Development of the First Potential Covalent Inhibitors of Anandamide Cellular Uptake

Aniello Schiano Moriello,[†] Laurence Balas,[‡] Alessia Ligresti,[†] Maria Grazia Cascio,[†,§] Thierry Durand,[‡] Enrico Morera,[||] Giorgio Ortar,[||] and Vincenzo Di Marzo*[,†]

Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, via dei Campi Flegrei 34, 80078 Pozzuoli (Napoli), Italy, UMR-CNRS 5074, Université Montpellier I, avenue Charles Flahault, 34093 Montpellier, France, Dipartimento di Scienze Farmaceutiche, Università degli Studi di Salerno, via Ponte Don Melillo, 84084 Fisciano (SA), Italy, and Dipartimento di Studi Farmaceutici, Università di Roma 'La Sapienza', piazzale Aldo Moro 5, 00185 Roma, Italy

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On the basis of the chemical structures of two previously developed metabolically stable and relatively potent inhibitors of anandamide uptake, **OMDM-1**,**2**, two series of potential covalent inhibitors of anandamide cellular reuptake, which might be used for the molecular characterization of the protein(s) involved in the membrane transport of endocannabinoids, have been designed and synthesized. Most of the compounds inhibited uptake to a varied extent and in a generally enantio-sensitive manner when co-incubated with [^{14}C]anandamide, but only three of them, the photoactivatable **1a** (OMDM-37**)**, **1b** (OMDM-39), and **8** (Lo395), also produced a significant inhibition of uptake following the preincubation only of the cells, and this effect was significantly enhanced following UV exposure only in the case of **8**. None of the new compounds inhibited [^{14}C]anandamide hydrolysis with $IC_{50} < 50$ μM, except for **1b**.

Introduction

To date, two G-protein-coupled receptors for *Cannabis* psychoactive principle Δ^9-tetrahydrocannabinol have been cloned: cannabinoid CB_1 and CB_2 receptors.[1] Endocannabinoids are defined as endogenous agonists of these receptors[2] and have been implicated in several physiological and pathological conditions in mammals.[3,4] The levels of the two major endocannabinoids, anandamide (AEA)[5] and 2-arachidonoylglycerol (2-AG)[6,7] are regulated by specific biosynthetic and degradative reactions catalyzed by enzymes that have been recently characterized and cloned.[3] The possible existence of a plasma membrane protein mediating both the release from the cells of endocannabinoids after biosynthesis on demand and the cellular re-uptake following the activation of CB_1 and CB_2 cannabinoid receptors, according to the AEA concentration gradient across the cell membrane, has been suggested but is still controversial.[2,8−13] Nevertheless, numerous synthetic substances are now available that can selectively inhibit the cellular re-uptake of AEA[14,15] without interfering with other proteins or the major enzyme involved in the degradation of this compound, fatty acid amide hydrolase (FAAH).[16] In some cases, very subtle changes in its chemical structure or the inversion of the stereochemistry of a chiral center can dramatically affect the capability of a certain compound to inhibit AEA re-uptake,[9,17,18] thus supporting the existence of a specific protein facilitating this process. Nevertheless, a protein capable of specifically binding AEA and other endocannabinoids with the ability to facilitate their transport across the cell membrane has not been identified yet.

We have previously shown that selective and metabolically stable inhibitors of AEA cellular uptake can be obtained by functionalizing the polar head of oleoylethanolamine with aromatic groups, as in the case of the two relatively potent enantiomers, **OMDM-1** and **OMDM-2**, and their analogues.[9,15,18] These compounds enhance some pharmacological actions of AEA,[19] elevate brain endocannabinoid levels,[20] and exert beneficial effects in animal models of disorders where endocannabinoids seem to play a protective function, for example, during both the symptoms and inflammatory consequences of experimental allergic encephalomyelitis.[19,21,22]

In the present study, we have designed and synthesized 21 structural analogues of **OMDM-1**,**2** (Figure 1) aiming to develop covalent inhibitors of the putative AEA membrane transporter. For this purpose, we have modified either the polar aromatic head or the alkyl tail of either compound by introducing chemical functions potentially capable of forming covalent bonds with amino acid residues. We have then examined the effects of the new compounds on AEA uptake from RBL-2H3 or C6 cells, where a putative AEA transporter has been preliminarily characterized,[23,24] either under normal cell culturing conditions or after brief exposure to UV light. We report data suggesting that the putative mechanism(s) mediating AEA transport across the cell membrane is indeed mediated by one or more photoaffinity labelable proteins.

Chemistry

The 21 compounds in Figure 1 were prepared as detailed below and as summarized in Schemes 1−5. The commercially available *N*-Boc-4-iodophenylalanines (*S*)-**9** and (*R*)-**9** were reduced to *N*-Boc-4-iodophenylalaninols (*S*)-**10** and (*R*)-**10** via mixed anhydrides. The alcoholic function has been protected as the acetate, and the resulting *N*-Boc-4-iodophenylalaninol acetates (*S*)-**11** and (*R*)-**11** have been converted into 4-trimethylstannyl analogues **12**. The carbonylative Stille reaction[25] of (*S*)-**12** and (*R*)-**12** with C_6H_5I or *t*-$BuOCOOC_6H_4I$ under atmospheric CO pressure in the presence of $PdCl_2/2PPh_3$ proceeded smoothly to give 4-benzoyl derivatives (*S*)-**13** and (*R*)-**13**. Alkaline hydrolysis of the ester group to give alcohols (*S*)-**14** and (*R*)-**14** followed by the removal of the Boc protecting group with $SOCl_2$−MeOH afforded amine hydrochlorides (*S*)-**15** and (*R*)-**15**, which were condensed with oleic acid using 1-hydroxybenzotriazole (HOBt)/*N*-ethyl-*N*′-(3-dimethylamino-

* To whom correspondence should be addressed. Phone: +39-81-8675093. Fax: +39-81-8041770. E-mail: vdimarzo@icmib.na.cnr.it.
[†] Institute of Biomolecular Chemistry.
[‡] Université de Montpellier.
[§] Università degli Studi di Salerno.
[||] Università di Roma 'La Sapienza'.

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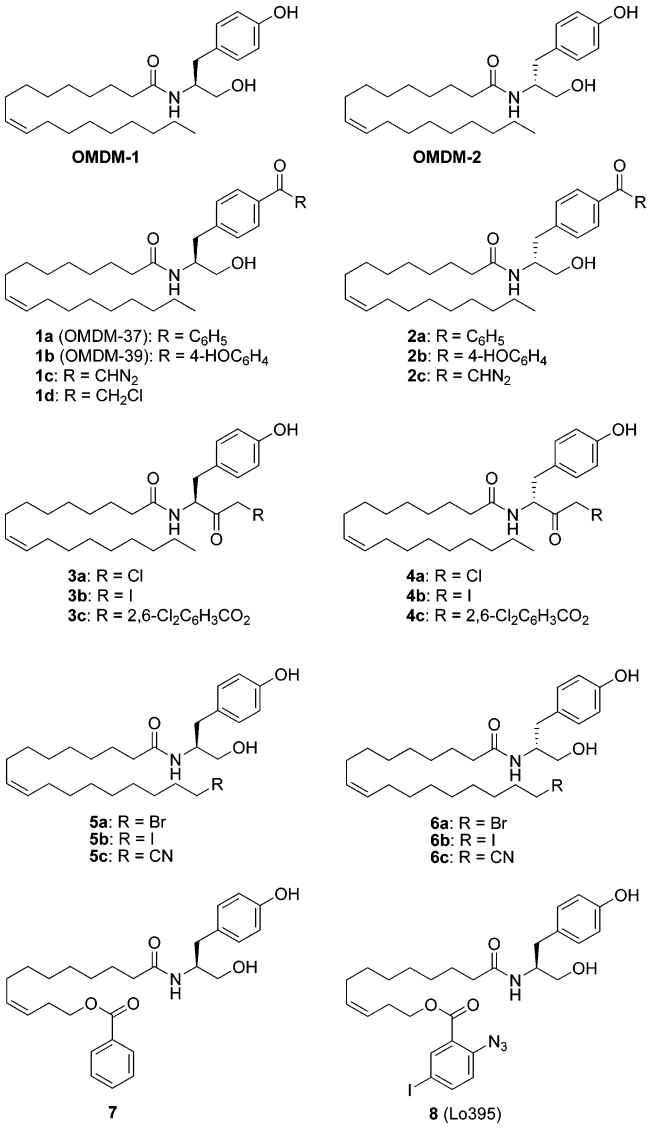


Figure 1. Structures of **OMDM-1**,**2** and the novel compounds synthesized and tested in this study.

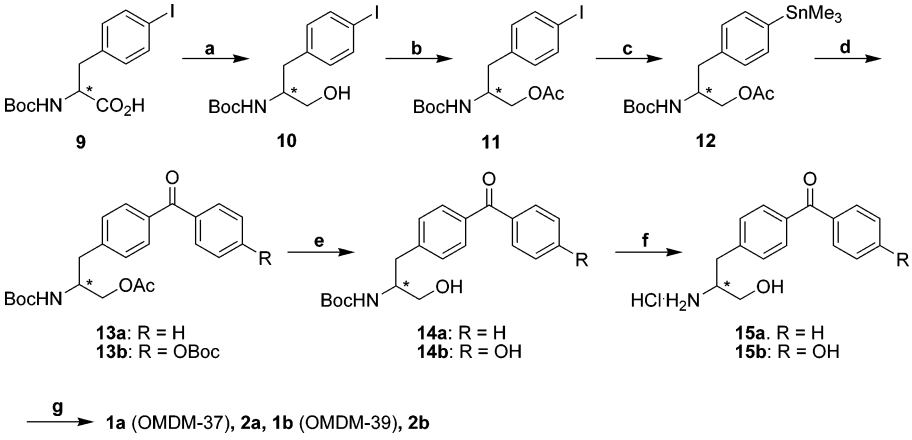
propyl)carbodiimide hydrochloride (EDC) as the carboxylate activator to give **1a** (OMDM-37), **2a**, **1b** (OMDM-39), and **2b** (Scheme 1).

Palladium-catalyzed alkoxycarbonylation of *N*-Boc-4-iodophenylalaninols (*S*)-**10** and (*R*)-**10** (see above) provided 4-carbethoxy analogues (*S*)-**16** and (*R*)-**16**. The removal of the Boc protecting group with dry HCl in AcOEt afforded amine hydrochlorides (*S*)-**17** and (*R*)-**17**, which were condensed with oleic acid using HOBt/EDC as the carboxylate activator to give amides (*S*)-**18** and (*R*)-**18**. Alkaline hydrolysis of the ester function and the protection of the alcohol group gave acids (*S*)-**19** and (*R*)-**19**. The reaction of (trimethylsilyl)diazomethane with the acyl chlorides derived from **19** by the action of oxalyl chloride in the presence of catalytic dimethylformamide (DMF) yielded diazoketones (*S*)-**20** and (*R*)-**20**, which were converted to **1c** and **2c** by the hydrolysis of the acetate group. The treatment of **1c** with dry HCl in AcOEt furnished chloromethyl ketone **1d** (Scheme 2).

Commercially available *N*-Boc-tyrosines (*S*)-**21** and (*R*)-**21** were converted to corresponding α-diazomethyl ketones (*S*)-**22** and (*R*)-**22** by the formation of the mixed anhydride with isobutyl chloroformate, followed by trapping with diazomethane.[26] The treatment of diazomethyl ketones **22** with a solution of dry HCl in AcOEt provided chloromethyl ketone derivatives (*S*)-**23** and (*R*)-**23**, which were subsequently converted to **3a** and **4a** by coupling with oleic acid activated as mixed anhydride by a treatment with isobutyl chloroformate. Nucleophilic displacement with sodium iodide in dry acetone afforded corresponding iodide derivatives **3b** and **4b**, which, in turn, were transformed into **3c** and **4c** by treatment with 2,6-dichlorobenzoic acid in DMF in the presence of potassium fluoride (Scheme 3).

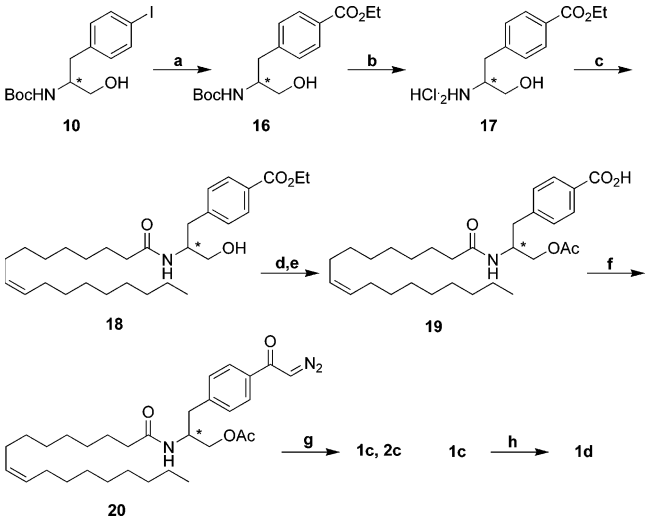
Commercially available 8-bromooctan-1-ol **24** was transformed into its corresponding tetrahydropyranyl (THP) and *t*-butyldimethylsilyl (TBDMS) ethers **25** and **26** as described previously.[27,28] Silyl ether **26** was converted to 10-[(*t*-butyldimethylsilyl)oxy]-1-decyne (**27**) by reaction with lithium acetylide-ethylenediamine complex according to a literature procedure.[28] Terminal alkyne **27** was alkylated with **25** to furnish 1-[(*t*-butyldimethylsilyl)oxy]-18-[(2-tetrahydropyranyl)oxy]-9-octadecyne (**28**). Stereoselective reduction of **28** with P-2 nickel[29] to give (*Z*)-alkene **29**, followed by the deprotection of the TBDMS protecting group with *n*-Bu_4NF and the oxidation of resulting alcohol **30** with pyridinium dichromate (DCC) in DMF afforded a carboxylic acid that was directly converted to corresponding methyl ester **31**. The deprotection of the THP protecting group with pyridinium *p*-toluenesulfonate[30] gave alcohol **32**, which was converted to bromide **33** by treatment with PPh_3/CBr_4.[31] Hydrolysis of the ester group with LiOH produced acid **34**, which was used in the condensation reactions

Scheme 1[a]



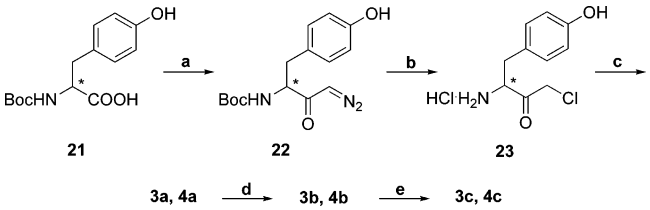
[a] Reagents and conditions: (a) *i*-BuOCOCl, *N*-Methylmorpholine, THF, −15 °C, 15 min, then $NaBH_4$, H_2O, −15 °C, 45 min; (b) $(CH_3CO)_2O$, pyridine, rt, 18 h; (c) $Pd(OAc)_2/2PPh_3$, $Me_3SnSnMe_3$, toluene, 100 °C, 15 min; (d) C_6H_5I or *t*-$BuOCOOC_6H_4I$, CO, $PdCl_2/2PPh_3$, DMF, 90 °C, 3.5 h; (e) 2N NaOH, MeOH, rt, 4 h; (f) $SOCl_2$, MeOH, 50 °C, 3 h; (g) oleic acid, HOBt/EDC, Et_3N, DMF, rt, 12 h.

Scheme 2[a]



[a] Reagents and conditions: (a) $Pd(OAc)_2/2PPh_3$, CO, EtOH, Et_3N, DMF, 80 °C, 12 h; (b) dry HCl, AcOEt, rt, 5 h; (c) oleic acid, HOBt/EDC, Et_3N, DMF, rt, 12 h; (d) 1M LiOH, THF−H_2O, 50 °C, 18 h; (e) $(CH_3CO)_2O$, pyridine, rt, 4 h; (f) $(COCl)_2$, DMF, 0 °C, 1h, then Me_3SiCHN_2, Et_3N, 0 °C, 12 h; (g) 1M LiOH, THF−H_2O, 0 °C, 3.5 h; (h) dry HCl, AcOEt, rt, 1 h.

Scheme 3[a]



[a] Reagents and conditions: (a) *i*-BuOCOCl, Et_3N, THF, −15 °C → rt, then CH_2N_2, rt, 2 h; (b) dry HCl, AcOEt, rt, 48 h; (c) oleic acid, *i*-BuOCOCl, *N*-Methylmorpholine, THF-DMF, −15 °C → rt, then **23**, rt, 24 h; (d) NaI, acetone, rt, 16 h; (e) KF, 2,6-dichlorobenzoic acid, DMF, rt, 16 h.

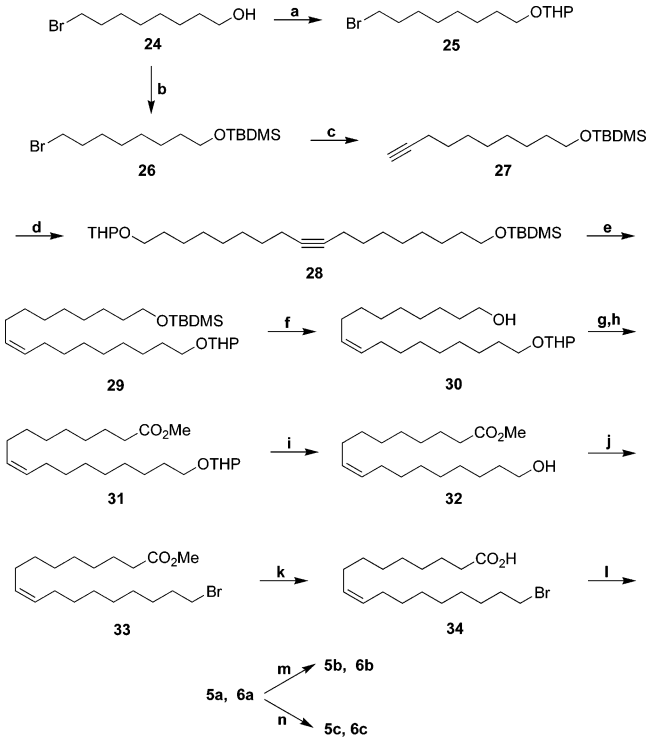
with (*S*)- and (*R*)-tyrosinol in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) to furnish **5a** and **6a**. Bromides **5a** and **6a** were converted to corresponding iodides **5b** and **6b** and nitriles **5c** and **6c** by treatment with NaI in acetone and KCN in DMSO, respectively (Scheme 4).

The synthesis of **8** and its noniodinated and nonphotoactivatable analogue **7** was carried out in 8 steps from azelaic acid monomethyl ester **35** via key common intermediate **39** (Scheme 5).[32] The first three steps to reach *Z*-derivative **37** are the reduction of carboxylic acid **35** using diborane followed by a Swern oxidation to afford aldehyde **36** according to Okuma and co-workers,[33] then a three carbon atom elongation in the presence of 3-(2-tetrahydropyranyloxy)propyl triphenylphosphonium bromide as described previously[34] to give *Z*-derivative **37**. After hydrolysis with LiOH in THF, the resulting carboxylic acid was coupled with di-*O*-*t*-butyldiphenylsilyl-L-tyrosinol (**38**) to give amide **39** using the anhydride activation procedure. After the removal of the THP group using classical acidic conditions, key alcohol **40** was obtained. Steglich esterification of **40** with benzoic acid, followed by fluoride cleavage of the silyl groups provided **7**. Application of the same esterification procedure using 2-azido-5-iodobenzoic acid[35] afforded photoactivatable **8** (Lo395).

Biological Evaluation

Three types of assays were used to investigate the activity of the novel compounds on the putative AEA membrane

Scheme 4[a]



[a] Reagents and conditions: (a) 3,4-dihydro-2H-pyran, pyridinium *p*-toluenesulfonate, CH_2Cl_2, rt, 18 h; (b) *t*-$BuMe_2SiCl$, Et_3N,DMAP, CH_2Cl_2, rt, 18 h; (c) lithium acetylide ethylenediamine complex, DMSO, rt, 24 h; (d) 1.2 M *n*-BuLi, THF, −25 °C, 15 min, then **25**, −25 °C, 2 h, then rt, 12 h; (e) P-2 Nickel, EtOH, rt, 2 h; (f) *n*-Bu_4NF, THF, rt, 2 h; (g) PDC, DMF, rt, 48 h; (h) CH_2N_2, Et_2O, 0 °C, 45 min; (i) pyridinium *p*-toluenesulfonate, EtOH, 55 °C, 12 h; (j) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 40 min; (k) 1 M LiOH, THF−H_2O, rt, 12 h; (l) (*S*)- or (*R*)-tyrosinol, DCC, DMF, rt, 12 h; (m) NaI, acetone, rt, 12 h; (n) KCN, DMSO, rt, 12 h.

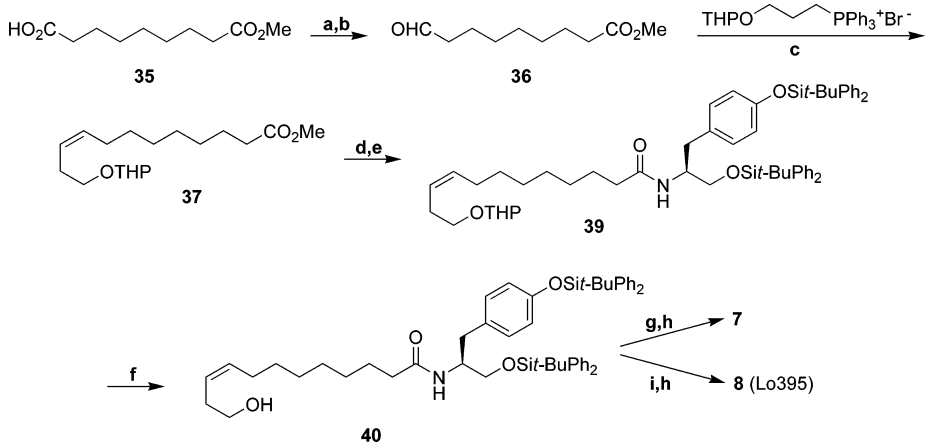
transporter in RBL-2H3 cells and C6 glioma cells. Protocol #1 was used to evaluate the affinity of all compounds for the putative protein(s) involved in cellular [^{14}C]AEA uptake and consisted of co-incubating RBL-2H3 cells with [^{14}C]AEA for 5 min and increasing the concentrations of the compounds. In some cases, the compounds were added 10 min prior to [^{14}C]-AEA. Protocols #2 and 3 were used only for those substances that showed some activity when protocol #1 was used and for nonphotoactivatable and UV-activatable compounds, respectively. Protocol #2 was carried out in RBL-2H3 cells preincubated with the inhibitors for 1 h, then thoroughly washed and incubated with [^{14}C]AEA for 5 min in the absence of inhibitors. Protocol #3 was carried out in C6 cells preincubated with the inhibitors for 8 min with or without exposure to UV light, then thoroughly washed and incubated with [^{14}C]AEA for 5 min in the absence of inhibitors. Finally, all compounds were assessed for their capability to inhibit [^{14}C]AEA hydrolysis using rat brain membranes.

Results and Discussion

The results are summarized in Tables 1 and 2 and described below.

OMDM-1,**2** analogues with headgroup modifications can ideally be divided into two subgroups. In the first subgroup, the ethanolamine moiety of **OMDM-1**,**2** was left unaltered, whereas in the aromatic region, the OH group was replaced by an electrophilic or a photoactivatable moiety. This yielded seven compounds, four of which (**1a**, **2a**, **1b**, and **2b**) were potentially capable of forming covalent bonds with proteins only after

Scheme 5[a]



[a] Reagents and conditions: (a) B_2H_6, THF; (b) $(COCl)_2$, DMSO, Et_3N; (c) KHMDS, THF, −78 °C; (d) LiOH, THF; (e) *i*-BuOCOCl, *N*-Methylmorpholine, Et_3N, then di-*O*-*t*-Butyldiphenylsilyl-L-tyrosinol (**38**); (f) TsOH·H_2O, MeOH; (g) $PhCO_2H$, DCC, DMAP, CH_2Cl_2; (h) *n*-Bu_4NF, THF; (i) 2-azido-5-iodobenzoic acid, DCC, DMAP.

Table 1. Inhibitory Effect of Compounds on [^{14}C]Anandamide Uptake by Intact RBL-2H3 Cells[a]

compd	protocol #1 (co-incubation only)	protocol #2 (1 h preincubation only)
1a	6.0 ± 0.9	N. T. (protocol #3)
2a*	10.0 ± 1.2[b]	N. T.
1b	10.1 ± 1.3	N. T. (protocol #3)
2b*	8.1 ± 0.8	N. T.
1c	>25	N. T.
2c*	>25	N. T.
1d	>25	N. T.
3a	10.0 ± 4.1	>25
4a*	>25[b]	N. T.
3b	>25	N. T.
4b*	>25	N. T.
3c	16.1 ± 2.6	>25
4c*	7.5 ± 1.5[b]	>25
5a	10.2 ± 1.4	>25
6a*	20.1 ± 2.3[b]	N. T.
5b	10.8 ± 1.5	>25
6b*	14.0 ± 1.1[b]	>25
5c	23.1 ± 2.6	N. T.
6c*	>25[b]	N. T
7	>25	N. T.
8 (Lo395)	11.0 ± 1.6	N. T. (protocol #3)

[a] Assessed by using protocol #1 (co-incubation of cells with inhibitors and [^{14}C]anandamide) and, only for those compounds exhibiting IC_{50} < 20 μM with protocol #1, also by using protocol #2 (1 h preincubation of cells with inhibitors only, followed by washing and incubation with [^{14}C]anandamide only; see Biological Evaluation and Experimental Section for a detailed description of the two protocols). N. T., not tested or, when indicated, tested with protocol #3 (Table 2). Asterisks denote those compounds that are the *R* enantiomers of the compounds preceding them in the list. Data are means ± SE of $N = 3$ experiments. [b] Denotes a mean significantly different from the IC_{50} value of the corresponding enantiomer using ANOVA followed by the Student Newman Keuls test, and $P < 0.05$ as the threshold of significance.

exposure to UV, whereas the other three, **1c**, **2c**, and **1d**, could form covalent bonds without UV light. Of these seven compounds, only the former four UV-sensitive derivatives inhibited [^{14}C]AEA uptake in RBL-2H3 cells with moderate potency when co-incubated with the radiolabeled substrate (IC_{50} values ranging between 6.0 and 10.1 μM, protocol #1) and little or no enantioselectivity. Two of the four potential UV-sensitive ligands, that is, **1a** and **1b**, still inhibited [^{14}C]AEA uptake with approximately the same potency when they were only preincubated with C6 cells for 8 min in the absence of the substrate and then washed before adding [^{14}C]AEA (protocol #3), thus pointing to a possible irreversible inhibition of the uptake mechanism. However, this effect of **1a** and **1b** did not seem to require exposure to UV light necessary to photoactivate the two compounds, although the low dose of **1b** tended to be more efficacious in the presence of UV light ($P = 0.1$). Finally, of the seven compounds of this subgroup, only **1b** exerted some inhibition of [^{14}C]AEA hydrolysis by rat brain membranes (IC_{50} = 10.2 ± 2.1 μM, mean ± SE, $N = 3$). This weak inhibitory effect was not improved after UV irradiation (data not shown).

Table 2. Inhibition of [^{14}C]Anandamide Uptake by C6 Cells by **1a**, **1b**, and **8**[a]

compd, concn, *N*	% inhibition, dark	% inhibition, UV
1a, 5 μM, $N = 3$	37.5 ± 1.5	30.3 ± 3.1 ($P > 0.1$)
1a, 10 μM, $N = 3$	65.8 ± 6.5	57.2 ± 5.5 ($N > 0.1$)
1b, 5 μM, $N = 3$	28.3 ± 0.9	68.6 ± 24.0 ($P = 0.1$)
1b, 10 μM, $N = 3$	73.6 ± 7.5	73.2 ± 6.9 ($P > 0.1$)
8, 10 μM, $N = 6$	32.8 ± 8.6	60.0 ± 13.9 ($P = 0.038$)

[a] According to protocol #3 (8 min preincubation of cells with inhibitors only, either in the dark or under UV irradiation, followed by washing of the cells, and incubation with [^{14}C]anandamide only; see Biological Evaluation and Experimental Section for a detailed description of this protocol). Data are means ± SE of $N = 3$ or 6 experiments. Statistically significant differences between dark and UV are shown and were calculated by ANOVA followed by the Student Newman Keuls test.

The second subgroup of headgroup-modified **OMDM-1**,**2** analogues, comprises compounds **3a**, **4a**, **3b**, **4b**, **3c**, and **4c**, where the aromatic region of **OMDM-1**,**2** was left unaltered, whereas the ethanolamine moiety was replaced by an electrophilic halo- or acyloxymethyl ketone group. Within this subgroup, only three compounds (**3a**, **3c**, and **4c**) exhibited moderate potency in inhibiting [^{14}C]AEA uptake in RBL-2H3 when co-incubated with the radiolabeled substrate (IC_{50} values ranging between 7.5 and 16.0 μM, protocol #1), whereas the other three did not inhibit the uptake up to a 25 μM concentration. However, **3a**, **3c**, and **4c** were no longer active when they were only preincubated with cells for up to 60 min in the absence of the substrate and then washed before adding [^{14}C]-AEA (protocol #2). This indicates that none of these putative covalent inhibitors binds stably to any of the potential proteins involved in AEA cellular uptake under our experimental conditions. Finally, none of the six compounds of this second group of headgroup-modified **OMDM-1**,**2** analogues inhibited [^{14}C]AEA hydrolysis by rat brain membranes ($IC_{50} > 50$ μM, data not shown).

To the group of **OMDM-1**,**2** analogues with alkyl tail modifications belong eight compounds, six of which were designed to covalently bind to the putative AEA membrane

transporter under normal cell culturing conditions and one, compound **8**, only after exposure to UV light. The eighth compound of this group, **7**, was synthesized as a noncovalent reference compound for **8**. All but one (i.e., **6c**) of the six potential covalent inhibitors exhibited affinity for putative transporter by inhibiting [^{14}C]AEA uptake in co-incubation experiments (IC_{50} values ranging between 10.2 and >25 μM, protocol #1), the most potent of which were **5a**, **5b**, and **6b** (IC_{50} = 10.2, 10.8, and 14.0 μM, respectively). In this series, a marked enantioselectivity was observed with all three couples of enantiomers similar to that previously reported for other **OMDM-1**,**2** analogues.[18] Interestingly, three more potent enantiomers in each couple, that is, **5a**, **5b**, and **5c**, became significantly more potent if preincubated with cells for 10 min and then co-incubated with [^{14}C]AEA (IC_{50} = 2.1 ± 0.3, 2.4 ± 0.3, and 2.5 ± 0.4 μM, respectively, mean ± SE, N = 3). This suggests that allowing more time to the compounds of these series to interact with the cells might sensibly improve their potency. However, none of these three compounds inhibited the uptake when they were only preincubated with cells for up to 1 h in the absence of [^{14}C]AEA and then washed prior to the introduction of the radiolabeled substrate in the incubation medium (protocol #2).

Compound **8** and not **7** exhibited some affinity for the putative transporter when using protocol #1 (IC_{50} = 11.0 μM) and was therefore tested using protocol #3 with and without exposure to UV light. In this case, 10 μM **8** could inhibit [^{14}C]AEA uptake when only preincubated with cells and then washed prior to introduction of [^{14}C]AEA, and UV exposure significantly enhanced this effect of the compound, thus suggesting a possible photoactivation of **8** binding to the protein(s) involved in AEA membrane transport.

Finally, none of the eight compounds of this second group of **OMDM-1**,**2** analogues inhibited [^{14}C]AEA hydrolysis by rat brain membranes under all conditions tested (IC_{50} >50 μM, either with or without UV irradiation; data not shown).

Of the headgroup derivatives, the ones whereupon the *p*-hydroxy-phenyl group of **OMDM-1**,**2** was substituted with a benzophenone group, either underivatized (**1a**, **2a**) or containing a *p*-hydroxy group (**1b**, **2b**), and the ones where the hydroxymethyl group of the ethanolamine portion was substituted with a 2-chloromethyl ketone group (**3a**) or an *o*,*o*′-dichloro benzoyloxymethyl ketone group (**4c**) were the ones with the highest affinity for the putative transporter. However, none of the new headgroup analogues was more potent than the parent compounds **OMDM-1**,**2**. These findings confirm that if there is any membrane protein specifically involved in AEA cellular reuptake its binding site has lower affinity for inhibitors with headgroups that are too big and/or polar and at the same time do not exhibit a high degree of aromatization.[36] Furthermore, even with those headgroups possessing several aromatic rings (**3c**, **4c**), or that are small but hydrophobic (**3a**, **4a**), a certain configuration (generally, but not always, *S*) is required for optimal activity, as previously shown for other analogues of **OMDM-1**,**2**.[18]

Regarding the alkyl chain derivatives of **OMDM-1**,**2**, again none of the new compounds developed here exhibited a higher affinity than the parent compounds for the putative AEA transporter, in agreement with previous findings with arvanil and its alkyl chain derivatives.[37,38] However, we found here that with some of the new derivatives belonging to this subgroup a short preincubation with the cells can significantly enhance their capability to inhibit AEA uptake and that a certain enantioselectivity of the chiral carbon atom (generally *S*) is required for optimal inhibitory activity.

Possibly the most novel finding of our present study is that although all novel compounds were designed to form covalent bonds with the putative AEA transporter either following long preexposure of the cells under normal light culturing conditions or after UV irradiation three of them were indeed capable of inhibiting AEA cellular uptake in a way that resisted thorough washes of the cells with a BSA-containing medium; therefore, this suggests a possible irreversible binding with the putative protein(s) mediating this process. In fact, the observation that out of 21 analogues with similar chemical properties the inhibitory effects of only 3 compounds were resistant to repeated washes validates our procedure as a possible means to assess covalent or at least stable bonds with inhibitors of AEA uptake. However, these three compounds, that is, **1a**, **1b**, and **8**, were designed to form covalent bonds with specific proteins only after UV irradiation, and only the inhibitory effect of the latter was significantly improved by UV irradiation, thus indicating that perhaps the resistance to repeated washes of the inhibitory effects is not always diagnostic of covalent inhibitors. However, it must be emphasized that at least at one of the two concentrations tested the inhibitory effect of **1b** showed a strong trend (P = 0.1) toward being enhanced following UV irradiation. It is therefore possible that photoactivatable labeling of the putative protein(s) mediating AEA cellular uptake can occur in parts of the binding site(s) that correspond to the positioning of both the headgroup and the alkyl chain of the inhibitor. However, because **8** did not inhibit AEA hydrolysis, either when co-incubated or when preincubated with rat brain membranes in the presence or absence of UV irradiation, it is very unlikely that its stable inhibition of AEA cellular uptake is due to the inhibition of intracellular AEA hydrolysis by FAAH.

In conclusion, we have reported here the development of several novel compounds designed with the purpose of obtaining covalent labeling of the putative AEA membrane transporter or the other protein(s) participating in AEA cellular uptake. Most of the new compounds exhibited an affinity for this process, as shown by their capability to inhibit the uptake of radiolabeled AEA when co-incubated with this compound. Furthermore, three UV-sensitive compounds, selected among those with the highest affinity for the putative AEA membrane transporter, stably inhibited AEA uptake even after repeated washes of the cells, and one of them did so more effectively following UV irradiation. A recent elegant study showed that high-affinity binding sites for some tetrazole-based urea derivatives are present on the membrane of RBL-2H3 cells and are responsible for the facilitated uptake of AEA by these cells.[39] However, the authors did not investigate the stable (possibly covalent) binding of any of their compounds to the putative membrane transporter. Therefore, our data simultaneously provide further evidence for the existence of specific protein(s) mediating AEA cellular uptake and new tools that might be useful for the isolation and molecular characterization of these proteins.

Experimental Section

Chemistry. All chemical reagents were commercially available. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured at 20 °C with a Schmidt-Haensch Polartronic D polarimeter (1 dm-cell) in 1% $CHCl_3$ solutions unless otherwise indicated. IR spectra were recorded on a Perkin-Elmer 1000 FT-IR spectrophotometer as KBr disks unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury 300 or a Bruker AMX300 spec-

trometer using $CDCl_3$ as the solvent unless otherwise indicated and TMS as the internal standard. The ESI mass spectra were run on a FINNIGAN LQC advantage spectrometer. FAB spectra were recorded on a JEOL JMX DX300 spectrometer. Satisfactory elemental analyses were obtained for the newly synthesized compounds (C, H, N ± 0.4%).

Compounds **25**,[27] **26**,[28] **27**,[28] **37**,[34] and 2-azido-5-iodobenzoic acid[35] have been described in the literature.

(*S*)-*N*-Boc-4-iodophenylalaninol ((*S*)-10). To a stirred solution of (*S*)-*N*-Boc-4-iodophenylalanine ((*S*)-**9**) (1.60 g, 4.10 mmol) in anhydrous THF (35 mL), *N*-methylmorpholine (4.5 mL, 4.10 mmol) and isobutyl chloroformate (0.55 mL, 4.10 mmol) were added at −15 °C. After stirring at −15 °C for 15 min, the solid was removed by filtration and washed with anhydrous THF, and the filtrate was treated dropwise with a solution of $NaBH_4$ (235 mg, 6.20 mmol) in H_2O (1.5 mL) at −15 °C under stirring. The reaction mixture was stirred for 30 min at −15 °C and then diluted with H_2O at room temperature. The resulting precipitate was filtered off after 30 min, washed with H_2O and hexane, and dried under vacuum (1.19 g, 89%). Mp 143−145 °C; $[\alpha]_D$ −23°; IR: 3377, 3273, 1659, 1549, 1318, 1175 cm^{-1}; ^1H NMR (300 MHz) δ: 1.40 (9H, s), 2.78 (2H, d, J = 6.9 Hz and 1H br s, overlapped), 3.52 (1H, dd, J = 11.1, 5.1 Hz), 3.62 (1H, dd, J = 11.1, 3.9 Hz), 3.82 (1H, m), 4.88 (1H, m), 6.97 (2H, d, J = 8.1 Hz), 7.61 (2H, d, J = 8.1 Hz); ^{13}C NMR (75 MHz): δ 28.32, 36.92, 53.41, 63.81, 79.86, 91.73, 128.53, 129.29, 131.39, 137.52, 156.04. Anal. ($C_{14}H_{20}INO_3$) C, H, N.

(*R*)-*N*-Boc-4-iodophenylalaninol ((*R*)-10). The title compound was prepared following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 83%; mp 144−146 °C; $[\alpha]_D$ +23°. Anal. ($C_{14}H_{20}INO_3$) C, H, N.

(*S*)-*N*-Boc-4-iodophenylalaninol Acetate ((*S*)-11). To a stirred solution of (*S*)-**10** (1.18 g, 3.13 mmol) in anhydrous pyridine (6.9 mL) was added acetic anhydride (3.4 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature and then poured into ice/water. The resulting solid was filtered off, washed with H_2O, and dried under vacuum to give 1.21 g (100%) of ester (*S*)-**11** as a white solid. Mp 118−120 °C; $[\alpha]_D$ −2°; IR: 3363, 2980, 1739, 1682, 1530, 1444, 1368, 1299, 1170, 1059 cm^{-1}; ^1H NMR (300 MHz) δ: 1.41 (9H, s), 2.08 (3H, s), 2.73 (1H, dd, J = 13.5, 8.4 Hz), 2.80 (1H, dd, J = 13.5, 6.0 Hz), 4.02 (2H, d, J = 4.0 Hz), 4.06 (1H, m), 4.65 (1H, m), 6.94 (2H, d, J = 8.4 Hz), 7.61 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz): δ 20.84, 28.33, 37.53, 50.58, 79.84, 131.30, 131.32, 136.94, 137.65, 155.02, 170.86. Anal. ($C_{16}H_{22}INO_4$) C, H, N.

(*R*)-*N*-Boc-4-iodophenylalaninol Acetate ((*R*)-11). The title compound was prepared following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 83%; mp 117−118 °C; $[\alpha]_D$ +2°. Anal. ($C_{16}H_{22}INO_4$) C, H, N.

(*S*)-*N*-Boc-4-trimethylstannylphenylalaninol Acetate ((*S*)-12). A stirred mixture of (*S*)-**11** (0.605 g, 1.44 mmol), $Me_3SnSnMe_3$ (0.42 mL, 2.02 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), and PPh_3 (30 mg, 0.12 mmol) in toluene (5.8 mL) was purged with N_2 for 15 min at room temperature and then heated at 100 °C for 15 min under N_2. The reaction mixture was then filtered through a short pad of silica gel, diluted with Et_2O, washed twice with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (0.73 g) was chromatographed on silica gel (22 g) using hexane/AcOEt = 9/1 as eluent to give 0.58 g (88%) of (*S*)-**12** as a white solid. Mp 60−62 °C; $[\alpha]_D$ −5°; IR ($CHCl_3$): 3367, 2982, 1731, 1689, 1529, 1263, 1173 cm^{-1}; ^1H NMR (300 MHz) δ: 0.27 (9H, t, J = 28.0 Hz), 1.41 (9H, s), 2.09 (3H, s), 2.77 (1H, dd, J = 13.5, 8.4 Hz), 2.87 (1H, dd, J = 13.5, 6.0 Hz), 4.02 (2H, d, J = 4.8 Hz), 4.09 (1H, m), 4.66 (1H, m), 7.16 (2H, d, J = 7.6 Hz), 7.42 (2H, d, J = 7.6 Hz); ^{13}C NMR (75 MHz): δ −9.59 (t, J = 175 Hz), 20.87, 28.35, 37.94, 50.60, 65.13, 79.29, 129.1, 136.08, 137.11, 140.19, 155.20, 170.92. Anal. ($C_{19}H_{31}NO_4Sn$) C, H, N.

(*R*)-*N*-Boc-4-trimethylstannylphenylalaninol Acetate ((*R*)-12). The title compound was prepared following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 86%; mp 57−61 °C; $[\alpha]_D$ +5°. Anal. ($C_{19}H_{31}NO_4Sn$) C, H, N.

(*S*)-*N*-Boc-4-benzoylphenylalaninol Acetate ((*S*)-13a). A mixture of (*S*)-**12** (209 mg, 0.5 mmol), C_6H_5I (0.062 mL, 0.55 mmol), $PdCl_2$ (5 mg, 0.025 mmol), and PPh_3 (13 mg, 0.05 mmol) in DMF (2 mL) was purged with carbon monoxide for 15 min and then stirred at 90 °C for 8 h under a CO baloon. The reaction mixture was then diluted with AcOEt (10 mL) and stirred at room temperature with saturated aqueous KF (1 mL) for 30 min. The precipitate was filtered off, and the organic phase was washed three times with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (252 mg) was chromatographed on silica gel (8 g) using hexane/AcOEt = 7/3 as eluent to give (*S*)-**13a** as a white solid (168 mg, 84%). Mp 92−94 °C; $[\alpha]_D$ −16°; IR: 3363, 2983, 1720, 1689, 1670, 1609, 1525, 1367, 1265, 1168 cm^{-1}; ^1H NMR (300 MHz) δ: 1.42 (9H, s), 2.11 (3H, s), 2.86−2.99 (2H, m), 4.07 (2H, d, J = 4.5 Hz), 4.15 (1H, m), 4.75 (1H, d, J = 7.8 Hz), 7.31−7.79 (9H, m); ^{13}C NMR (75 MHz): δ 20.79, 28.28, 38.03, 50.51, 65.04, 79.64, 128.05, 128.99, 129.73, 130.21, 132.12, 135.84, 137.43, 142.11, 154.87, 170.53, 195.95. Anal. ($C_{23}H_{27}NO_5$) C, H, N.

(*R*)-*N*-Boc-4-benzoylphenylalaninol Acetate ((*R*)-13a). Prepared following the same procedure that was used for the synthesis of (*S*)-enantiomer. Yield 79%; mp 90−92 °C; $[\alpha]_D$ +16°. Anal. ($C_{23}H_{27}NO_5$) C, H, N.

(*S*)-*N*-Boc-4-benzoylphenylalaninol ((*S*)-14a). To a solution of (*S*)-**13a** (150 mg, 0.38 mmol) in MeOH (1.5 mL), 2 N NaOH (0.38 mL) was added, and the mixture was stirred at room temperature for 4 h, diluted with water, and extracted with AcOEt. The organic solution was washed with water, dried (Na_2SO_4), and evaporated under vacuum. The residue (121 mg) was chromatographed on silica gel (3.5 g) using hexane/AcOEt = 1/1 as eluent to give (*S*)-**14a** as a white solid (112 mg, 84%). Mp 122−124 °C; $[\alpha]_D$ −28°; IR: 3356, 2970, 1686, 1655, 1527, 1278, 1170, 1007 cm^{-1}; ^1H NMR (300 MHz) δ: 1.41 (9H, s), 2.56 (1H, br s), 2.95 (2H, d, J = 7.8 Hz), 3.59 (1H, dd, J = 11.0, 5.1 Hz), 3.69 (1H, dd, J = 11.0, 3.9 Hz), 3.92 (1H, m), 4.88 (1H, m), 7.33−7.79 (9H, m); ^{13}C NMR (75 MHz): δ 28.36, 37.50, 53.53, 64.10, 79.86, 128.30, 128.31, 129.31, 130.00, 130.44, 132.40, 135.91, 137.69, 143.18, 156.01, 196.53. Anal. ($C_{21}H_{25}NO_4$) C, H, N.

(*R*)-*N*-Boc-4-benzoylphenylalaninol ((*R*)-14a). The title compound was prepared following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 93%; mp 121−123 °C; $[\alpha]_D$ +28°. Anal. ($C_{21}H_{25}NO_4$) C, H, N.

(*S*)-4-Benzoylphenylalaninol Hydrochloride ((*S*)-15a). To a solution of (*S*)-**14a** (102 mg, 0.29 mmol) in anhydrous MeOH (1 mL), $SOCl_2$ (0.022 mL, 0.29 mmol) was added, and the mixture was stirred at 50 °C for 3 h. Evaporation of the solution under vacuum furnished (*S*)-**15a** as a white solid (84 mg, 100%), which was used without further purification in the next step.

(*R*)-4-Benzoylphenylalaninol Hydrochloride ((*R*)-15a). The title compound was prepared following the same procedure that was used for the synthesis of the (*S*)-enantiomer.

(*Z*)-*N*-{(1*S*)-2-Hydroxy-1-[(4-benzoylphenyl)methyl]ethyl}-9-octadecenamide (1a). To a stirred solution of oleic acid (81 mg, 0.29 mmol) in DMF (1 mL) were added at 0 °C HOBt (41 mg, 0.30 mmol) and EDC (58 mg, 0.30 mmol). The mixture was stirred for 15 min at 0 °C and for 1 h at room temperature, and (*S*)-**15a** (84 mg, 0.29 mmol) and Et_3N (0.040 mL, 0.29 mmol) were added, and the mixture was stirred overnight at room temperature. The mixture was diluted with brine and extracted with AcOEt. The organic phase was washed with 10% citric acid solution, saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (145 mg) was chromatographed on silica gel (6 g) using hexane/AcOEt = 7/3 as eluent to give 96 mg (64%) of **1a** as a white solid. Mp 69−70 °C; $[\alpha]_D$ −16°; IR: 3296, 2925, 1646, 1541, 1446, 1317, 1277, 1176 cm^{-1}; ^1H NMR (300 MHz) δ: 0.88 (3H, t, J = 6.6 Hz), 1.26 (20H, m), 1.55−1.59 (2H, m), 1.99 (4H, m), 2.15 (2H, t, J = 7.6 Hz), 2.96−2.99 (2H, m), 3.18 (1H, br s), 3.61 (1H, dd, J = 11.0, 5.1 Hz), 3.66 (1H, dd, J = 11.0, 3.9 Hz), 4.21 (1H, m), 6.00 (1H, d, J = 7.9 Hz), 7.34−7.78 (9H, m); ^{13}C NMR (75 MHz): δ 14.12, 22.68, 25.73, 27.17, 27.23, 29.14, 29.21, 29.27, 29.31, 29.33, 29.53, 29.72, 29.77, 31.90, 36.82, 37.03, 52.43, 63.74,

128.31, 129.24, 129.70, 129.97, 130.01, 130.46, 132.44, 135.95, 137.60, 143.11, 173.80, 196.48. Anal. ($C_{34}H_{49}NO_3$) C, H, N.

(*R*)-*N*-{(1*S*)-2-Hydroxy-1-[(4-benzoylphenyl)methyl]ethyl}-9-octadecenamide (2a). The title compound was prepared following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 66%; mp 70−71 °C; $[\alpha]_D$ +16°. Anal. ($C_{34}H_{49}NO_3$) C, H, N.

(*S*)-*N*,*O*-BisBoc-4-(4-hydroxybenzoyl)phenylalaninol Acetate ((*S*)-13b). A mixture of (*S*)-**12** (228 mg, 0.5 mmol), *O*-Boc-4-hydroxy-1-iodobenzene (176 mg, 0.55 mmol), $PdCl_2$ (5 mg, 0.025 mmol), and PPh_3 (13 mg, 0.05 mmol) in DMF (2 mL) was purged with carbon monoxide for 15 min and then stirred at 90 °C for 3.5 h under a CO baloon. The reaction mixture was then diluted with AcOEt (10 mL) and stirred at room temperature with a saturated aqueous KF solution (1 mL) for 30 min. The precipitate was filtered off, and the organic phase was washed three times with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (336 mg) was chromatographed on silica gel (14 g) using hexane/AcOEt = 75/25 as eluent to give (*S*)-**13b** as a white solid (133 mg, 52%). Mp 72−75 °C; $[\alpha]_D$ −13°; IR: 3358, 2982, 1759, 1720, 1685, 1607, 1525, 1370, 1272, 1148, 1047 cm^{-1}; ^1H NMR (300 MHz) δ: 1.42 (9H, s), 1.58 (9H, s), 2.09 (3H, s), 2.87−2.94 (2H, m), 4.07 (2H, d, J = 4.4 Hz), 4.15 (1H, m), 4.72 (1H, m), 7.27−7.84 (8H, m); ^{13}C NMR (75 MHz): δ 20.83, 27.69, 28.33, 38.06, 50.57, 65.16, 79.80, 84.21, 121.12, 129.28, 130.36, 131.56, 135.00, 135.97, 142.45, 151.21, 154.19, 170.85, 195.09. Anal. ($C_{28}H_{35}NO_8$) C, H, N.

(*R*)-*N*,*O*-BisBoc-4-(4-hydroxybenzoyl)phenylalaninol Acetate ((*R*)-13b). The title compound was prepared following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 54%; mp 75−77 °C; $[\alpha]_D$ +13°. Anal. ($C_{28}H_{35}NO_8$) C, H, N.

(*S*)-*N*-Boc-4-(4-hydroxybenzoyl)phenylalaninol ((*S*)-14b). To a solution of (*S*)-**13b** (114 mg, 0.22 mmol) in MeOH (2 mL), 2 N NaOH (0.5 mL) was added, and the mixture was stirred at room temperature for 4 h, diluted with water, acidified with 2 N HCl to pH 3−4, and extracted with AcOEt. The organic solution was washed with water until neutral pH, dried (Na_2SO_4), and evaporated under vacuum to give 80 mg (98%) of (*S*)-**14b** as a white solid. Mp 210−212 °C; $[\alpha]_D$ −31° ($CHCl_3$/MeOH = 1/1, c 1.0); IR: 3351, 3180, 2971, 1686, 1638, 1517, 1278, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$ = 1/1) δ: 1.40 (9H, s), 2.87 (1H, dd, J = 13.5, 6.0 Hz), 2.96 (1H, dd, J = 13.5, 8.4 Hz), 3.54 (1H, dd, J = 11.2, 4.8 Hz), 3.59 (1H, dd, J = 11.2, 4.4 Hz), 3.87 (1H, m), 5.75 (1H, m), 6.88−7.76 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 1/1): δ 28.43, 37.76, 53.80, 63.53, 79.85, 115.48, 129.21, 129.58, 130.24, 133.25, 136.69, 143.60, 156.74, 156.78, 162.27. Anal. ($C_{21}H_{25}NO_5$) C, H, N.

(*R*)-*N*-Boc-4-(4-hydroxybenzoyl)phenylalaninol ((*R*)-14b). The title compound was prepared following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 99%; mp 213-215 °C; $[\alpha]_D$ +32° ($CHCl_3$/MeOH = 1/1, c 1.0). Anal. ($C_{21}H_{25}NO_5$) C, H, N.

(*S*)-4-(4-Hydroxybenzoyl)phenylalaninol Hydrochloride ((*S*)-15b). The title compound was prepared following the same procedure that was used for the synthesis of (*S*)-**15a**.

(*R*)-4-(4-Hydroxybenzoyl)phenylalaninol Hydrochloride ((*R*)-15b). The title compound was prepared following the same procedure that was used for the synthesis of (*R*)-**15a.**

(*Z*)-*N*-{(1*S*)-2-Hydroxy-1-[[4-(4-hydroxybenzoyl)phenyl]methyl]etil}-9-octadecenamide (1b). The title compound was prepared from (*S*)-**15b**, following the same procedure that was used for the synthesis of **1a.** Yield 65%; mp 115−116 °C; $[\alpha]_D$ −14°; IR: 3302, 3145, 2923, 1645, 1602, 1541, 1318, 1297, 1168, 1044 cm^{-1}; ^1H NMR (300 MHz) δ: 0.87 (3H, t, J = 6.6 Hz), 1.26 (20H, m), 1.57 (2H, m), 1.98 (4H, m), 2.17 (2H, t, J = 7.2 Hz), 2.49 (2H, m), 2.86−2.99 (2H, m), 3.55 (1H, dd, J = 11.1, 4.5 Hz), 3.63 (1H, dd, J = 3.9 Hz), 4.19 (1H, m), 5.26−5.38 (2H, m), 6.42 (1H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.7 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.62 (2H, d, J = 7.8 Hz), 7.68 (2H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz): δ 14.12, 22.70, 25.78, 27.19, 27.23, 29.16, 29.22, 29.27, 29.33, 29.55, 29.73, 29.78, 31.92, 36.74, 36.79, 36.99, 52.33, 52.42, 63.24, 115.31, 128.97, 129.12, 129.73, 130.04, 130.11, 132.92, 136.63, 142.43, 161.66, 174.47, 196.01. Anal. ($C_{34}H_{49}NO_4$) C, H, N.

(*Z*)-*N*-{(1*R*)-2-Hydroxy-1-[[4-(4-hydroxybenzoyl)phenyl]methyl]ethyl}-9-octadecenamide (2b). The title compound was prepared from (*R*)-**15b**, following the same procedure that was used for the synthesis of **1a**. Yield 62%; mp 114−116 °C; $[\alpha]_D$ +14°. Anal. ($C_{34}H_{49}NO_4$) C, H, N.

(*S*)-*N*-Boc-4-(ethoxycarbonyl)phenylalaninol ((*S*)-16). A mixture of (*S*)-**10** (2.45 g, 6.49 mmol), $Pd(OAc)_2$ (44 mg, 0.19 mmol), PPh_3 (102 mg, 0.39 mmol), EtOH (7.6 mL, 130 mmol), and Et_3N (1.82 mL, 13 mmol) in DMF (26 mL) was purged with carbon monoxide for 5 min at room temperature and then stirred under a CO baloon at 80 °C overnight. The mixture was diluted with brine and extracted with AcOEt. The organic phase was washed three times with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (2.64 g) was chromatographed on silica gel (105 g) using hexane/AcOEt = 75/25 as eluent to give 1.13 g (54%) of (*S*)-**16** as a white solid. Mp 103−104 °C; $[\alpha]_D$ −25°; IR: 3351, 2981, 1718, 1684, 1611, 1529, 1446, 1368, 1276, 1179, 1104, 1006 cm^{-1}; ^1H NMR (300 MHz) δ: 1.39 (3H, t, J = 7.0 Hz), 1.40 (9H, s), 2.64 (1H, br s), 2.91 (2H, d, J = 6.6 Hz), 3.54 (1H, dd, J = 11.0, 4.6 Hz), 3.65 (1H, dd, J = 11.0, 3.7 Hz), 3.88 (1H, br s), 4.37 (2H, q, J = 7.0 Hz), 4.88 (1H, m), 7.30 (2H, d, J = 8.2 Hz), 7.97 (2H, d, J = 8.2 Hz); ^{13}C NMR (75 MHz): δ 14.34, 28.33, 37.43, 53.47, 60.93, 63.97, 79.88, 128.80, 129.33, 129.79, 143.41, 156.02, 166.60. Anal. ($C_{17}H_{25}NO_5$) C, H, N.

(*R*)-*N*-Boc-4-(ethoxycarbonyl)phenylalaninol ((*R*)-16). The title compound was prepared following the same procedure that was used for the synthesis of (*S*)-**16**. Yield 53%; mp 102−104 °C; $[\alpha]_D$ +25°. Anal. ($C_{17}H_{25}NO_5$) C, H, N.

(*S*)-4-(Ethoxycarbonyl)phenylalaninol Hydrochloride ((*S*)-17). To a solution of (*S*)-**16** (1.021 g, 3.16 mmol) in AcOEt (6.7 mL) was added a saturated solution of anhydrous HCl in AcOEt (13.5 mL). The solution was stirred at room temperature overnight and then evaporated under vacuum to leave 880 mg (100%) of (*S*)-**17** as a white powder, which was used in the next step without further purification.

(*R*)-4-(Ethoxycarbonyl)phenylalaninol Hydrochloride ((*R*)-17). The title compound was prepared following the same procedure that was used for the synthesis of (*S*)-**17**. Yield 100%.

(*Z*)-*N*-{(1*S*)-2-Hydroxy-1-[[4-(ethoxycarbonyl)phenyl]methyl]etil}-9-octadecenamide ((*S*)-18). To a stirred solution of oleic acid (741 mg, 2.62 mmol) in DMF (10 mL) was added at 0 °C HOBt (466 mg, 2.76 mmol) and EDC (529 mg, 2.76 mmol). The mixture was stirred for 15 min at 0 °C and for 1 h at room temperature, then a solution of (*S*)-**17** (883 mg, 3.16 mmol) in DMF (10 mL) and Et_3N (0.44 mL, 3.16 mmol) was added, and the mixture was stirred overnight at room temperature. The mixture was diluted with brine and extracted with AcOEt. The organic phase was washed with 10% citric acid solution, saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (1.77 g) was chromatographed on silica gel (55 g) using CH_2Cl_2/AcOEt = 1/1 as eluent to give 944 mg (74%) of (*S*)-**18** as an oil. $[\alpha]_D$ −17°; IR: 3435, 2928, 2856, 1711, 1658, 1509, 1465, 1280, 1207, 1180 cm^{-1}; ^1H NMR (300 MHz) δ: 0.88 (3H, t, J = 6.6 Hz), 1.26 (20H, m), 1.38 (3H, t, J = 7.2 Hz), 1.52−1.59 (2H, m), 1.97−2.01 (4H, m), 2.13 (2H, t, J = 7.5 Hz), 2.87−3.00 (2H, m), 3.53 (1H, br s), 3.56 (1H, dd, J = 11.1, 4.8 Hz), 3.64 (1H, dd, J = 11.1, 3.7 Hz), 4.16−4.22 (1H, m), 4.33 (2H, q, J = 7.2 Hz), 5.28−5.39 (2H, m), 6.08 (1H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.96 (2H, d, J = 8.1 Hz). ^{13}C NMR (75 MHz): δ 14.13, 14.33, 22.69, 25.74, 27.19, 27.24, 29.15, 29.19, 29.28, 29.34, 29.54, 29.74, 29.78, 31.92, 36.81, 37.02, 52.38, 60.96, 63.62, 128.86, 129.28, 129.70, 129.81, 130.02, 143.38, 166.56, 173.83. Anal. ($C_{30}H_{49}NO_4$) C, H, N.

(*Z*)-*N*-{(1*R*)-2-Hydroxy-1-[[4-(ethoxycarbonyl)phenyl]methyl]etil}-9-octadecenamide ((*R*)-18). The title compound was prepared following the same procedure that was used for the synthesis of (*S*)-**18**. Yield 70%; $[\alpha]_D$ +16°. Anal. ($C_{30}H_{49}NO_4$) C, H, N.

(*Z*)-*N*-{(1*S*)-2-Hydroxy-1-[(4-carboxyphenyl)methyl]etil}-9-octadecenamide Acetate ((*S*)-19). To a stirred solution of (*S*)-**18** (544 mg, 1.18 mmol) in THF/H_2O = 5/1 (19.5 mL) was added a 1 N LiOH solution (1.8 mL) dropwise at room temperature. The mixture was stirred overnight at 50 °C, acidified to pH 4 with 2 N HCl, and extracted with AcOEt. The organic phase was washed twice with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue of the crude hydroxy acid (541 mg, 100%) was dissolved in anhydrous pyridine (9.3 mL), and acetic anhydride (0.52 mL, 5.5 mmol) was added, and the solution was stirred for 4 h at room temperature. The mixture was poured into ice/water, and the resulting suspension was stirred for 30 min at room temperature and extracted with AcOEt. The organic phase was washed with 2 N HCl and brine until neutral, dried (Na_2SO_4), and evaporated under vacuum. The residue (560 mg) was chromatographed on silica gel (17 g) using CH_2Cl_2/AcOEt = 7/3 as eluent to give 363 mg (65%) of (*S*)-**19** as a colorless oil. $[\alpha]_D$ −3°; IR: 3439, 2928, 2856, 1736, 1693, 1666, 1508, 1235, 1203, 1042 cm^{-1}; ^1H NMR (300 MHz) δ: 0.88 (3H, t, J = 6.6 Hz), 1.26 (20H, m), 1.55−1.59 (2H, m), 1.97−2.01 (4H, m), 2.11 (3H, s), 2.16 (2H, t, J = 7.2 Hz), 2.86−3.00 (2H, m), 4.05 (1H, dd, J = 11.4, 4.2 Hz), 4.13 (1H, dd, J = 11.4, 5.6 Hz), 4.51 (1H, m), 5.28−5.39 (2H, m), 5.75 (1H, d, J = 8.7 Hz), 7.31 (2H, d, J = 8.1 Hz), 8.04 (2H, d, J = 8.1 Hz); ^{13}C NMR (75 MHz): δ 14.12, 20.84, 22.69, 25.64, 27.16, 27.22, 29.13, 29.25, 29.32, 29.53, 29.72, 29.77, 31.90, 36.77, 37.65, 49.32, 64.87, 128.16, 129.35, 129.73, 130.00, 130.50, 143.27, 170.97, 171.19, 173.17. Anal. ($C_{30}H_{47}NO_5$) C, H, N.

(*Z*)-*N*-{(1*R*)-2-Hydroxy-1-[(4-carboxyphenyl)methyl]etil}-9-octadecenamide Acetate ((*R*)-19). The title compound was prepared following the same procedure that was used for the synthesis of (*S*)-**19**. Yield 57%; $[\alpha]_D$ +4°. Anal. ($C_{30}H_{49}NO_4$) C, H, N.

(*Z*)-*N*-{(1*S*)-2-Hydroxy-1-[[4-(2-diazoacetyl)phenyl]methyl]-etil}-9-octadecenamide (1c). To a solution of (*S*)-**19** (408 mg, 0.82 mmol) in anhydrous CH_2Cl_2 (7.6 mL) were added DMF (26 μL, 0.33 mmol) and oxalyl chloride (0.28 mL, 3.28 mmol) at 0 °C under stirring. The mixture was stirred for 1 h at 0 °C, evaporated under vacuum at room temperature, redissolved in DMF (7.6 mL), and treated with Et_3N (0.34 mL, 2.46 mmol) and a 2 M ethereal solution of Me_3SiCHN_2 (1.23 mL) at 0 °C. The mixture was stirred for 5 h at 0 °C and then partitioned between brine and AcOEt. The organic phase was washed twice with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (478 mg) was chromatographed on silica gel (16 g) with CH_2Cl_2/AcOEt = 9/1 as eluent to give 56 mg (13%) of (*S*)-**20**. Intermediate (*S*)-**20** was dissolved in THF/H_2O = 5/1 (2 mL), and a 1 N LiOH solution (0.24 mL) was added under stirring at 0 °C. The mixture was stirred at 0 °C for 3.5 h, diluted with water, and extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (54 mg) was chromatographed on silica gel (16 g) with CH_2Cl_2/AcOEt = 1/1 as eluent to give 24 mg (68%) of **1c** as a white solid. Mp 72−74 °C; $[\alpha]_D$ −28°; IR: 3437, 2928, 2110, 1659, 1619, 1508, 1465, 1363, 1236 cm^{-1}; ^1H NMR (300 MHz) δ: 0.88 (3H, t, J = 6.7 Hz), 1.26 (20H, m), 1.55 (2H, m), 2.00 (4H, m), 2.13 (2H, t, J = 6.6 Hz), 2.87−3.00 (2H, m), 3.54 (1H, dd, J = 10.9, 4.3 Hz), 3.62 (1H, dd, J = 10.9, 3.6 Hz), 4.18 (1H, m), 5.28−5.39 (2H, m), 5.94 (1H, s), 6.19 (1H, d, J = 8.1 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.67 (2H, d, J = 8.1 Hz); ^{13}C NMR (75 MHz): δ 14.12, 22.69, 25.74, 27.19, 27.24, 29.17, 29.20, 29.30, 29.33, 29.53, 29.75, 29.77, 31.91, 36.78, 36.97, 52.33, 54.28, 63.45, 126.96, 129.62, 129.69, 130.04, 134.96, 143.58, 173.81, 186.21. Anal. ($C_{29}H_{45}N_3O_3$) C, H, N.

(*Z*)-*N*-{(1*R*)-2-Hydroxy-1-[[4-(2-diazoacetyl)phenyl]methyl]-etil}-9-octadecenamide (2c). The title compound was prepared following the same procedure that was used for the synthesis of **1c**. Overall yield 8%; mp 72−74 °C; $[\alpha]_D$ +27°. Anal. ($C_{29}H_{45}N_3O_3$) C, H, N.

(*Z*)-*N*-{(1*S*)-2-Hydroxy-1-[[4-(2-chloroacetyl)phenyl]methyl]-etil}-9-octadecenamide (1d). To a solution of **1c** (21 mg, 0.04 mmol) in AcOEt (1 mL) was added a saturated solution of anhydrous HCl in AcOEt (21 μL). The mixture was stirred at room temperature for 1 h and then evaporated under vacuum. The residue (22 mg) was chromatographed on silica gel (900 mg) using CH_2Cl_2/AcOEt = 1/1 as eluent to give 15 mg of **1d** as a white solid. Mp 82−83 °C; $[\alpha]_D$ −5 °C; IR: 3436, 2928, 1660, 1606, 1507, 1465, 1234 cm^{-1}; ^1H NMR (300 MHz) δ: 0.88 (3H, t, J = 6.6 Hz), 1.26 (20H, m), 1.54 (2H, m), 2.00 (4H, m), 2.14 (2H, t, J = 7.5 Hz), 2.52 (1H, br s), 2.96 (2H, d, J = 6.6 Hz), 3.57−3.69 (2H, m), 4.22 (1H, m), 4.69 (2H, s), 5.28−5.40 (2H, m), 5.91 (1H, d, J = 6.6 Hz), 7.37 (2H, d, J = 7.9 Hz), 7.89 (2H, d, J = 7.9 Hz); ^{13}C NMR (75 MHz): δ 14.12, 22.69, 25.70, 27.19, 27.25, 29.15, 29.19, 29.27, 29.34, 29.54, 29.73, 29.78, 31.92, 36.82, 37.14, 45.86, 52.26, 63.77, 128.90, 129.70, 129.82, 130.07, 132.76, 144.86, 173.74, 190.74. Anal. ($C_{29}H_{46}ClNO_3$) C, H, N.

(1*S*)-*N*-Boc-1-amino-3-azo-1-{[(4-hydroxyphenyl)methyl]propan-2-one} ((*S*)-22). To a solution of (*S*)-**21** (737 mg, 2.6 mmol) in anhydrous THF (9 mL) were added *i*-butyl chloroformate (0.38 mL, 2.9 mmol) and Et_3N (0.75 mL, 5.3 mmol) at −15 °C under a nitrogen atmosphere, and the mixture was stirred for 30 min at room temperature. An ethereal solution of diazomethane (24 mL, ca. 12 mmol) was added, and after stirring for a further 2 h, the solvent was evaporated under vacuum, and the residue was diluted with saturated $NaHCO_3$ and extracted with Et_2O. The organic phase was washed two times with brine, dried (Na_2SO_4), and evaporated under vacuum. Chromatography of the residue (961 mg) on silica gel (30 g) using hexane/AcOEt = 6/4 as eluent afforded (*S*)-**22** (544 mg, 68%) as a white solid. Mp 132−133 °C (lit.[26] 136−137 °C); $[\alpha]_D$ +12°; IR (KBr): 3369, 3074, 2123, 1676, 1607, 1591, 1526, 1453, 1339, 1253, 1172 cm^{-1}; ^1H NMR (300 MHz) δ: 1.42 (9H, s), 2.93 (2H, d, J = 6.6 Hz), 4.36 (1H, m), 5.22 (2H, m), 6.49 (1H, s), 6.75 (2H, d, J = 8.4 Hz), 7.01 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz): δ 28.32, 37.87, 54.81, 58.66, 80.45, 115.62, 126.69, 130.48, 155.20, 155.41, 193.77. Anal. ($C_{15}H_{19}N_3O_4$) C, H, N.

(1*R*)-*N*-Boc-1-amino-3-azo-1-{[(4-hydroxyphenyl)methyl]propan-2-one} ((*R*)-22). The title compound was prepared following the same procedure that was used for the synthesis of (*S*)-**22**. Yield 60%; mp 132−133 °C; $[\alpha]_D$ −14°. Anal. ($C_{15}H_{19}N_3O_4$) C, H, N.

(1*S*)-1-Amino-3-chloro-1-[(4-hydroxyphenyl)methyl]propan-2-one Hydrochloride ((*S*)-23). (*S*)-**22** (507 mg, 1.66 mmol) was dissolved in a 0.6 M solution of HCl in AcOEt (18 mL). The reaction mixture was stirred for 48 h at room temperature. The resulting precipitate was filtered off, washed with anhydrous diethyl ether, and dried under vacuum to give (*S*)-**23** (331 mg, 80%), which was used in the next step without further purification.

(1*R*)-1-Amino-3-chloro-1-[(4-hydroxyphenyl)methyl]propan-2-one Hydrochloride ((*R*)-23). The title compound was prepared from (*R*)-**22** following the same procedure that was used for the synthesis of (*S*)-enantiomer. Yield 76%.

(*Z*)-*N*-{(1*S*)-3-Chloro-1-[(4-hydroxyphenyl)methyl]propan-2-one}-9-octadecenamide (3a). To a stirred solution of oleic acid (374 mg, 1.32 mmol) in anhydrous THF (7 mL) were added *i*-butyl chloroformate (0.17 mL, 1.32 mmol) and *N*-methylmorpholine (0.29 mL, 2.64 mmol) at −15 °C under a nitrogen atmosphere. After 15 min, a solution of (*S*)-**23** (331 mg, 1.32 mmol) in DMF (1 mL) was added, and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with water and extracted with AcOEt. The organic phase was dried (Na_2SO_4) and evaporated under vacuum. The residue (734 mg) was chromatographed on silica gel (29 g) using hexane/AcOEt = 8/2 as eluent to provide **3a** (550 mg, 87%) as a white solid. Mp 89−91 °C; $[\alpha]_D$ +26°; IR (KBr): 3369, 2921, 2852, 1735, 1611, 1515, 1268, 1202 cm^{-1}; ^1H NMR (300 MHz) δ: 0.87 (3H, t, J = 6.8 Hz), 1.26 (20H, m), 1.57 (2H, m), 2.00 (4H, m), 2.16 (2H, t, J = 7.6 Hz), 2.90−3.04 (2H, m), 3.96 (1H, d, J = 16.2 Hz), 4.14 (1H, d, J = 16.2 Hz), 4.92−4.99 (1H, m), 5.28−5.40 (2H, m), 6.08 (1H, d, J = 7.6 Hz), 6.30 (1H, br s), 6.77 (2H, d, J = 8.4 Hz), 7.00 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz): δ 14.13, 22.69, 25.49, 27.17, 27.23, 29.10, 29.13, 29.19, 29.33, 29.53, 29.71, 29.77, 31.91, 36.30, 36.98, 47.59, 57.26, 115.97, 126.56, 129.73, 130.05, 130.19, 155.67, 173.76, 201.33. Anal. ($C_{28}H_{44}ClNO_3$) C, H, N.

(*Z*)-*N*-{(1*R*)-3-Chloro-1-[(4-hydroxyphenyl)methyl]propan-2-one}-9-octadecenamide (4a). The title compound was prepared

from oleic acid and (*R*)-**23**, following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 79%; mp 86−87 °C; $[\alpha]_D$ −27°. Anal. ($C_{28}H_{44}ClNO_3$) C, H, N.

(*Z*)-*N*-{(1*S*)-3-Iodo-1-[(4-hydroxyphenyl)methyl]propan-2-one}-9-octadecenamide (3b). A mixture of **3a** (300 mg, 0.63 mmol) and NaI (900 mg, 6.3 mmol) in acetone (6 mL) was stirred for 16 h at room temperature. The mixture was diluted with water and extracted with AcOEt. The organic phase was washed twice with water, dried (Na_2SO_4), and evaporated under vacuum. The residue (448 mg) was chromatographed on silica gel (14 g, hexane/AcOEt = 9/1) to provide **3b** (218 mg, 61%) as a white solid. Mp 87−89 °C; $[\alpha]_D$ +19°; IR (KBr): 3358, 2922, 2851, 1723, 1610, 1540, 1513, 1325, 1266, 1217 cm^{-1}; ^1H NMR (300 MHz) δ: 0.88 (3H, t, J = 6.8 Hz), 1.26 (20H, m), 1.58 (2H, m), 2.00 (4H, m), 2.18 (2H, t, J = 7.2 Hz), 3.00−3.03 (2H, m), 3.74 (1H, d, J = 10.8 Hz), 3.78 (1H, d, J = 10.8 Hz), 5.08 (1H, m), 5.33−5.36 (2H, m), 6.08 (1H, d, J = 7.2 Hz), 6.28 (1H, br s), 6.78 (2H, d, J = 8.4 Hz), 7.02 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz): δ 4.40, 14.13, 22.69, 25.49, 27.18, 27.24, 29.11, 29.14, 29.21, 29.34, 29.54, 29.71, 29.78, 31.91, 36.44, 37.72, 57.01, 115.90, 129.54, 129.73, 130.05, 130.23, 155.42, 173.34, 201.71. Anal. ($C_{28}H_{44}INO_3$) C, H, N.

(*Z*)-*N*-{(1*R*)-3-Iodo-1-[(4-hydroxyphenyl)methyl]propan-2-one}-9-octadecenamide (4b). The title compound was prepared from **4a** following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 55%; mp 86−88 °C; $[\alpha]_D$ −18°. Anal. ($C_{28}H_{44}INO_3$) C, H, N.

(*Z*)-*N*-{(1*S*)-3-(2,6-Dichlorobenzoyloxy)-1-[(4-hydroxyphenyl)-methyl]propan-2-one}-9-octadecenamide (3c). A mixture of **3b** (66 mg, 0.114 mmol) and KF (13 mg, 0.23 mmol) in DMF (0.5 mL) was stirred for 1 min at room temperature. 2,6-Dichlorobenzoic acid (44 mg, 0.23 mmol) was then added and stirring was continued for 16 h at room temperature. The mixture was partitioned between water and AcOEt. The organic phase was washed twice with water, dried (Na_2SO_4), and evaporated under vacuum. The residue (103 mg) was chromatographed on silica gel (3 g, hexane/AcOEt = 8/2 as eluent) to provide **3c** (52 mg, 72%) as an oil. $[\alpha]_D$ +23°; IR ($CHCl_3$): 3424, 3011, 2928, 2855, 1737, 1667, 1515, 1434, 1264, 1206 cm^{-1}; ^1H NMR (300 MHz) δ: 0.87 (3H, t, J = 6.7 Hz), 1.26 (20H, m), 1.56 (2H, m), 2.00 (4H, m), 2.18 (2H, t, J = 7.2 Hz), 2.97 (1H, dd, J = 14.0, 6.8 Hz), 3.11 (1H, dd, J = 14.0, 6.8 Hz), 4.92 (2H, m), 5.00 (1H, m), 5.32−5.35 (2H, m), 6.17 (1H, d, J = 7.6 Hz), 6.74 (2H, d, J = 7.6 Hz), 7.02 (2H, d, J = 7.6 Hz), 7.33 (3H, m); ^{13}C NMR (75 MHz): δ 14.13, 22.70, 25.52, 27.21, 27.26, 29.13, 29.17, 29.18, 29.33, 29.55, 29.73, 29.79, 31.92, 36.42, 56.70, 68.07, 115.86, 126.72, 128.06, 129.79, 129.97, 130.04, 131.42, 132.26, 132.29, 155.59, 164.00, 173.66, 201.38. Anal. ($C_{35}H_{47}Cl_2NO_5$) C, H, N.

(*Z*)-*N*-{(1*R*)-3-(2,6-Dichlorobenzoyloxy)-1-[(4-hydroxyphenyl-)methyl]propan-2-one}-9-octadecenamide (4c). The title compound was prepared from **4b** following the same procedure that was used for the synthesis of **3c**. Yield 61%; $[\alpha]_D$ −24°. Anal. ($C_{35}H_{47}Cl_2NO_5$) C, H, N.

1-[(*t*-Butyldimethylsilyl)oxy]-18-[2-(tetrahydropyranyl)oxy]-9-octadecyne (28). To a stirred solution of **27**[28] (1.19 g, 5 mmol) in anhydrous THF (10 mL), a solution of 1.2 M *n*-BuLi in hexane (5 mL, 6 mmol) was added dropwise at −25 °C under nitrogen. After the mixture was stirred for 10 min at −25 °C, anhydrous hexamethylphosporamide (10 mL) was added, followed by a dropwise addition of a solution of **25**[27] (1.62 g, 5 mmol) in anhydrous THF (10 mL). The mixture was maintained at −25 °C for an additional 2 h, then stirred overnight at room temperature, and poured into ice/water (50 mL). Extraction with AcOEt, followed by three washings with brine, drying (Na_2SO_4), and evaporation under vacuum afforded a residue (2.51 g) that was chromatographed on silica gel (100 g) using hexane/AcOEt = 97/3 as eluent to give 1.95 g (81%) of **28** as a colorless liquid. ^1H NMR (300 MHz) δ: 0.03 (3H, s), 0.87 (9H, s), 1.28−1.87 (30H, m), 2.11 (4H, t, J = 6.9 Hz), 3.35 (1H, td, J = 9.9, 6.6 Hz), 3.48 (1H, m), 3.57 (2H, t, J = 6.6 Hz), 3.71 (1H, td, J = 9.9, 6.6 Hz), 3.85 (1H, m), 4.55 (1H, m); ^{13}C NMR (75 MHz): δ −4.88, 18.70, 19.10, 20.03, 25.86, 26.11, 26.32, 26.55, 29.15, 29.48, 29.67, 29.71, 30.07, 31.11, 33.19, 62.54, 63.55, 67.89, 80.39, 80.41, 99.00. Anal. ($C_{29}H_{56}O_3Si$) C, H, N.

(*Z*)-1-[(*t*-Butyldimethylsilyl)oxy]-18-[2-(tetrahydropyranyl)-oxy]-9-octadecene (29). To a stirred solution of $Ni(OAc)_2 \cdot 4H_2O$ (77 mg, 0.3 mmol) in 95% EtOH (5.2 mL), a 1 M solution of $NaBH_4$ in 95% EtOH (0.3 mL) was added at room temperature under nitrogen. To the suspension of the in situ generated catalyst, a solution of **28** (1.21 g, 2.5 mmol) in 95% EtOH (10 mL) was added after 30 min. The mixture was hydrogenated at room temperature for 2 h under atmospheric pressure, then filtered through a Celite pad, and evaporated under vacuum to afford 1.18 g (97%) of **29** as a colorless liquid. ^1H NMR (300 MHz,) δ: 0.04 (6H, s), 0.89 (9H, s), 1.25−1.85 (30H, m), 1.98−2.02 (4H, m), 3.37 (1H, td, J = 9.9, 6.6 Hz), 3.49 (1H, m), 3.59 (2H, t, J = 6.6 Hz), 3.73 (1H, td, J = 9.9, 6.6 Hz), 3.87 (1H, m), 4.57 (1H, m), 5.34 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.84, 18.73, 20.06, 25.88, 26.16, 26.34, 26.60, 27.56, 29.61, 29.77, 29.84, 30.10, 31.14, 33.23, 62.58, 63.59, 67.94, 99.04, 130.03. Anal. ($C_{29}H_{58}O_3Si$) C, H, N.

(*Z*)-1-Hydroxy-18-[2-(tetrahydropyranyl)oxy]-9-octadecene (30). Compound **29** (1.18 g, 2.4 mmol) was treated under stirring with a 1 M solution of *N*-tetrabutylammonium fluoride in THF (12.2 mL) for 2 h at room temperature under nitrogen. The solution was concentrated and partitioned between AcOEt and water. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (1.50 g) was chromatographed on silica gel (45 g) using CH_2Cl_2/AcOEt = 95/5 as eluent to give 0.83 g (92%) of **30** as a colorless liquid. ^1H NMR (300 MHz) δ: 1.24−1.84 (30H, m), 1.97−2.01 (4H, m), 3.37 (1H, td, J = 9.9, 6.6 Hz), 3.49 (1H, m), 3.61 (2H, t, J = 6.6 Hz), 3.72 (1H, td, J = 9.9, 6.6 Hz), 3.86 (1H, m), 4.57 (1H, m), 5.33 (1H, m); ^{13}C NMR (75 MHz): δ 20.03, 25.84, 26.11, 26.57, 27.53, 29.57, 29.81, 30.07, 31.11, 33.13, 62.61, 63.23, 67.98, 99.06, 130.05. Anal. ($C_{23}H_{44}O_3$) C, H, N.

(*Z*)-18-[2-(Tetrahydropyranyl)oxy]-9-octadecenoic Acid Methyl Ester (31). A mixture of **30** (605 mg, 1.64 mmol) and pyridinium dichromate (3.70 g, 9.84 mmol) in DMF (33 mL) was stirred at room temperature for 48 h and then was partitioned between AcOEt and water. The organic phase was washed three times with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (657 mg) was treated with an excess of an ethereal solution of diazomethane at 0 °C for 45 min. The ether was evaporated under vacuum and the residue (663 mg) was chromatographed on silica gel (15 g) with CH_2Cl_2 as eluent to give 553 mg (85%) of **31** as a colorless oil. ^1H NMR (300 MHz) δ: 1.22−1.81 (28H, m), 1.97−1.99 (4H, m), 2.27 (2H, t, J = 7.5 Hz), 3.35 (1H, td, J = 9.9, 6.6 Hz), 3.47 (1H, m), 3.64 (3H, s), 3.70 (1H, td, J = 9.9, 6.6 Hz), 3.84 (1H, m), 4.55 (1H, m), 5.31 (2H, m); ^{13}C NMR (75 MHz): δ 19.67, 24.91, 25.49, 26.21, 27.12, 27.17, 29.08, 29.11, 29.22, 29.45, 29.64, 29.71, 30.75, 34.04, 51.31, 62.20, 67.55, 98.65, 129.53, 129.70, 173.95. Anal. ($C_{24}H_{44}O_4$) C, H, N.

(*Z*)-18-Hydroxy-9-octadecenoic Acid Methyl Ester (32). A solution of **31** (1.05 g, 2.65 mmol) and pyridinium *p*-toluenesulfonate (67 mg, 0.27 mmol) in EtOH (22 mL) was stirred overnight at 55 °C. The solvent was evaporated under vacuum, and the residue was filtered through a short pad of silica gel using CH_2Cl_2 as the eluent to give 797 mg (96%) of **32** as a colorless oil. ^1H NMR (300 MHz) δ: 1.30 (18H, m), 1.52−1.64 (4H, m), 1.93 (1H, br s), 1.98−2.02 (4H, m), 2.30 (2H, t, J = 7.5 Hz), 3.62 (2H, t, J = 6.6 Hz), 3.66 (3H, s), 5.34 (2H, m); ^{13}C NMR (75 MHz): δ 24.91, 25.74, 27.12, 27.15, 29.04, 29.09, 29.11, 29.18, 29.39, 29.46, 29.63, 29.69, 32.75, 34.04, 51.36, 62.82, 129.56, 129.69, 174.07. Anal. ($C_{19}H_{36}O_3$) C, H, N.

(*Z*)-18-Bromo-9-octadecenoic Acid Methyl Ester (33). To a solution of **32** (797 mg, 2.55 mmol) in anhydrous CH_2Cl_2 (28 mL) were added at 0 °C CBr_4 (1.11 g, 3.34 mmol) and PPh_3 (938 mg, 3.58 mmol), and the mixture was stirred at 0 °C for 40 min. The solution was concentrated under vacuum and partitioned between AcOEt and water. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (1.97 g) was chromatographed on silica gel (40 g) using hexane/CH_2Cl_2 = 6/4 as eluent to give 889 mg (94%) of **33** as a colorless oil. ^1H NMR

(300 MHz) δ: 1.25−1.44 (18H, m), 1.59−1.64 (2H, m), 1.80−1.90 (2H, m), 1.98−2.02 (4H, m), 3.40 (2H, t, J = 6.9 Hz), 3.66 (3H, s), 5.34 (2H, m); ^{13}C NMR (75 MHz): δ 24.91, 27.13, 28.13, 28.70, 29.12, 29.28, 29.40, 29.64, 32.78, 33.87, 34.04, 51.32, 129.61, 173.93. Anal. ($C_{19}H_{35}BrO_2$) C, H, N.

(*Z*)-*N*-{(1*S*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl}-18-bromo-9-octadecenamide (5a). To a solution of **33** (210 mg, 0.56 mmol) in THF/H_2O = 5/1 (9.4 mL), a 1 M aqueous solution of LiOH (0.94 mL) was added, and the mixture was stirred overnight at room temperature. The solution was acidified to pH 4−5 with 2 N HCl and extracted with AcOEt. The organic phase was washed with water until neutral, dried (Na_2SO_4), and evaporated under vacuum. To a stirred solution of the residue of the (*Z*)-18-bromo-9-octadecenoic acid (**34**) (202 mg, 0.56 mmol) in DMF (3 mL), a solution of L-tyrosinol (127 mg, 0.62 mmol) in DMF (2 mL) and DCC (129 mg, 0.62 mmol) were added. The mixture was stirred overnight at room temperature and then partitioned between AcOEt and brine. The organic phase was washed with a 2 N HCl, water, saturated $NaHCO_3$, and water until neutral, dried (Na_2SO_4), and evaporated under vacuum. The residue (375 mg) was chromatographed on silica gel using CH_2Cl_2/AcOEt = 6/4 as eluent to give 118 mg (82%) of **5a** as a white solid. Mp 63−65 °C; $[\alpha]_D$ −13° ($CHCl_3$, c 1.0); IR ($CHCl_3$): 3432, 3343, 2929, 2855, 1652, 1614, 1513, 1464, 1242, 1194, 1172 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25−1.55 (20H, m), 1.80−1.89 (2H, m), 1.99 (4H, m), 2.14 (2H, t, J = 7.5 Hz), 2.66−2.80 (2H, m), 3.40 (2H, t, J = 6.9 Hz), 3.52 (1H, dd, J = 11.1, 5.1 Hz), 3.62 (1H, dd, J = 11.1, 3.6 Hz), 3.91 (1H, br s), 4.12 (1H, br s), 5.33 (2H, m), 6.06 (1H, d, J = 7.3 Hz), 6.72 (2H, d, J = 8.2 Hz), 6.98 (2H, d, J = 8.2 Hz), 8.14 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.70, 27.16, 28.12, 28.69, 29.12, 29.21, 29.65, 32.78, 34.01, 36.22, 36.77, 52.94, 63.79, 115.43, 128.49, 129.63, 129.65, 129.94, 154.91, 174.25. Anal. ($C_{27}H_{44}BrNO_3$) C, H, N.

(*Z*)-*N*-{(1*R*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl}-18-bromo-9-octadecenamide (6a). The title compound was prepared following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 74%; mp 63−65 °C; $[\alpha]_D$ +13°. Anal. ($C_{27}H_{44}BrNO_3$) C, H, N.

(*Z*)-*N*-{(1*S*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl}-18-iodo-9-octadecenamide (5b). A solution of **5a** (102 mg, 0.2 mmol) and NaI (150 mg, 1 mmol) in acetone (2 mL) was stirred overnight at room temperature, diluted with water, and extracted with AcOEt. The organic phase was dried (Na_2SO_4) and evaporated under vacuum to give 110 mg (99%) of **5b** as a white solid. Mp 67−68 °C; $[\alpha]_D$ −14°; IR ($CHCl_3$): 3433, 3345, 2928, 2855, 1654, 1514, 1465, 1234, 1199, 1172 cm^{-1}; ^{1}H NMR (300 MHz) δ: 1.25−1.54 (20H, m), 1.76−1.85 (2H, m), 1.99 (4H, m), 2.13 (2H, t, J = 7.5 Hz), 2.65−2.78 (2H, m), 3.17 (2H, t, J = 6.9 Hz), 3.51 (1H, dd, J = 11.1, 5.1 Hz), 3.60 (1H, dd, J = 11.1, 3.6 Hz), 3.80 (1H, br s), 4.11 (1H, br s), 5.33 (2H, m), 6.19 (1H, d, J = 7.8 Hz), 6.71 (2H, d, J = 8.1 Hz), 6.97 (2H, d, J = 8.1 Hz), 8.09 (1H, br s); ^{13}C NMR (75 MHz): δ 7.35, 25.69, 27.15, 28.44, 29.11, 29.20, 29.25, 29.62, 30.42, 33.48, 36.19, 36.75, 52.89, 63.60, 115.41, 128.44, 129.60, 129.63, 129.93, 154.90, 174.33. Anal. ($C_{27}H_{44}INO_3$) C, H, N.

(*Z*)-*N*-{(1*R*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl}-18-iodo-9-octadecenamide (6b). The title compound was prepared from **6a** following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 99%; mp 67−68 °C; $[\alpha]_D$ +14°. Anal. ($C_{27}H_{44}INO_3$) C, H, N.

(*Z*)-*N*-{(1*S*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl}-18-cyano-9-octadecenamide (5c). A solution of **5a** (102 mg, 0.2 mmol) and KCN (26 mg, 0.4 mmol) in DMSO (2 mL) was stirred overnight at room temperature, diluted with water, and extracted with AcOEt. The organic phase was washed twice with water, dried (Na_2SO_4), and evaporated under vacuum to give 91 mg (100%) of **5c** as a white solid. Mp 34−36 °C; $[\alpha]_D$ −12°; IR ($CHCl_3$): 3433, 3345, 2929, 2856, 2247, 1654, 1514, 1465, 1234, 1172 cm^{-1}; ^{1}H NMR (300 MHz) δ: 1.23−1.69 (22H, m), 1.99 (4H, m), 2.13 (2H, t, J = 7.6 Hz), 2.33 (2H, t, J = 6.9 Hz), 2.66−2.79 (2H, m), 3.51 (1H, dd, J = 11.1, 5.1 Hz), 3.60 (1H, dd, J = 11.1, 3.6 Hz), 3.90 (1H, br s), 4.11 (1H, m), 5.33 (2H, m), 6.26 (1H, d, J = 8.4 Hz), 6.72 (2H, d, J = 8.5 Hz), 6.98 (2H, d, J = 8.5 Hz), 8.17 (1H, br s); ^{13}C NMR (75 MHz): δ 17.05, 25.25, 25.70, 27.07, 27.14, 28.57, 28.65, 29.01, 29.09, 29.17, 29.57, 29.65, 36.13, 36.70, 52.91, 63.54, 115.37, 119.75, 128.45, 129.55, 129.67, 129.94, 154.99, 162.44, 174.28. Anal. ($C_{28}H_{44}N_2O_3$) C, H, N.

(*Z*)-*N*-{(1*R*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl}-18-cyano-9-octadecenamide (6c). The title compound was prepared from **6a**, following the same procedure that was used for the synthesis of the (*S*)-enantiomer. Yield 99%; mp 34−36 °C; $[\alpha]_D$ +12°. Anal. ($C_{26}H_{44}N_2O_3$) C, H, N.

Di-O-*t*-butyldiphenylsilyl-L-tyrosinol (38). To a solution of L-tyrosinol (1.52 g, 7.45 mmol) in CH_2Cl_2 (15 mL), Et_3N (4.36 mL, 31.29 mmol) and 4-(dimethylamino)pyridine (90.4 mg, 0.74 mmol) were added at room temperature. The reaction mixture was stirred for 30 min at room temperature, and then upon cooling at −4 °C, *t*-butyldiphenyl chloride (5.4 mL, 20.86 mmol, 2.8 eq) was added dropwise. An immediate precipitate was formed, and the reaction was stirred for 16 h at 25 °C. Upon cooling at 0 °C and dilution with CH_2Cl_2 (45 mL), the reaction mixture was quenched with ice/water (15 mL) and then acidified with 5% HCl (10 mL). After stirring for 15 min and the addition of a saturated Na_2CO_3 solution (10 mL), the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. The residue (375 mg) was chromatographed on silica gel using CH_2Cl_2/CH_3-OH = 95/5 as eluent to give 4.03 g (84%) of **38** as a pale-yellow oil. IR: 3071, 3053, 2931, 2857, 1608, 1589, 1508, 1472, 1427, 1390, 1361, 1254, 1189, 1172, 1111, 1007, 998, 918, 821, 740, 699 cm^{-1}; MS (FAB+, NBA) *m*/*z*: 645 [M + H$^+$], 567 [M − Ph]; ^{1}H NMR (300 MHz) δ: 1.06 (9H, s), 1.10 (9H, s), 2.44 (1H, dd, J = 8.2, 13.5 Hz), 2.66 (1H, dd, J = 5.4, 13.5 Hz), 2.72 (2H, br s), 3.00−3.11 (1H, m), 3.49 (1H, dd, J = 6.4, 9.9 Hz), 3.60 (1H, dd, J = 4.4, 9.9 Hz), 6.67 (2H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.4 Hz), 7.30−7.50 (12H, m), 7.60−7.68 (4H, m), 7.68−7.75 (4H, m); ^{13}C NMR (75 MHz): δ 19.17, 19.34, 26.47, 26.82, 39.00, 54.14, 67.59, 119.54, 127.61, 129.59, 129.74, 129.80, 130.97, 132.93, 133.32 135.41, 153.94. Anal. ($C_{41}H_{49}NO_2Si_2$) C, H, N.

(*Z*)-*N*-[(1*S*)-2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1-[[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]phenyl]methyl]ethyl]-12-[(tetrahydro-2H-pyran-2-yl)oxy]-9-dodecenamide (39). A 0.5 M aqueous solution of LiOH (0.5M, 3.84 mL) was added dropwise to a stirred solution of ester **37**[32] (200 mg, 0.64 mmol) in THF (6.4 mL) at 0 °C under argon. The ice bath was removed, and the mixture was stirred for 3 h at 30 °C. Upon cooling at 0 °C, the reaction was quenched with 1 M $NaHSO_4$ (1.92 mL). The pH was adjusted to 5−6. The solution was extracted with AcOEt. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated under vacuum to give 204 mg (100%) of the carboxylic acid as a colorless liquid, which was used in the subsequent step without further purification. IR: 3372−2460 (br), 3007, 2925, 2854, 3078, 1708, 1440, 1410, 1352, 1260, 1200, 1183, 1136, 1119, 1075, 1031, 984, 922, 905, 869, 814, 725 cm^{-1}; ^{1}H NMR (300 MHz) δ: 1.23−1.41 (8H, m), 1.42−1.90 (8H, m), 1.95−2.09 (2H, m), 2.20−2.30 (2H, m), 2.30−2.40 (2H, m), 3.32−3.43 (1H, m), 3.43−3.55 (1H, m), 3.65−3.75 (1H, m), 3.80−3.94 (1H, m), 4.53−4.64 (1H, m), 5.29−5.49 (2H, m), 10.74 (1H, br s); ^{13}C NMR (75 MHz): δ 19.46, 24.68, 25.39, 27.18, 27.87, 28.95, 29.01, 29.45, 30.61, 34.44, 62.16, 67.05, 98.63, 125.48 131.81, 179.80. To a solution of the carboxylic acid (191 mg, 0.64 mmol) in CH_3CN (3.8 mL) were added *N*-methylmorpholine (141 μL, 1.28 mmol) and *i*-butyl chloroformate (116 μL, 0.90 mmol) at −4 °C. After stirring for 60 min at −5 °C (thick white suspension), a solution of **38** (494 mg, 0.77 mmol) in CH_3CN (2.0 mL) was cannulated. The resulting mixture was stirred for 1 h at room temperature, then diluted with AcOEt (15 mL), and quenched with water (1 mL). The organic layer was washed twice with brine. The combined aqueous phases were extracted with AcOEt. The combined organic extracts were dried ($MgSO_4$) and evaporated under vacuum. Chromatography of the residue on silica gel using cyclohexane/AcOEt = 99/1 to 90/10 as eluent provided amide **39** (491 mg, 83%) as a colorless oil.

IR: 3301, 3071, 2929, 2856, 1641, 1608, 1541, 1508, 1472, 1427, 1390, 1361, 1253, 1200, 1112, 1070, 1031, 997, 984, 919, 869, 821, 739 cm-1; MS (FAB+, NBA) *m/z*: 947 [M + Na+], 923 [M − H+], 867 [M − tBu], 841 [M + 2H+ − THP], 685 [M − TBDPS]; ^{1}H NMR (300 MHz) δ: 1.05 (9H, s), 1.07 (9H, s), 1.20−1.30 (8H, m), 1.40−1.90 (8H, m), 1.95−2.06 (4H, m), 2.32 (2H, q, J = 6.8 Hz), 2,74 (2H, d, J = 7.2 Hz), 3.33−3.43 (1H, m), 3.43−3.50 (1H, m), 3.50−3.57 (2H, m), 3.65−3.76 (1H, m), 3.80−3.90 (1H, m), 4.03−4.15 (1H, m), 4.54−4.62 (1H, m), 5.30−5.49 (2H, m), 5.54 (1H, d, J = 8.7 Hz), 6.61 (2H, d, J = 8.4 Hz), 6.85 (2H, d, J = 8.4 Hz), 7.26−7.43 (12H, m), 7.52−7.63 (4H, m), 7.64−7.72 (4H, m); ^{13}C NMR (75 MHz): δ 19.31, 19.39, 19.53, 25.44, 25.61, 26.50, 26.92, 27.26, 27.92, 29.06, 29.19, 29.56, 30.67, 36.27, 36.81, 51.33, 62.20, 63.49, 67.04, 98.67, 119.54, 125.53, 127.64, 127.71, 129.78, 130.01, 130.32, 131.82, 133.02, 133.25, 135.47, 154.05, 172.15. Anal. ($C_{58}H_{77}NO_5Si_2$) C, H, N.

(*Z*)-*N*-[(1*S*)-2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1-[[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]phenyl]methyl]ethyl]-12-hydroxy-9-dodecenamide (40). A solution of *p*-toluenesulfonic acid (1.2 mg, 6 μmol) in MeOH (1.0 mL) was added dropwise to a stirred solution of **39** (250 mg, 0.27 mmol) in MeOH (1.4 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 2.5 h, concentrated under vacuum, and diluted with Et_2O. The mixture was neutralized with a few drops of a saturated $NaHCO_3$ solution, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated under vacuum. The residue was chromatographed on silica gel using heptanes/AcOEt = 7/3 as eluent to give **40** as a colorless oil (205 mg, 51%). IR: 3600−3100 (br), 3068, 3050, 2930, 2855, 1645, 1509, 1428, 1255, 1113, 921, 822 cm^{-1}; MS (FAB+, NBA) *m/z*: 840 [M], 763 [M − Ph], 627 [M − TBDPS], 569 [M − TBDPS − *t*Bu]; ^{1}H NMR (300 MHz) δ: 1.06 (9H, s), 1.08 (9H, s), 1.18−1.39 (8H, m), 1.45−1.70 (3H, m), 1.95−2.10 (4H, m), 2.30 (2H, dd, J = 6.8, 13.5 Hz), 2.75 (2H, d, J = 7.2 Hz), 3.53 (2H, d, J = 3.3 Hz), 3.61 (2H, t, J = 6.5 Hz), 4.04−4.16 (1H, m), 5.28−5.40 (1H, m), 5.47−5.62 (2H, m), 6.62 (2H, d, J = 8.2 Hz), 6.86 (2H, d, J = 8.3 Hz), 7.26−7.45 (12H, m), 7.53−7.64 (4H, m), 7.64−7.73 (4H, m); ^{13}C NMR (75 MHz): δ 19.36, 19.45, 25.59, 26.54, 26.97, 27.25, 28.97, 29.12, 29.54, 29.69, 30.84, 36.31, 36.82, 51.38, 62.31, 63.53, 119.60, 125.12, 127.69, 127,77, 129.83, 130.06 130.34, 133.07, 133.27, 135.52, 154.10, 172.24. Anal. ($C_{53}H_{69}NO_4Si_2$) C, H, N.

(*Z*)-*N*-[(1*S*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl]-12-(benzoyloxy)-9-dodecenamide (7). A solution of DCC (29 mg, 142 μmol), DMAP (4 mg, 32 μmol), **40** (54 mg, 64 μmol), and benzoic acid (12 mg, 96 μmol) in CH_2Cl_2 (1.3 mL) was stirred for 16 h at room temperature. The mixture was diluted with CH_2Cl_2, filtered over silica gel, and concentrated in vacuo. The residue was chromatographed on silica gel using heptanes/AcOEt = 9/1 as eluent to give (*Z*)-*N*-[(1*S*)-2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-[[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]phenyl]methyl]ethyl]-12-(benzoyloxy)-9-dodecenamide (30.1 mg, 50%) as a colorless oil. IR: 3400−3200, 3071, 2930, 2857, 1720, 1643, 1608, 1509, 1472, 1428, 1270, 1113, 1070, 998, 920, 822 cm^{-1}; MS (FAB+, NBA) *m/z*: 945 [M + H]; ^{1}H NMR (300 MHz) δ: 1.06 (9H, s), 1.08 (9H, s), 1.19−1.40 (8H, m), 1.45−1.57 (2H, m), 1.95−2.12 (4H, m), 2.50 (2H, q, J = 6.8 Hz), 2.76 (2H, d, J = 7.2 Hz), 3.54 (2H, d, J = 3.4 Hz), 4.05−4.17 (1H, m), 4.30 (2H, t, J = 6.8 Hz), 5.35−5.53 (2H, m), 5.57 (1H, d, J = 8.7 Hz), 6.62 (2H, d, J = 8.4 Hz), 6.86 (2H, d, J = 8.4 Hz), 7.26−7.45 (14 H, m), 7.48−7.64 (5H, m), 7.65−7.73 (4H, m), 8.03 (2H, d, J = 7.2 Hz); ^{13}C NMR (75 MHz): δ 19.30, 19.40, 25.59, 26.50, 26.91, 27.27, 29.03, 29.16, 29.50, 36.27, 36.80, 51.35, 63.49, 64.39, 119.55, 124.32, 127.64, 127.72, 128.24, 129.50, 129.78, 130.00 130.30, 132.76, 132.88, 133.02, 135.47, 154.06, 166.52, 172.20. A 1 M solution of *N*-tetrabutylammonium fluoride (TBAF) in THF (89 μL, 89 μmol) was added to a solution of the benzoate ester (28 mg, 29.6 μmol) in THF (500 μL) at 0 °C. The mixture was stirred for 5 min at 0 °C, then for 1 h at 20 °C, and evaporated under vacuum. The residue was filtered on silica gel, using CH_2Cl_2/CH_3OH = 98/2 as eluent to give **7** (14 mg, 98%) as a colorless oil. $[\alpha]_D$ = + 3.1 (c = 0.05, CH_2Cl_2); IR 3600−3080 (br), 1717, 1704 cm^{-1}; MS (electrospray): positive 468.4 (M + 1), negative 466.7 (M − 1), MS2 positive = 346 (M − PhCOO), 450.2 (M − H_2O), 468.1 (M + 1); ^{1}H NMR (300 MHz) δ: 1.43−1.10 (8H, m), 1.45−1.60 (2H, m), 1.95−2.05 (2H, m), 2.10 (2H, t, J = 7.5 Hz), 2.40−2.55 (2H, m), 2.62−2.85 (2H, m), 3.54 (1H, dd, J = 11.1, 5.2 Hz), 3.63 (1H, dd, J = 11.1, 3.3 Hz), 4.00−4.20 (1H, m), 4.29 (2H, t, J = 6.9 Hz), 5.35−5.60 (2H, m), 5.85−6.05 (1H, m), 6.73 (2H, d, J = 8.1 Hz), 6.99 (2H, d, J = 8.1 Hz), 7.40 (2H, t, J = 7.3 Hz), 7.53 (1H, tt, J = 1.3, 7.3 Hz), 8. 01 (2H, dd, J = 7.3, 1.3 Hz); ^{13}C NMR (75 MHz): δ 25.64, 26.94, 27.25, 29.00, 29.08, 29.46, 29.66, 36.18, 36.77, 53.07, 64.30, 64.59), 115.60, 124.22,128.34, 128.76, 129.56, 130.13, 130.28 132.95, 133.07, 155.25, 166.92, 174.38. Anal. ($C_{28}H_{37}NO_5$) C, H, N.

(*Z*)-*N*-[(1*S*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl]-12-[(2-azido-5-iodo)benzoyloxy]-9-dodecenamide (8). To a stirred solution of DCC (37 mg, 177 μmol), DMAP (5 mg, 40 μmol), and 2-azido-5-iodobenzoic acid[35] (35 mg, 120 μmol) in CH_2Cl_2 (0.9 mL) was added a solution of **40** (60 mg, 72 μmol) in CH_2Cl_2 (1.3 mL) at 0 °C. After stirring at room temperature for 15 h in the dark, the mixture was diluted with CH_2Cl_2 and filtered through a short pad of silica gel using cyclohexane/Et_2O = 7/3 as eluent in the dark. The residue was chromatographed on fluorisil (1.5 g) using cyclohexane/Et_2O = 95/5 to 50/50 as eluent to give **8** (65.4 mg, 82%) as a colorless oil. MS *m/z*: (ESI >0) 1133.2 [M + Na$^+$]; IR: 3298, 3071, 2929, 2856, 2125, 2095, 1728, 1644, 1509, 1472, 1428, 1290, 1250, 1113, 1089, 920, 822 cm^{-1}; ^{1}H NMR (300 MHz) δ: 1.06 (9H s), 1.07 (9H, s), 1.15−1.38 (8H, m), 1.43−1.57 (2H, m), 1.95−2.10 (4H, m), 2.48 (2H, q, J = 6.9 Hz), 2.75 (2H, d, J = 7.2 Hz), 3.53 (2H, d, J = 3.4 Hz), 4.03−4.15 (1H, m), 4.27 (2H, t, J = 6.7 Hz), 5.32−5.45 (1H, m), 5.45−5.55 (1H, m), 5.55 (1H, d, J = 8.9 Hz), 6.61 (2H, d, J = 8.5 Hz), 6.85 (2H, d, J = 8.5 Hz), 6.95 (1H, d, J = 8.5 Hz), 7.20−7.45 (12H, m), 7.51−7.63 (4H, m), 7.63−7.72 (4H, m), 7.77 (1H, dd, J = 2.1, 8.5 Hz), 8.11 (1H, d, J = 2.1 Hz); ^{13}C NMR (75 MHz): δ 19.35, 19.44, 25.65, 26.54, 26.83, 26.96, 27.34, 29.12, 29.24, 29.56, 29.67, 36.31, 36.85, 51.38, 63.51, 65.07, 87.33, 119.60, 121.75, 124.06, 127.69, 127.77, 129.83, 130.06, 130.34, 133.07, 133.20, 135.52, 139.98, 140.32, 141.71, 154.10, 163.68, 172.22. A 1 M solution of *N*-tetrabutylammonium fluoride (TBAF) in THF (525 μL) was added in the dark to a solution of the 2-azido 5-iodobenzoate ester (58 mg, 53 μmol) in THF at 0 °C. The mixture was stirred at 0 °C for 10 min, then at 20 °C for 1 h, and evaporated under vacuum. The residue was filtered through a short pad of silica gel using CH_2Cl_2/CH_3OH = 98/2 as eluent. Evaporation under vacuum and chromatography on silica gel of the filtrate with CH_2Cl_2/CH_3OH = 99/1 to 97/3 as eluent gave **8** (25.0 mg, 75%) as a pale yellow oil. $[\alpha]_D$ = +2.8 (c = 0.05, CH_2Cl_2); IR: 3600−3100, 3017, 2927, 2855, 2125, 1717, 1642, 1539, 1515, 1475, 1380, 1295, 1240, 1132, 1089, 814 cm^{-1}; MS (electrospray): positive 657.1 (M + 23), negative 633.3 (M − 1), MS2 positive = 502.3 (M − N_2I); 629.2 (M − N_2), 657.1 (M + 23); ^{1}H NMR (300 MHz) δ: 1.05−1.43 (8H, m), 1.45−1.60 (2H, m), 1.72 (1H, br s), 1.90−2.10 (2H m), 2.12 (2H, t, J = 7.4 Hz), 2.40−2.55 (2H, m), 2.60−2.85 (2H, m), 3.00 (1H, br s), 3.55 (1H, dd, J = 10.8, 4.8 Hz), 3.65 (1H, dd, J = 10.8, 3.0 Hz), 4.05−4.20 (1H, m), 4.27 (2H, t, J = 6.9 Hz), 5.30−5.44 (1H, m), 5.45−5.60 (1H, m), 5.87 (1H, d, J = 7.6 Hz), 6.73 (d, 2H, d, J = 8.3 Hz), 6.95 (d, 1H, d, J = 8.5 Hz), 6.99 (d, 2H, d, J = 8.3 Hz), 7.77 (1H, dd, J = 2.1, 8.5 Hz), 8.10 (1H, d, J = 2.1 Hz); ^{13}C NMR (75 MHz): δ 25.64, 26.81, 27.28, 29.03, 29.11, 29.48, 36.19, 36.78, 53.07, 64.39, 65.17, 87.34, 115.60, 121.75, 123.96, 124.35, 128.85, 130.14, 133.31, 140.00, 140.32, 141.80, 155.12, 163.94, 174.33. Anal. ($C_{28}H_{35}IN_4O_5$) C, H, N.

Assay of AEA Cellular Reuptake. The effect of compounds on the uptake of [^{14}C]AEA by rat basophilic leukemia (RBL-2H3) cells was studied by using 2.4 μM (10,000 cpm) of [^{14}C]AEA. Three protocols were used. In the first case (protocol #1), a previously described procedure was used.[23] This consisted of incubating the cells with [^{14}C]AEA for 5 min at 37 °C in the presence or absence of varying concentrations of the inhibitors. In some cases, a 10 min preincubation of the cells with the inhibitors preceded the addition of the radiolabeled substrate. The second protocol (protocol

#2) consisted of preincubating RBL-2H3 cells at room temperature (25 °C) for 60 min under normal laboratory lighting conditions with nonphotoactivatable compounds. The preincubation was then followed by 3 washes of the cells with a cell culture medium containing 0.2% BSA, 2 washes with BSA-free culture medium, and finally, by a 5 min incubation with [^{14}C]AEA in the absence of inhibitors. The third protocol (protocol #3) consisted of preincubating rat C6 glioma cells at room temperature (25 °C) for either 8 min in the presence of UV light (315−400 nm, 125W) or for 8 min in the dark with photoactivatable compounds. The preincubation was then followed by 3 washes of the cells with a cell culture medium containing 0.2% BSA, 2 washes with BSA-free culture medium, and finally, by a 5 min incubation with [^{14}C]AEA in the absence of inhibitors. One or two fixed concentrations of the inhibitors, roughly corresponding to their IC_{50} values obtained using protocol #1, were used for protocol #2 or #3. In the case of protocol #3, cell viability after UV exposure was checked after each experiment, and the incubation time of 8 min was selected as the longest time interval that did not cause cell damage as assessed with trypan blue. C6 cells were used instead of RBL-2H3 cells because they were more resistant to UV exposure. In all cases, residual [^{14}C]AEA in the incubation medium after extraction with $CHCl_3$/CH_3OH 2:1 (by volume), determined by scintillation counting of the lyophilized organic phase, was used as a measure of the amount of AEA that was taken up by the cells.[40] Data are expressed as the concentration exerting 50% inhibition of AEA uptake (IC_{50}) calculated by GraphPad. Nonspecific binding of [^{14}C]AEA to cells and plastic dishes was determined in the presence of 100 μM AEA and was never higher than 40% of total uptake with both RBL-2H3 and C6 cells.

Assay of Fatty Acid Amide Hydrolase (FAAH). The effect of compounds on the enzymatic hydrolysis of AEA was studied as described previously,[23] using membranes prepared from rat brain, incubated with the test compounds and [^{14}C]AEA (2.4 μM) in 50 mM Tris-HCl at pH 9 for 30 min at 37 °C. The [^{14}C]ethanolamine produced from [^{14}C]AEA hydrolysis was measured by scintillation counting of the aqueous phase after extraction of the incubation mixture with 2 volumes of $CHCl_3$/CH_3OH 2:1 (by volume). Some experiments were likewise performed by preincubating membranes from C6 cells with **1b** and **8** for 10 min at 37 °C, in the dark or with concomitant exposure to UV light, followed by the addition of [^{14}C]AEA in the presence of the inhibitors. With active compounds, data are expressed as the concentration exerting 50% inhibition of AEA hydrolysis (IC_{50}) calculated by GraphPad.

Supporting Information Available: Elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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