# Articles

## Synthesis, Structure–Affinity Relationships, and Biological Activities of Ligands Binding to Retinoic Acid Receptor Subtypes

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The retinoic acid receptors (RARs) transduce retinoid dependant gene regulation, and many biological effects of retinoids are mediated through binding and activation of three closely related receptor subtypes (RARα, RARβ, and RARγ). In order to investigate the role of receptor subtypes, we have carried out a chemical synthesis program to seek selective retinoids for these receptors. We measured receptor binding affinity using recombinant RARα, -β, and -γ proteins and assessed cellular differentiating activity in F9 murine teratocarcinoma cells (F9 cells). This research has identified the 4-substituted-3-(1-adamantyl)phenyl moiety as a new pharmacophore which can replace the β-cyclogeranylidene ring of the naturally ocurring *all-trans*-retinoic acid. Two chemical series derived from the general structures 6-(3-tertioalkylphenyl)-2-naphthoic acid (series I) and 4-[(*E*)-2-(3-tertioalkylphenyl)propenyl]benzoic acid (series II) were developed. In particular, we have obtained the RARγ selective derivatives 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid (**7**) [$K_i$(RARα) = 6500 nM, $K_i$(RARβ) = 2480 nM, $K_i$(RARγ) = 77 nM] and 4-[(*E*)-2-[3-(1-adamantyl)-4-hydroxyphenyl]propenyl]benzoic acid (**19**) [$K_i$(RARα) = 1 144 nM, $K_i$(RARβ) = 1245 nM, $K_i$(RARγ) = 53 nM]. In series I, the presence of a phenol group, irrespective of the nature of tertioalkyl group, imparted at least partial RARγ selectivity, whereas in series II, the presence of both adamantyl and phenol groups is needed to confer RARγ selectivity. The RARγ selective ligands induce differentiation in F9 cells (**7**, $AC_{50}$ = 33 nM; **19**, $AC_{50}$ = 66 nM). From series I, a mixed RARβ–γ agonist with potent cellular differentiating activity was selected for development as a topical antiacne agent, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid (**5**, CD 271) [$K_i$(RARα) = 1100 nM, $K_i$(RARβ) = 34 nM, $K_i$(RARγ) = 130 nM, $AC_{50}$(F9) = 37 nM]. Finally, from series II, we have obtained a weak antagonist in the F9 cellular differentiation assay, 4-[(*E*)-2-(3-*tert*-butyl-4-hydroxyphenyl)propenyl]benzoic acid (**15**, $IC_{50}$ = 700 nM).

### Introduction

Retinoids, natural and synthetic analogues of vitamin A, play a major role in controlling cell proliferation and differentiation.[1] These properties confer on this class of substances a high potential for the treatment of various hyperproliferative diseases.[2] *all-trans*-Retinoic acid (AtRA), 13-*cis*-retinoic acid, and synthetic analogues are widely used by both the topical and oral routes of administration in the management of dermatological diseases such as acne, psoriasis, and other disorders in which abnormal patterns of keratinization are found.[3] Moreover, retinoids are under study for treatment and prevention of some forms of cancers,[4] including acute promyelocytic leukemia which responds to treatment with AtRA.[5] Many biological effects of retinoids are mediated by activation of nuclear receptors (RARs) which are ligand dependent gene transcription factors. Three distinct receptor subtypes (RARα, -β, and -γ) which display >75% homology in their ligand-binding domain have been identified. These receptors are 55 kDa proteins located in the cell nucleus. After complexation with a ligand, RARs exert their gene transcriptional activity as a heterodimer formed with retinoid X receptors (RXRs). The RXR receptors also belong to the same steroid/thyroid hormone superfamily sharing high homolgy in the DNA-binding domain with the RARs and other members. RARs bind AtRA, and the 9-cis stereoisomer of AtRA whereas RXRs only bind the 9-cis stereoisomer.[6]

Side effects such as mucocutaneous irritation, hypervitaminosis A, and teratogenicity are drawbacks in the therapeutic use of retinoids.[7] The discovery of RAR subtypes has stimulated medicinal chemists to seek new drugs with an improved therapeutic index. In normal skin, RARα and predominantly RARγ are present in the keratinocytes of the epidermis.[8] RARβ is neither expressed nor induced in this skin layer. In contrast, in the dermis, the fibroblast does express RARβ, and in addition the gene encoding RARβ is also inducible by retinoic acid in this cell type. As the expression of RAR subtypes is tissue specific, we and others[9–12] speculated that receptor specific ligands will activate some, but not all, of the multiple pathways involved in the biological response of the parent compound. Consequently, in the field of dermatology, selective compounds for the RARγ subtype might act preferentially in the epidermis and thus present an improved benefit/risk ratio. However, RARβ-mediated action may also lead to response in

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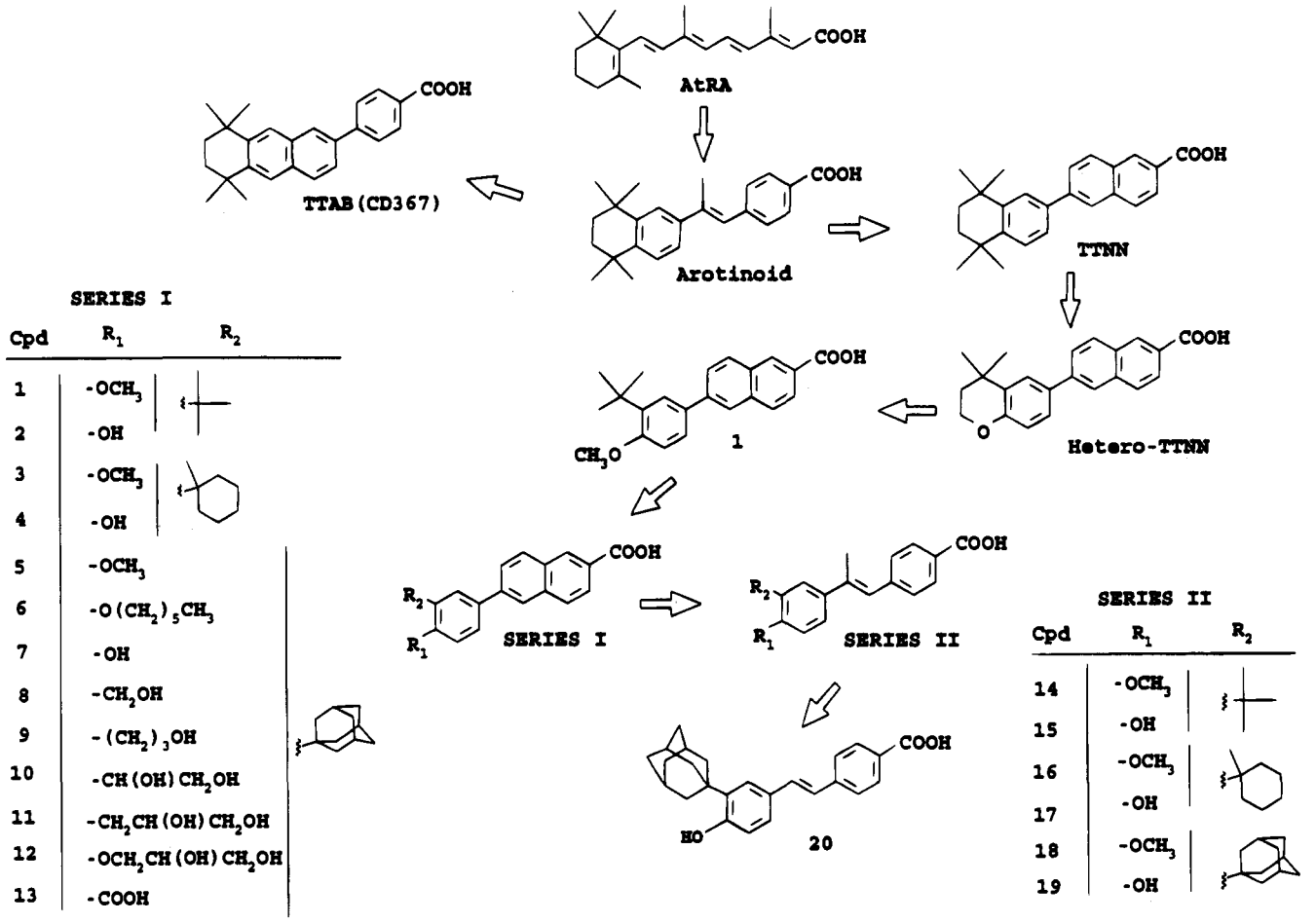
**Scheme 1.** Structural Evolution from AtRA to Aromatic Retinoids of Series I and II



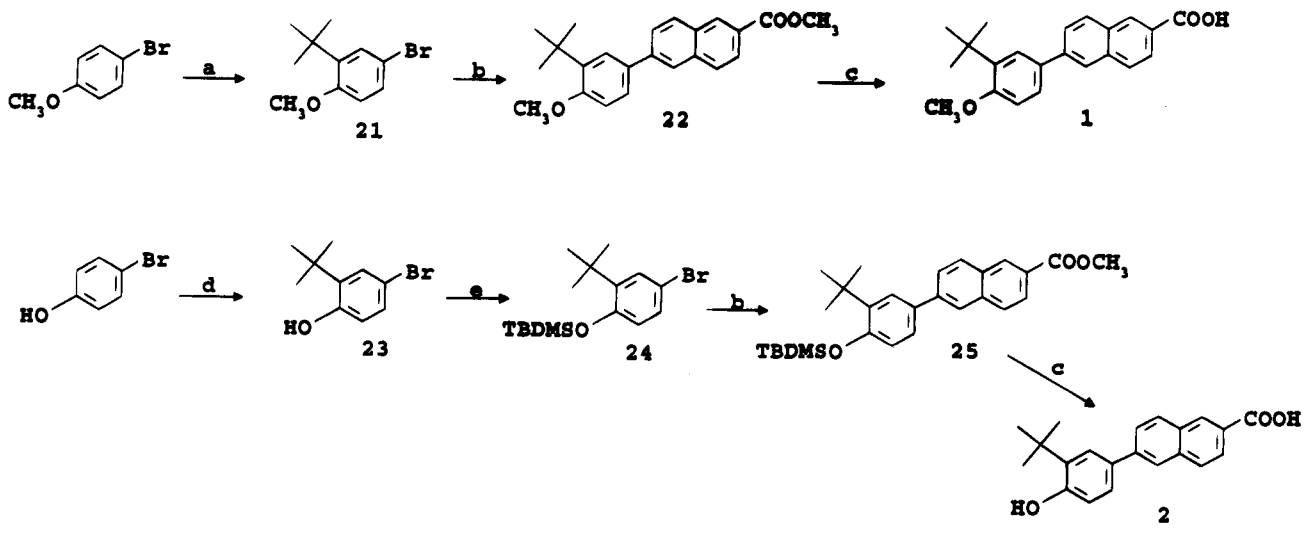

fibroblasts; thus, for skin diseases, molecules with mixed RAR$\beta-\gamma$ profiles may be preferred. Finally, receptor specific ligands provide pharmacological tools to probe the biological role of receptor subtypes.

Agonists[9] and antagonists[10] of RAR$\alpha$, mixed RAR$\beta-\gamma$ ligands,[9b] RAR$\gamma$ selective compounds,[11] and, recently, selective ligands for the RXR subfamily have been described.[12] In this paper, we report the synthesis of naphthoic and propenylbenzoic acid derivatives of series I and II, respectively (Scheme 1) and their RARs binding affinities and F9 cell-differentiating activities (Table 1).

## Chemistry

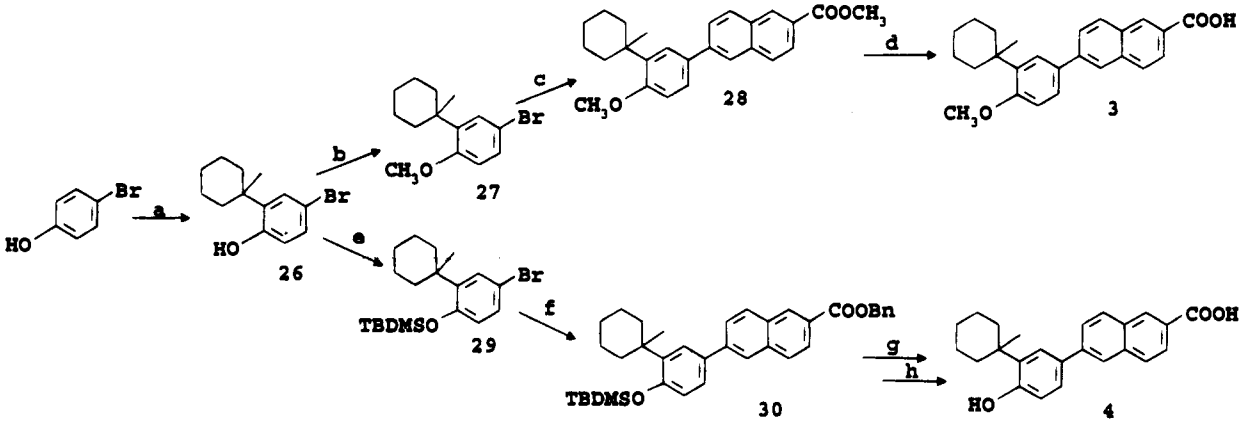
Compounds **1**–**7** and **12** were obtained as outlined in Schemes 2–4. First, a Friedel–Crafts alkylation with appropriate tertioalkyl derivatives led to compounds **21**, **23**, **26**, and **32**. The phenol groups of these derivatives were protected by either methoxy, (*tert*-butyldimethyl-

**Scheme 2**[a]



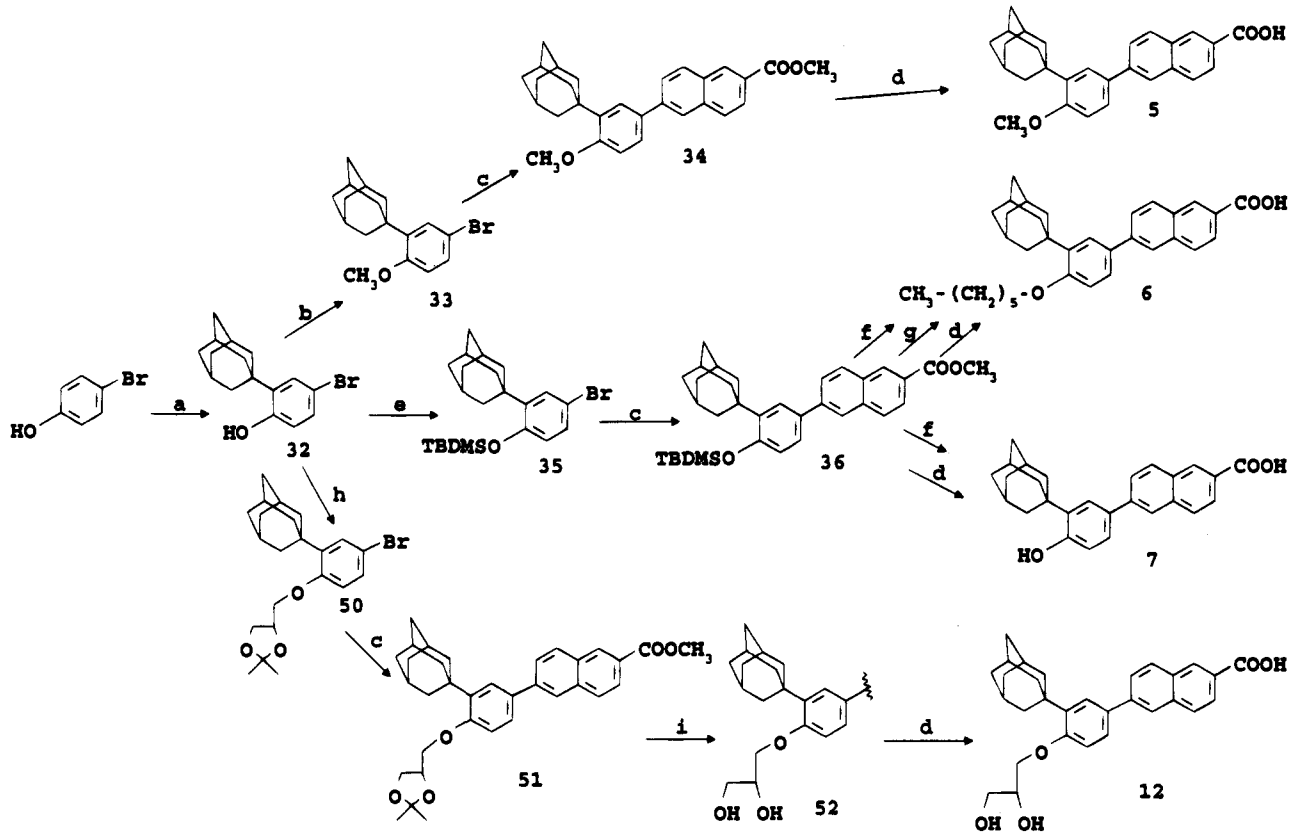

[a] (a) *t*-BuCl, $AlCl_3$; (b) (1) Mg/THF, (2) $ZnCl_2$, (3) methyl 6-bromo-2-naphthoate, $NiCl_2$/DPPE; (c) NaOH, MeOH; (d) isobutylene, Dowex resin; (e) TBDMSCl, $Et_3N$, DMAP, DMF.

**Scheme 3**[a]



[a] (a) 1-Methylcyclohexanol, $H_2SO_4$, $CH_2Cl_2$; (b) $CH_3I$, NaH, THF; (c) (1) Mg/THF, (2) $ZnCl_2$, (3) methyl 6-bromo-2-naphthoate, $NiCl_2$/DPPE; (d) NaOH, MeOH; (e) TBDMSCl, $Et_3N$, DMAP, DMF; (f) (1) Mg/THF, (2) $ZnCl_2$, (3) benzyl 6-bromo-2-naphthoate, $NiCl_2$/DPPE; (g) TBAF, THF; (h) $H_2$, Pd–C, dioxane.

**Scheme 4**[a]

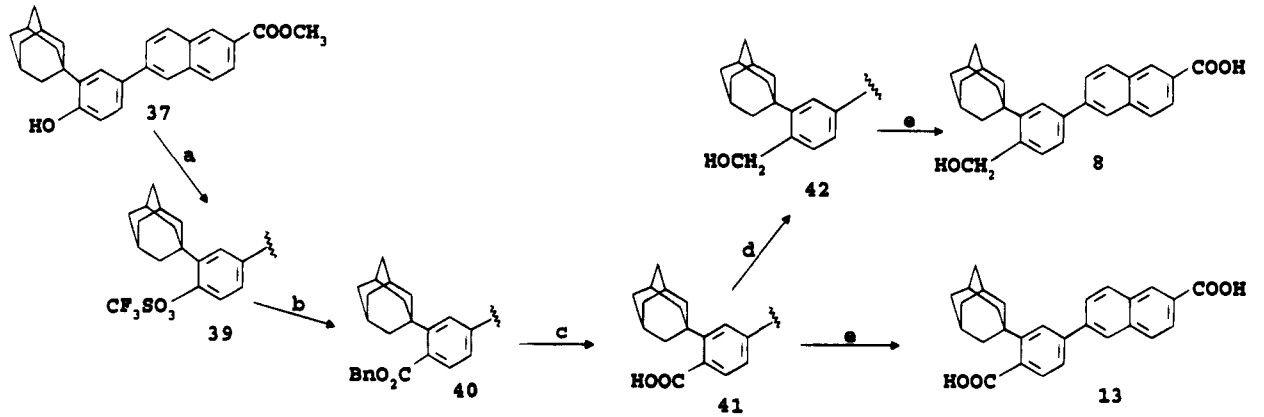


[a] (a) 1-Adamantanol, $H_2SO_4$, $CH_2Cl_2$; (b) $CH_3I$, NaH, THF; (c) (1) Mg/THF, (2) $ZnCl_2$, (3) methyl 6-bromo-2-naphthoate, $NiCl_2$/DPPE; (d) NaOH, MeOH; (e) TBDMSCl, $Et_3N$, DMAP, DMF; (f) TBAF, THF; (g) NaH, $CH_3(CH_2)_5Br$, DMF; (h) 3-(tosyloxy)-1,2-propanediol acetonide, $K_2CO_3$, DMF; (i) HCOOH, $H_2O$.

silyl)oxy (TBDMS), or acetonide group. Compounds **21**, **24**, **27**, **29**, **33**, **35**, and **50** were converted into zincate derivatives and then condensed to benzyl or methyl 6-bromo-2-naphthoate by a nickel-catalyzed cross-coupling.[13] Acid hydrolysis of the acetonide group of **51** with aqueous formic acid solution[14] furnished the diol derivative **52**. The carboxylic acids derivatives **1**–**3**, **5**–**7**, and **12** were obtained through saponification of their corresponding esters. The carboxylic acid derivative **4** was obtained through catalytic hydrogenation of the benzyl ester group.

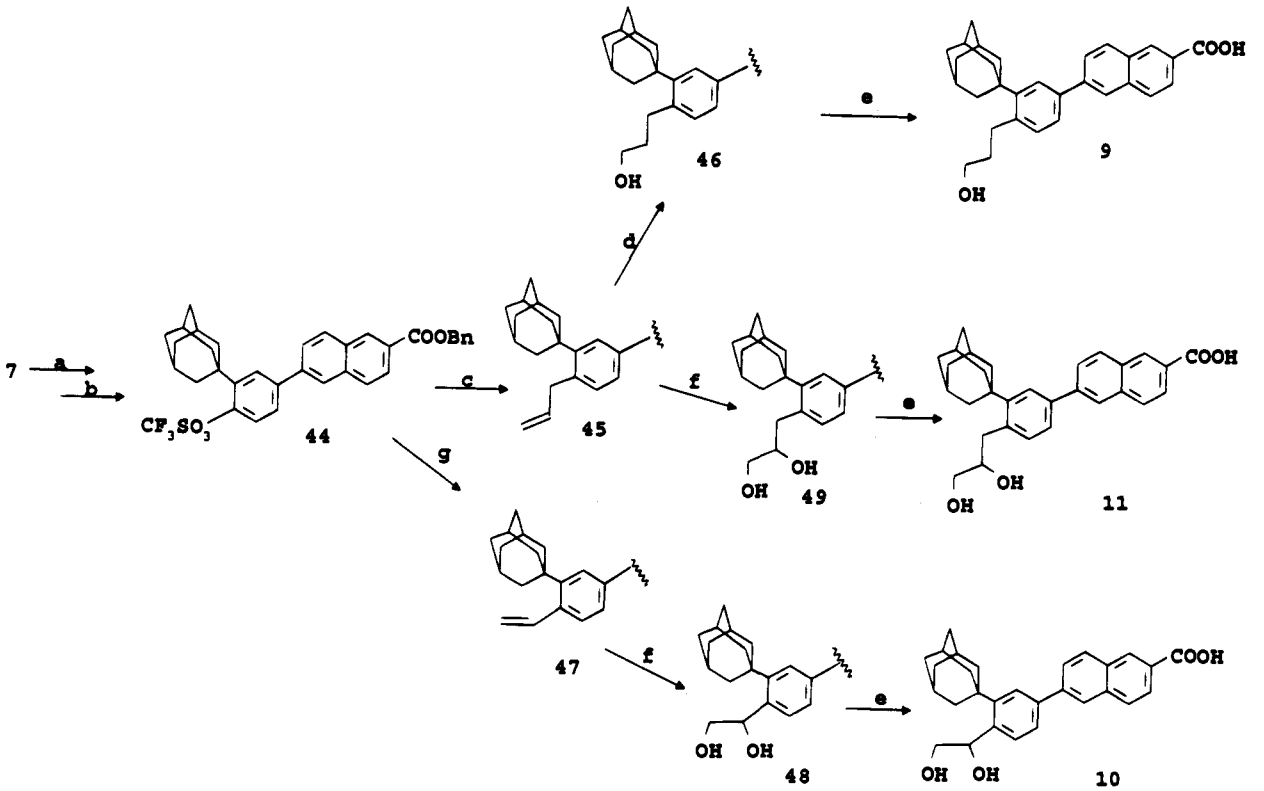
Synthesis of compounds **8**–**11** and **13** is outlined in Schemes 5 and 6. Phenols **37** and **43** were treated with triflic anhydride to give compounds **39** and **44**, respectively. Palladium-catalyzed carbonylation of the triflate **39** led to the benzyloxycarbonyl derivative **40**.[15] Catalytic hydrogenation of **40** afforded the benzoic acid **41** which was subsequently selectively reduced with $BH_3$ to give **42**. Free naphthoic acids **8** and **13** were then obtained by saponification. Palladium-catalyzed cross-coupling of the triflate **44** with allyltin and vinyltin reagents led respectively to **45** and **47**.[16] Hydroboration of the propenyl side chain of **45** with 9-borabicyclo[3.3.1]-nonane (9-BBN) gave **46**.[17] Oxidation of vinyl and propenyl side chains with catalytic osmium tetraoxide gave respectively the diols **48** and **49**.[18] Finally, removal

**Scheme 5**[a]




[a] (a) $Tf_2O$, DMAP, pyridine; (b) CO, $Et_3N$, $Pd(OAc)_2$, DPPF, benzyl alcohol, DMF; (c) $H_2$, Pd–C, dioxane; (d) $BH_3$, THF; (e) NaOH, MeOH.

**Scheme 6**[a]

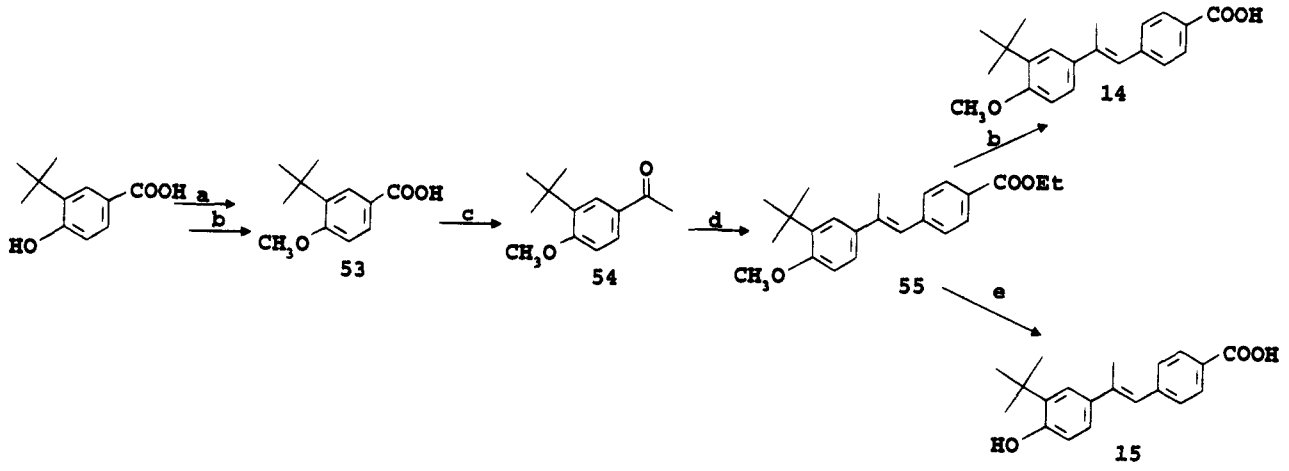



[a] (a) Benzyl bromide, NaH, DMF; (b) $Tf_2O$, DMAP, pyridine; (c) $CH_2{=}CHCH_2SnBu_3$, $(PPh_3)_2PdCl_2$, LiCl, DMF; (d) 9-BBN, THF, NaOH, $H_2O_2$; (e) $H_2$, Pd–C, dioxane; (f) $(CH_3)_3NO$, $OsO_4$, pyridine, $H_2O$; (g) $CH_2{=}CHSnBu_3$, $(PPh_3)_2PdCl_2$, LiCl, DMF.

of benzyl ester groups by catalytic hydrogenation led to the naphthoic acids **9**–**11**.

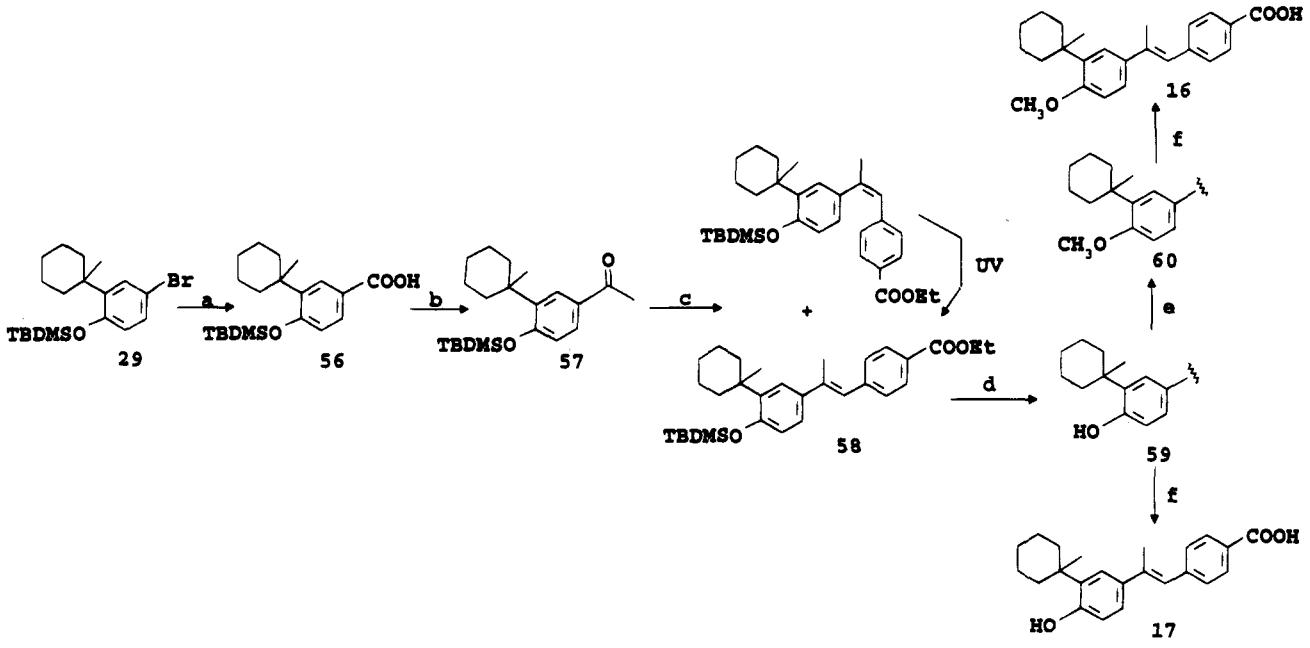
Synthesis of compounds **14**–**20** is illustrated in Schemes 7–9. Carboxylic acids **56** and **61** are prepared through standard reaction of a Grignard reagent with carbon dioxide. The *m*-tertioalkylphenylcarboxylic acid derivatives **53** and **56** are converted into methyl phenyl ketones using methyllithium to give **54** and **57**, respectively. The methyl phenyl ketone derivative **62** is obtained via palladium-catalyzed cross-coupling of tetramethyltin reagent on the acyl chloride derivative of **61**.[19] The bromide **35** is converted into its lithium derivative which is condensed with DMF to give carboxaldehyde **64**. Horner–Emmons olefination of ketones **54**, **57**, and **62** with diethyl [4-(ethoxycarbonyl)-benzyl]phosphonate using NaH as the base led to the stilbene derivatives **55**, **58**, and **63**.[20] In the case of the methylcyclohexyl derivative **58** whose phenol is protected with a TBDMS group, a 4:1 (*Z*/*E*) mixture of geometric isomers was obtained, whereas with compounds **55** and **63**, the *E* isomer was preponderant. Accordingly, isomeric mixture of **58** was irradiated (Hanovia lamp) to give a 1:1 (*Z*/*E*) mixture. The geometric configuration was assigned using NMR experiments by comparing NOE effects between the methyl vinylic and ethylenic protons. Furthermore, chemical shifts of ethylenic protons were in agreement with these configurations. Compound **20** was obtained also through Horner–Emmons olefination in the same conditions as for obtention of the above stilbene derivatives. In this case, we obtained exclusively *E* isomer whose configuration was assigned through vinylic coupling constant (16 Hz). Free carboxylic methoxy derivatives **14**, **16**, **18**, and **20** were obtained after saponification. Free

**Scheme 7**[a]




[a] (a) $Me_2SO_4$, $K_2CO_3$, 2-butanone; (b) NaOH, MeOH; (c) $CH_3Li$, $Et_2O$; (d) 4-$(EtO)_2P(O)CH_2$-$C_6H_4$-$CO_2Et$, NaH, 15-crown-5, THF; (e) LiSMe, DMF.

**Scheme 8**[a]




[a] (a) Mg, THF, $CO_2$; (b) $CH_3Li$, $Et_2O$; (c) 4-$(EtO)_2P(O)CH_2$-$C_6H_4$-$CO_2Et$, NaH, 15-crown-5, THF; (d) TBAF, THF; (e) NaH, $CH_3I$, THF; (f) NaOH, MeOH.

carboxylic phenol derivatives **15** and **19** were obtained after deprotection with sodium or lithium methoxide.[21]

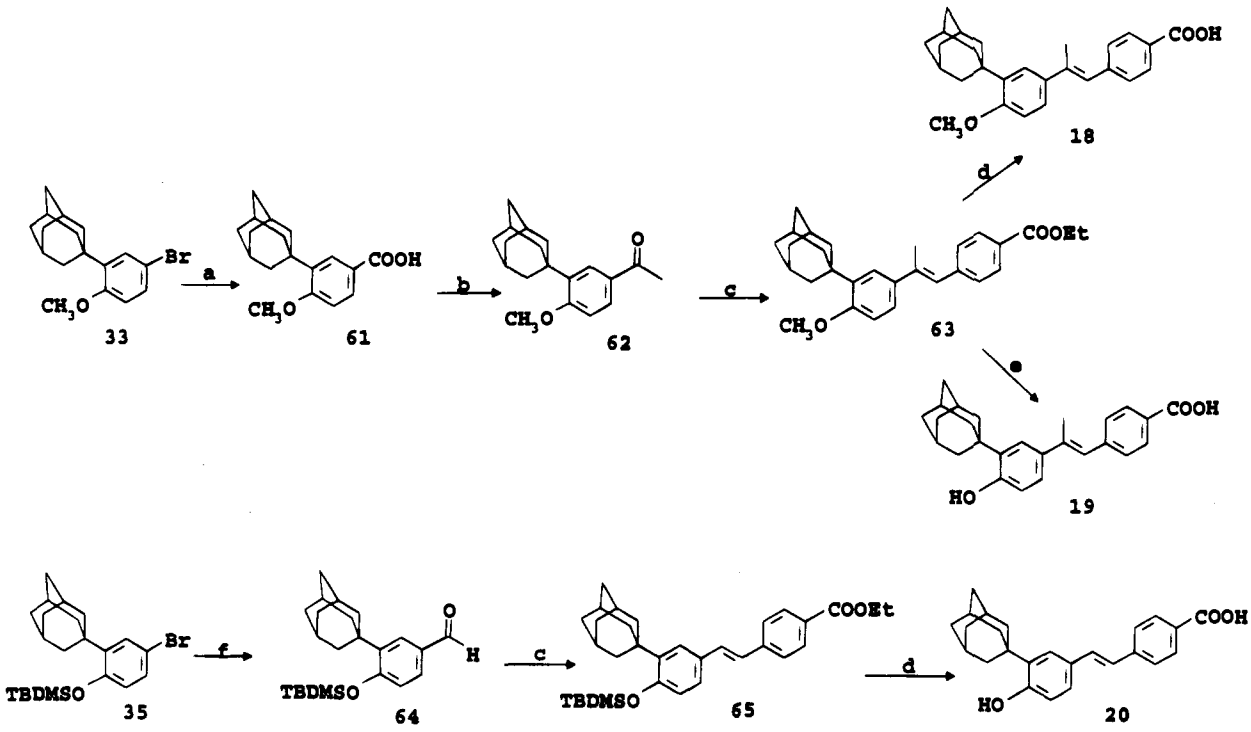
## Biological Results and Discussion

Scheme 1 outlines the progression of structure from AtRA to aromatic retinoids. Incorporation of all but one of the double bonds in the linker region into aromatic rings led to the stilbene derivative arotinoid.[22] A key feature of this molecule was the replacement of the $\beta$-cyclogeranylidene group present in the naturally occurring retinoids by the tetrahydrotetramethylnaphthalene moiety. This structure could be constrained further by rendering the lipophilic part of the molecule aromatic to give the anthracenyl derivative TTAB (CD 367).[23] Arotinoid and CD 367 both elicit binding profiles similar to that of AtRA, characterized by a high affinity for each receptor subtype. Consequently, the highly constrained TTAB structure probably represents the bioactive conformation of the flexible natural ligand AtRA. Moreover, this implies that this conformation may be the same for each receptor subtype. In view of the above, tritiated CD 367 was developed as a radioligand[24] and used as such in the binding experiments described here.

The arotinoid skeleton can also be rendered fully aromatic by constructing the naphthoic acids exemplified by TTNN.[25] In contrast to the anthracenyl derivative CD 367, TTNN possessed reduced affinity for RAR$\alpha$ and, to a lesser extent, RAR$\gamma$.

In the absence of three-dimensional structural data on the binding sites of RARs, we designed new target compounds reasoning by analogy with arotinoid and the established leads, CD 367 and TTNN. We have synthesized molecules whose structures can be thought to evolve from TTNN to 6-(substituted-phenylnaphthoic acid derivatives of series I and then to (phenylpropenyl)-benzoic derivatives of series II. The replacement of the tetrahydrotetramethylnaphthalene ring by open-ring chain analogues gave rise to molecules where a 3,4-

**Scheme 9**[a]




[a] (a) Mg, THF; $CO_2$; (b) (1) $SOCl_2$, toluene, (2) $SnMe_4$, $PhCH_2Pd(PPh_3)_2Cl$, HMPA; (c) 4-$(EtO)_2P(O)CH_2$-$C_6H_4$-$CO_2Et$, NaH, 15-crown-5, THF; (d) NaOH, MeOH; (e) NaSMe, DMF; (f) *n*-BuLi, DMF, THF.

**Table 1.** Binding Affinities to RARs and F9 Teratocarcinoma Cell-Differentiating Activities of Retinoids

| | binding: $K_i$ (nM)[a] | | | F9 differentiation | |
|---|---|---|---|---|---|
| compd | RARα | RARβ | RARγ | $AC_{50}$ (nM)[a] | $IC_{50}$ (nM)[a,b] |
| AtRA | 16 ± 3 | 7 ± 3 | 3 ± 1 | 200 ± 15 | |
| arotinoid | 21 ± 1 | 5 ± 1.5 | 5 ± 0.1 | 0.78 ± 0.38 | |
| CD 367 | 5.3 ± 0.7 | 3 ± 0.5 | 2 ± 0.1 | 0.46 ± 0.11 | |
| TTNN | 580 ± 140 | 13 ± 2 | 40 ± 17 | 15 ± 5 | |
| hetero-TTNN | 8500 ± 2300 | 210 ± 30 | 860 ± 40 | 300 ± 100 | |
| 1 | 6500 ± 2500 | 36 ± 8 | 426 ± 16 | 200 ± 80 | |
| **2** | >10 000 | 3550 ± 540 | 200 ± 30 | NA | NA |
| 3 | 1120 ± 200 | 26 ± 5 | 160 ± 23 | 150 ± 21 | |
| **4** | >10 000 | 660 ± 150 | 121 ± 6 | 175 ± 25 | |
| **5** | 1100 ± 70 | 34 ± 4 | 130 ± 25 | 37 ± 7 | |
| **6** | >10 000 | >10 000 | >10 000 | NA | |
| **7** | 6500 ± 570 | 2480 ± 620 | 77 ± 18 | 33 ± 27 | |
| **8** | >10 000 | 156 ± 32 | 386 ± 65 | 460 ± 43 | |
| **9** | 695 ± 248 | 21 ± 6 | 72 ± 2 | 7.5 ± 4 | |
| **10** | >10 000 | 288 ± 30 | 153 ± 27 | 73 ± 30 | |
| **11** | >10 000 | 158 ± 6 | 34 ± 5 | 100 ± 39 | |
| **12** | 5000 | 89 ± 12 | 151 ± 45 | 83 ± 28 | |
| **13** | >10 000 | >10 000 | >10 000 | 2000 ± 350 | |
| **14** | 130 ± 50 | 12 ± 4 | 13 ± 2.5 | 30 ± 5 | |
| **15** | 834 ± 54 | 105 ± 35 | 85 ± 10 | NA | 700 ± 125 |
| **16** | 420 ± 110 | 17 ± 2 | 29 ± 15 | 30 ± 16 | |
| **17** | 1056 ± 88 | 90 ± 20 | 27 ± 12 | 300 ± 60 | |
| **18** | 460 ± 100 | 105 ± 45 | 95 ± 15 | 100 ± 29 | |
| **19** | 1144 ± 67 | 1245 ± 30 | 53 ± 7 | 66 ± 24 | |
| **20** | 610 ± 29 | 70 ± 29 | 20 ± 6 | 1 ± 0.41 | |

[a] Results are the mean ±SEM of three separate experiments. [b] Protocol to assay inhibiting concentration was only performed with compounds **2** and **15**. NA = not active.

disubstituted phenyl ring is linked to the naphthoic acid at C6. The *p*-methoxy-*m*-tertioalkyl-substituted compounds **1**, **3**, and **5** are ligands which have higher affinities for RARβ and RARγ than RARα. Replacement of the *tert*-butyl group by 1-methylcyclohexyl or 1-adamantyl does not alter the affinity for RARβ, while the affinities for RARα and RARγ are lower for the compounds which contain the *tert*-butyl group than for compounds containing the corresponding 1-methylcyclohexyl and 1-adamantyl derivatives. When the methoxy group of the 4-substituted-3-(1-adamantyl)phenyl pharmacophore was replaced by a hexyloxy group (**6**), high-affinity binding to each receptor was lost. Comparing the $K_i$ values for the *tert*-butyl derivative **1** with TTNN and hetero-TTNN,[26] the replacement of a *gem*-dimethyl group in TTNN by an oxygen atom to give hetero-TTNN resulted in a marked reduction of the affinity on the three receptors. Interestingly, opening the chroman ring of hetero-TTNN to give the methoxy-*tert*-butylphenyl derivative **1** induced an enhancement

in affinity for RARβ. This effect is possibly due to a difference of availability of oxygen for interaction with receptors. In the case of hetero-TTNN, this oxygen, included in the chroman ring, is more exposed outward than the oxygen atom of compound **1** which is less accessible, due to the masking effect of methyl in the flexible methoxy group. This suggests that affinity to RARβ is reduced by the presence of an exposed oxygen atom in this portion of the ligand, replacing the methoxy group able to contribute by the methyl group to the interaction with RARβ.

Replacement of the methoxy group by phenol led to molecules **2**, **4**, and **7** that have reduced affinity for RARα and RARβ and comparable or perhaps slightly enhanced affinity for RARγ. The adamantylphenol-substituted naphthalene **7** showed the highest selectivity for RARγ. In order to further explore the factors which govern this specific recognition, we replaced the phenol by other polar functions while maintaining the adamantyl group in the same position. When the phenol group is replaced with an aliphatic chain bearing one (**8** and **9**) or two hydroxyl groups (**10**–**12**), an enhancement of affinity for RARβ, accompanied by a loss of selectivity, resulted. Absence of RARγ selectivity could be related to difference in acidity between a phenol and hydroxyl groups located on an aliphatic chain. Introduction of a carboxylic group at this site led to compound **13**, which did not bind to any RAR.

To further explore the ligand interactions with RARs, we prepared the propenylbenzoic derivatives (series II). The stilbene methoxy derivatives **14**,[26] **16**, and **18** are also characterized by a mixed RARβ–γ-binding profile. Moreover, the $K_i$ values for RARα and -γ are lower than for corresponding analogues in series I. Affinities for RARβ are similar in both series for *tert*-butyl and methylcyclohexyl derivatives and lower in the case of adamantyl substitution in series II compared to series I. Replacement of the methoxy group by a phenol (**15**, **17**, **19**) also induced a reduction of affinity on RARα and -β, and only in the case of the adamantyl substitution (**19**) is the RARγ selectivity again observed.

In conclusion, when we compare compounds of series I and II bearing the same substituents (methoxy and phenol), it is interesting to note the higher affinities for RARα and RARγ for compounds in series II. This suggests that the presence of the naphthyl group, independently of the nature of substituents in the para or meta position on the phenyl ring, is sufficient to diminish interaction with both RARα and -γ subtypes. In the case of the naphthalene series I, the presence of a phenol group is sufficient to induce at least a partial RARγ selectivity irrespective of the nature of the *m*-alkyl group. In contrast, in the stilbene series, the presence of both adamantyl and phenol groups is needed to confer RARγ selectivity. In order to investigate the role of volume requirements in the central portion of the compound, we synthesized the stilbene derivative **20**, devoid of the methyl group on the propenyl linker. This modification enhanced affinity, especially toward RARβ, suggesting that, in addition to adamantyl and phenol groups, some degree of hindrance in the linker unit of the stilbene series is required to gain RARγ selectivity.

Compounds were also tested for their ability to induce differentiation of F9 cells as estimated by plasminogen activator (PA) secretion.[27] These cells express high basal levels of RARα and RARγ, whereas RARβ, expressed at a low level in undifferentiated cells, is inducible by treatment with AtRA.[28] The RARγ selective compounds **7** and **19** induced plasminogen activator secretion with a half-maximal induction potency ($AC_{50}$) in the same range as their $K_i$ values for this receptor subtype. Thus, this pharmacological response could be mediated through this receptor. This is in agreement with the effects of the related methoxy derivatives **5** and **18** which are mixed RARβ–γ ligands. The differences in potency in the F9 cell assay between **5** vs **7** and **18** vs **19** are not affected by an enhancement of affinity for RARβ. This suggests that PA secretion is unrelated to induction of RARβ during the differentiation process and, consequently, that this pharmacological response is predominantly RARγ mediated with these compounds. With other compounds which are mainly mixed RARβ–γ ligands, $AC_{50}$ values in the F9 cell assay are in agreement with a mediation of this response through the RARγ receptor, but affinities and activities do not strictly correlate. We have previously shown that a RARα selective compound is also a potent inducer of PA in F9 cells.[29] Taken together, these results suggest that under these conditions, both receptor subtypes, RARα and -γ , are able to mediate PA induction in F9 cells, but we cannot exclude a role for RARβ after its induction. By generation of F9 cell lines in which RARα or RARγ is disrupted, it has been recently shown[30] that each of the RARs, α and γ, exhibits some specificity with respect to the regulation of differentiation—specific gene expression. However, loss of RARγ is associated with more dramatic alterations in gene expression than loss of RARα.

It is still difficult to define the exact role of the receptors in this bioassay. Studies have shown that RARs alone do not mediate the biological responses of retinoids. A key role for RXR as a dimer partner with RARs and the presence of different profiles of cognate hormone response elements in the target cell genes could be major factors influencing retinoid action and potency.[31,32] Apparently, small changes in structure can have a pronounced influence on the binding profiles and biological activity of these molecules. The pharmacological response is certainly dependant on other parameters, such as metabolic stability and the concentration of the ligand in the cell nucleus.

Two compounds, **2** and **15**, exhibiting moderate and high affinities for RARγ, respectively, are inactive in this assay. These compounds were evaluated as potential antagonists, and one compound, **15**, effectively exhibited a low antagonist activity. Finally, in order to further understand structure–activity of these series, we have reversed substituents $R_1$ and $R_2$ of compound **18**. The resulting compound (4-[(*E*)-2-[3-methoxy-4-(1-adamantyl)phenyl]propenyl]benzoic acid) exhibited a more potent antagonistic activity ($IC_{50}$ = 300 nM) in F9 cell differentiation assay than compound **15**. Further work is in progress in our laboratory to obtain more potent antagonists.

This research program has provided several compounds that were further screened in other in vitro and in vivo assays. Compounds **7** and **19** have shown a potent inhibitory effect of the proliferation of human melanoma cells.[11c] The mixed RARβ–γ compound **5**

(CD 271) showed high potency in the rhino mouse model of comedolysis.[33] Furthermore, CD 271 (INN adapalene) which was well tolerated[34] and efficient[35] in clinical studies has been developed as a topical treatment for acne.

Through this work, we can gain further insight into the structural features linking biological activity and receptor selectivity in the field of retinoids. The present structure–affinity data will provide a significant basis for future molecular modeling studies. Moreover, compounds **7** and **19**, which are the most RAR$\gamma$ selective described to date, are invaluable tools to investigate the respective contribution of the RAR$\gamma$ subtype in the pleiotropic response induced by retinoids in cultured cells, embryos, and whole animals.

## Experimental Section

The abbreviations which were used are as follows: DMAP, 4-(*N*,*N*-dimethylamino)pyridine; DMF, dimethylformamide; DPPE, 1,2-bis(diphenylphosphino)ethane; DPPF, 1,1′-bis(diphenylphosphino)ferrocene; HMPA, hexamethylphosphoramide; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; $Tf_2O$, trifluoromethanesulfonic anhydride; THF, tetrahydrofuran.

## Chemistry

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. 3-*tert*-Butyl-4-hydroxybenzoic acid was obtained from NIPA Laboratories Ltd. Reactions were carried out under a nitrogen or argon atmosphere. Reactions were monitored by thin-layer chromatography using Merck silica gel $60F_{254}$ plates (0.25 mm thickness) visualized with UV. Flash column chromatography was performed using Merck silica gel (230–400 mesh). Proton magnetic spectra were obtained on either a 90 or 250 MHz Brucker spectrometer using TMS as an internal standard. Infrared spectra were recorded on either a 1420 Perkin-Elmer or a 1600 FTIR Perkin-Elmer spectrometer. Mass spectra were recorded on a Hewlett Packard 5989A spectrometer using chemical ionization (CI) or electronic impact (EI) mode. Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses were obtained at CNRS (Vernaison, France) and are within ±0.4% of calculated values. Standard workup: organic layer washed with water or brine, dried ($MgSO_4$), and evaporated (Rotavapor).

**4-Bromo-2-*tert*-butylanisole (21).** $AlCl_3$ (3.10 g, 22.6 mmol) was added, all at once, to a mixture of 63.5 g (339 mmol) of *p*-bromoanisole and 31.4 g (339 mmol) of *tert*-butyl chloride. The mixture was stirred at ambient temperature until the evolution of gas ceased (about 15 min) and then heated to 80 °C for 15 min. The mixture was poured into 300 mL of iced water and extracted with $Et_2O$. After workup and purification by chromatography (hexane/$CH_2Cl_2$, 9:1), 31.9 g (39%) of **21** was obtained as a colorless oil which crystallized on cooling: mp <30 °C; $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 1.35 (s, 9H), 3.8 (s, 3H), 6.73 (d, 1H, $J$ = 7.6 Hz), 7.29 (dd, 1H, $J$ = 7.6, 2 Hz), 7.52 (br s, 1H); IR (KBr) 1220, 1290 cm$^{-1}$; MS (EI) *m/z* 243 ($M^+$). Anal. ($C_{11}H_{15}BrO$) C,H.

**Methyl 6-(3-*tert*-Butyl-4-methoxyphenyl)-2-naphthoate (22).** A solution of **21** (18.8 g, 77.5 mmol) in THF (100 mL) was added drop by drop to 2.26 g (93 mmol) of magnesium turnings and a crystal of iodine. Once the addition was complete, the mixture was heated at 40 °C for 30 min. To this solution cooled at room temperature was added 12.7 g (93 mmol) of zinc chloride in THF (100 mL), and the resulting mixture was stirred for 30 min at room temperature. There were then successively added methyl 6-bromo-2-naphthoate (12.1 g, 46 mmol) and 300 mg of $NiCl_2$/DPPE complex. The resulting mixture was then stirred for 10 h at room temperature. After evaporation of THF, addition of 200 mL of water, and extraction with $CH_2Cl_2$, the organic layer was worked up. The residue was purified by chromatography (hexane/$CH_2Cl_2$, 1:1) to give 11.5 g (72%) of **22**: mp 160 °C; $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 1.44 (s, 9H), 3.90 (s, 3H), 4 (s, 3H), 7 (d, 1H, $J$ = 7.5 Hz), 7.5–8.1 (m, 7H), 8.6 (br s, 1H); MS (EI) *m/z* 348 ($M^+$). Anal. ($C_{23}H_{24}O_3$) C,H.

**6-(3-*tert*-Butyl-4-methoxyphenyl)-2-naphthoic Acid (1).** Compound **22** (6.96 g, 20 mmol) was treated with 400 mL of a 2 N NaOH solution in methanol under reflux for 8 h. After evaporation of methanol and addition of 300 mL of water, the mixture was acidified until pH 1 with 6 N HCl and extracted with $Et_2O$. After workup and recrystallization in $Et_2O$, 6 g (90%) of 1 as a white solid was obtained: mp 263 °C; $^1$H NMR (90 MHz, Pyr-$d_5$) $\delta$ 1.53 (s, 9H), 3.8 (s, 3H), 7.1 (d, 1H, $J$ = 8.4 Hz), 7.75 (dd, 1H, $J$ = 8, 2 Hz), 7.7–8.4 (m, 5H), 8.55 (dd, 1H, $J$ = 8, 2 Hz), 8.72 (s, 1H); IR (KBr) 1690, 1290, 1225 cm$^{-1}$; MS (EI) *m/z* 334 ($M^+$). Anal. ($C_{22}H_{22}O_3$) C,H.

**4-Bromo-2-*tert*-butylphenol (23).** To 51.9 g (0.3 mol) of *p*-bromophenol was added 4.5 g of resin DOWEX (50 × 12). The resulting suspension was saturated with isobutylene and heated to 95 °C for 6 h under continuous bubbling of isobutylene. After allowing evaporation of excess of isobutylene, the resulting mixture was purified by chromatography (hexane/$CH_2Cl_2$, 50:50) to give 51.4 g (75%) of **23** as a colorless oil: $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 1.4 (s, 9H), 4.8 (s, 1H), 6.55 (d, 1H, $J$ = 8.6 Hz), 7.15 (dd, 1H, $J$ = 8, 2 Hz), 7.35 (d, 1H, $J$ = 2 Hz); MS (EI) *m/z* 239 ($M^+$).

**4-[(*tert*-Butyldimethylsilyl)oxy]-3-*tert*-butyl-1-bromobenzene (24).** Compound **23** in solution in DMF (250 mL) was treated with 34.4 mL (247 mmol) of triethylamine, 1.1 g (9 mmol) of DMAP, and 37.2 g (247 mmol) of *tert*-butyldimethylsilyl chloride and the resulting mixture stirred for 4 h at room temperature. The mixture was poured into iced water and extracted with $Et_2O$. After standard workup and chromatography (hexane), 63 g (82%) of **24** was obtained as a colorless oil: $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 0.3 (s, 6H), 1.1 (s, 9H), 1.35 (s, 9H), 6.65 (d, 1H, $J$ = 8.5 Hz), 7.15 (dd, 1H, $J$ = 8.5, 2 Hz), 7.35 (d, 1H, $J$ = 2 Hz); MS (EI) *m/z* 343 ($M^+$).

**Methyl 6-[3-*tert*-Butyl-4-[(*tert*-butyldimethylsilyl)oxy]-phenyl]-2-naphthoate (25).** Compound **24** (11.3 g, 33 mmol) was transformed into zincate derivative and condensed with methyl 6-bromo-2-naphthoate (5.1 g, 19.3 mmol) using exactly the same procedure as for preparation of **22**. After purification by chromatography (hexane/$CH_2Cl_2$, 70:30), 7.8 g (91%) of **25** as a white solid was obtained: mp 114–115 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.38 (s, 6H), 1.07 (s, 9H), 1.47 (s, 9H), 3.98 (s, 3H), 6.94 (d, 1H, $J$ = 8 Hz), 7.44 (dd, 1H, $J$ = 8, 2 Hz), 7.65 (d, 1H, $J$ = 2 Hz), 7.89–8.08 (m, 5H), 8.6 (br s, 1H); MS (EI) *m/z* 448 ($M^+$). Anal. ($C_{28}H_{36}O_3Si$) C,H.

**6-(3-*tert*-Butyl-4-hydroxyphenyl)-2-naphthoic Acid (2).** Compound **25** (7.4 g, 16.5 mmol) was saponified as described for 1. After the same workup, 5.1 g (97%) of **2**, as a white solid, was obtained: mp 252–253 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.47 (s, 9H), 6.98 (d, 1H, $J$ = 8 Hz), 7.5–8.2 (m, 7H), 8.63 (br s, 1H); IR (KBr) 1785, 1290 cm$^{-1}$; MS (EI) *m/z* 320 ($M^+$). Anal. ($C_{21}H_{20}O_3$) C,H.

**2-(1-Methylcyclohexyl)-4-bromophenol (26).** *p*-Bromophenol (52 g, 30 mmol) and 58.6 mL (45 mmol) of 1-methylcyclohexanol dissolved in 500 mL of $CH_2Cl_2$ were treated with 24 mL (42 mmol) of concentrated sulfuric acid (98%). The mixture was refluxed for 4 days. Organic layer was then washed with water, neutralized with $NaHCO_3$, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography (hexane/$CH_2Cl_2$, 80:20) to give 33.3 g (41%) of **26** as an oil: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.30 (s, 3H), 1.38–1.70 (m, 8H), 2.05 (m, 2H), 6.53 (d, 1H, $J$ = 8.5 Hz), 7.15 (dd, 1H, $J$ = 8.5, 2 Hz), 7.35 (d, 1H, $J$ = 2.2 Hz); MS (EI) *m/z* 269 ($M^+$).

**2-(1-Methylcyclohexyl)-4-bromoanisole (27).** To a suspension of sodium hydride (80% in oil, 0.5 g, 16.9 mmol) in 20 mL of DMF was slowly added, while maintaining the temperature at 20 °C, 4.1 g (15.3 mmol) of **26**. The mixture was stirred for 1 h at room temperature at which point $CH_3I$ (0.96 mL, 15.4 mmol) was added. The mixture was then stirred for 2 h at 20 °C, poured into water, and extracted with $Et_2O$. After standard workup followed by chromatography (hexane), 3.7 g (85%) of **27** as a yellow oil was obtained: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.26 (s, 3H), 1.45–170 (m, 8H), 2.0 (m, 2H), 3.78 (s,

3H), 6.73 (d, 1H, $J$ = 8.5 Hz), 7.26 (dd, 1H, $J$ = 8.5, 2 Hz), 7.35 (d, 1H, $J$ = 2.5 Hz); MS (EI) $m/z$ 283 ($M^+$).

**Methyl 6-[3-(1-Methylcyclohexyl)-4-methoxyphenyl]-2-naphthoate (28).** Compound **27** (3.6 g, 12.9 mmol) was transformed into zincate derivative and condensed with methyl 6-bromo-2-naphthoate (2.3 g, 8.7 mmol), following exactly the same procedure as for preparation of **22**. After chromatography (hexane/$CH_2Cl_2$, 60:40), 3.14 g (93%) of **28** was obtained: mp 145 °C; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 1.35 (s, 3H), 1.56 (m, 6H), 1.79 (m, 2H), 2.18 (m, 2H), 3.88 (s, 3H), 3.98 (s, 3H), 7.0 (d, 1H, $J$ = 8 Hz), 7.53 (dd, 1H, $J$ = 8 Hz), 7.6 (s, 1H), 7.78 (dd, 1H, $J$ = 8 Hz), 7.89 (dd, 1H, $J$ = 8 Hz), 7.92 (dd, 1H, $J$ = 8 Hz), 7.95 (s, 1H), 8.06 (dd, 1H, $J$ = 8 Hz), 8.60 (s, 1H); IR (KBr) 1715, 1295 $cm^{-1}$; MS (EI) 388 ($M^+$). Anal. ($C_{26}H_{28}O_3$) C,H.

**6-[3-(1-Methylcyclohexyl)-4-methoxyphenyl]-2-naphthoic Acid (3).** Compound **28** (3.1 g, 8 mmol) was saponified as described for 1. After evaporation of the solvent, addition of water, and acidification with 6 N HCl, the solid was filtered and dried under vacuum over phosphoric anhydride. Recrystallization in methanol gave 2.0 g (67%) of **3** as a white solid: mp 259 °C; $^1H$ NMR (250 MHz, Pyr-$d_5$) $\delta$ 1.1 (s, 3H), 1.2 (m, 6H), 1.5 (m, 2H), 1.89 (m, 2H), 3.41 (s, 3H), 6.76 (d, 1H, $J$ = 8.5 Hz), 7.39 (dd, 1H, $J$ = 8.5, 2 Hz), 7.57 (br s, 1H), 7.66 (dd, 1H, $J$ = 8.5, 2 Hz), 7.74 (d, 1H, $J$ = 8.5 Hz), 7.78 (d, 1H, $J$ = 8.5 Hz), 8.01 (s, 1H), 8.18 (dd, 1H, $J$ = 8.5, 2 Hz), 8.75 (s, 1H); IR (KBr) 1685, 1240 $cm^{-1}$; MS (EI) $m/z$ 374 ($M^+$). Anal. ($C_{25}H_{26}O_3$) C,H.

**4-Bromo-2-(1-methylcyclohexyl)-1-[(*tert*-butyldimethylsilyl)oxy]benzene (29).** To a solution of compound **26** (33.2 g, 124 mmol) in 250 mL of DMF were added $Et_3N$ (19 mL, 136 mmol), DMAP (755 mg, 6.2 mmol), and a solution of *tert*-butyldimethylsilyl chloride (20.5 g, 136 mmol) in DMF (100 mL). The mixture was stirred at room temperature for 4 h, poured into water, and extracted with $Et_2O$. After standard workup and chromatography (hexane), 42.5 g (85%) of **29**, as a yellow oil, was obtained: $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0 (s, 6H), 0.71 (s, 9H), 0.97 (s, 3H), 1.15–1.39 (m, 8H), 1.76 (m, 2H), 6.36 (d, 1H, $J$ = 8.5 Hz), 6.84 (dd, 1H, $J$ = 8.5, 2 Hz), 7.05 (d, 1H, $J$ = 2.5 Hz); MS (EI) 383 ($M^+$).

**Benzyl 6-[3-(1-Methylcyclohexyl)-4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-2-naphthoate (30).** Compound **29** (12 g, 31 mmol) was converted into zincate derivative and then condensed with benzyl 6-bromo-2-naphthoate (7.56 g, 22 mmol) following the same procedure as for preparation of **22**. Standard workup and chromatography (hexane/$CH_2Cl_2$, 70:30) afforded 9.3 g (75%) of **30**, as an amorphous solid: $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0.36 (s, 6H), 1.05 (s, 9H), 1.36 (s, 3H), 1.50 (m, 6H), 1.79 (m, 2H), 2.22 (m, 2H), 5.43 (s, 2H), 6.92 (d, 1H, $J$ = 8.2 Hz), 7.25–7.49 (m, 6H), 7.65 (d, 1H, $J$ = 2 Hz), 7.75 (dd, 1H, $J$ = 8, 2 Hz), 7.90 (d, $J$ = 8 Hz), 7.96 (d, 1H, $J$ = 8 Hz), 7.99 (s, 1H), 8.07 (dd, 1H, $J$ = 8.5, 2 Hz), 8.63 (s, 1H); MS (EI) $m/z$ 564 ($M^+$).

**Benzyl 6-[3-(1-Methylcyclohexyl)-4-hydroxyphenyl]-2-naphthoate (31).** Compound **30** (9.28 g, 16 mmol) in solution in 50 mL of THF was treated with 16 mL (18 mmol) of a 1.1 M solution of TBAF in THF. The mixture was stirred for 1.5 h at ambient temperature and then poured into iced water and extracted with $Et_2O$. Standard workup, followed by trituration in hexane, gave 6.9 g (95%) of **31** as a white solid: mp 142 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.40 (s, 3H), 1.57 (m, 6H), 1.80 (m, 2H), 2.23 (m, 2H), 5.07 (s, 1H), 5.44 (s, 2H), 6.77 (d, 1H, $J$ = 8 Hz), 7.33–7.52 (m, 6H), 7.65 (d, 1H, $J$ = 2 Hz), 7.75 (dd, 1H, $J$ = 8.5, 2 Hz), 7.88 (d, 1H, $J$ = 8 Hz), 7.96 (d, 1H, $J$ = 8 Hz), 7.99 (s, 1H), 8.11 (dd, 1H, $J$ = 8.5, 2 Hz), 8.64 (s, 1 H); MS (EI) $m/z$ 450 ($M^+$). Anal. ($C_{31}H_{30}O_3$).

**6-[3-(1-Methylcyclohexyl)-4-hydroxyphenyl]-2-naphthoic Acid (4).** Compound **31** (2.25 g, 5 mmol) in 50 mL of dioxane was hydrogenated under 7 bars of $H_2$ in the presence of 0.67 g of Pd–C (10%) for 3 h at room temperature. After filtration on Celite and evaporation, the residue was recrystallized in diisopropyl ether to give 1.16 g (79%) of **4** as a white solid: mp 209 °C; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.34 (s, 3H), 1.48 (m, 6H), 1.72 (m, 2H), 2.23 (m, 2H), 6.94 (d, 1H, $J$ = 8 Hz), 7.50 (d, 1H, $J$ = 8 Hz), 7.60 (d, 1H, $J$ = 2 Hz), 7.85 (dd, 1H, $J$ = 8, 2 Hz), 7.95 (d, 1H, $J$ = 8 Hz), 7.98 (d, 1H, $J$ = 8 Hz), 8.07 (d, 1H, $J$ = 8 Hz), 8.16 (s, 1H), 8.59 (s, 1H), 9.60 (s, 1H), 13 (br s, 1 H); IR (KBr) 1672, 1290 $cm^{-1}$; MS (EI) $m/z$ 360 ($M^+$). Anal. ($C_{24}H_{24}O_3$) C,H.

**2-(1-Adamantyl)-4-bromophenol (32).** 4-Bromophenol (34.6 g, 0.2 mol) and 30.4 g (0.2 mol) of 1-adamantanol were dissolved in 100 mL of dichloromethane. To the resulting solution was slowly added 11 mL (0.2 mol) of concentrated sulfuric acid (98%). The mixture was stirred for 8 h at ambient temperature, poured into water, neutralized with sodium bicarbonate, extracted with dichloromethane, dried over $MgSO_4$, and evaporated. After recrystallization in isooctane, 52.8 g (86%) of **32** as a white solid was obtained; mp 148–149 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.76 (s, 6H), 2.08 (s, 9H), 4.80 (s, 1H), 6.52 (d, 1H, $J$ = 8.2 Hz), 7.14 (dd, 1H, $J$ = 8.2, 2 Hz), 7.28 (d, 1H, $J$ = 2 Hz); MS (EI) $m/z$ 307 ($M^+$). Anal. ($C_{16}H_{19}BrO$) C,H.

**2-(1-Adamantyl)-4-bromoanisole (33).** Compound **32** (36.8 g, 120 mmol) was treated with $CH_3I$ (9 mL, 144 mmol) as described for preparation of **27** to give, after chromatography (hexane/$CH_2Cl_2$, 90:10) and recrystallization in hexane, 26.2 g (68%) of **33** as a white solid: mp 138–139 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.75 (s, 6H), 2.05 (s, 9H), 3.80 (s, 3H), 6.72 (d, 1H, $J$ = 8 Hz), 7.24 (dd, 1H, $J$ = 2, 8 Hz), 7.28 (d, 1H, $J$ = 2 Hz); MS (EI) $m/z$ 321 ($M^+$). Anal. ($C_{17}H_{21}BrO$) C,H.

**Methyl 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoate (34).** Compound **33** (14.5 g, 45.3 mmol) was converted into zincate derivative and then condensed with methyl 6-bromo-2-naphthoate (7.95 g, 30 mmol) following procedure described in preparation of compound **22**. After the same workup, the residue was purified by chromatography (heptane/$CH_2Cl_2$,70:30) and then recrystallized in ethyl acetate to give 12.2 g (78%) of **34** as a white solid; mp 222–223 °C; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 1.8 (s, 6H), 2.2 (br s, 9H), 3.9 (s, 3H), 4 (s, 3H), 7 (d, 1H, $J$ = 8.2 Hz), 7.55 (dd, 1H, $J$ = 8.2, 2 Hz), 7.6 (s, 1H), 7.7–8.15 (m, 5H), 8.6 (br s, 1H); IR (KBr) 1715, 1295 $cm^{-1}$; MS (EI) $m/z$ 426 ($M^+$). Anal. ($C_{29}H_{30}O_3$) C,H.

**6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic Acid (5).** Compound **34** (10.5 g, 24.6 mmol) was saponified as described for 1. After the same treatment as for isolation of **3** and recrystallization in a THF/ethyl acetate mixture, 8.2 g (81%) of **5** as a white solid was obtained: mp 319–322 °C; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.75 (s, 6H), 2.06 (s, 3H), 2.13 (s, 6H), 3.86 (s, 3H), 7.11 (d, 1H, $J$ = 8.5 Hz), 7.57 (d, 1H, $J$ = 2 Hz), 7.65 (dd, 1H, $J$ = 8.5, 2 Hz), 7.88 (dd, 1H, $J$ = 8.5, 2 Hz), 7.97 (dd, 1H, $J$ = 8.5, 2 Hz), 8.07 (d, 1H, $J$ = 8.5 Hz), 8.15 (d, 1H, $J$ = 8.5 Hz), 8.22 (br s, 1H), 8.60 (br s, 1H); IR (KBr) 1690, 1300, 1235 $cm^{-1}$; MS (EI) $m/z$ 412 ($M^+$). Anal. ($C_{28}H_{28}O_3$) C,H.

**2-(1-Adamantyl)-4-bromo-1-[(*tert*-butyldimethylsilyl)oxy]benzene (35).** Compound **32** (30.7 g, 100 mmol) was treated with *tert*-butyldimethylsilyl chloride (15.7 g, 104 mmol) as described for preparation of **24**. After the same workup, the residue was purified by chromatography (hexane) to give 32.6 g (86%) of **35** as a white solid: mp 111 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0.32 (s, 6H), 1.02 (s, 9H), 1.75 (s, 6H), 2.06 (s, 9H), 6.65 (d, 1H, $J$ = 8.7 Hz), 7.13 (dd, 1 H, $J$ = 8.7, 2.5 Hz), 7.28 (d, 1 H, $J$ = 2.5 Hz); MS (EI) $m/z$ 421 ($M^+$). Anal. ($C_{22}H_{33}BrOSi$) C,H.

**Methyl 6-[3-(1-Adamantyl)-4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-2-naphthoate (36).** Compound **35** (33.3 g, 79 mmol) was converted into zincate derivative and condensed with methyl 6-bromo-2-naphthoate (10.5 g, 39.5 mmol), using the procedure described for synthesis of **22**. After the same workup and purification by chromatography (heptane/ether, 70:30), 18.5 g (90%) of **36** was obtained as a white solid: mp 152–153 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0.39 (s, 6H), 0.88 (s, 9H), 1.8 (s, 6H), 2.1 (s, 3H), 2.19 (s, 6H), 3.98 (s, 3H), 6.91 (d, 1H, $J$ = 8.5 Hz), 7.42 (dd, 1H, $J$ = 8.5, 2.5 Hz), 7.60 (d, 1H, $J$ = 2.2 Hz), 7.78 (dd, 1H, $J$ = 8.5, 2 Hz), 7.88–8.08 (m, 4H), 8.60 (s, 1H); MS (EI) $m/z$ 526 ($M^+$).

**Methyl 6-[3-(1-Adamantyl)-4-hydroxyphenyl]-2-naphthoate (37).** Compound **36** (23 g, 43.7 mmol) was deprotected with TBAF as described for preparation of **31** to give, after trituration in hexane, 17.8 g (99%) of **37** as a white solid: mp 263–264 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.72 (s, 6 H), 2.12 (s, 3H), 2.23 (s, 6H), 3.98 (s, 3H), 6.90 (d, 1H, $J$ = 8.2 Hz),

7.40 (dd, 1H, $J$ = 8.2, 2 Hz), 7.56 (d, 1H, $J$ = 2 Hz), 7.78 (dd, 1H, $J$ = 8.5, 2 Hz), 7.90 (d, 1H, $J$ = 8.5 Hz), 7.95 (d, 1H, $J$ = 8.5 Hz), 8.03 (s, 1H), 8.05 (dd, 1H, $J$ = 8.5, 2 Hz), 8.59 (s, 1H); MS (EI) $m/z$ 412 ($M^+$). Anal. ($C_{28}H_{28}O_3$) C,H.

**Methyl 6-[3-(1-Adamantyl)-4-(hexyloxy)phenyl]-2-naphthoate (38).** Compound **37** (5.3 g, 12.8 mmol) was treated with iodohexane (2.3 mL, 15.4 mmol) as described for preparation of **27**. Chromatography (hexane/$CH_2Cl_2$, 50:50) and recrystallization in isooctane gave 5.5 g (87%) of **38** as a white solid: mp 129–130 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.90 (t, 3H), 1.39 (m, 4H), 1.57 (m, 2H), 1.80 (s, 6H), 1.90 (m, 2H), 2.11 (s, 3H), 2.21 (s, 6H), 3.98 (s, 3H), 4.04 (m, 2H), 6.98 (d, 1H, $J$ = 8.5 Hz), 7.56 (dd, 1H, $J$ = 8.5, 2 Hz), 7.60 (d, 1H, $J$ = 2 Hz), 7.79 (dd, 1H, $J$ = 8.5, 2 Hz), 7.90 (d, 1H, $J$ = 8.5 Hz), 7.97 (d, 1H, $J$ = 8.5 Hz), 8.00 (d, 1H, $J$ = 2 Hz), 8.06 (dd, 1H, $J$ = 8.5, 2 Hz); MS $m/z$ 496 ($M^+$). Anal. ($C_{34}H_{40}O_3$) C,H.

**6-[3-(1-Adamantyl)-4-(hexyloxy)phenyl]-2-naphthoic Acid (6).** Compound **38** (4.2 g, 8.4 mmol) was saponified as described for 1. Recrystallization in AcOEt afforded 3.8 g (95%) of **6** as a white solid: mp 266–267 °C; $^1$H NMR (90 MHz, Pyr-$d_5$) $\delta$ 0.90 (t, 3H), 1.35 (m, 4H), 1.50 (m, 1H), 1.85 (s, 6H), 2 (m, 2H), 2.15 (s, 3H), 2.4 (s, 6H), 4 (t, 2H), 7.15 (d, 1H, $J$ = 8.5 Hz) 7.7 (dd, 1H, $J$ = 8, 2 Hz), 8.0 (dd, 1H, $J$ = 8, 2 Hz), 8.1–8.4 (m, 3H), 8.4 (br s, 1H), 8.5 (dd, 1H, $J$ = 8.5, 2 Hz), 9.1 (s, 1H); IR (KBr) 1230, 1290, 1690 cm$^{-1}$; MS $m/z$ 482 ($M^+$). Anal. ($C_{33}H_{38}O_3$) C,H.

**6-[3-(1-Adamantyl)-4-hydroxyphenyl]-2-naphthoic Acid (7).** Compound **37** (5 g, 12 mmol) was saponified as described for 1. Recrystallization in diisopropyl ether afforded 3.8 g (79%) of compound **7**, as a white solid: mp 274–275 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.76 (s, 6H), 2.07 (s, 3H), 2.17 (s, 6H), 6.92 (d,1 H, $J$ = 8.2 Hz), 7.50 (d, 1H, $J$ = 8.2 Hz), 7.52 (s, 1H), 7.86 (dd, 1H, $J$ = 8.5, 2 Hz), 7.97 (dd, 1H, $J$ = 8.5, 2 Hz), 8.06 (d, 1H, $J$ = 8.5 Hz), 8.09 (d, 1H, $J$ = 8.5 Hz), 8.17 (s, 1H), 8.59 (s, 1H); IR (KBr) 1690, 1230 cm$^{-1}$; MS $m/z$ 398 ($M^+$). Anal. ($C_{27}H_{26}O_3$) C,H.

**Methyl 6-[3-(1-Adamantyl)-4-[[(trifluoromethyl)sulfonyl]oxy]phenyl]-2-naphthoate (39).** To a solution of compound **37** (10.3 g, 25 mmol) in $CH_2Cl_2$ (100 mL) were added pyridine (6 mL, 74 mmol) and DMAP (30 mg, 0.25 mmol). To the resulting mixture cooled at −70 °C was added dropwise a solution of triflic anhydride (5 mL, 30 mmol) in $CH_2Cl_2$. After standard workup and chromatography (hexane/$CH_2Cl_2$, 40:60), 12.5 g (92%) of **39** as a white solid was obtained: mp 185–186 °C; $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 1.81 (s, 6H), 2.16 (s, 9H), 3.99 (s, 3H), 7.46 (d, 1H, $J$ = 8.5 Hz), 7.58 (dd, 1H, $J$ = 8.5, 2 Hz), 7.74 (d, 1H, $J$ = 8.5 Hz), 7.75 (s, 1H), 7.94 (d, 1H, $J$ = 8.5 Hz), 8.01 (s, 1H), 8.03 (dd, 1H, $J$ = 8.5, 2 Hz), 8.10 (d, 1H, $J$ = 8.5 Hz), 8.64 (s, 1H); MS (CI) $m/z$ 545 ($MH^+$).

**Methyl 6-[3-(1-Adamantyl)-4-(benzyloxycarbonyl)phenyl]-2-naphthoate (40).** A mixture of **39** (13.1 g, 24 mmol), $Et_3N$ (6.7 mL, 48 mmol), Pd $(OAc)_2$ (0.27 g, 1.2 mmol), and DPPF (1.33 g, 2.4 mmol) in DMF (100 mL) and benzyl alcohol (24 mL) was stirred for 6 h at 70 °C under 6 bars of CO pressure. The reaction mixture was then diluted with brine, extracted with ether, washed with 1 N HCl and then brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue (hexane/$CH_2Cl_2$, 50:50) gave 9.15 g (72%) of **40** as a white solid: mp 170 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.63 (s, 3H), 2.0 (s, 3H), 2.7 (s, 6H), 3.99 (s, 3H), 5.39 (s, 2H), 7.36–7.55 (m, 7H), 7.77 (d, 1H, $J$ = 8.5 Hz), 7.79 (s, 1H), 7.93 (d, 1H, $J$ = 8.5 Hz), 8.01 (d, 1H, $J$ = 8.5 Hz), 8.03 (s, 1H), 8.09 (d, 1H, $J$ = 8.5 Hz), 8.63 (s, 1H); MS (EI) $m/z$ 530 ($M^+$). Anal. ($C_{36}H_{34}O_4$) C,H.

**Methyl 6-[3-(1-Adamantyl)-4-carboxyphenyl]-2-naphthoate (41).** To a solution of **40** (9.0 g, 17 mmol) in dioxane (90 mL) and acetic acid (0.5 mL) was added 900 mg of Pd–C (10%). The resulting mixture was hydrogenated under 7 bars of pressure of hydrogen for 4 h at 70 °C. After filtration of the mixture on Celite and evaporation, the solid residue was triturated in hexane to give 6.8 g (91%) of **41** as a white solid: mp 239–240 °C; $^1$H NMR (250 MHz, Pyr-$d_5$) $\delta$ 1.45 (m, 6H), 1.79 (s, 3H), 2.23 (s, 6H), 3.66 (s, 3H), 7.48 (d, 1H, $J$ = 8 Hz), 7.65 (d, 1H, $J$ = 8.5 Hz), 7.74 (d, 1H, $J$ = 8.5 Hz), 7.82 (s, 1H), 7.84 (d, 1H, $J$ = 8.5 Hz), 7.92 (d, 1H, $J$ = 8.5 Hz), 8.0 (d, 1H, $J$ = 8.5 Hz), 8.13 (s, 1H), 8.58 (s, 1H); MS (EI) $m/z$ 440 ($M^+$). Anal. ($C_{29}H_{28}O_4$) C,H.

**Methyl 6-[3-(1-Adamantyl)-4-(hydroxymethyl)phenyl]-naphthoate (42).** To a solution of compound **41** (6.2 g, 14 mmol) in THF (30 mL) was added dropwise 49 mL of a 1 M $BH_3$ solution in THF. The mixture was heated under reflux for 12 h. Evaporation of the solvent, neutralization by 1 N HCl, extraction with AcOEt, standard workup, and chomatography in $CH_2Cl_2$ gave 4.45 g (75%) of **42** as a white solid: mp 212 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.72 (s, 6H), 2.15 (s, 9H), 3.99 (s, 3H), 5.07 (s, 2H), 7.60 (m, 2H), 7.71 (br s, 1H), 7.79 (dd, 1H, $J$ = 8.5, 2 Hz), 7.92 (d, 1H, $J$ = 8.5 Hz), 7.99–8.10 (m, 3H), 8.62 (s, 1H); MS (EI) 426 ($M^+$). Anal. ($C_{29}H_{30}O_3$) C,H.

**6-[3-(1-Adamantyl)-4-(hydroxymethyl)phenyl]-2-naphthoic Acid (8).** Compound **42** (4.4 g, 10.3 mmol) was saponified as described for preparation of 1. After the same treatment as described for isolation of **3**, followed by a recrystallization in EtOH–water mixture, 3 g (68%) of **8** was obtained as a white solid: mp 277–278 °C; $^1$H NMR (250 MHz, Pyr-$d_5$) $\delta$ 1.34 (s, 6H), 1.65 (s, 3H), 1.83 (s, 6H), 5.05 (s, 2H), 7.44 (dd, 1H, $J$ = 8, 2 Hz), 7.56 (br s, 1H), 7.66 (dd, 1H, $J$ = 8.5, 2 Hz), 7.77–7.87 (m, 3H), 8.05 (s, 1H), 8.20 (dd, 1H, $J$ = 8.5, 2 Hz), 8.76 (s, 1H); IR (KBr) 1710, 1290 cm$^{-1}$; MS (EI) 412 ($M^+$). Anal. ($C_{28}H_{28}O_3$) C,H.

**Benzyl 6-[3-(1-Adamantyl)-4-hydroxyphenyl]-2-naphthoate (43).** Compound **7** (7.5 g, 18.8 mmol) was treated with benzyl bromide (2.5 mL, 21 mmol) as described for the preparation of **27** to give, after the same treatment, chromatography (hexane/$CH_2Cl_2$, 30:70) and recrystallization in hexane, 7.9 g (86%) of **43** as a white solid: mp 186 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.80 (6H), 2.12 (s, 3H), 2.21 (s, 6H), 5.07 (s, 1H), 5.44 (s, 2H), 6.78 (d, 1H, $J$ = 8.5 Hz), 7.36–7.44 (m, 5H), 7.49 (s, 1H), 7.50 (dd, 1H, $J$ = 8.5, 2 Hz), 7.58 (d, 1H, $J$ = 2 Hz), 7.76 (dd, 1H, $J$ = 8.2 Hz), 7.90 (d, 1H, $J$ = 8.7 Hz), 7.96 (d, 1H, $J$ = 8.7 Hz), 7.98 (s, 1H), 8.10 (dd, 1H, $J$ = 8.7 Hz, $J$ = 2 Hz), 8.64 (s, 1H); MS (EI) $m/z$ 488 ($M^+$). Anal. ($C_{34}H_{32}O_3$) C,H.

**Benzyl 6-[3-(1-Adamantyl)-4-[[(trifluoromethyl)sulfonyl]oxy]phenyl]-2-naphthoate (44).** A solution of compound **43** (39 g, 80 mmol) was treated with $Tf_2O$ (16 mL, 96 mmol) as described for preparation of **39**. After same workup and chromatography ($CH_2Cl_2$/hexane, 40:60), 44.1 g (89%) of **44** was obtained as a white solid: mp 132 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.81 (s, 6H), 2.15 (s, 9H), 5.44 (s, 2H), 7.36–7.59 (m, 7H), 7.74 (m, 2H), 7.94 (d, 1H, $J$ = 8.7 Hz), 8.00 (s, 1H), 8.02 (d, 1H, $J$ = 8.7 Hz), 8.13 (dd, 1H, $J$ = 8.7, 2 Hz), 8.66 (s, 1H); MS (CI) $m/z$ 621 ($MH^+$).

**Benzyl 6-[3-(1-Adamantyl)-4-(2-propenyl)phenyl]-2-naphthoate (45).** Compound **44** (33 g, 53 mmol) in DMF (180 mL) was treated with allyltributyltin (16.5 mL, 53 mmol), LiCl (4.5 g, 0.1 mol), and $(PPh_3)_2PdCl_2$ (0.74 g, 1.0 mmol). The mixture was stirred at 100 °C for 40 min and then poured into iced water, extracted with ether, washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography ($CH_2Cl_2$/hexane, 40:60) to give 26.3 g (97%) of **45** as a white solid: mp 121 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.80 (s, 6H), 2.15 (s, 9H), 3.81 (d, 2H, $J$ = 5.7 Hz), 5.08 (d, 1H, $J$ = 16.7 Hz), 5.12 (d, 1H, $J$ = 9.5 Hz), 5.43 (s, 2H), 6.03 (m, 1H), 7.30 (d, 1H, $J$ = 8 Hz), 7.35–7.44 (m, 3H), 7.49 (m, 3H), 7.69 (s, 1H), 7.80 (d, 1H, $J$ = 8.5 Hz), 7.91 (d, 1H, $J$ = 8.5 Hz), 7.99 (d, 1H, $J$ = 8.5 Hz), 8.04 (s, 1H), 8.10 (d, 1H, $J$ = 8.5 Hz), 8.64 (s, 1H); MS (EI) $m/z$ 512 ($M^+$). Anal. ($C_{37}H_{36}O_2$) C,H.

**Benzyl 6-[3-(1-Adamantyl)-4-(3-hydroxypropyl)phenyl]-2-naphthoate (46).** A solution of compound **45** (5.1 g, 10 mmol) in THF (20 mL) was cooled to 0 °C and treated by a dropwise addition of 30 mL of a 0.5 M solution of 9-BBN in THF. The mixture was stirred 1 h at 0 °C and 1 h at ambient temperature. To this precedent mixture cooled at 0 °C were added 25 mL of a 1 M solution of NaOH in water and 20 mL of a solution of $H_2O_2$ (30%) in water. The resulting mixture stirred for 1 h at 0 °C and 2 h at ambient temperature. After evaporation of THF and extraction with $CH_2Cl_2$, the organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography ($CH_2Cl_2$/hexane, 80:0) to give 4.67 g (88%) of **46** as a white solid: mp 176 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.81 (s, 6H), 1.95 (m, 2H), 2.16

(s, 9H), 3.10 (m, 2H), 3.82 (t, 2H), 5.43 (s, 2H), 7.32 (d, 1H, $J$ = 8 Hz), 7.36–7.52 (m, 6H), 7.68 (br s, 1H), 7.80 (dd, 1H, $J$ = 8.5, 2 Hz), 7.91 (d, 1H, $J$ = 8.5 Hz), 7.99 (d, 1H, $J$ = 8.5 Hz), 8.09 (br s, 1H), 8.10 (dd, 1H, $J$ = 8.5, 2 Hz), 8.65 (s, 1H); MS (EI) $m/z$ 530 ($M^+$). Anal. ($C_{37}H_{38}O_3$) C,H.

**6-[3-(1-Adamantyl)-4-(3-hydroxypropyl)phenyl]-2-naphthoic Acid (9).** Compound **46** (2.67 g, 5 mmol) was hydrogenated as described for preparation of **4**. The same workup followed by crystallization in a EtOH/water mixture afforded 1.78 g (81%) of **9** as a white solid: mp 262–263 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.77 (br s, 8H), 2.11 (s, 9H), 2.98 (m, 2H), 3.55 (m, 2H), 7.32 (d, 1H, $J$ = 8 Hz), 7.58 (d, 1H, $J$ = 8 Hz), 7.65 (s, 1H), 7.90 (d, 1H, $J$ = 8.7 Hz), 7.99 (d, 1H, $J$ = 8.7 Hz), 8.09 (d, 1H, $J$ = 8.7 Hz), 8.18 (d, 1H, $J$ = 8.7 Hz), 8.25 (s, 1H), 8.62 (s, 1H); IR (KBr) 1715, 1260, 1220 cm$^{-1}$; MS (EI) $m/z$ 440 ($M^+$). Anal. ($C_{30}H_{32}O_3$) C,H.

**Benzyl 6-[3-(1-Adamantyl-4-ethenylphenyl]-2-naphthoate (47).** Compound **44** (13.8 g, 22 mmol) was treated with vinyltributyltin (9.4 mL, 31 mmol) in the conditions described for preparation of **45**. After the same workup followed by chromatography ($CH_2Cl_2$/hexane, 30:70), 4.5 g (41%) of **47** was obtained as a white solid: mp 158–160 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.80 (s, 6H), 2.18 (s, 9H), 5.30 (d, 1H, $J$ = 11 Hz), 5.43 (s, 2H), 5.51 (d, 1H, $J$ = 17 Hz), 7.24–7.65 (m, 8H), 7.69 (s, 1H), 7.81 (d, 1H, $J$ = 8.5 Hz), 7.92 (d, 1H, $J$ = 8.5 Hz), 8.01 (d, 1H, $J$ = 8.5 Hz), 8.05 (s, 1H), 8.11 (d, 1H, $J$ = 8.5 Hz), 8.65 (s, 1H); MS $m/z$ 498 ($M^+$). Anal. ($C_{36}H_{34}O_2$) C,H.

**Benzyl 6-[3-(1-Adamantyl)-4-(1,2-dihydroxyethyl)phenyl]-2-naphthoate (48).** A solution of compound **47** (2.5 g, 5 mmol) and trimethylamine $N$-oxide dihydrate (0.76 g, 6.8 mmol) in pyridine (0.4 mL) and water (5 mL) was treated with $OsO_4$ (25 mg, 0.1 mmol). The resulting mixture was stirred under reflux for 6 h. After cooling to 20 °C, followed by addition of $NaHSO_3$ (0.29 g) and water (10 mL), the mixture was stirred for 30 min at room temperature. Extraction with AcOEt, followed by standard workup and chromatography ($CH_2Cl_2$/$Et_2O$, 9:1), led to 1.92 g (72%) of **48** as a white solid: mp 193 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.82 (s, 6H), 2.11 (m, 9H), 3.80 (m, 2H), 5.43 (s, 2H), 5.77 (m, 1H), 7.36–7.76 (m, 9H), 7.77 (dd, 1H, $J$ = 8.5, 2 Hz), 7.92 (d, 1H, $J$ = 8.5 Hz), 7.96 (d, 1H, $J$ = 8.5 Hz), 7.98 (d, 1H, $J$ = 2 Hz), 8.10 (dd, 1H, $J$ = 8.5, 2 Hz), 8.65 (s, 1H); IR (KBr) MS (EI) $m/z$ 532 ($M^+$). Anal. ($C_{36}H_{36}O_4$) C,H.

**6-[3-(1-Adamantyl)-4-(1,2-dihydroxyethyl)phenyl]-2-naphthoic Acid (10).** Compound **48** (1.90 g, 3.5 mmol) in dioxane (50 mL) was treated with 0.6 g of Pd–C (10%) and hydrogenated under 7 bars of $H_2$ pressure for 4 h at 50 °C. The mixture was filtered on Celite and evaporated to give, after recrystallization in water–EtOH mixture, 1.1 g (70%) of **10** as a white solid: mp 248 °C; $^1$H NMR (250 MHz, Pyr-$d_5$) $\delta$ 1.63 (s, 6H), 1.93 (s, 3H), 2.23 (m, 6H), 4.26 (m, 1H), 4.36 (m, 1H), 6.27 (m, 1H), 7.83 (d, 1H, $J$ = 8 Hz), 7.91 (s, 1H), 8.03 (dd, 1H, $J$ = 8, 2 Hz), 8.16 (d, 1H, $J$ = 8 Hz), 8.21 (d, 1H, $J$ = 8 Hz), 8.26 (d, 1H, $J$ = 8 Hz), 8.42 (s, 1H), 8.56 (dd, 1H, $J$ = 8, 2 Hz), 9.12 (s, 1H); IR (KBr) 1700, 1295 cm$^{-1}$; MS (EI) $m/z$ 442 ($M^+$). Anal. ($C_{29}H_{30}O_4$) C,H.

**Benzyl 6-[3-(1-Adamantyl)-4-(2,3-dihydroxypropyl)-phenyl]-2-naphthoate (49).** A solution of compound **45** (5.13 g, 10 mmol) was treated with trimethylamine $N$-oxide dihydrate (1.51 g, 13.6 mmol) and $OsO_4$ (20 mg, 0.078 mmol) as described for the preparation of **48**. After the same workup, the residue was purified by chromatography ($CH_2Cl_2$/$Et_2O$, 80:20) to give, after trituration in hexane, 4 g (74%) of **49** as a white solid: mp 199–200 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.77 (s, 6H), 2.13 (br s, 9H), 3.3 (m, 2H), 3.65 (m, 2H), 4.7 (m, 1H), 5.43 (s, 2H), 7.37–7.60 (m, 7 H), 7.67 (s, 1H), 7.93 (d, 1H, $J$ = 8 Hz), 8.03 (d, 1H, $J$ = 8 Hz), 8.14 (d, 1H, $J$ = 8.5 Hz), 8.22 (d, 1H, $J$ = 8 Hz), 8.28 (s, 1H), 8.68 (s, 1H); MS (EI) $m/z$ 546 ($M^+$). Anal. ($C_{37}H_{38}O_4$) C,H.

**6-[3-(1-Adamantyl)-4-(2,3-dihydroxypropyl)phenyl]-2-naphthoic Acid (11).** Compound **49** (4 g, 7.3 mmol) was hydrogenated as described for **10**. Recrystallization in a dioxane–water mixture gave 3 g (90%) of 11 as a white solid: mp 258 °C; $^1$H NMR (250 MHz, Pyr-$d_5$) $\delta$ 1.40 (q, 6H), 1.70 (s, 3H), 1.95 (s, 6H), 3.3 (m, 2H), 3.88 (m, 2H), 4.19 (m, 1H), 7.35 (d, 1H, $J$ = 8 Hz), 7.6–7.71 (m, 3H), 7.83 (d, 1H, $J$ = 8 Hz), 7.86 (d, 1H, $J$ = 8 Hz), 8.07 (s, 1H), 8.22 (d, 1H, $J$ = 8 Hz), 8.78 (s, 1H); IR (KBr) 1690, 1300 cm$^{-1}$; MS (EI) $m/z$ 456 ($M^+$). Anal. ($C_{30}H_{32}O_4$) C,H.

**3-(1-Adamantyl)-4-[[(2,3-dimethyl-1,3-dioxolan-4-yl)-methyl]oxy]bromobenzene (50).** To a solution of compound **32** (10 g, 32.5 mmol) in DMF (140 mL) containing 4.95 g (35.8 mmol) of potassium carbonate was added dropwise 11.2 g (39 mmol) of 3-(tosyloxy)-1,2-propanediol acetonide. The mixture was stirred at 100 °C for 12 h and then poured into iced water and extracted with ether. Standard workup and chromatography ($CH_2Cl_2$/hexane, 50:50) afforded 7.5 g (55%) of **50** as a white solid: mp 90–91 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.40 (s, 3H), 1.45 (s,3H), 1.75 (s, 6H), 2.05 (s, 9H), 3.95 (m, 2H), 4.07 (m, 1H), 4.22 (m, 1H), 4.53 (m, 1H), 6.72 (d, 1H, $J$ = 8.7 Hz), 7.26 (m, 2H); MS (EI) $m/z$ 421 ($M^+$). Anal. ($C_{22}H_{29}BrO_3$) C,H.

**Methyl 6-[3-(1-Adamantyl)-4-[[(2,3-dimethyl-1,3-dioxolan-4-yl)methyl]oxy]phenyl]-2-naphthoate (51).** Compound **50** (7.4 g, 17.6 mmol) was converted into zincate derivative and condensed with methyl 6-bromo-2-naphthoate (9.97 g, 37.6 mmol) following exactly the same procedure as for the preparation of **22**. After the same workup followed by chromatography (hexane/dichloromethane 70:30), 8.3 g (89%) of compound **51** was obtained as a white solid: mp 116–118 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.43 (s, 3H), 1.48 (s, 1H), 1.60 (s, 6H), 2.11 (s, 3H), 2.17 (s, 6H), 3.99 (s, 3H), 4.02 (m, 2H), 4.22 (m, 2H), 4.58 (m, 1H), 6.98 (d, 1H, $J$ = 8.2 Hz), 7.52 (d, 1H, $J$ = 8.5 Hz), 7.60 (s, 1H), 7.78 (d, 1H, $J$ = 8.2 Hz), 7.91 (d, 1H, $J$ = 8.2 Hz), 7.98 (d, 1H, $J$ = 8.5 Hz), 8.2 (s, 1H), 8.06 (d, 1H, $J$ = 8.2 Hz), 8.61 (s, 1H); MS (EI) $m/z$ 526 ($M^+$). Anal. ($C_{34}H_{38}O_5$) C,H.

**Methyl 6-[3-(1-Adamantyl)-4-[(2,3-dihydroxypropyl)-oxy]phenyl]-2-naphthoate (52).** Compound **51** (4.8 g, 9.15 mmol) was placed in 90 mL of a solution of formic acid (40%) in water, and the mixture was heated for 48 h at 100 °C. The mixture was then poured into water and extracted with AcOEt. Standard workup and chromatography ($CH_2Cl_2$/THF, 90:10) afforded 3.2 g (72%) of **52** as a white solid: mp 209–210 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.75 (s, 6H), 2.07 (s, 3H), 2.14 (s, 6H), 3.48 (m, 1H), 3.80 (m, 2H), 4.15 (m, 2H), 6.98 (d, 1H, $J$ = 8.5 Hz), 7.48 (dd, 1H, $J$ = 8.5, 2 Hz), 7.54 (br s, 1H), 7.74 (dd, 1H, $J$ = 8.5, 2 Hz), 7.86 (dd, 1H, $J$ = 8.5, 2 Hz), 7.92 (d, 1H, $J$ = 8.5 Hz), 7.95 (s, 1H), 8.01 (d, 1H, $J$ = 8.5 Hz), 8.55 (s, 1H); IR (KBr) 1720, 1290, 1225 cm$^{-1}$; MS (EI) $m/z$ 486 ($M^+$). Anal. ($C_{31}H_{34}O_5$) C,H.

**6-[3-(1-Adamantyl)-4-[(2,3-dihydroxypropyl)oxy]phenyl]-2-naphthoic Acid (12).** Compound **52** (3 g, 6.17 mmol) was treated by 60 mL of a 1 N sodium hydroxide solution in methanol and refluxed for 24 h. After evaporation of methanol, the residue was taken up in water and acidified with 2 N HCl and the mixture was extracted by AcOEt. After standard workup and recrystallization in AcOEt, 2.67 g (92%) of **12** as a white solid was obtained: mp 278 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.66 (s, 6H), 1.87 (s, 3H), 2.06 (s, 6H), 3.48 (m, 2H), 3.84–3.93 (m, 3H), 6.98 (d, 1H, $J$ = 8.5 Hz), 7.47 (s, 1H), 7.52 (dd, 1H, $J$ = 8.5, 2 Hz), 7.78 (dd, 1H, $J$ = 8.5, 2 Hz), 7.86 (d, 1H, $J$ = 8.5 Hz), 7.97 (d, 1H, $J$ = 8.5 Hz), 8.04 (d, 1H, $J$ = 8.5 Hz), 8.11 (s, 1H), 8.48 (s, 1H); IR (KBr) 1700, 1235 cm$^{-1}$; MS (EI) $m/z$ 472 ($M^+$). Anal. ($C_{30}H_{32}O_5$) C,H.

**6-[3-(1-Adamantyl)-4-carboxyphenyl]-2-naphthoic Acid (13).** Compound **41** (0.95 g, 2.17 mmol) was saponified as described for 1 to give, after recrystallization in a AcOEt/THF mixture, 0.74 g (80%) of **13** as a white solid: mp 333–335 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.74 (s, 6H), 1.99 (s, 3H), 2.17 (s, 6H), 7.42 (d, 1H, $J$ = 8 Hz), 7.71 (d, 1H, $J$ = 8 Hz), 7.86 (s, 1H), 7.94 (d, 1H, $J$ = 8.5 Hz), 8.01 (d, 1H, $J$ = 8.5 Hz), 8.13 (d, 1H, $J$ = 8.5 Hz), 8.22 (d, 1H, $J$ = 8.5 Hz), 8.33 (s, 1H), 8.64 (s, 1H); IR (KBr) 1690 cm$^{-1}$; MS (EI) $m/z$ 426 ($M^+$). Anal. ($C_{28}H_{26}O_4$) C,H.

**3-*tert*-Butyl-4-methoxybenzoic Acid (53).** A solution of 3-*tert*-butyl-4-hydroxybenzoic acid (NIPA Fine Chemicals; 8.45 g, 43.5 mmol) in 2-butanone (200 mL) was treated by $K_2CO_3$ (24 g, 174 mmol) and $Me_2SO_4$ (9.05 mL, 95.5 mmol). The resulting mixture was heated at 70 °C for 3.5 h. After evaporation of solvents, the residue was taken up in water and extracted with ether. The organic layer was then washed,

dried, and evaporated to give 9.64 g (100%) of methyl 3-*tert*-butyl-4-methoxybenzoate as a yellow oil: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.38 (s, 9H), 3.88 (s, 3H), 3.89 (s,3H), 6.87 (d, 1H, $J$ = 8.5 Hz), 7.89 (d, 1H, $J$ = 8.5 Hz), 7.97 (s, 1H); MS (EI) $m/z$ 222 ($M^+$).

Methyl 3-*tert*-butyl-4-methoxybenzoate (9.64 g, 43.4 mmol) was saponified as described for 1 to give, after recrystallization in ethanol, 8.38 g (93%) of **53** as a white solid: mp 194 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.38 (s, 9H), 3.91 (s, 3H), 7.10 (d, 1H, $J$ = 8.5 Hz), 7.85 (d, 1H, $J$ = 8.5 Hz), 7.87 (s, 1H); MS (EI) $m/z$ 208 ($M^+$). Anal. ($C_{12}H_{16}O_3$) C,H.

**(3-*tert*-Butyl-4-methoxyphenyl)ethanone (54).** Compound **53** (6.23 g, 30 mmol) in $Et_2O$ (60 mL) was treated at −20 °C with 37.5 mL of a solution of $CH_3Li$ (1.6 M in $Et_2O$). The mixture was allowed to warm up to 20 °C during the night under stirring and then poured into iced water and extracted with $Et_2O$. Standard workup and chromatography in hexane afforded 6 g (97%) of **54** as a colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.39 (s, 9H), 2.56 (s, 3H), 6.89 (d, 1H, $J$ = 8.5 Hz), 7.82 (dd, 1H, $J$ = 8.5, 2 Hz), 7.94 (d, 1H, $J$ = 2 Hz); MS (EI) $m/z$ 206 ($M^+$).

**Ethyl 4-[(*E*)-2-(3-*tert*-Butyl-4-methoxyphenyl)propenyl]benzoate (55).** To a suspension of NaH (80%) in oil (1.14 g, 38 mmol) in THF (30 mL) was added dropwise a solution containing **54** (6 g, 29 mmol), diethyl [4-(ethoxycarbonyl)-benzyl]phosphonate (10.5 g, 35 mmol), and 15-crown-5 (1.27 g, 5.8 mmol) in THF (80 mL). The reaction mixture was then stirred at room temperature for the night and then diluted with water and extracted with $Et_2O$. Standard workup and chromatography (hexane/$Et_2O$, 95:5) afforded 3.86 g (38%) of ethyl 4-[(*Z*)-2-(3-*tert*-butyl-4-methoxyphenyl)propenyl]benzoate as a colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.23 (s, 9H), 1.38 (t, 3H), 2.22 (s, 3H), 3.83 (s, 3H), 4.35 (q, 2H), 6.44 (s, 1H), 6.78 (d, 1H, $J$ = 8 Hz), 7.0 (m, 4H), 7.77 (d, 2H, $J$ = 8 Hz); MS (EI) $m/z$ 352 ($M^+$).

Also obtained was 5.42 g (53%) of **55** as a white solid: mp 71.5 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.37 (s, 9H),1.43 (t, 3H), 2.28 (s, 3H), 3.86 (s, 3H), 4.38 (q, 2H), 6.77 (s, 1H) 6.87 (d, 1H, $J$ = 8 Hz), 7.34 (dd, 1H, $J$ = 8, 2 Hz), 7.40 (d, 2H, $J$ = 8 Hz), 7.46 (d, 1H, $J$ = 2 Hz), 8.03 (d, 2H, $J$ = 8 Hz); MS (EI) $m/z$ 352 ($M^+$). Anal. ($C_{23}H_{28}O_3$) C,H.

**4-[(*E*)-2-(3-*tert*-Butyl-4-methoxyphenyl)propenyl]benzoic Acid (14).** Compound **55** (1.4 g, 4 mmol) was saponified as described for preparation of 1 to give, after recrystallization in AcOEt, 1.3 g (92%) of **14** as a white solid: mp 238−240 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.26 (s, 9H), 2.14 (s, 3H), 3.73 (s, 3H), 6.63 (s, 1H), 6.74 (d, 1H, $J$ = 8 Hz), 7.21 (dd, 1H, $J$ = 8, 2 Hz), 7.26 (d, 2H, $J$ = 8 Hz), 7.31 (d, 1H, $J$ = 2 Hz), 7.89 (d, 2H, $J$ = 8 Hz); IR (KBr) 1680, 1295, 1180 cm$^{-1}$; MS (EI) $m/z$ 324 ($M^+$). Anal. ($C_{21}H_{24}O_3$) C,H.

**4-[(*E*)-2-(3-*tert*-Butyl-4-hydroxyphenyl)propenyl]benzoic Acid (15).** Compound **55** (2 g, 5.6 mmol) in solution in DMF (40 mL) was treated with LiSMe (1.8 g, 34 mmol) prepared as described.[21] The mixture was stirred at 120 °C for 4 h and then poured into iced water, acidified to pH 1 with 1 N HCl, and extracted with $Et_2O$. Standard workup, chromatography ($Et_2O$/hexane, 80:20), and recrystallization in a hexane−diisopropyl ether mixture afforded 0.78 g (45%) of **15** as a white solid: mp 209 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.44 (s, 9H), 2.27 (s, 3H), 6.75 (s, 1H), 6.81 (d, 1H, $J$ = 8 Hz), 7.21 (d, 1H, $J$ = 8 Hz), 7.40 (d, 2H, $J$ = 8 Hz),7.42 (s, 1H), 8.04 (d, 2H, $J$ = 8 Hz); IR (KBr) 1680, 1290, 1100 cm$^{-1}$; MS (EI) $m/z$ 310 ($M^+$). Anal. ($C_{20}H_{22}O_3$) C,H.

**3-(1-Methylcyclohexyl)-4-[(*tert*-butyldimethylsilyl)oxy]-benzoic Acid (56).** Compound **29** (42.5 g, 0.11 mol) in THF (150 mL) was converted into organomagnesium reagent as decribed in the synthesis of **22**. The resulting solution was then cooled to −70 °C and submitted to bubbling with $CO_2$ (gas) for 1 h. Temperature was then increased up to 20 °C during the night. The mixture was neutralized with saturated $NH_4Cl$ and extracted with $Et_2O$. Organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give, after recrystallization in $Et_2O$, 28.8 g (74%) of **56**: mp >340 °C; $^1$H NMR (250 MHz, Pyr-$d_5$) $\delta$ 0.15 (s, 6H), 0.77 (s, 9H), 1.15 (s, 3H), 1.20−1.50 (m, 8H), 2.0 (m, 2H), 6.65 (d, 1H, $J$ = 8 Hz), 8.02 (d, 1H, $J$ = 8 Hz), 8.32 (br s, 1H); MS (EI) $m/z$ 348 ($M^+$).

**3-(1-Methylcyclohexyl)-4-[(*tert*-butyldimethylsilyl)oxy]-ethanone (57).** Compound **56** (28.8 g, 83 mmol) was treated with 104 mL of a 1.6 M solution of $CH_3Li$ in hexane by the same conditions as for the preparation of **53** to give, after chromatography ($CH_2Cl_2$), 22 g (76%) of **57** as a yellow oil; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.36 (s, 6H), 1.04 (s, 9H), 1.32 (s, 3H), 1.53−1.78 (m, 8H), 2.16 (m, 2H), 2.56 (s, 3H), 6.84 (d, H, $J$ = 8 Hz), 7.72 (dd, 1H, $J$ = 8, 2 Hz), 7.99 (d, 1H, $J$ = 2 Hz); MS (EI) $m/z$ 346 ($M^+$). Anal. ($C_{21}H_{34}O_2Si$).

**Ethyl 4-[(*E*)-2-[3-(1-Methylcyclohexyl)-4-[(*tert*-butyldimethylsilyl)oxy]phenyl]propenyl]benzoate (58).** Compound **57** (21 g, 60 mmol) was condensed with diethyl [4-(ethoxycarbonyl)benzyl]phosphonate (18 g, 60 mmol) following the same procedure as for the synthesis of **55**. After the same treatment and chromatography (hexane/$CH_2Cl_2$, 70:30), 12.9 g (44%) of **58** was obtained as a 4:1 *Z*/*E* miture which was subsequently placed in THF (900 mL) and irradiated with a medium pressure Hannovia Hg arc lamp for 48 h to give a 1:1 mixture of *Z* and *E* isomers. Chromatography (hexane/ether, 95:5) followed by crystallization in hexane gave 5.4 g (18.4%) of **58**: mp 58 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.33 (s, 6H), 1.03 (s, 9H), 1.31 (s, 3H), 1.37 (t, 3H), 1.40−1.75 (m, 8H), 2.16 (m, 2H), 2.28 (s, 3H), 4.37 (m, 2H), 6.76 (s, 1H), 6.80 (d, 1H, $J$ = 8 Hz), 7.23 (dd, 1H, $J$ = 8, 2 Hz), 7.40 (d, 2H, $J$ = 8 Hz), 7.48 (d, 1H, $J$ = 2 Hz), 8.03 (d, 2H, $J$ = 8 Hz); MS (EI) $m/z$ 492 ($M^+$). Anal. ($C_{31}H_{44}O_3Si$) C,H.

**Ethyl 4-[(*E*)-2-[3-(1-Methylcyclohexyl)-4-hydroxyphenyl]propenyl]benzoate (59).** Compound **58** (5.3 g, 10.7 mmol) was deprotected as described for preparation of **31**. After the same treatment, followed by a recrystallization in hexane, 3 g (76%) of **59** was obtained: mp 131 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.27 (s, 3H), 1.33 (t, 3H), 1.43−1.64 (m, 8H), 2.07 (m, 2H), 2.16 (s, 3H), 4.28 (m, 2H), 6.57 (d, 1H, $J$ = 8 Hz), 6.66 (s, 1H), 7.12 (dd, 1H, $J$ = 8, 2 Hz), 7.29 (d, 2H, $J$ = 8.5 Hz), 7.36 (d, 1H, $J$ = 2 Hz), 7.92 (d, 2H, $J$ = 8.5 Hz); MS (EI) $m/z$ 378 ($M^+$). Anal. ($C_{25}H_{30}O_3$) C,H.

**Ethyl 4-[(*E*)-2-[3-(1-Methylcyclohexyl)-4-methoxyphenyl]propenyl]benzoate (60).** Compound **59** (2.2 g, 5.8 mmol) was converted into methoxy derivative using $CH_3I$ (0.36 mL, 5.86 mmol) as described for **27**. After the same workup, followed by chromatography ($CH_2Cl_2$/hexane, 6:4) and recrystallization in hexane, 1.86 g (81%) of **60** as white solid was obtained: mp 60−62 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.32 (s, 3H), 1.40 (t, 3H), 1.43−1.76 (m, 8H), 2.12 (m, 2H), 2.28 (s, 3H), 3.84 (s, 3H), 4.38 (m, 2H), 6.78 (s, 1H), 6.88 (d, 1H, $J$ = 8 Hz), 7.34 (dd, 1H, $J$ = 8, 2 Hz), 7.41 (d, 2H, $J$ = 8 Hz), 7.49 (d, 1H, $J$ = 2 Hz), 8.03 (d, 2H, $J$ = 8 Hz); MS (EI) $m/z$ 392 ($M^+$). Anal. ($C_{26}H_{32}O_3$) C,H.

**4-[(*E*)-2-[3-(1-Methylcyclohexyl)-4-methoxyphenyl]propenyl]benzoic acid (16).** Compound **60** (1.71 g, 4.36 mmol) was saponified as described for preparation of 1. Recrystallization ($Et_2O$) afforded 1.2 g (75%) of **16** as a white solid: mp 242−244 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.18 (s, 3H), 1.35−1.40 (m, 6H), 1.62 (m, 2H), 1.97 (m, 2H), 2.16 (s, 3H), 3.72 (s, 3H), 6.74 (s, 1H), 6.91 (d, 1H, $J$ = 8.5 Hz), 7.32 (d, 1H, $J$ = 8.5 Hz), 7.34 (s, 1H), 7.40 (d, 2H, $J$ = 8 Hz), 7.85 (d, 2H, $J$ = 8 Hz); IR (KBr) 1680, 1290, 1250, 1175 cm$^{-1}$; MS (EI) $m/z$ 364 ($M^+$). Anal. ($C_{24}H_{28}O_3$) C,H.

**4-[(*E*)-2-[3-(1-Methylcyclohexyl)-4-hydroxyphenyl]propenyl]benzoic acid (17).** Compound **59** (0.75 g, 2 mmol) was saponified as described for 1. Chromatography ($CH_2Cl_2$/MeOH, 95:5) and recrystallization in hexane/$Et_2O$ mixture gave 0.49 g (70%) of **17** as a white solid: mp183−185 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.32 (s, 3H), 1.40−1.60 (m, 6H), 1.75 (m, 2H), 2.17 (m, 2H), 2.24 (s, 3H), 6.72 (s, 1H), 6.76 (d, 1H, $J$ = 8 Hz), 7.17 (d, 1H, $J$ = 8 Hz), 7.37 (d, 2H, $J$ = 7 Hz), 7.40 (s, 1H), 8.01 (d, 2H, $J$ = 7 Hz); IR (KBr) 1675, 1210, 1250 cm$^{-1}$; MS (EI) $m/z$ 350 ($M^+$). Anal. ($C_{23}H_{26}O_3$).

**3-(1-Adamantyl)-4-methoxybenzoic Acid (61).** Compound **33** (20 g, 62.4 mmol) was converted into the corresponding organomagnesium derivative and then reacted with $CO_2$ as described for preparation of **56** to give, after crystallization in AcOEt, 15.9 g (89%) of **61**: mp 238−239 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.76 (s, 6H), 2.09 (br s, 9H), 3.89 (s, 3H), 6.88 (d, 1H, $J$ = 8.5 Hz), 7.91 (dd, 1H, $J$ = 8.5, 2 Hz), 7.95 (d, 1H, $J$ = 2 Hz); MS (EI) $m/z$ 286 ($M^+$). Anal. ($C_{18}H_{22}O_3$).

**[3-(1-Adamantyl)-4-methoxyphenyl]ethanone (62).** To a solution of compound **61** (28.7 g, 0.1 mmol) in toluene (280 mL) was added thionyl chloride (14.5 mL, 0.2 mol), and the mixture was heated at 100 °C for 3.5 h. After evaporation of excess thionyl chloride, the residue was dissolved in HMPA (100 mL). To this solution were added $Sn(Me)_4$ (15.1 mL, 0.21 mol) and $PhCH_2Pd(PPh_3)_2Cl$ (76 mg). Reaction mixture was heated under stirring at 60 °C for 12 h and then poured into iced water. After extraction with $Et_2O$, standard workup, chromatography ($CH_2Cl_2$/hexane, 60:40), and recrystallization in AcOEt/hexane mixture gave 21.1 g (74%) of **62** as a white solid: mp 140 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.77 (s, 6H), 2.1 (s, 9H), 2.56 (s, 3H), 3.90 (s, 3H), 6.88 (d, 1H, $J$ = 8 Hz), 7.81 (dd, 1H, $J$ = 8, 2 Hz), 7.89 (d, 1H, $J$ = 2 Hz); MS (EI) $m/z$ 284 ($M^+$). Anal. ($C_{19}H_{24}O_2$) C,H.

**Ethyl 4-[(*E*)-2-[3-(1-Adamantyl)-4-methoxyphenyl]propenyl]benzoate (63).** Compound **62** (4.27 g, 15 mmol) was condensed with diethyl [4-(ethoxycarbonyl)benzyl]phosphonate (5.4 g, 18 mmol) as described for preparation of **55** to give, after chomatography (hexane/AcOEt/$CH_2Cl_2$, 94:3:3) and recrystallization in AcOEt/hexane mixture, 0.53 g (8%) of ethyl 4-[(*Z*)-2-[3-(1-adamantyl)-4-methoxyphenyl]propenyl]benzoate as a white solid: mp 120–122 °C; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.30 (t, 3H), 1.64 (s, 6H), 1.82 (s, 6H), 1.93 (s, 3H), 2.2 (s, 3H), 3.80 (s, 3H), 4.27 (m, 2H), 6.48 (s, 1H), 6.83 (s, 1H), 6.87 (d, 1H, $J$ = 8 Hz), 7.02 (m, 3H), 7.70 (d, 2H, $J$ = 8 Hz); MS (EI) $m/z$ 430 ($M^+$).

Also obtained was 2.87 g (44%) of **63** as a white solid: mp 104–106 °C; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.33 (t, 3H), 1.74 (s, 6H), 2.08 (br s, 9H), 2.24 (s, 3H), 3.82 (s, 3H), 4.31 (m, 2H), 6.84 (s, 1H), 6.97 (d, 1H, $J$ = 8 Hz), 7.35 (br s, 1H), 7.39 (dd, 1H, $J$ = 8, 2 Hz), 7.51 (d, 2H, $J$ = 8 Hz), 7.95 (d, 2H, $J$ = 8 Hz); MS (EI) $m/z$ 430 ($M^+$). Anal. ($C_{29}H_{34}O_3$) C,H.

**4-[(*E*)-2-[3-(1-Adamantyl)-4-methoxyphenyl]propenyl]benzoic Acid (18).** Compound **63** (1 g, 2.3 mmol) was saponified as described for preparation of 1 and worked up as described for isolation of **3** to give, after recrystallization in EtOH, 0.7 g (75%) of **18** as a white solid: mp 307–308 °C; $^1H$ NMR (250 MHz, Pyr-$d_5$) $\delta$ 1.68 (m, 6H), 1.97 (s, 3H), 2.15 (s, 6H), 2.29 (s, 3H), 3.70 (s, 3H) 6.91 (d, 1H, $J$ = 8.5 Hz), 7.02 (s, 1H), 7.42 (dd, 1H, $J$ = 8.5, 2 Hz), 7.45 (m, 3H), 7.52 (d, 1H, $J$ = 2 Hz), 7.55 (d, 2H, $J$ = 8 Hz), 8.42 (d, 2H, $J$ = 8 Hz); IR (KBr) 1685, 1295, 1240, 1180 $cm^{-1}$; MS (EI) $m/z$ 402 ($M^+$). Anal. ($C_{27}H_{30}O_3$) C,H.

**4-[(*E*)-2-[3-(1-Adamantyl)-4-hydroxyphenyl]propenyl]benzoic Acid (19).** Compound **63** (1.8 g, 4.2 mmol) was deprotected as described for preparation of **15** using NaSMe (Fluka; 2.3 g, 33.5 mmol). After the same workup followed by chromatography (hexane/AcOEt, 1:1) and recrystallization in hexane/AcOEt mixture, 1 g (62%) of **19** was obtained as a white solid: mp 243–245 °C; $^1H$ NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.54 (s, 6H), 1.85 (s, 3H), 1.91 (s, 6H), 2.02 (s, 3H), 6.57 (d, 1H, $J$ = 8 Hz), 6.60 (s, 1H), 7.06 (dd, 1H, $J$ = 8, 2 Hz), 7.09 (d, 1H, $J$ = 2 Hz), 7.28 (d, 2H, $J$ = 8.2 Hz), 7.73 (d, 2H, $J$ = 8.2 Hz); IR (KBr) 1680, 1195, 1240 $cm^{-1}$; MS (EI) $m/z$ 388 ($M^+$). Anal. ($C_{26}H_{28}O_3$).

**3-(1-Adamantyl)-4-[(*tert*-butyldimethylsilyl)oxy]benzenecarboxaldehyde (64).** A solution of compound **35** (30 g, 71 mmol) in THF (300 mL) was cooled to −70 °C and treated by a dropwise addition of $n$-butyllithium (49 mL, 1.6 M in hexane). The resulting mixture was stirred for 45 min at −70 °C and further submitted at −40 °C to a dropwise addition of DMF (5.5 mL, 71 mmol). The resulting mixture was then allowed to warm up to room temperature under stirring. After the same treatment as for isolation of **27**, followed by recrystallization in hexane, 16.6 g (82%) of **64** was obtained as a yellow solid: mp 115–116 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0.39 (s, 6H), 1.05 (s, 9H), 1.77 (s, 6H), 2.12 (m, 9H), 6.88 (d, 1H, $J$ = 8 Hz), 7.60 (dd, 1H, $J$ = 8, 2 Hz), 779 (d, 1H, $J$ = 2 Hz); MS (EI) $m/z$ 370 ($M^+$). Anal. ($C_{23}H_{34}O_2Si$) C,H.

**Ethyl 4-[(*E*)-2-[3-(1-Adamantyl)-4-[(*tert*-butyldimethylsilyl)oxy]phenyl]ethenyl]benzoate (65).** Compound **64** (7.41 g, 20 mmol) was treated with diethyl [4-(ethoxycarbonyl)benzyl]phosphonate (7.2 g, 24 mmol) as described for preparation of **55** to give, after chromatography (heptane/AcOEt, 95:5) and recrystallization in hexane/AcOEt mixture, 5.2 g (51%) of **65** as a white solid: mp 125–126 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0.36 (s, 3H), 1.05 (s, 9H), 1.39 (t, 3H), 1.78 (s, 6H), 2.09 (s, 3H), 2.14 (s, 6H), 4.37 (m, 2H), 6.79 (d, 1H, $J$ = 8 Hz), 6.95 (d, 1H, $J$ = 16 Hz), 7.16 (d, 1H, $J$ = 16 Hz), 7.26 (dd, 1H, $J$ = 8, 2 Hz), 7.39 (d, 1H, $J$ = 2 Hz), 7.52 (d, 2H, $J$ = 8.2 Hz), 8.00 (d, 2H, $J$ = 8.2 Hz); MS (EI) $m/z$ 516 ($M^+$). Anal. ($C_{33}H_{44}O_3Si$) C,H.

**4-[(*E*)-2-[3-(1-Adamantyl)-4-hydroxyphenyl]ethenyl]benzoic Acid (20).** Compound **65** (2.4 g, 4.6 mmol) was saponified as described for preparation of 1 to give, after chromatography ($Et_2O$/hexane, 60:40) and recrystallization in AcOEt/hexane mixture, 1.26 g (73%) of **20** as a white solid: mp 279–280 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.78 (s, 6H), 2.08 (s, 3H), 2.17 (s, 6H), 6.80 (d, 1H, $J$ = 8 Hz), 6.93 (d, 1H, $J$ = 16 Hz), 7.16 (d, 1H, $J$ = 16 Hz), 7.22 (dd, 1H, $J$ = 8, 2 Hz), 7.34 (d, 1H, $J$ = 2 Hz), 7.51 (d, 2H, $J$ = 8 Hz), 8.01 (d, 2H, $J$ = 8 Hz); IR (KBr) 1680, 1190 $cm^{-1}$; MS (EI) $m/z$ 374 ($M^+$). Anal. ($C_{25}H_{26}O_3$) C,H.

**Binding Assays.** Binding assays were performed as previously described.[11a] Briefly, COS-7 cells were transfected with the different pSG-derived expression vectors of human RARs (pSG1 for RAR$\alpha$ and pSG5 for RAR$\beta$ and -$\gamma$) using the polybrene technique. Cells were lysed, and the nuclear extracts were recovered by centrifugation (5 min at 10000$g$) and submitted to DNase I digestion and high-salt extractions (NaCl, 0.4 M). After 5 min of centrifugation at 10000$g$, the supernatant was used for binding studies.

Competition experiments were performed as described previously[24b] using [$^3$H]CD 367 (2 nM) as the radioligand. Separation of bound and free ligand was performed by high-performance size exclusion chromatography (HPSEC) on GF250 columns (250 × 9.4 mm; DuPont de Nemours). The competition binding curves were analyzed by computer-assisted nonlinear regression analysis (MINSQ, MicroMath scientific software).

**Differentiation Assay in F9 Cells. (A) Agonist Activity.** Differentiating activity was measured as previously described.[27] Briefly, F9 murine teratocarcinoma cells were grown in Dubelcco's modified Eagle medium (DMEM) supplemented with 15% fetal bovine serum and treated for 3 days with different concentrations of retinoids. Cell differentiation was quantified by assaying plasminogen activator (PA) secretion. The retinoid concentration eliciting half-maximal PA secretion ($AC_{50}$) was calculated by means of nonlinear regression analysis.

**(B) Antagonist Activity.** Following the above protocol, cells were coincubated with both a fixed concentration ($10^{-8}$ M) of the reference agonist retinoid *N*-(4-carboxybenzyl)-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-amine[36] (F9 $AC_{50}$ = 4 nM) and various concentrations of the retinoid to be tested. The $IC_{50}$ was defined as the concentration of antagonist inhibiting 50% of the agonist response.

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## References

(1) Gudas, L. J.; Sporn, M. B.; Roberts, A. B. Cellular biology and biology and biochemistry of the retinoids. In *The Retinoids, Biology, Chemistry and Medicine*; Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven Press: New York, 1994; pp 443–520.

(2) Pawson, B. A.; Ehmann, C. W.; Itri, L. M.; Sherman, M. I. Retinoids at the threshold: Their biological significance and therapeutic potential. *J. Med. Chem.* **1982**, *25*, 1269–1277.

(3) Boyd, A. S. An Overview of Retinoids. *Am. J. Med.* **1989**, *86*, 568–574.

(4) Hong, W. K.; Itri, L. M. Retinoids and human cancer. In *The Retinoids, Biology, Chemistry and Medicine;* Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven Press: New York, 1994; pp 597–630.
(5) Chomienne, C.; Ballerini, P.; Balitrand, N.; Amor, M.; Bernard, J. F.; Boivin, P.; Daniel, M. T.; Berger, R.; Castaigne, S.; Degos, L. Retinoic acid therapy for promyelocytic leukaemia. *Lancet* **1989**, *ii*, 746–747.
(6) Mangelsdorf, D. J.; Umesono, K.; Evans, R. M. The retinoid receptors. In *The Retinoids, Biology, Chemistry and Medicine;* Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven Press: New York, 1994; pp 319–349.
(7) Amstrong, R. B.; Ashenfelter, K. O.; Eckhoff, C.; Levin, A. A.; Shapiro, S. S. General and reproductive toxicology of retinoids. In *The Retinoids, Biology, Chemistry and Medicine;* Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven Press: New York, 1994; pp 545–572.
(8) (a) Zelent, A.; Krust, A.; Petkovich, M.; Kastner, P.; Chambon, P. Cloning of murine α and β retinoic acid receptors and a novel receptor predominantly expressed in skin. *Nature* **1989**, *339*, 714–717. (b) Fisher, G. J.; Talwar, H. S.; Xiao, J. H.; Datta, S. C.; Reddy, A. P.; Gaub, M. P.; Rochette-Egly, C.; Chambon, P.; Voorhees, J. J. Immunological identification and functional quantitation of retinoic acid and retinoid X receptor proteins in human skin. *J. Biol. Chem.* **1994**, *269*, 20629–20635.
(9) (a) Hashimoto, Y.; Kagechika, H.; Shudo, K. Expression of retinoic acid receptor genes and the ligand-binding selectivity of retinoic acid receptors (RAR's). *Biochem. Biophys. Res. Commun.* **1990**, *166*, 1300–1307. (b) Delescluse, C.; Cavey, M. T.; Martin, B.; Bernard, B. A.; Reichert, U.; Maignan, J.; Darmon, M.; Shroot, B. Selective high affinity retinoic acid receptor α or β-γ ligands. *Mol. Pharmacol.* **1991**, *40*, 556–562.
(10) Apfel, C.; Bauer, F.; Crettaz, M.; Forni, L.; Kamber, M.; Kaufmann, F.; LeMotte P.; Pirson, W.; Klaus, M. A retinoic acid receptor alpha antagonist selectively counteracts retinoic acid effects. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7129–7133.
(11) (a) Martin, B.; Bernardon, J. M.; Cavey, M. T.; Bernard, B.; Carlavan, I.; Charpentier, B.; Pilgrim, W. R.; Shroot, B.; Reichert, U. Selective synthetic ligands for human nuclear retinoic acid receptors. *Skin Pharmacol.* **1992**, *5*, 57–65. (b) Bernard, B. A.; Bernardon, J. M.; Delescluse, C.; Martin, B.; Lenoir, M. C., Maignan, J.; Charpentier, B.; Pilgrim, W. R.; Reichert, U.; Shroot, B. Identification of synthetic retinoids with selectivity for human nuclear retinoic acid receptor γ. *Biochem. Biophys. Res. Commun.* **1992**, *186*, 977–983. (c) Schadendorf, D.; Worm, M.; Jurgovsky, K.; Dippel, E.; Michel, S.; Charpentier, B.; Bernardon, J. M.; Reichert, U.; Czarnetzki, B. M. Retinoic acid receptor-γ-selective retinoids exert antiproliferative effects on human melanoma cell growth *in vitro*. *Int. J. Oncol.* **1994**, *5*, 1325–1331.
(12) (a) Lehmann, J. M.; Jong, L.; Fanjul, A.; Cameron, J. F.; Lu, X. P.; Haefner, P.; Dawson, M. I.; Pfahl, M. Retinoids selective for retinoid X receptor response pathway. *Science* **1992**, *258*, 1944–1946. (b) Chandraratna, R. World Pat. Appl. 17796, February 11, 1993. (c) Boehm, M. F.; Zhang, L.; Badea, B. A.; White, S. K.; Mais, D. E.; Berger, E.; Suto, C. M.; Goldman, M. E.; Heyman, R. A. Synthesis and structure-activity relationships of novel retinoid X receptor-selective retinoids. *J. Med. Chem.* **1994**, *37*, 2930–2941.
(13) Negishi, E. I. Palladium- or nickel-catalyzed cross-coupling. A new selective method for carbon-carbon bond formation. *Acc. Chem. Res.* **1982**, *15*, 340–348.
(14) Duval, D.; Predine, J.; Charpentier, B.; Emiliozzi, R. Synthesis of 7α- and β-carboxymethyl derivatives of cortisol, corticosterone, deoxycorticosterone and cortisone. Immunogenic properties of cortisol, corticosterone and deoxycorticosterone derivatives. *J. Steroid. Biochem.* **1985**, *22*, 67–78.
(15) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. Palladium-catalyzed carbonylation of aryl triflates. Synthesis of arenecarboxylic acid derivatives from phenols. *Tetrahedron Lett.* **1986**, *27*, 3931–3934.
(16) Stille, J. K. The palladium-catalyzed cross-coupling reactions of organotin reagents with organic electrophiles. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.
(17) Knights, E. F.; Brown, H. C. 9-Borabicyclo[3.3.1]nonane as a convenient selective hydroborating agent. *J. Am. Chem. Soc.* **1968**, *90*, 5281–5283.
(18) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. An improved catalytic $OsO_4$ oxidation of olefins to cis-1,2-glycols using tertiary amine oxides as the oxidant. *Tetrahedron Lett.* **1976**, *23*, 1973–1976.
(19) Heck, R. F. Palladium reagent in organic synthesis. In *Best Synthetic Methods*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: New York, 1985.
(20) Baker, R.; Sims, R. J. A convenient modification of the Wadsworth-Emmons method of olefin formation using a crown ether. *Synthesis* **1981**, 117–118.
(21) Kelly, T. R.; Dali, H. M.; Tsang, W. G. Lithium thiomethoxide: a convenient mercaptide reagent. *Tetrahedron Lett.* **1977**, 3859–3860.
(22) Loeliger, P.; Bollag, W.; Mayer, H. Arotinoids, a new class of highly active retinoids. *Eur. J. Med. Chem. Chim. Ther.* **1980**, *15*, 9–15.
(23) (a) Shroot, B.; Eustache, J.; Watts, O.; Bernardon, J. M.; Nédoncelle, P. Eur. Pat. Appl. 210929, July 25, 1985. (b) Dawson, M. I.; Hobbs, P. D.; Derdzinski, K. A.; Chao, W. R.; Frenking, G.; Loew, G. H.; Jetten, A. M.; Napoli, J. L.; Williams, J. B.; Sani, B. P.; Wille, J. J., Jr.; Schiff, L. J. Effect of structural modifications in the C7-C11 region of the retinoid skeleton on biological activity in a series of aromatic retinoids. *J. Med. Chem.* **1989**, *32*, 1504–1517.
(24) (a) Shroot, B.; Darmon, Y. M.; Nédoncelle, P.; Martin, C. Eur. Pat. Appl. 359 621, September 1, 1988. (b) Cavey, M. T.; Martin, B.; Carlavan, I.; Shroot, B. In vitro binding of retinoids to the nuclear retinoic acid receptor α. *Anal. Biochem.* **1990**, *186*, 19–23. (c) Dawson, M. I.; Hobbs, P. D.; Rhee, S. W.; Morimoto, H.; Williams, P. G. Synthesis of [1′,3′,4′-$^3H_3$]4-(5′,6′,7′,8′-tetrahydro-5′,5′,8′,8′-tetramethyl-2′-anthracenyl)benzoic acid for binding studies of retinoic acid receptor. *J. Labelled Compd. Radiopharm.* **1993**, *33*, 633–637.
(25) Dawson, M. I.; Chan, R. L.; Derdzinski, K.; Hobbs, P. D.; Chao, W. R.; Schiff, L. J. Synthesis and pharmacological activity of 6-[(E)-2-(2,6,6-trimethyl-1-cyclohexen-1-yl)ethen-1-yl]- and 6-(1,2,3,4-Tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)-2-naphthalene-carboxylic acids. *J. Med. Chem.* **1983**, *26*, 1653–1656.
(26) Schiff, L. J.; Okamura, W. H.; Dawson, M. I.; Hobbs, P. D. Structure-biological activity relationships of new synthetic retinoids on epithelial differentiation of cultured hamster trachea. In *Chemistry and Biology of Synthetic Retinoids;* Dawson, M. I., Okamura, W. H., Eds.; CRC Press, Inc.: Boca Raton, FL, 1990; pp 308–363.
(27) (a) Strickland, S.; Mahdavi, V. The induction of differentiation in teratocarcinoma stem cells by retinoic acid. *Cell* **1978**, *15*, 393–403. (b) Darmon, M.; Rocher, M.; Cavey, M. T.; Martin, B.; Rabilloud, T.; Delescluse, C.; Shroot, B. Biological activity of retinoids correlates with affinity for nuclear receptors, but not for cytosolic binding protein. *Skin Pharmacol.* **1988**, *1*, 161–175.
(28) Hu, L.; Gudas, L. J. Cyclic AMP analogs and retinoic acid influence the expression of retinoic acid receptor alpha, beta and gamma mRNAs in F9 teratocarcinoma cells. *Mol. Cell. Biol.* **1990**, *10*, 391–396.
(29) RARα selective compound (Am 580) 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid; $K_i$: RARα = 8 nM, RARβ = 131 nM, RARγ = 450 nM; F9 $AC_{50}$ = 20 nM.
(30) Boylan, J. F.; Lufkin, T.; Achkar, C. C.; Taneja, R.; Chambon, P.; Gudas, L. J. Targeted disruption of retinoic acid receptor α (RARα) and RAR γ results in receptor-specific alterations in retinoic acid-mediated differentiation and retinoic acid metabolism. *Mol. Cell. Biol.* **1995**, *15*, 843–851.
(31) Zhang, X. K.; Pfahl, M. Hetero- and homodimeric receptors in thyroid hormone and vitamin A action. *Receptor* **1993**, *3*, 183–191.
(32) In a RXRα functional transactivation assay, as described in ref 12c, none of the compounds was active at a concentration of 1 μM.
(33) Bernerd, F.; Ortonne, J. P.; Bouclier, M.; Chatelus, A.; Hensby, C. The rhino mouse model: The effects of topically applied all-*trans* retinoic acid and CD 271 on the fine structure of the epidermis and utricle wall of pseudocomedones. *Arch. Dermatol. Res.* **1991**, *283*, 100–107.
(34) Griffiths, C. E. M.; Elder, J. T.; Bernard, B. A.; Rossio, P.; Cromie, A. M.; Finkel, L. J.; Shroot, B.; Voorhees, J. J. Comparison of CD 271 (adapalene) and all-*trans* retinoic acid in human skin: dissociation of epidermal effects and CRABP-II mRNA expression. *J. Invest. Dermatol.* **1993**, *101*, 325–328.
(35) Verschoore, M.; Langner, A.; Wolska, H.; Jablonska, S.; Czernielewski, J.; Schaefer, H. Efficacy and safety of CD 271 alcoholic gels in the topical treatment of *acne vulgaris*. *Br. J. Dermatol.* **1991**, *124*, 368–371.
(36) Janssen, B.; Wuest, H. H. Eur. Pat. 386452, February 10, 1989.

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