArH), 7.76–7.25 (m, 5H, ArH), 6.81–6.60 (m, 3H, ArH), 5.48 (m, 2H, 2×C=CH), 4.99 (s, 2H, $ArCH_2O$), 4.54 (q, $J=7$ Hz, 2H, CO_2CH_2), 4.39 (m, 4H, $2\times OCH_2C=C$), 1.70 (s, 6H, $2\times CH_3$), 1.69 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.38 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$).

2-[(3,4-Biscyclopentyloxy)phenyl]methoxy-3′-carboethoxy-[1,1′-biphenyl]-6-carboxaldehyde (41c). 41% yield: chromatographed on silica gel using CH_2Cl_2:hexane, then CH_2Cl_2, then 5% EtOAc:CH_2Cl_2 to afford an oil; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H, CHO), 8.15–7.66 (m, 10H, ArH), 4.98 (s, 2H, $ArCH_2O$), 4.70 (b, 2H, $2\times R_2CHOR$), 4.35 (q, $J=7$ Hz, 2H, CO_2CH_2), 1.82–1.58 (m, 16H, cyclopentyl), 1.38 (t, $J=7$ Hz, 3H, $CO_2CH_2CH_3$).

Synthesis of (*E*)-2-[(3,4-bispentyloxy)phenyl]methoxy-6-[methyl(3-propenoate)]-1,1′-biphenyl-3′-carboxylic acid, methyl ester (42a). Aldehyde **41a** was converted to diester **42a** using general procedure H (63% yield): chromatographed on silica gel using CH_2Cl_2:hexane to afford an oil; UV_{max} (EtOH) 208 nM (ε = 47,562), 232 nm (ε = 36,190), 284 nM (ε = 19,436); ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, $J=8$ Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.51–7.34 (m, 6H, ArH and C=CH), 7.06 (dd, $J=5$, 5 Hz, 1H, ArH), 6.61 (s, 1H, ArH), 6.37 (d, $J=16$ Hz, 1H, C=CH), 4.94 (s, 2H, $ArCH_2O$), 3.97 (t, $J=7$ Hz, 2H, OCH_2R), 3.95 (s, 3H, OCH_3), 3.77 (t, $J=7$ Hz, 2H, OCH_2R), 3.70 (s, 3H, OCH_3), 1.81–0.90 (m, 18 H, pentyl); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.02 (C=O), 166.88 (C=O), 156.10, 149.20, 149.04, 143.01, 136.05, 134.60, 132.46, 131.02, 131.59, 130.17, 129.96, 129.30, 128.91, 128.65, 128.09, 119.46, 119.07, 114.82, 113.76, 112.10, 70.34, 69.29, 68.92, 52.09, 51.59, 29.07, 28.99, 28.27, 28.22, 22.51, 22.48, 14.07; IR (KBr) 2960, 2870, 1750, 1690, 1510, 1280, 1200 cm^{-1}; MS (DCI) *m/e* 575 (MH^+), 543, 295, 263. Anal. ($C_{35}H_{42}O_7 \cdot 0.25\ H_2O$) C, H.

Also obtained in this fashion were the following:

(*E*)-2-[3,4-Bis(3-methyl-2-butenyloxy)phenyl]methoxy-6-[methyl(3-propenoate)]-1,1′-biphenyl-3′-carboxylic acid, methyl ester (42b). 36% yield: chromatographed on silica gel using CH_2Cl_2:hexane to afford an oil; UV_{max} (EtOH) 206 nM (ε = 64,456), 232 nM (ε = 38,475), 284 nM (ε = 19,713); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J=8$ Hz, 1H, ArH), 8.00 (s, 1H, ArH), 7.51–7.06 (m, 5H, ArH and C=CH), 6.79 (d, $J=8$ Hz, 1H, ArH), 6.70–6.60 (m, 3H, ArH), 6.37 (d, $J=16$ Hz, 1H, C=CH), 5.49 (m, 2H, $2\times OCH_2CH=C$), 4.92 (s, 2H, $ArCH_2O$), 4.55 (d, $J=6$ Hz, 2H, $OCH_2CH=C$), 4.39 (d, $J=6$ Hz, 2H, $OCH_2CH=C$), 3.90 (s, 3H, CO_2CH_3), 3.69 (s, 3H, CO_2CH_3), 1.75 (s, 6H, $2\times CH_3$), 1.66 (s, 6H, $2\times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.02 (C=O), 166.87 (C=O), 156.09, 148.86, 148.27, 143.02, 137.56, 137.09, 136.00, 135.51, 134.56, 131.93, 131.55, 129.95, 129.29, 128.92, 128.66, 128.08, 120.27, 119.92, 119.45, 119.15, 119.08, 114.34, 113.66, 112.34, 70.28, 65.93, 65.64, 52.09, 51.59, 25.77, 18.19; IR (KBr) 2900, 1730 (C=O), 1663 (C=O), 1510, 1430, 1255, 1230 cm^{-1}; MS (DCI) *m/e* 571 (MH^+), 539, 503, 471, 449, 435, 313, 259. Anal. ($C_{35}H_{36}O_7 \cdot 0.1\ CH_2Cl_2$) C, H.

(*E*)-2-[(3,4-Biscyclopentyloxy)phenyl]methoxy-6-[methyl(3-propenoate)]-1,1′-biphenyl-3′-carboxylic acid, methyl ester (42c). 57% yield: chromatographed on silica gel using CH_2Cl_2:hexane to afford an oil; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, $J=8$ Hz, 1H, ArH), 7.99 (s, 1H, ArH), 7.46–7.04 (m, 6H, ArH and C=CH), 6.79 (d, $J=8$ Hz, 1H, ArH), 6.68 (d, $J=8$ Hz, 1H, ArH), 6.63 (s, 1H, ArH), 6.37 (d, $J=13$ Hz, 1H, C=CH), 3.93 (s, 2H, $ArCH_2O$), 4.69–4.52 (m, 2H, $2\times R_2CHOR$), 3.90 (s, 3H, CO_2CH_3), 3.70 (s, 3H, CO_2CH_3), 1.82-1.58 (m, 16H, cyclopentyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.03 (C=O), 166.88 (C=O), 156.91, 148.86, 148.36, 143.04, 136.03, 135.34, 134.59, 131.89, 131.52, 129.94, 129.47, 128.91, 128.64, 128.09, 119.44, 119.33, 119.03, 116.49, 115.18, 114.22, 81.06, 80.79, 70.29, 52.09, 51.59, 32.77, 23.90.

Synthesis of 2-[(3,4-bis(pentyloxy)phenyl]methoxy-3′-carboxy-[1,1′-biphenyl]-6-[(*E*)-3-propenoic acid] (43a). Diester **42a** was hydrolyzed using general procedure F to afford diacid **43a** (73% yield): recrystallized using ether:hexane; mp = 191–193 °C; UV_{max} (EtOH) 206 nM (ε = 49,197), 232 nm (ε = 36,853), 282 nM (ε = 20,355); ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, $J=2$, 2, 8 Hz, 1H, ArH), 7.91 (dd, $J=2$, 2 Hz, 1H, ArH), 7.43–7.27 (m, 5H, ArH and $CH=CHCO_2H$), 7.01 (dd, $J=4$, 8 Hz, 1H, ArH), 6.69 (d, $J=8$ Hz, 1H, ArH), 6.61 (dd, $J=2$, 8 Hz, 1H, ArH), 6.55 (d, $J=2$ Hz, 1H, ArH), 6.22 (d, $J=16$ Hz, 1H, $CH=CHCO_2H$), 4.87 (s, 2H, $ArCH_2O$), 3.93–3.66 (m, 4H, $2\times RCH_2O$), 1.76–0.82 (m, 18H, pentyl); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 169.11 (C=O), 168.92 (C=O), 155.98, 149.05, 148.37, 143.69, 135.91, 135.43, 134.52, 132.26, 131.53, 130.05, 129.39, 128.87, 127.96, 119.74, 119.16, 119.09, 118.75, 114.35, 113.60, 112.15, 70.31, 69.35, 68.99, 28.87, 28.81, 28.16, 28.10, 22.40, 13.93; IR (KBr) 3400 (OH), 2950, 1685 (C=0), 1625, 1513, 1257, 1140 cm^{-1}; MS (DCI) *m/e* 547 (MH^+), 529 (M−OH), 299, 281, 267. Anal. ($C_{33}H_{38}O_7 \cdot 0.5\ H_2O$) C, H.

Also obtained in this fashion were the following:

2-[3,4-Bis(3-methyl-2-butenyloxy)phenyl]methoxy-3′-carboxy-[1,1′-biphenyl]-6-[(*E*)-3-propenoic acid] (43b). 70% yield: recrystallized using CH_2Cl_2:hexane; mp = 175–179 °C; UV_{max} (EtOH) 208 nM (ε = 55,237), 232 nM (ε = 36,495), 282 nM (ε = 18,975); ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8 Hz, 1H, ArH), 7.83 (s, 1H, ArH), 7.44 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.35–7.24 (m, 4H, ArH and C<u>H</u>=CHCO$_2$H), 7.07 (d, *J* = 8 Hz, 1H, ArH), 6.74–6.61 (m, 3H, ArH), 6.26 (d, *J* = 16 Hz, 1H, C=C<u>H</u>CO$_2$H), 5.33 (m, 2H, 2×OCH$_2$C<u>H</u>=C), 4.86 (s, 2H, Ar<u>C</u>H$_2$O), 4.47 (d, *J* = 6 Hz, 2H, OC<u>H</u>$_2$CH=C), 4.34 (d, *J* = 6 Hz, 2H, OC<u>H</u>$_2$CH=C), 1.66 (s, 6H, 2×CH$_3$), 1.61 (s, 6H, 2×CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.82, (C=O), 169.51 (C=O), 156.68, 149.36, 148.70, 143.85, 138.52, 138.14, 136.76, 135.85, 132.79, 131.26, 130.46, 129.56, 129.33, 128.53, 120.68, 120.58, 120.25, 120.08, 119.74, 115.11, 114.77, 113.31, 70.91, 66.72, 66.36, 25.94, 25.92, 18.34, 18.30; IR (KBr) 3240 (OH), 2900, 1680 (C=O), 1630, 1510, 1250 cm^{-1}; MS (DCI) *m/e* 517, 267, 259. Anal. ($C_{33}H_{34}O_7 \cdot 0.75\ H_2O$) C, H.

2-[(3,4-Bis(cyclopentyloxy)phenyl]methoxy-3′-carboxy-[1,1′-biphenyl]-6-[(*E*)-3-propenoic acid] (43c). 75% yield: recrystallized using ether:hexane; mp = 215–216 °C; UV_{max} (EtOH) 208 nM (ε = 47,271), 232 nm (ε = 35,149), 282 nM (ε = 18,855); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.91 (dd, *J* = 2, 2 Hz, 1H, ArH), 7.51–7.31 (m, 5H, ArH and C<u>H</u>=CHCO$_2$H), 7.14 (dd, *J* = 2, 8 Hz, 1H, ArH), 6.79 (d, *J* = 6 Hz, 1H, ArH), 6.68 (dd, *J* = 2, 6 Hz, 1H, ArH), 6.61 (d, *J* = 2 Hz, 1H, ArH), 6.35 (d, *J* = 16 Hz, 1H, C=C<u>H</u>CO$_2$H), 4.92 (s, 2H, ArCH$_2$O), 4.70–4.68 (m, 1H, R$_2$C<u>H</u>OAr) 4.52–4.49 (m, 1H, R$_2$C<u>H</u>OAr) 1.77–1.56 (m, 16H, cyclopentyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.70 (C=O), 172.33 (C=O), 159.92, 152.48, 151.80, 146.90, 140.24, 139.09, 138.22, 135.73, 135.35, 134.43, 133.94, 132.80, 132.33, 131.78, 123.57, 123.24, 122.65, 120.27, 118.65, 118.11, 84.95, 84.47, 73.72, 36.18, 27.42, 27.31; IR (KBr) 3420, 2960, 1685, 1630, 1250 cm^{-1}; MS (DCI) *m/e* 543 (MH^+), 457 (M−C_4H_8O), 281, 267, 259. Anal. ($C_{33}H_{34}O_7 \cdot 0.75\ H_2O$) H; C, calcd, 71.46; found, 71.04.

Synthesis of 3′-carboethoxy-2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]methoxy-[1,1′-biphenyl]-6-[(*E*)-3-propenoic acid], methyl ester (44). Aldehyde **27** (0.965 , 2.05 mmol) was dissolved in 15.6 mL of CH_2Cl_2, and methyl(triphenylphosphoranylidene)acetate (2.74 g, 8.20 mmol) is added. The mixture was stirred at room temperature for 24 h. Thin-layer chromatographic analysis at this time indicated the reaction was incomplete. More methyl(triphenylphosphoranylidene)acetate (0.246 g, 0.736 mmol) was added and stirring continued for another 20 h. The mixture was poured into water and EtOAc, and the aqueous phase was extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude material was chromatographed using EtOAc:hexane (5%–10%–20%) to afford diester **44** (0.694 g, 1.32 mmol, 64%) as a clear oil: UV_{max} ($CHCl_3$) 242 nM (ε = 31,760), 286 nM (ε = 23,380), 656 nM (ε = 4992); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.98 (dd, *J* = 2, 2 Hz, 1H, ArH), 7.50 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.43 (m, 1H, ArH), 7.41 (d, *J* = 16 Hz, 1H, C=CH), 7.33 (m, 2H, ArH), 7.17 (d, *J* = 8 Hz, 1H, ArH), 7.06 (dd, *J* = 2, 8 Hz, 1H, ArH), 7.00 (d, *J* = 2 Hz, 1H, ArH), 6.90 (dd, *J* = 2, 8 Hz, 1H, ArH), 6.32 (d, *J* = 16 Hz, 1H, C=CH), 4.95 (s, 2H, ArCH$_2$O), 4.34 (q, *J* = 7 Hz, 2H, CO$_2$CH$_2$), 3.68 (s, 3H, CO$_2$CH$_3$), 1.61 (s, 4H, CH$_2$CH$_2$), 1.35 (t, *J* = 7 Hz, 3H, CO$_2$CH$_2$C<u>H</u>$_3$), 1.21 (s, 6H, 2×CH$_3$), 1.10 (s, 6H, 2×CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.07 (C=O), 166.48 (C=O), 156.27, 144.89, 144.23, 143.37, 143.09, 135.93, 135.15, 134.66, 133.58, 131.79, 131.63, 130.35, 128.89, 128.78, 128.16, 126.47, 124.52, 123.73, 119.44, 118.95, 113.90, 70.28, 60.94, 51.61, 34.98, 34.16, 34.06, 31.80, 31.68, 14.33; IR (film) 2958, 2928, 1720, 1636, 1570, 1460, 1294, 1258, 1230, 1170 cm^{-1}; MS (DCI) *m/e* 527 (MH^+), 495 (M−CH_3O), 481 (M−C_2H_5O), 201 ($C_{15}H_{21}^+$). HRMS (FAB) *m/e* 549.2611 [$(M + Na)^+$ calcd for $C_{34}H_{38}O_5Na$: 549.2617].

Synthesis of 3′-carboxy-2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]methoxy-[1,1′-biphenyl]-6-propanoic acid (45). Diester **44** (0.629 g, 1.20 mmol) was dissolved in 10 mL of EtOAc, and 10% palladium on carbon (0.100 g, 0.094 mmol) was added. The suspension was hydrogenated using a balloon of hydrogen for 3.5 h. The mixture was filtered through a pad of Florisil, eluting with ether and ethyl acetate. The filtrate was evaporated, and the crude material was chromatographed on silica gel using 5% EtOAc:hexane to yield 3′-carboethoxy-2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl] methoxy-[1,1′-biphenyl]-6-[3-propanoic acid], methyl ester (0.608 g, 1.15 mmol, 96%) as a clear oil: UV_{max} ($CHCl_3$) 242 nM (ε = 9776), 278 nM (ε = 3210); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 2, 2, 8 Hz, 1H, ArH), 7.97 (dd, *J* = 2, 2 Hz, 1H, ArH), 7.45 (m, 2H, ArH), 7.28 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.16 (d, *J* = 8 Hz, 1H, ArH), 6.97 (d, *J* = 2 Hz, 1H, ArH), 6.93 (d, *J* = 3 Hz, 1H, ArH), 6.90 (d, *J* = 3 Hz, 1H, ArH), 6.86 (dd, *J* = 2, 8 Hz, 1H, ArH), 4.91 (s, 2H, ArCH$_2$O), 4.35 (q, *J* = 7 Hz, 2H, CO$_2$CH$_2$), 3.57 (s, 3H, CO$_2$CH$_3$), 2.73 (dd, *J* = 8, 8 Hz, 2H, ArC<u>H</u>$_2$CH$_2$CO$_2$), 2.39 (dd, *J* = 8, 8 Hz, 2H, ArCH$_2$-C<u>H</u>$_2$CO$_2$), 1.61 (s, 4H, CH$_2$CH$_2$), 1.36 (t, *J* = 7 Hz, 3H, CO$_2$CH$_2$C<u>H</u>$_3$), 1.21 (s, 6H, 2×CH$_3$), 1.09 (s, 6H, 2×CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.15 (C=O), 166.60 (C=O), 156.16, 144.81, 144.03, 140.06, 137.40, 134.67, 133.95, 131.14, 130.54, 130.47, 128.77, 128.34, 128.25, 126.36, 124.43, 123.63, 121.41, 110.60, 69.97, 60.92, 51.55, 34.99, 34.15, 34.03, 31.80, 31.66, 28.42, 14.33; IR (film) 2958, 2928, 1738, 1718, 1580, 1456, 1364, 1296, 1258, 1230, 1080, 758 cm^{-1}; MS (DCI) *m/e* 529 (MH^+), 483 (M−C_2H_5O), 201 ($C_{15}H_{21}^+$). Anal. ($C_{34}H_{40}O_5$) C, H.

The above saturated diester (0.548 g, 1.04 mmol) was

hydrolyzed using general procedure F to afford diacid **45** (0.306 g, 0.630 mmol, 61%) as a white solid: recrystallized from CH_2Cl_2:pentane; mp = 160–161 °C; UV_{max} ($CHCl_3$) 242 nM (ε = 11,222), 278 nM (ε = 3474); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H, ArH), 7.49 (m, 2H, ArH), 7.29 (dd, *J* = 8, 8 Hz, 1H, ArH), 7.15 (d, *J* = 8 Hz, 1H, ArH), 6.98 (d, *J* = 2 Hz, 1H, ArH), 6.93 (d, *J* = 8 Hz, 1H, ArH), 6.91 (d, *J* = 8 Hz, 1H, ArH), 6.85 (dd, *J* = 2, 8 Hz, 1H, ArH), 4.91 (s, 2H, $ArCH_2O$), 2.72 (m, 2H, $ArCH_2CH_2CO_2$), 2.49 (m, 2H, $ArCH_2CH_2CO_2$), 1.59 (s, 4H, CH_2CH_2), 1.20 (s, 6H, 2×CH_3), 1.08 (s, 6H, 2xCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.38 (C=O), 172.41 (C=O), 156.14, 145.85, 144.85, 144.05, 139.77, 137.49, 135.78, 133.87, 132.05, 130.40, 129.23, 128.90, 128.30, 126.37, 124.46, 123.66, 121.19, 110.61, 70.00, 35.13, 34.99, 34.13, 34.03, 31.79, 31.65, 27.87; IR (KBr) 3414, 2960, 2928, 1704, 1580, 1458, 1260, 1078 cm^{-1}; MS (DCI) *m/e* 487 (MH^+), 469 (M−OH), 201 ($C_{15}H_{21}^+$). Anal. ($C_{31}H_{34}O_5 \cdot 0.7\ H_2O$) C, H.

Synthesis of 3′-carboxy-2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]methoxy-[1,1′-biphenyl]-6-[(*E*)-3-propenoic acid] (46). Diester **44** (0.246 g, 0.467 mmol) was hydrolyzed using general procedure F to afford diacid **46** (0.194 g, 0.401 mmol, 86%) as a white solid: recrystallized from EtOAc:hexane; mp = 247–249 °C; UV_{max} (EtOH) 204 nM (ε = 34,000), 220 nM (ε = 30,186), 280 nM (ε = 15,343); ^1H NMR (300 MHz, DMSO-d_6) δ 12.70 (b, 2H, 2×CO_2H), 7.97 (bd, *J* = 8 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 7.61–7.40 (m, 4H, ArH), 7.27 (d, *J* = 8 Hz, 1H, ArH), 7.19 (d, *J* = 8 Hz, 1H, ArH), 7.15 (d, *J* = 16 Hz, 1H, C=CH), 7.03 (s, 1H, ArH), 6.94 (d, *J* = 8 Hz, 1H, ArH), 6.42 (d, *J* = 16 Hz, 1H, C=CH), 5.00 (s, 2H, $ArCH_2O$), 1.56 (s, 4H, CH_2CH_2), 1.16 (s, 6H, 2×CH_3), 1.06 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.26 (C=O), 167.14 (C=O), 155.67, 144.20, 143.55, 141.43, 135.90, 134.94, 133.73, 133.65, 131.23, 130.70, 129.25, 128.48, 128.40, 126.15, 124.49, 124.12, 120.61, 118.81, 114.16, 69.43, 34.51, 33.74, 33.70, 31.56, 31.46; IR (KBr) 3422, 2962, 2926, 1688, 1626, 1570, 1464, 1310, 1254 cm^{-1}; MS (DCI) *m/e* 467 (M−OH), 201 ($C_{15}H_{21}^+$). Anal. ($C_{31}H_{32}O_5 \cdot 0.75\ H_2O$) C, H.

Acknowledgement

We thank the Department of Analytical Research in Wallingford, CT for analytical data in support of this work.

References

1. (a) Davies, P.; MacIntyre, D. E. In *Inflammation: Basic Principles and Clinical Correlates*, 2nd ed.; Gallin, J. I.; Goldstein, I. M.; Snyderman, R., Eds.; Raven Press: New York, 1992; pp 123–138. (b) Lam, B. K.; Austen, K. F. In *Inflammation: Basic Principles and Clinical Correlates*, 2nd ed.; Gallin, J. I.; Goldstein, I. M.; Snyderman, R., Eds.; Raven Press: New York, 1992; pp 139–148. (c) Zimmerman, G. A.; Prescott, S. M., McIntyre, T. M. In *Inflammation: Basic Principles and Clinical Correlates*, 2nd ed.; Gallin, J. I.; Goldstein, I. M.; Snyderman, R., Eds.; Raven Press: New York, 1992; pp 149–176. (d) Pruzanski, W.; Vadas, P. *Immunology Today* **1991**, *12*, 143. (e) Vadas, P.; Pruzanski, W. *Lab. Invest.* **1986**, *55*, 391.
2. Henderson, Jr., W. R. *Am. Rev. Respir. Dis.* **1991**, *143*, S86.
3. Pruzanski, W.; Vadas, P. *J. Rheumatol* **1988**, *15*, 1601.
4. Forster, S.; Ilderton, E.; Norris, J. F.; Summerly, R.; Yardley, H. J. *Br. J. Dermatol* **1985**, *112*, 135.
5. ; Nevalainen, T. *Scand. J. Gastroenterol* **1980**, *15*, 641.
6. (a) Gregson, N. A. *Biochem. Soc. Trans.* **1989**, *17*, 280. (b) Trotter, J.; Smith, M. A. *Clin. Biol. Res.* **1984**, *146*, 55.
7. Vadas, P. J. *Lab. Clin. Med.* **1984**, *104*, 873–881.
8. Ford, D. A.; Hazen, S. L.; Saffitz, J. E.; Gross, R. W. J. *Clin. Invest.* **1991**, *88*, 331.
9. Van den Bosch, H. *Biochim. Biophys. Acta* **1980**, *604*, 191.
10. Axelrod, J. *Chem. Senses* **1989**, *1*, 1; Brand, J. G. Ed.; Dekker: New York.
11. Di Marzo, V.; Galadari, S. H. I.; Tippins, J. R.; Morris, H. R. *Life Sci.* **1991**, *49*, 247.
12. Arita, H.; Hanasaka, K.; Nakano, T.; Oka, S.; Teroka, H.; Matsumoto, K. *J. Biol. Chem.* **1991**, *266*, 19139.
13. Gupta, C. *Proc. Soc. Exp. Biol. Med.* **1988**, *188*, 489.
14. Fry, M. R.; Ghosh, S. S.; East, J. M.; Franson, R. C. *Biology Of Reproduction* **1992**, *47*, 751.
15. Elsbach, P.; Weiss, J. *Biochem. Biophys. Acta* **1988**, *947*, 29.
16. Regelson, W.; Franson, R. *Ann. N.Y. Acad. Sci.* **1991**, *621*, 262.
17. (a) Clark, J. D.; Milona, N.; Knopf, J. L. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 7708. (b) Kramer, R. M.; Roberts, E. F.; Manetta, J.; Putnam, J. E. *J. Biol. Chem.* **1991**, *266*, 5268. (c) Clark, J. D.; Lin, L.-L.; Kriz, R. W.; Ramesha, C. S.; Sultzman, L. A.; Lin, A. Y.; Milona, N.; Knopf, J. L. *Cell* **1991**, *65*, 1043. (d) Sharp, J. D.; White, D. L.; Chiou, X. G.; Goodson, T.; Gamboa, G. C.; McClure, D.; Burgett, S.; Hoskins, J.; Skatrud, P. L.; Sportsman, J. R.; Becker, G. W.; Kang, L.H.; Roberts, E. F.; Kramer, R. M. *J. Biol. Chem.* **1991**, *266*, 14850.
18. (a) Hazen, S. L.; Hall, C. R.; Ford, D. A.; Gross, R. W. *J. Clin. Invest.* **1993**, *91*, 2513. (b) Hazen, S. L.; Gross, R. W. *Biochem. J.* **1991**, *280*, 581.
19. Nishijima, J.; Okamoto, M.; Ogawa, M.; Kosaki, G.; Yamano, T. *J. Biochem.* **1983**, *94*, 137.
20. (a) Hara, S.; Kudo, I.; Chang, H. W.; Matsuta, K.; Miyamoto, T.; Inoue, K. *J. Biochem.* **1989**, *105*, 395. (b) Seilhamer, J. J.; Pruzanski, W.; Vadas, P.; Plant, S.; Miller, J. A.; Kloss, J.; Johnson, L. K. *J. Biol. Chem.* **1989**, *264*, 5335. (c) Kramer, R. M.; Hession, C.; Johansen, B.; Hayes, G.; McGray, P.; Chow, E. P.; Tizard, R.; Pepinsky, R. B. *J. Biol. Chem.* **1989**, *264*, 5768.
21. (a) Wery, J.-P.; Schevitz, R. W.; Clawson, D. K.; Bobbitt, J. L.; Dow, E. R.; Gamboa, G.; Goodson, Jr., T.; Hermann, H. B.; Kramer, R. M.; McClure, D. B.; Mihelich, E. D.; Putnam, J. E.; Sharp, J. D.; Stark, D. H.; Teater, C.; Warrick, M. W.; Jones, N. D. *Nature* **1991**, *352*, 79. (b) Scott, D. L.; White, S. P.; Browning, J. L.; Rosa, J. J.; Gelb, M. H.; Sigler, P. B. *Science* **1991**, *254*, 1007.
22. A group at Lilly has recently reported the elegant use of related structural information in the design of indole-based PLA_2 inhibitors; see: Schevitz, R. W.; Bach, N. J.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Dillard, R. D.; Draheim, S. E.; Hartley, R. W.; Jones, N. D.; Mihelich, E. D.; Olkowski, J. L.; Snyder, D. W.; Sommers, C.; Wery, J.-P. *Nature Structural Biology* **1995**, *2*, 458.
23. (a) Jain, M. K.; Ghomaschi, F.; Yu, B.-Z.; Bayburt, T.; Murphy, D.; Houck, D.; Brownell, J.; Reid, J. C.; Solowiej, J. E.; Wong, S.-M.; Mocek, U.; Jarrell, R.; Sasser, M.; Gelb, M. H. *J. Med. Chem.* **1992**, *35*, 3584. (b) Gelb, M. H.; Jain, M. K.; Berg, O. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1335. (c) Yu, L.; Dennis, E. A. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1343. (d) For general comments regarding lipase interactions

with organized lipid surfaces see: Blow, D. *Nature* **1991**, *351*, 444.
24. For examples see: (a) Musser, J. H.; Kreft, A. F.; Failli, A. A.; Demerson, C. A.; Shah, U. S.; Nelson, J. A. International Patent Publication **1991**, WO91/06537. (b) Failli, A. A.; Kreft, A. F.; Musser, J. H.; Banker, A. L.; Nelson, J. A.; Shah, U. S. US Patent **1991**, 5,071,988. (c) Djuric, S. W.; Haack, R. A.; Miyashiro, J. M. International Patent Publication, **1992**, WO92/21644. (d) Tramposch, K. M.; Steiner, S. A.; Stanley, P. L.; Nettleton, D. O.; Franson, R. C.; Lewin, A. H.; Carroll, F. I. *Biochem. Biophys. Res. Commun.* **1992**, *189*, 272. (e) Kohler, T.; Heinisch, M.; Kirchner, M.; Peinhardt, G.; Hirschelmann, R.; Nuhn, P. *Biochemical Pharmacology* **1992**, *44*, 805. (f) LeMahieu, R. A.; Carson, M.; Han, R.-J.; Madison, V. S.; Hope, W. C.; Chen, T.; Morgan, D. W.; Hendrickson, H. S. *J. Med. Chem.* **1993**, *36*, 3029. (g) Beaton, H. G.; Bennion, C.; Connolly, S.; Cook, A. R.; Gensmantel, N. P.; Hallam, C.; Hardy, K.; Hitchin, B.; Jackson, C. G.; Robinson, D. H. *J. Med. Chem.* **1994**, *37*, 557. (h) Carson, M.; Han, R.-J.; LeMahieu, R. A.; Madison, V. S. US Patent **1994**, 5,298,652. (i) Pisabarro, M. T.; Ortiz, A. R.; Palomer, A.; Cabre, F.; Garcia, L.; Wade, R. C.; Gago, F.; Mauleon, D.; Carganico, G. *J. Med. Chem.* **1994**, *37*, 337. (j) Wheeler, T. N.; Blanchard, S. G.; Andrews, R. C.; Fang, F.; Gray-Nunez, Y.; Harris, C. O.; Lambert, M. H.; Mehrotra, M. M.; Parks, D. J.; Ray, J. A.; Smalley, Jr., T. L. *J. Med. Chem.* **1994**, *37*, 4118. (k) Potts, B. C. M.; Faulkner, D. J. *J. Nat. Prod.* **1992**, *55*, 1701. (l) Tanaka, K.; Matsutani, S.; Kanda, A.; Kato, T.; Yoshida, T. *J. Antibiotics* **1994**, *47*, 631. (m) Barnette, M. S.; Rush, J.; Marshall, L. A.; Foley, J. J.; Schmidt, D. B.; Sarau, H. M. *Biochem. Pharmacol.* **1994**, *47*, 1661. (n) Carganico, G.; Mauelon, D.; Garcia, M. L. International Patent Publication **1993**, WO93/21211. (o) Marki, F.; Breitenstein, W.; Beriger, E.; Bernasconi, R.; Caravatti, G.; Francis, J. E.; Paioni, R.; Wehrli, H. U.; Wiederkehr, R. *Agents Actions* **1993**, *38*, 202. (p) Pruzanski, W.; Greenwald, R. A.; Street, I. P.; Laliberte, F.; Stefanski, E.; Vadas, P. *Biochem. Pharmacol.* **1992**, *44*, 1165. (q) Garst, M. E. *Curr. Opin. Ther. Pat.* **1992**, 400. (r) Schiehser, G. A.; Von Burg, G. F. US Patent **1991**, 5,070207. (s) Marshall, L. A.; Steiner, K. E.; Schiehser, G. A. US Patent **1990**, 4,933,365.
25. (a) Burke, J. R.; Gregor, K. R.; Tramposch, K. M. *J. Biol. Chem.* **1995**, *270*, 274. (b) For a complete discussion of the 'scooting-mode' assay see: Gelb, M. H.; Berg, O.; Jain, M. K. *Curr. Opin. Struct. Biol.* **1991**, *1*, 836.
26. Springer, D. M.; Luh, B.-Y.; Greene, K. M.; Bronson, J. J.; Mansuri, M. M. Biaryl Phospholipase A_2 Inhibitors. US Patent **1995**, 5,391,817.
27. Kessar, S. V.; Gupta, Y. P.; Mohammad, T.; Khurana, A.; Sawal, K. K. *Heterocycles* **1984**, *22*, 2723.
28. We initially attempted a more concise strategy for the synthesis of compounds in the $n=2$ unsaturated series illustrated by **43**. Wittig reaction of aldehyde **8** provided the expected unsaturated diester (an intermediate in the synthesis of **38**). It was hoped that demethylation of this intermediate would provide a phenol suitable for Mitsunobu coupling to a variety of alcohols. Unfortunately, treatment of the above Wittig product with Me_2BBr resulted in the loss of the olefin, with retention of the methoxy group. (It is possible that intramolecular Friedel–Crafts cyclization of the unsaturated ester occurred to give products containing a fluorene nucleus, but this has not been rigorously determined.)
29. For comparison purposes, the IC_{50} of manoalide has been determined to be 20 nM against the non-pancreatic 14 kDa PLA_2 isolated from human synovial fluid; Marshall, L. A.; Bauer, J.; Sung, M. L.; Chang, J. Y. *J. Rheumatol.* **1991**, *18*, 59), and 3.2 μM against the non-pancreatic enzyme isolated from human polymorphonuclear leukocytes (Marki, F.; Breitenstein, W.; Beriger, E.; Bernasconi, R.; Caravatti, G.; Francis, J. E.; Paioni, R.; Wehrli, H. U.; Wiederkehr, R. *Agents Actions* **1993**, *38*, 202.
30. (a) Tramposch, K. M.; Chilton, F. H.; Stanley, P. L.; Franson, R. C.; Havens, M. B.; Nettleton, D. O.; Davern, L. D.; Darling, I. M.; Bonney, R. J. *J. Pharmacol. Expt. Therapeut.* **1994**, *271*, 852. (b) Stanley, P. L.; Steiner, S.; Havens, M.; Tramposch, K. M. *Skin Pharmacol.* **1991**, *4*, 262.
31. Bradley, P. P.; Priebat, D. A.; Christensen, R. D.; Rothstein, G. *J. Invest. Derm* **1982**, *78*, 206.
32. The compounds tested in the chronic inflammation in vivo assay (**2**, **4**, **28**, **36b**, **36i**) were not evaluated as potential inhibitors of MPO in a control experiment. Thus, the possibility exists that some (or all) of the in vivo activity reported for these compounds in the tables is a consequence of direct inhibition of the enzyme marker MPO rather than a reflection of reduced influx of neutrophils (PMNs). However, animals treated with compound **28** had significant, dose-dependent ear weight reductions that paralleled the measured reduction of myeloperoxidase activity. This implies that the drug is reducing general hyperplasia (and inflammation), and that it is not acting simply as a MPO inhibitor. Many other structurally similar (but non-biaryl) compounds were evaluated in the chronic assay for both ear weight reduction and inhibition of MPO activity. The compounds tested almost always displayed ear weight reductions that paralleled the measured reduction of myeloperoxidase activity.
33. In general, compounds with IC_{50}s against the human enzyme <20 μM were resynthesized for evaluation in the chronic in vivo assay. However, since compound **28** was one of the first compounds synthesized from this general biaryl structural class, and it was easy to synthesize on the 250 mg scale required for evaluation of a compound in the 10-day chronic assay, it was tested despite the poor IC_{50} against the human enzyme. Compound **36h**, the most active derivative in vitro reported here ($IC_{50}=2$ μM), was not evaluated in vivo in the chronic assay due to its erratic behavior in a whole-cell assay that measured arachidonic acid release from PMNs stimulated with ionophore A23187 (calcimycin). (For details regarding this assay see ref 30. The erratic behavior (non-dose response) of **36h** in this assay was attributed to possible toxicity due to surfactant effects on the PMN cell membranes.) Many compounds were tested in the PMN arachidonic acid release assay from different structural series, but only four compounds from the biaryl diacid class were tested. The IC_{50} for **36h** could not be determined, but the remaining IC_{50}s are as follows: **2** = 4 μM; **36i** = 2 μM; and **36b** = 20 μM. Activity in this assay can be viewed as evidence for cellular penetration of the test compounds, and inhibitory activity towards the desired enzymatic target (PLA_2), although other explanations are possible.
34. Saa, J. M. *J. Org. Chem.* **1992**, *57*, 678.
35. Dawson, M. I.; Hobbs, P. D.; Dorsky, A.; Morimoto, H. *J. Labelled Compounds and Radiopharmaceuticals* **1990**, *28*, 89.