Articles

(Carboxyalkyl)benzyl Propargyl Ethers as Selective Inhibitors of Leukocyte-Type 12-Lipoxygenases

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A series of (carboxyalkyl)benzyl propargyl ethers was synthesized and tested as inhibitors of 12-lipoxygenase (12-LO) from porcine leukocyte cytosol. Optimum activity was displayed by 3-[4-[(2-tridecynyloxy)methyl]phenyl]propanoic acid. Altering the length of the alkyl side chain attached to the acetylenic group reduced activity. Changing the substitution pattern in the (carboxyalkyl)benzyl group from *para* to *meta* or *ortho* also reduced activity. Analogs in which the triple bond was replaced by a double bond or an allene displayed reduced activity, whereas fully saturated analogs were inactive. High concentrations (10 μM) of the most potent acetylenic (carboxylalkyl)benzyl ethers did not inhibit human platelet 12-LO, human neutrophil 5-LO, rabbit reticulocyte 15-LO, or soybean 15-LO. Thus, this class of compounds represents the first example of isoform specific LO inhibitors.

Lipoxygenases (LO) are among the oldest and most extensively studied enzymes of plant and animal metabolism.[1,2] The reaction they catalyze is the stereospecific oxygenation of polyunsaturated fatty acids to hydroperoxy fatty acids (Figure 1).[3] Multiple isoforms exist in both the plant and animal kingdom that differ in substrate specificity and position of oxygenation.[4−8] Mammalian LO's preferentially oxygenate arachidonic acid, and different LO's insert oxygen at the 5, 8, 12, and 15 positions.[7] All LO's are non-heme iron-containing proteins (one atom per molecule), and the mammalian enzymes are approximately 70 kDa in size.[7,8] The iron cycles between the ferric and ferrous oxidation states during catalytic turnover, and the ferric form represents the catalytically active form of the resting enzyme.[9,10]

The physiological function of individual mammalian LO's is uncertain aside from 5-LO, which catalyzes the first step of leukotriene biosynthesis.[11] Potential functions for the products of other mammalian LO's include control of cell proliferation, platelet aggregation, cell adhesion, tumor metastasis, and atherosclerosis *inter alia*.[12−15] Our laboratories have been particularly interested in 12-LO's because of their potential involvement in cell adhesion, endothelial cell retraction, and tumor metastasis.[16−19] Two isoforms of 12-LO exist in mammals that are the products of different genes and exhibit differences in tissue distribution, substrate specificity, and immunochemical reactivity.[7,20] The leukocyte-type enzyme is the product of an 8-kb gene that is expressed in inflammatory cells, small intestine, and neural tissue.[21,22] The enzyme oxygenates a number of polyunsaturated fatty acids at nearly equivalent rates,[23] The platelet-type enzyme is the product of a 15-kb gene that is expressed in platelet and epidermis.[24−27] This enzyme oxygenates arachidonic acid at a higher rate than other polyunsaturated fatty acids.[28] There is 58% identity between leukocyte-type and platelet-type 12-LO.[21]

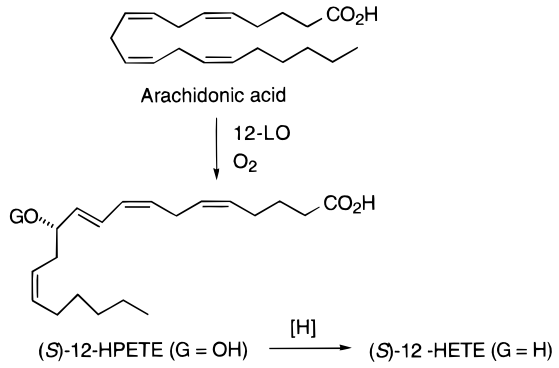

Figure 1. Oxidation of arachidonic acid to (*S*)-12-hydroperoxyeicosatetraenoic acid (HPETE) and conversion to (*S*)-12-hydroxyeicosatetraenoic acid (HETE).

Specific 12-LO inhibitors would be useful tools for differentiating the physiological roles of the two enzymes and may serve as lead compounds for drug development. No specific 12-LO inhibitors have been described, and in fact, many inhibitors that are specific for a given LO exhibit some activity against other LO isoforms.[29−31] Therefore, we attempted to design a series of molecules that would be selective inhibitors of 12-LO's but not of 5- or 15-LO's. Since phenols and hydroxamates react with the iron center of the enzymes,[29,32] we felt they would be poor choices as potentially specific inhibitors. The other major class of molecules that inhibit lipoxygenases is acetylenic fatty acid analogs.[33] These molecules are believed to be substrates for oxidation by lipoxygenases that lead to enzyme inactivation during turnover.[33−35] Most of the acetylenic fatty acids that have been described inhibit a range of lipoxygenases, but Corey and associates have reported that certain monoacetylenic fatty acids selec-

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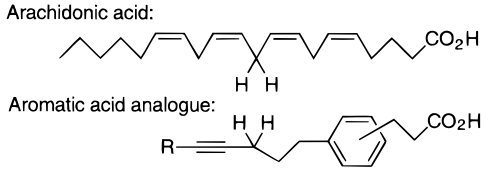
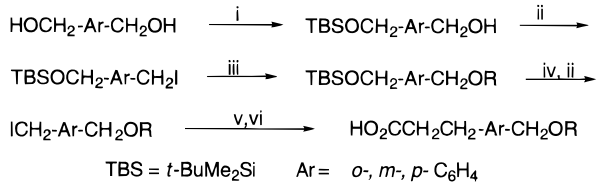


Figure 2. Design of arachidonic acid analogs as 12-LO substrate mimics.

Scheme 1. Method A[a]



[a] (i) TBSCl, imidazole, DMF, 12 h, 25 °C; (ii) Ph_3P, imidazole, I_2, CH_3CN-Et_2O, 1 h, 25 °C; (iii) RONa, THF, 12 h, 25 °C; (iv) HF, pyridine, CH_3CN, 12 h, 25 °C; (v) CH_3COO-*t*-Bu, lithium diisopropylamide, THF, −78 °C, 1 h; (vi) CF_3CO_2H, CH_2Cl_2, 20 h, 25 °C.

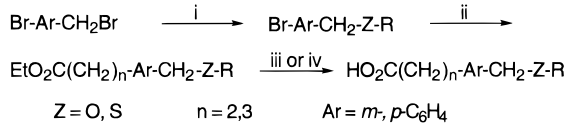
tively inactivate individual lipoxygenases.[36−38] Thus, we designed acetylenic substrate analogs that might serve as mechanism-based inactivators. Since 12-LO abstracts the 10(*pro-S*)-hydrogen atom in the first step of arachidonic acid oxygenation, we introduced a potentially reactive hydrogen atom appropriately positioned in a fatty acid analog (Figure 2). The methylene group containing this hydrogen atom was positioned between an acetylenic group and a heteroatom to increase the reactivity of the methylene hydrogen. Finally, we introduced a phenyl ring at a position approximately equivalent to the 5,6-double bond of arachidonic acid. Elaboration of this model quickly identified a series of molecules that were not only specific for 12-LO but, in fact, were nearly a 1000-fold selective for leukocyte-type 12-LO as opposed to platelet-type 12-LO.

Results

Chemistry. 1. Phenylpropanoic and Phenylbutanoic Acids. In the first approach (Scheme 1, method A), benzenedimethanols were monoprotected by treatment with 1 equiv of TBSCl followed by treatment with triphenylphosphine/iodine/imidazole[39] to produce benzyl iodides. Ethers were prepared by a standard Williamson synthesis. Subsequent removal of the silyl protection with hydrofluoric acid in acetonitrile was followed by iodination of the resulting alcohols. The final elongations were carried out in THF at −78 °C using 1.1 equiv of the lithium enolate of *tert*-butyl acetate and quenching at the same temperature after 1 h. The resulting esters were hydrolyzed by treatment with trifluoroacetic acid in dichloromethane or lithium hydroxide in methanol and water to afford the propanoic acid.

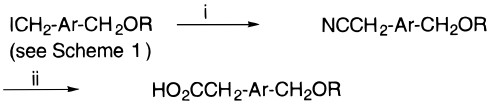
In the second approach (Scheme 2, method B), bromobenzyl bromides were converted to ethers or sulfides utilizing previously prepared long chain alcohols or thiols. The zinc reagents from ethyl 3-iodopropanoate and ethyl 4-iodobutanoate were prepared by treatment with an excess of zinc−copper couple.[40] This was followed by the addition of the aryl bromide and a catalytic amount of palladium(0). The reaction mixture was stirred at reflux for a 12-h period. The success of this palladium(0) coupling procedure was found to be

Scheme 2. Method B[a]



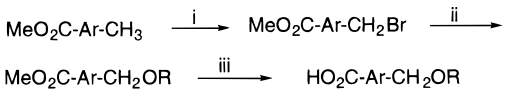
[a] (i) RZNa, THF, 12 h, 25 °C; (ii) $I(CH_2)_nCOOEt$, ZnCu, toluene−dimethylacetamide, 4 h, 60 °C, $Pd(Ph_3P)_4$, 24 h; (iii) NaOH, MeOH, 5 h, 25 °C; (iv) LiOH, THF, H_2O, 12 h, Δ.

Scheme 3. Method C[a]



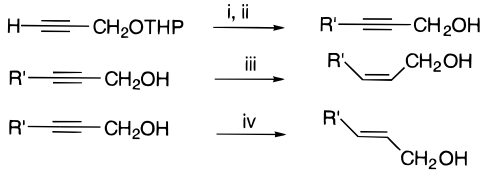
[a] (i) NaCN, DMF, 10 h, 25 °C; (ii) KOH, MeOH, H_2O, 24 h, Δ.

Scheme 4. Method D[a]



[a] (1) NBS, benzoyl peroxide, CCl_4, 12 h, Δ; (ii) R-ONa, THF, 12 h, 25 °C; (iii) LiOH, THF, H_2O, 15 h, 25 °C.

Scheme 5[a]



[a] (i) *n*-BuLi, RI, THF, hexamethylphosphoramide (HMPA), 1 h, 0 °C; (ii) *p*-TsOH, MeOH, 25 °C; (iii) H_2, $Pd/CaCO_3$ (lead poisoned), EtOAc, 25 °C, 10 h; (iv) $LiAlH_4$, Et_2O, reflux, 24 h.

strongly dependent upon the length and position of the lipophilic chain. The best results were obtained for the smallest lipophilic chains in a *para* position relative to the bromide. *Ortho*-substituted starting materials were found resistant to the coupling conditions and were fully recovered after treatment. The syntheses of arylpropanoic or arylbutanoic acid derivatives were completed by alkaline hydrolyses of the corresponding esters in methanol.

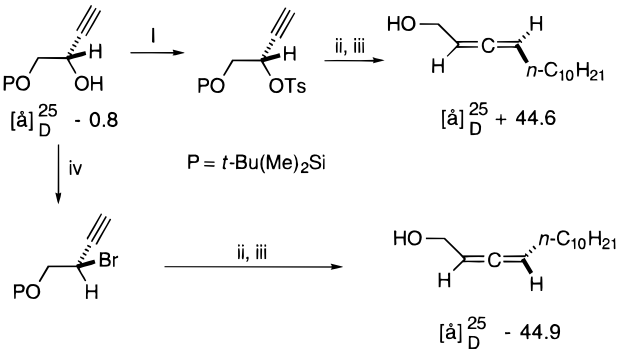
2. Phenylacetic Acids. Various phenylacetic acids were prepared by treatment of the appropriate benzyl iodide (see Scheme 1) with NaCN followed by hydrolysis with KOH/MeOH (Scheme 3, method C).

3. Benzoic Acids. The sequence was started with the NBS bromination of methyl 4-methylbenzoate. The resulting benzyl bromides were treated with the appropriate alcoholate side chain followed by alkaline hydrolysis to provide the desired benzoic acid derivatives (Scheme 4, method D).

4. Lipophilic Side Chains. Various alkynol side chains were elaborated from the readily available THP derivative of propargyl alcohol (Scheme 5). The related *cis*-allylic alcohols were obtained by partial hydrogenation, whereas the corresponding *trans*-alcohols were prepared by treatment of the alkynols with a 2-fold excess of $LiAlH_4$.[41]

On the basis of the precedent that various organometallic reagents react with chiral propargylic derivatives to form optically active allenes,[42] it was decided to base our approach on the previously described propargyl alcohol[42] shown in Scheme 6. To prepare the dextrorotatory allene, the alcohol was treated with

Scheme 6[a]



[a] (i) TsCl, Et_3N, CH_2Cl_2, 25 °C, 17 h; (ii) *n*-$C_{10}H_{21}$MgBr, CuBr–dimethyl sulfide, tetrahydrofuran, 0 °C, 0.25 h; (iii) tetrabutylammonium fluoride, THF, 25 °C, 2 h; (iv) Ph_3P, pyridine, CBr_4, THF, 25 °C, 1 h.

p-toluenesulfonyl chloride and triethylamine in dichloromethane to give the tosylate. The latter was subsequently subjected to copper-catalyzed Grignard addition of decylmagnesium bromide to afford the protected α-allenic alcohol. Further treatment with tetrabutylammonium fluoride in THF gave the desired dextrorotatory allenoic alcohol. (The enantiomeric purity was determined to be >98% ee by ^{19}F (282 MHz) NMR spectroscopy of the corresponding Mosher ester.[43]) The levorotatory form was prepared by bromination of the starting propargyl alcohol using carbon tetrabromide–triphenylphosphine[44] in THF containing pyridine. The resulting bromide was converted to the enantiomeric allenic alcohol by the same procedure as described above.

Enzymology. Cytosolic fractions from porcine leukocytes and human platelets were used in a radiochemical assay that measured the conversion of [1-^{14}C]-arachidonic acid to 12-HPETE and its reduction product 12-HETE. An amount of enzyme was used that would convert approximately 30–50% of 5 μM arachidonate to products. This concentration is near the K_m's of both enzymes so that competitive as well as irreversible inhibitors could be detected. Inhibitor and enzyme were preincubated for 5 min at 37 °C; then arachidonate was added. Reactions were terminated after 15 min, and the products and remaining starting material were extracted and separated by TLC. The extent of conversion was determined with a TLC radioactivity scanner. Compounds were initially evaluated at 1 and 10 μM concentrations, and if inhibition was observed, an IC_{50} was determined. All incubations were carried out in triplicate, and IC_{50}'s were repeated to verify their accuracy.

The initial compound tested was **1a**; the features that went into its design are outlined above. Compound **1a** exhibited very weak activity, but substitution of O for sulfur as in **1b** improved the inhibitory potency somewhat (Table 1). The ability to inhibit 12-LO was quite dependent on the orientation of the propanoic acid residue on the phenyl ring, as indicated by the compounds **1c**, **2**, and **3d** (Table 2). *Para* substitution led to the most potent inhibitors and *ortho* substitution the least potent.

A dramatic dependence on the length of the alkyl side chain was observed (Table 2). A 60-fold increase in potency accompanied the lengthening of the chain from hexyl to decyl (**3b** vs **3d**). Increasing the length beyond

Table 1. *Meta*- and *Ortho*-Substituted Phenylpropanoic Acids

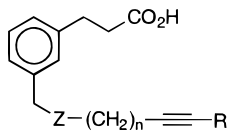
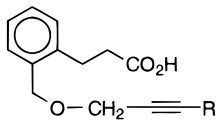
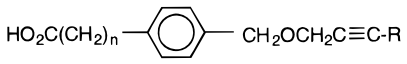
Compound				Method	IC_{50} (μm)
					
1	Z	n	R		
a	S	1	*n*-C_8H_{17}	A	>10
b	O	1	*n*-C_8H_{17}	A	10
c	O	1	*n*-$C_{10}H_{21}$	B	0.32
d	O	1	*n*-C_6H_{13}	B	>10
e	O	2	*n*-C_5H_{11}	B	>10
					
2	R = *n*-$C_{10}H_{21}$			A	5

Table 2. *Para*-Substituted Phenylbutanoic, Phenylpropanoic, Phenylacetic, and Benzoic Acids **3**



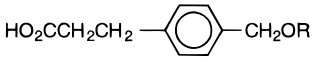
3

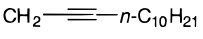
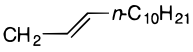
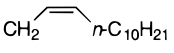
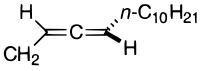
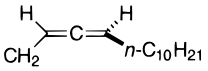
compound				
	n	R	method	IC_{50} (μM)
3a	3	*n*-$C_{10}H_{21}$	B	>10
3b	2	*n*-C_6H_{13}	A	2.0
3c	2	*n*-C_8H_{17}	A	0.10
3d	2	*n*-$C_{10}H_{21}$	B	0.035
3e	2	*n*-$C_{12}H_{25}$	A	0.32
3f	2	*n*-$C_{14}H_{29}$	A	>10
3g	2	$Ph(CH_2)_4$	A	5.0
3h	1	*n*-$C_{10}H_{21}$	C	0.05
3i	0	*n*-$C_{10}H_{21}$	D	0.06
3j	0	*n*-C_7H_{15}	D	6.0
3k	0	*n*-$C_{14}H_{29}$	D	>10

decyl, e.g., **3e**,**f**, reduced inhibitor efficacy. Thus, in most subsequent syntheses, the length of the ω alkyl chain was fixed at 10 carbons. Substitution of phenyl in the alkyl chain, see **3g**, produced a relatively poor inhibitor. Shortening the carboxyalkyl chain from arylpropionyl to benzoyl had relatively little effect on inhibitory potency (**3d**,**h**,**i**), whereas lenghthening it to arylbutyryl significantly decreased potency (**3a**).

The importance of the triple bond was investigated with the series of compounds listed in Table 3. Substitution of a double bond for the triple bond, cf. **4** and **5** vs **3d**, reduced activity approximately 10–100-fold. The *trans*-isomer **4** was approximately 6 times more active than the *cis*-isomer **5**. Complete reduction to the hydrocarbon as in **8** eliminated activity up to 10 μM. Enantiomeric allenes **6** and **7** were synthesized that demonstrated approximately 10-fold less activity than **3d**. However, these compounds each contain one extra carbon in the ω side chain of the molecule relative to **3d**, and as discussed above, inhibitory potency was very sensitive to the length of this side chain. Incorporation of the extra carbon may have contributed to the decrease in activity. The data in Table 3 indicate that for

Table 3. Effect of Various Unsaturations in the Lipophilic Chain



	R	Method	IC_{50} (μm)
3d		B	0.035
4		A	0.04
5		A	2.5
6	 (*S*)	A	0.28
7	 (*R*)	A	0.45
8	$CH_2CH_2CH_2$-*n*-$C_{10}H_{21}$	A	> 10

maximal activity a double or triple bond is required in a side chain.

All of the compounds described above were also tested against the human platelet cytosol 12-LO. No inhibition of activity was detected with any of the compounds at concentrations as high as 10 μM. A limited number of the more potent inhibitors of leukocyte-type 12-LO were also tested against human neutrophil 5-LO and rabbit reticulocyte 15-LO but were inactive at 10 μM. Thus, the (carboxyalkyl)benzyl propargyl ethers described herein appeared to be highly selective for leukocyte-type 12-LO. For comparison, 5,8,11,14-eicosatetraynoic acid (ETYA) was tested against our porcine leukocyte and human platelet 12-LO's preparations. ETYA inhibited leukocyte-type 12-LO with an IC_{50} of 0.05 μM and platelet-type 12-LO with an IC_{50} of 0.5 μM. These findings underscore the potency and selectivity of the acetylenic (carboxyalkyl)benzyl ethers against porcine leukocyte 12-LO.

Discussion

Acetylenic analogs of polyunsaturated fatty acids have long been recognized as inhibitors of fatty acid oxygenases such as lipoxygenase and cyclooxygenase.[33,35,45] In most cases, these acetylenic compounds inhibit one or more LO's and cyclooxygenase, but certain acetylenic arachidonic acid analogs have been described as selective inhibitors of different LO isoenzymes.[36−38,46,47] The series of substituted (carboxyalkyl)benzyl ethers described in the present study represent a series of potent and selective inhibitors of leukocyte-type 12-LO. The key structural features required for potent inhibition include a methylene group between the benzyl ether and a site of unsaturation (preferably a triple bond), a decyl side chain attached to the acetylenic group, and *para* substitution in the substituted benzyl ether.

A high degree of selectivity within this series of compounds was observed for inhibition of leukocyte-type 12-LO. No inhibition of human platelet-type 12-LO, human neutrophil 5-LO, rabbit reticulocyte 15-LO, soybean 15-LO, or sheep seminal vesicle cyclooxygenase was observed at concentrations as high as 10 μM. This series of compounds appears to be the most selective group of LO inhibitors described to date. Particularly striking is the lack of inhibitory activity against the platelet-type 12-LO. Substrate specificity studies of the two LO isoenzymes indicate that the leukocyte-type enzyme will act on a much broader range of polyunsaturated fatty acid than will the platelet-type enzyme.[5,7,23] This suggests that the leukocyte-type enzyme has a more accommodating substrate access channel than the platelet-type enzyme. Thus, the leukocyte-type enzyme may bind substrate analogs more easily than the platelet-type enzyme does.

Acetylenic inhibitors of LO and cyclooxygenase are believed to act as reactive substrate analogs that generate oxidants during turnover leading to loss of enzyme activity.[33−35] The (carboxyalkyl)benzyl ethers prepared in this study were designed based on this premise, and the structure−activity for inhibition that we have determined is consistent with the hypothesis that they are mechanism-based inhibitors.

Deuteration of the methylene group between the ether oxygen and the triple bond in the parent compound **3d** did not affect inhibitory potency, which one might have expected if oxidation of the methylene group was a key step in LO inhibition (G. Gorin and L. Kuhnert, unpublished results). For example, 15-LO from soybeans exhibits an extraordinarily high isotope effect ($k_H/k_D \sim 80$) for hydrogen removal from linoleic acid.[48] However, the magnitude of the isotope effect observed depends on temperature, viscosity, etc.[48] Furthermore, detailed kinetic studies similar to those reported for the plant LO's have not been reported for any of the mammalian LO's so the magnitude of kinetic isotope effects for hydrogen removal from substrates or potential inhibitors is not known. Thus, it is hard to predict whether deuteration should alter the rate of inhibitor oxidation and LO inactivation.

The present work defines the structural requirements for inhibition of leukocyte-type 12-LO by a novel series of acetylenic arachidonic acid analogs that are the first to display specificity for a single LO isoform. These compounds or derivatives elaborated from them should be useful in exploring the role of leukocyte 12-LO in physiological and pathophysiological processes.

Experimental Section

Materials. Enzymology: Preparation of Porcine Leukocyte and Human Platelet Cytosol. The assay mixture contained porcine leukocyte or human platelet cytosol (75 μg/mL) in 100 mM HEPES, 2 mM $CaCl_2$, and 1 mM $MgCl_2$, pH 8.0, in a total volume of 100 μL. Inhibitors were added in 3 μL of DMSO and preincubated for 5 min at 37 °C. [1-^{14}C]-Arachidonic acid was added to a final concentration of 5 μM, and the reactions were allowed to proceed for 15 min. Dilute HCl was added to acidify, and unlabeled 12-HETE (5 μM) and arachidonic acid (100 μM) were added as carrier. The samples were extracted with water-saturated ethyl acetate, and an aliquot was spotted onto silica gel TLC plates. The plates were developed with dichloromethane/ethyl acetate/acetic acid, 70/30/1. The R_f's of 12-HETE and arachidonic acid in this solvent system were 0.30 and 0.45, respectively. The percentage conversion to 12-HETE was calculated from the percentage of the total ^{14}C on the TLC plate that coleuted with a standard of 12-HETE.

Synthesis. Phenylpropanoic Acid Derivatives. Method A: [4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]phenyl]methanol. A flask was charged with 3.00 g of a 60% dispersion of NaH in oil. The dispersion was washed with three 10-mL portions of THF. The NaH was suspended in 70 mL of THF and cooled to 0 °C, followed by the slow addition of a solution of 1,4-benzenedimethanol (Aldrich) (8.50 g, 62 mmol) in THF

(10 mL) to the mixture. After 25 min at 0 °C, an additional 40-mL portion of THF was added to the mixture, and the cold bath was removed. The reaction mixture was stirred at 25 °C for 30 min and then recooled to 0 °C. At this time, *tert*-butyldimethylsilyl chloride (10.19 g, 68.20 mmol, 1.1 equiv) was added to the mixture. The solution was allowed to warm to 25 °C over a 1-h period and was stirred at this temperature for an additional 12 h. The mixture was poured into 50 mL of water and extracted with three 50-mL portions of ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a yellow oil. Purification by flash silica gel chromatography (85:15 petroleum ether/EtOAc) yielded 9.6 g (50%) of the monoprotected title compound as a clear oil: R_f 0.62 (8:2 petroleum ether/EtOAc); IR (neat) 3550−3100 (b, OH), 3000, 2800, 1600, 1493, 1256, 1192, 1131, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (s, 4 H), 4.75 (s, 2 H), 4.60 (d, J = 5.4 Hz, 2 H), 2.60 (s, 1 H), 0.97 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 140.89, 139.77, 127.12, 126.39, 65.07, 64.95, 26.11, 18.57, −5.08. Anal. ($C_{14}H_{24}O_2Si$) C, H.

1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4-(iodomethyl)benzene. A flask was charged with Ph_3P (3.93 g, 15 mmol, 1.5 equiv), imidazole (1.24 g, 20 mmol, 2 equiv), and a 3/1 mixture of Et_2O/CH_3CN (100 mL). The mixture was stirred until dissolution was complete. At this time, I_2 (3.81 g, 15 mmol, 1.5 equiv) was added, and vigorous stirring was continued until a yellow suspension formed. A solution of the above benzyl alcohol (3.58 g, 10 mmol) in 10 mL of the same solvent was then added. After 1 h, the mixture was concentrated in vacuo, the resulting crude material was taken up into 100 mL of hexane, and the solution was washed with 100 mL of a saturated solution of sodium bisulfite. The aqueous solutions were back-extracted with two 100-mL portions of hexane. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a yellow oil. Purification by flash silica gel chromatography (95:5 petroleum ether/EtOAc) afforded 4.40 g (93%) of the iodo derivative as a clear colorless oil: R_f 0.85 (9:1 petroleum ether/EtOAc); IR (neat) 2957, 2929, 2858, 1470, 1372, 1252, 1047, 836, 780, 667, 562, 527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2 H), 7.26 (d, J = 8.1 Hz, 2 H), 4.71 (s, 2 H), 4.47 (s, 2 H), 0.96 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 141.28, 137.78, 128.63, 126.39, 64.60, 25.95, 5.89, −5.25.

***cis*-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4-[(2-tridecenyloxy)methyl]benzene.** A flask was charged with 60 mg of a 60% dispersion of NaH in oil. The dispersion was washed with three 2-mL portions of THF. The NaH was suspended in 5 mL of THF and cooled to 0 °C. A solution of *cis*-2-tridecen-1-ol (206 mg, 1.1 mmol, 1.1 equiv) in THF (1 mL) was slowly added to the mixture. After 25 min the cold bath was removed, and stirring was continued for an additional 10 min. At this time a solution of the above benzyl iodide (361 mg, 1 mmol) in THF (1 mL) was added, and stirring was continued for 12 h. The mixture was poured into water (20 mL) and ether (25 mL). The organic layer was separated and washed with three 10-mL portions of water. The ether extract was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield a yellow oil. Purification by flash silica gel chromatography (95:5 petroleum ether/EtOAc) afforded 341 mg (85%) of the title compound as a clear colorless oil: R_f 0.80 (9:1 petroleum ether/EtOAc); IR (neat) 3013, 2929, 2851, 1682, 1654, 1463, 1252, 1090, 836, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (s, 4 H), 5.61 (m, 2 H), 4.76 (s, 2 H), 4.52 (s, 2 H), 4.08 (d, J = 4.8 Hz, 2 H), 2.05 (m, 2 H), 1.29 (m, 16 H), 0.97 (s, 9 H), 0.91 (t, J = 6.9 Hz, 3 H), 0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 140.76, 137.04, 127.71, 126.04, 125.98, 71.86, 65.58, 64.80, 31.92, 29.62, 29.56, 29.52, 29.24, 29.36, 27.61, 25.94, 22.69, 18.57, 14.12, −5.25. Anal. ($C_{27}H_{48}O_2Si$) C, H.

***cis*-[4-[(2-Tridecenyloxy)methyl]phenyl]methanol.** To a solution of the above silyl ether (341 mg, 0.84 mmol) in CH_3CN (10 mL) was added 50% aqueous HF (1 mL); the mixture was stirred at room temperature for 15 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (50 mL) and ether (75 mL). The organic layer was separated, washed with two 50-mL portions of water, dried ($MgSO_4$), and concentrated to yield the title compound (290 mg, 98%) as a colorless oil: R_f 0.24 (9:1 petroleum ether/EtOAc); IR (neat) 3393, 3013, 2921, 2851 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 4 H), 5.60 (m, 2 H), 4.63 (s, 2 H), 4.49 (s, 2 H), 4.07 (d, J = 5.1 Hz, 2 H), 2.39 (s, 2 H), 2.04 (q, J = 6.6 Hz, 2 H), 1.27 (m, 16 H), 0.89 (t, J = 6.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 140.49, 137.82, 134.24, 128.10, 127.12, 125.94, 71.88, 65.85, 65.03, 32.03, 29.76, 29.66, 29.48, 29.37, 27.73, 22.82, 14.24. Anal. ($C_{21}H_{34}O_2$) C, H.

***cis*-1-(Iodomethyl)-4-[(2-tridecenyloxy)methyl]benzene.** A flask was charged with Ph_3P (314 mg, 1.2 mmol, 1.5 equiv), imidazole (109 mg, 1.6 mmol, 2 equiv), and 10 mL of a 3/1 mixture of Et_2O/CH_3CN. The resulting mixture was stirred until dissolution was complete. At this time, I_2 (305 mg, 1.2 mmol, 1.5 equiv) was added, and vigorous stirring was continued until a yellow suspension formed, and a solution of the above alcohol (250 mg, 0.8 mmol) in 1 mL of the same solvent was then added. After 1 h, the mixture was concentrated in vacuo, and the resulting yellow oil was taken up into 50 mL of hexane and 30 mL of a saturated solution of sodium bisulfite; this was extracted with two 30-mL portions of hexane. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a yellow oil. Purification by flash silica gel chromatography (95:5 petroleum ether/EtOAc) afforded 350 mg (93%) of the title iodo derivative as a clear colorless oil: R_f 0.75 (9:1 petroleum ether/EtOAc); ^1H NMR ($CDCl_3$) δ 7.33 (d, J = 8.1 Hz, 2 H), 7.18 (d, J = 8.1 Hz, 2 H), 5.62 (m, 2 H), 4.45 (s, 2 H), 4.40 (s, 2 H), 4.05 (d, J = 5.1 Hz, 2 H), 2.05 (m, 2 H), 1.37 (m, 16 H), 0.91 (t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.50, 138.69, 134.26, 128.91, 128.28, 125.97, 71.74, 66.02, 32.06, 29.78, 29.70, 29.51, 29.38, 27.78, 22.86, 14.30, 5.66.

***tert*-Butyl *cis*-3-[4-[(2-Tridecenyloxy)methyl]phenyl]-propanoate.** A solution of *tert*-butyl acetate (0.2 mL, 1.5 mmol, 2 equiv) in dry THF (1 mL) was added to a solution of LDA. (The latter was prepared by adding *n*-BuLi (0.68 mL, 2.5 M in hexane, 1.72 mmol) to a solution of diisopropylamine (0.10 mL, 1.89 mmol) in THF (4 mL) at −78 °C and stirring for 30 min.) The resulting mixture was stirred for 30 min at −78 °C, and the above iodide (350 mg, 0.75 mmol) in THF (1 mL) was added. After 1 h, the reaction mixture was allowed to warm to 0 °C and immediately poured into water (20 mL) and ether (30 mL). The organic layer was separated and washed with three 15-mL portions of water. The ether extract was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Flash chromatography eluted by 95:5 petroleum ether/EtOAc furnished the title ester (250 mg, 78%) as a colorless oil: R_f 0.68 (9:1 petroleum ether/EtOAc); ^1H NMR ($CDCl_3$) δ 7.27 (d, J = 8.1 Hz, 2 H), 7.17 (d, J = 8.1 Hz, 2 H), 5.59 (m, 2 H), 4.47 (s, 2 H), 4.06 (d, J = 4.5 Hz, 2 H), 2.90 (t, J = 7.8 Hz, 2 H), 2.53 (t, J = 7.8 Hz, 2 H), 2.04 (m, 2 H), 1.42 (s, 9 H), 1.27 (m, 16 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.32, 140.26, 136.38, 134.02, 128.44, 128.07, 126.13, 80.38, 71.96, 65.78, 37.18, 32.03, 30.95, 29.74, 29.67, 29.63, 29.47, 29.36, 28.18, 27.73, 22.79, 14.24. Anal. ($C_{27}H_{44}O_3$) C, H.

***cis*-3-[4-[(2-Tridecenyloxy)methyl]phenyl]propanoic Acid (5).** A solution of the above ester (250 mg, 0.6 mmol) in a 1:5 mixture of trifluoroacetic acid and CH_2Cl_2 (10 mL) was stirred at 25 °C for 12 h and evaporated to dryness in vacuo at room temperature. Purification by flash silica gel chromatography (25:1 CH_2Cl_2/MeOH) afforded 205 mg (95%) of the title phenylpropanoic acid derivative as a white solid: mp 35−36 °C; R_f 0.35 (20:1 CH_2Cl_2/MeOH); IR (neat) 3400, 2951, 2921, 2851, 1703, 1442, 1111, 942, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.50 (s, 1 H), 7.30 (d, J =

and cooled to 0 °C. A solution of 3-nonyn-1-ol (152 mg, 1.1 mmol, 1.1 equiv) in THF (1 mL) was slowly added. After 25 min the cold bath was removed, and stirring was continued for an additional 10 min. At this time a solution of 3-bromobenzyl bromide (250 mg, 1 mmol) in THF (1 mL) was added and stirring continued for 12 h. The mixture was poured into water (20 mL) and ether (25 mL). The organic layer was separated and washed with three 10-mL portions of water. The ether extract was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield a yellow oil. Purification by flash silica gel chromatography (95:5 petroleum ether/EtOAc) afforded 262 mg (85%) of the title product as a clear colorless oil: R_f 0.88 (9:1 petroleum ether/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 4 H), 4.55 (s, 2 H), 3.56 (t, J = 6.9 Hz, 2 H), 2.48 (tt, J_1 = 6.9 Hz, J_2 = 2.4 Hz, 2 H), 2.15 (tt, J_1 = 7.2 Hz, J_2 = 2.4 Hz, 2 H), 1.40 (m, 6 H), 0.89 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.82, 130.78, 130.65, 130.09, 126.12, 122.68, 81.81, 72.74, 69.29, 31.20, 28.80, 22.35, 20.29, 18.86, 14.12.

Ethyl 3-[3-[(3-Nonynyloxy)methyl]phenyl]propanoate. A flask was charged with Zn−Cu couple (200 mg, 3 mmol), and a solution of ethyl 3-iodopropanoate (510 mg, 2 mmol) in dry toluene (4 mL) and dry *N*,*N*-dimethylacetamide (2 mL) was added. The mixture was vigorously stirred for 1 h at room temperature and then heated at gentle reflux for 4.5 h. After the mixture was cooled to 60 °C, a solution of tetrakis-(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol) in toluene (2 mL) was added over 1 min, and stirring was continued for 5 min at the same temperature. A solution of the above aryl bromide (309 mg, 1 mmol) in dry toluene (2 mL) was added, and the mixture was refluxed for 12 h. The reaction mixture was allowed to cool to 25 °C and filtered through a Celite pad. The filter cake was washed with ether (50 mL). The filtrate was successively washed with a solution of 1 N ammonium chloride (10 mL), a solution of saturated sodium hydrogen carbonate (10 mL), and a solution of saturated sodium chloride (10 mL). The aqueous phases were back-extracted with ether (30 mL); the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield a yellow oil. Purification by flash silica gel chromatography (97:3 petroleum ether/EtOAc) afforded the title ester (165 mg, 51%) as a colorless oil: R_f 0.44 (95:5 petroleum ether/EtOAc); IR (neat) 2929, 2858, 1738, 1449, 1374, 1160, 1111, 787, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.19 (m, 4 H), 4.51 (s, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 3.55 (t, J = 7.2 Hz, 2 H), 2.94 (t, J = 8.1 Hz, 2 H), 2.61 (t, J = 8.1 Hz, 2 H), 2.46 (tt, J_1 = 6.9 Hz, J_2 = 2.1 Hz, 2 H), 2.13 (tt, J_1 = 7.2 Hz, J_2 = 2.4 Hz, 2 H), 1.40 (m, 6 H), 1.22 (t, J = 7.2 Hz, 3 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173 01, 140.87, 138.58, 128.68, 127.75, 81.64, 76.67, 72.99, 69.15, 60.53, 36.02, 31.01, 31.18, 28.81, 22.34, 20.28, 18.85, 14.32, 14.12. Anal. ($C_{20}H_{30}O_3$) C, H.

3-[3-[(3-Nonynyloxy)methyl]phenyl]propanoic Acid (1e). A solution of the above ester (150 mg, 0.45 mmol) in a mixture of MeOH (4 mL) and 1 N NaOH (1 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo, H_2O (20 mL) was added, and the pH was adjusted to 4 with 10% AcOH. Ether (30 mL) was added. The organic layer was separated and washed with water (20 mL). The ether extract was dried ($MgSO_4$) and concentrated by rotary evaporation. Purification by flash silica gel chromatography (20:1 CH_2Cl_2/MeOH) afforded **1e** (129 mg, 95%) as a colorless oil: R_f 0.31 (20:1 CH_2Cl_2/MeOH); IR (neat) 3500, 2929, 2858, 2245, 1710, 1104, 731, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.5 (s, 1 H), 7.21 (m, 4 H), 4.55 (s, 2 H), 3.57 (t, J = 6.9 Hz, 2 H), 2.97 (t, J = 8.1 Hz, 2 H), 2.69 (t, J = 8.1 Hz, 2 H), 2.49 (tt, J_1 = 7.2 Hz, J_2 = 2.4 Hz, 2 H), 2.15 (tt, J_1 = 6.9 Hz, J_2 = 2.1 Hz, 2 H), 1.40 (m, 6 H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.20, 140.47, 138.62, 128.78, 127.73, 125.93, 81.69, 76.67, 72.95, 69.15, 35.70, 31.21, 30.63, 28.83, 22.36, 20.27, 18.86, 14.12. Anal. ($C_{19}H_{26}O_3$) C, H.

1-Bromo-4-[(2-tridecynyloxy)methyl]benzene: colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 2 H), 7.23 (d, J = 8.4 Hz, 2 H), 4.53 (s, 2 H), 4.15 (t, J = 2.1 Hz, 2 H), 2.23 (tt, J_1 = 7.2 Hz, J_2 = 2.1 Hz, 2 H), 1.40 (m, 16 H), 0.88 (t, J = 6.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 136.74, 131.44, 129.59, 121.57, 87.60, 75.50, 70.45, 57.84, 31.86, 29.53, 29.30, 29.10, 28.86, 28.59, 22 65, 18.74, 14.10; HRMS calcd for $C_{20}H_{29}BrO$ ($M^{\bullet+}$) 364.1402, found 364.1408.

Ethyl 3-[4-[(2-tridecynyloxy)methyl]phenyl]propanoate: colorless oil; IR (neat) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28 (d, J = 7.8 Hz, 2 H), 7.19 (d, J = 7.8 Hz, 2 H), 4.55 (s, 2 H), 4.14 (m, 4 H), 2.95 (t, J = 8.1 Hz, 2 H), 2.60 (t, J = 8.1 Hz, 2 H), 2.23 (m, 2 H), 1.27 (m, 19 H), 0.88 (t, J = 6.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.03, 140.14, 135.54, 128.32, 87.15, 75.90, 71.04, 60.39, 57.63, 35.88, 31.85, 30.64, 29.52, 29.30, 29.11, 28.86, 28.60, 22.65, 18.76, 14.16, 14.09; HRMS calcd for $C_{25}H_{38}O_3$ ($M^{\bullet+}$) 386.2821, found 386.2826.

3-[4-[(2-Tridecynyloxy)methyl]phenyl]propanoic acid (3d): white crystals; mp 49 °C; IR (neat) 3250, 2957, 2921, 2851, 2302, 2238, 1696, 1463, 1259, 1069, 1020, 942, 801 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.50 (s, 1 H), 7.30 (d, J = 8.1 Hz, 2 H), 7.19 (d, J = 8.1 Hz, 2 H), 4.56 (s, 2 H), 4.15 (t, J = 1.8 Hz, 2 H), 2.96 (t, J = 7.8 Hz, 2 H), 2.68 (t, J = 7.8 Hz, 2 H), 2.23 (tt, J_1 = 7.2 Hz, J_2 = 2.1 Hz, 2 H), 1.27 (m, 16 H), 0.88 (t, J = 6.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 178.86, 139.88, 135.88, 128.59, 128.45, 87.52, 75.90, 71.16, 57.81, 35.66, 32.02, 30.41, 29.89, 29.44, 29.27, 29.02, 28.77, 22.80, 18.91, 14.24; HRMS calcd for $C_{23}H_{34}O_3$ ($M^{\bullet+}$) 358.2507, found 358.2511. Anal. ($C_{23}H_{34}O_3$) C, H.

The corresponding dideutero compound (-CÿCCD$_2$-O-) was prepared by reduction of methyl 2-tridecynoate with $LiAlD_4$ in diethyl ether at room temperature followed by coupling of the corresponding propargyl alcohol with 4-bromobenzyl bromide and proceeding as in the preparation of **3d**. The ^{1}H NMR spectrum of **3d**-d_2 matched that above except for the absence of the triplet at 4.15.

Arylacetic Acid Derivatives. Method C: [4-[(2-Tridecynyloxy)methyl]phenyl]acetonitrile. A solution of 1-(iodomethyl)-4-[(2-tridecynyloxy)methyl]benzene (100 mg, 0.23 mmol) and NaCN (20 mg, 1.5 equiv) in DMF (2 mL) was stirred for 5 h at 25 °C. The resulting mixture was poured in water (20 mL) and ether (25 mL). The organic layer was separated and washed with two 10-mL portions of water. The ether extract was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield a yellow oil. Purification by flash silica gel chromatography (95:5 petroleum ether/EtOAc) afforded the title nitrile (66 mg, 95%) as a clear oil: R_f 0.3 (9:1 petroleum ether/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J = 8.1 Hz, 2 H), 7.31 (d, J = 8.1 Hz, 2 H), 4.59 (s, 2 H), 4.17 (t, J = 2.1 Hz, 2 H), 3.74 (s, 2 H), 2.24 (tt, J_1 = 6.9 Hz, J_2 = 1.8 Hz, 2 H), 1.35 (m, 16 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.99, 129.44, 128.86, 128.10, 117.95, 87.74, 75.73, 70.80, 58.04, 32.01, 29.67, 29.44, 29.25, 29.01, 28.74, 23.48, 22.80, 18.89, 14.23.

4-[(2-Tridecynyloxy)methyl]phenylacetic Acid (3h). The above nitrile (66 mg) was dissolved in MeOH (1 mL) and water (1 mL). LiOH (50 mg) was added, and the resulting mixture was refluxed for 35 h. The mixture was allowed to cool to 25 °C, acidified, extracted with ether (25 mL), dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield a yellow oil. Purification by flash silica gel chromatography (96:4 CH_2Cl_2/MeOH) afforded **3h** (50 mg, 90%) as a clear oil: R_f 0.4 (95:5 CH_2Cl_2/MeOH); IR (neat) 3400, 2921, 2851, 1696, 1463, 1407, 1076, 991, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.5 (s, 1 H), 7.27 (m, 4 H), 4.57 (s, 2 H), 4.14 (s, 2 H), 3.62 (s, 2 H), 2.22 (m, 2 H), 1.34 (m, 16 H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.20, 136.78, 132.74, 129.38, 128.32, 70.83, 57.67, 40.74, 31.86, 29.52, 29.29, 29.10, 28.86, 28.60, 22.33, 18.75, 14.09. Anal. ($C_{22}H_{32}O_3$) C, H.

Benzoic Acid Derivatives. Method D: Methyl 4-(Bromomethyl)benzoate. A solution of methyl 4-methylbenzoate (1.50 g, 10 mmol), *N*-bromosuccinimide (1.78 g, 10 mmol, 1.0 equiv), and a catalytic amount of benzoyl peroxide (30 mg, 0.12 mmol) in CCl_4 (50 mL) was stirred at gentle reflux for 15 h. The resulting mixture was allowed to cool to 25 °C and filtered. The solvent was removed by rotary evaporation. The resulting slurry was chromatographed on silica gel (98:2 petroleum ether/ethyl acetate) to afford a mixture of brominated compounds. Recrystallization of the crude mixture from petroleum ether afforded the title compound as white crystals (1.8 g, 80%): mp 53−54 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 8.1 Hz, 2 H), 7.44 (d, J = 8.1 Hz, 2 H), 4.48 (s, 2 H), 3.90 (s, 3 H); ^{13}C

NMR ($CDCl_3$) δ 166.48, 142.57, 130.03, 129.00, 52.20, 32.22. Anal. ($C_9H_9BrO_2$) C, H.

Methyl 4-[(2-Decynyloxy)methyl]benzoate. A flask was charged with 50 mg of a 60% dispersion of NaH in oil. The dispersion was washed with three 2-mL portions of THF. The NaH was suspended in 5 mL of THF and cooled to 0 °C. A solution of 2-decyn-1-ol (169 mg, 1.1 mmol, 1.1 equiv) in THF (1 mL) was slowly added. After 25 min the cold bath was removed, and stirring was continued for an additional 10 min. At this time a solution of methyl 4-(bromomethyl)benzoate (229 mg, 1 mmol) in THF (1 mL) was added and stirring continued for 12 h. The mixture was poured into water (20 mL) and ether (25 mL). The organic layer was separated and washed with three 10-mL portions of water. The ether extract was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield a yellow oil. Purification by flash silica gel chromatography (95:5 petroleum ether/EtOAc) afforded 181 mg (60%) of the title ester as a clear colorless oil: R_f 0.76 (9:1 petroleum ether/EtOAc); ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 8.1 Hz, 2 H), 7.42 (d, J = 8.1 Hz, 2 H), 4.63 (s, 2 H), 4.18 (t, J = 2.1 Hz, 2 H), 3.90 (s, 3 H), 2.22 (tt, J_1 = 6.9 Hz, J_2 = 1.8 Hz, 2 H), 1.50 (m, 2 H), 1.30 (m, 8 H), 0.87 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.89, 143.04, 129.64, 129.37, 127.47, 87.70, 75.44, 70.62, 58.13, 52.05, 31.72, 28.79, 28.56, 22.60, 18.73, 14.05.

4-[(2-Decynyloxy)methyl]benzoic Acid (3j). A mixture of the above ester (300 mg, 1 mmol), water (2 mL), THF (2 mL), and 0.1 N NaOH (2 mL) was stirred for 30 h at 25 °C. The resulting solution was acidified and extracted with ether (25 mL). The ether extract was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield **3j** as white crystals (250 mg, 87%): mp 33−34 °C; IR (neat) 3400, 2921, 2851, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12 (s, 1 H), 8.1 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 2 H), 4.68 (s, 2 H), 4.22 (t, J = 1.8 Hz, 2 H), 2.24 (tt, J_1 = 6.9 Hz, J_2 = 1.8 Hz, 2 H), 1.52 (m, 2 H), 1.30 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 172.10, 144.29, 130.49, 128.69, 127.72, 127.63, 75.55, 70.74, 58.36, 31.85, 28.96, 28.92, 28.71, 22.73, 18.89, 14.19. Anal. ($C_{18}H_{24}O_3$) C, H.

Supporting Information Available: Details on the preparation of various lipophilic side chains and compound characterization of **1a**−**d**, **3a**−**c**,**f**,**g**,**i**,**k**, **4**, and **6**−**8** as well as various key intermediates leading to these compounds (27 pages). Ordering information can be found on any current masthead page.

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