Retinoic Acid Receptor β,γ-Selective Ligands: Synthesis and Biological Activity of 6-Substituted 2-Naphthoic Acid Retinoids

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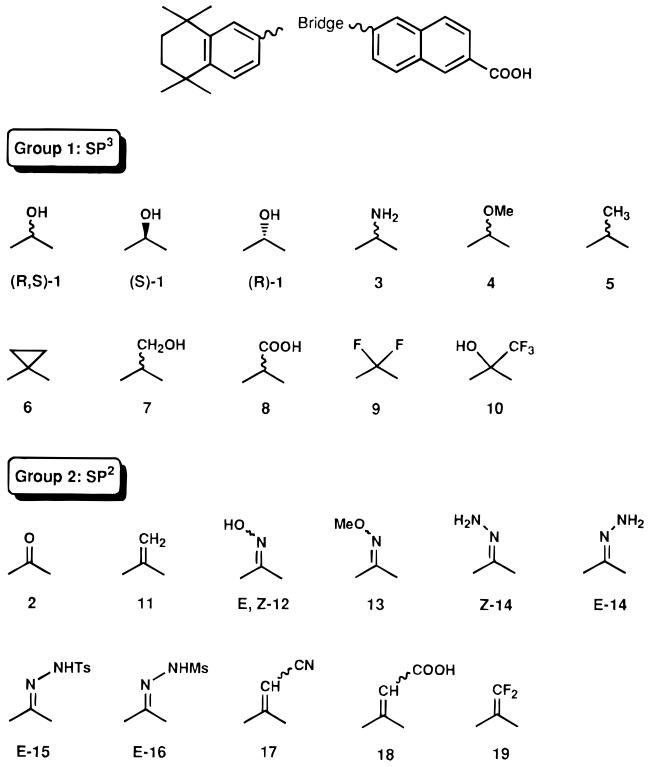
In search for retinoic acid receptor (RAR) selective ligands, a series of 6-substituted 2-naphthoic acid retinoids were synthesized and evaluated *in vitro* in a transactivation assay and a competition binding assay for all RARs. These derivatives, in general, showed RAR β,γ selectivity. Among these naphthoic acids, oxime derivative **12** was identified as a potent RAR γ-selective retinoid, while olefinic derivative **11** was found to be comparable to retinoic acid and slightly RAR β,γ selective. For the bioassays, a general correlation was observed between the binding affinity of the ligand to the receptors and the potency of the compounds in the transactivation assay. The structure−activity relationship of these naphthoic acids will be discussed.

Introduction

Retinoic acid, a metabolite of retinol (vitamin A), is known to be involved in many essential life processes.[1] Particularly, because of its functions in cell proliferation and differentiation, retinoic acid and its derivatives (retinoids) have been extensively studied and show excellent beneficial effects in the treatment of cancers and several dermatological diseases.[2−4] Despite knowledge of their profound pharmacological effects in biological systems, the mechanism of action of the retinoids is still not clear. Evidence has indicated that retinoic acid might exert its functions through gene regulation mediated by at least two classes of nuclear receptors, retinoic acid receptors (RAR α, β, γ) and retinoid X receptors (RXR α, β, γ).[5−7] Studies of the distribution of mRNA for these receptors in rodents and man revealed that RAR α widely exists in most tissues, while RAR γ is found predominantly in lung and skin, and RAR β is inducible by retinoic acid in most tissues.[8,9] Current research efforts in this field have focused on searching for receptor-specific ligands in order to elucidate the biological functions of each receptor.[10−14] Furthermore, development of receptor-specific retinoids may have the advantage of avoiding unacceptable side effects caused by retinoids, such as skin irritation, teratogenesis, and hypervitaminosis-A.

Among the RAR-selective ligands previously prepared, racemate **1** (Chart 1) has been reported to be RAR γ selective.[11] Recently we have verified the RAR γ selectivity of the alcohol and extended this finding to demonstrate that the majority of the biological activity of this racemate resides in the *S*-enantiomer ((***S***)-**1**).[15] The superior activity of **(*S*)-1** over **(*R*)-1** was identified in both RAR binding and transactivation assays *in vitro* as well as in the Rhino mouse utriculi reduction assay *in vivo*. The differential biological activity of the enantiomers led us to hypothesize that the linkage between the tetrahydrotetramethylnaphthalene and the naphthoic acid may be involved in potency and/or RAR receptor selectivity. Consequently, we have prepared a series of 6-naphthoic acid derivatives to study the structure−activity relationship (SAR) as a function of variation within the linkage between the naphthalenes. The derivatives prepared (Chart 1, **1**−**19**) are divided into two groups depending on the bond order of the center atom: Group 1 has an sp^3 configuration, while group 2 has an sp^2 configuration at the center. We herein detail the preparation of the enantiomers of **1** and report the SAR studies of these naphthoic acids.

Chart 1



Chemistry

Early attempts in the preparation of the enantiomers **(*R*)-1** and **(*S*)-1** by stereoselective reduction of the

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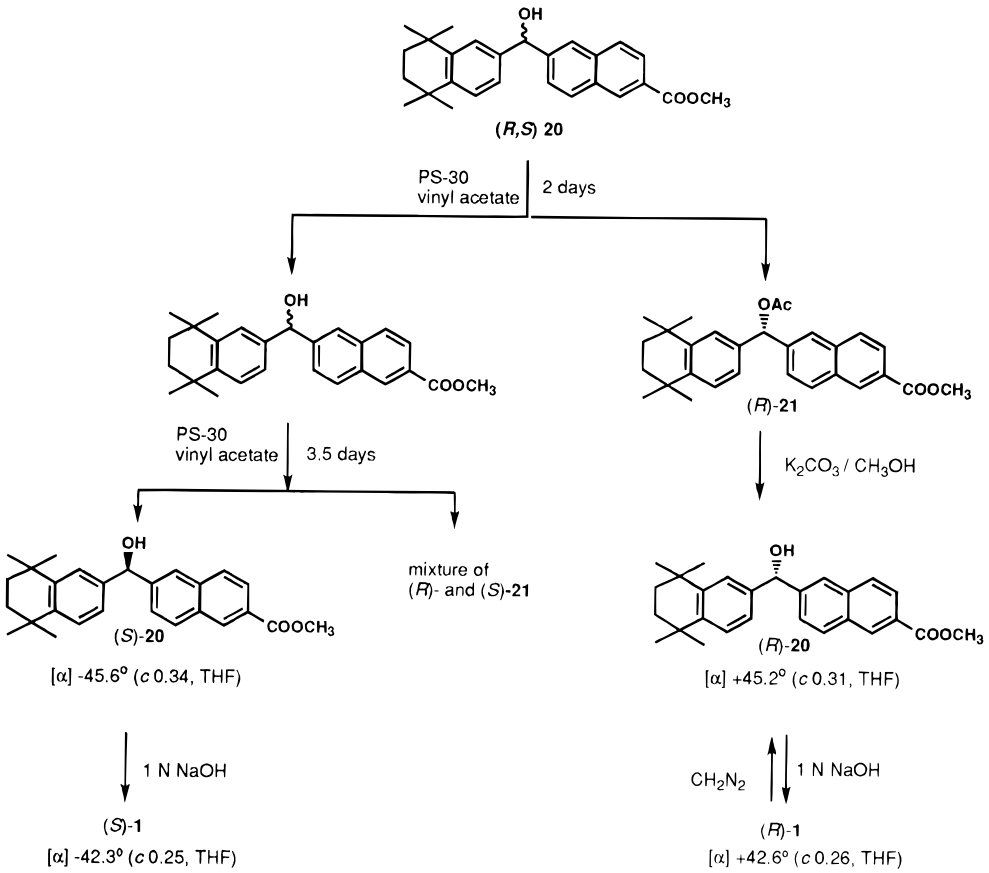
Scheme 1

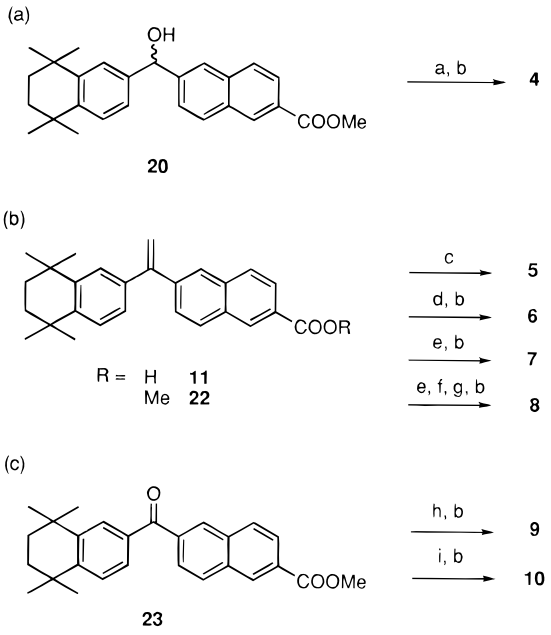


corresponding ketone ester **23**[16] proved fruitless. Direct resolution of acid **(*R,S*)-1** by several lipases was also unsuccessful. Surprisingly, the corresponding racemic alcohol ester **(*R,S*)-20** was easily resolved in DME using *Pseudomonas* lipase, PS-30, and vinyl acetate as the acyl donor (Scheme 1).[17] The acetylated product, **(*R*)-21**, was readily separated from unreacted alcohol by silica gel chromatography. Hydrolysis with K_2CO_3 provided **(*R*)-20** in 31% conversion yield with >98% enantiomeric excess (ee). The unreacted alcohol recovered from the previous chromatography was resubjected to the acetylation procedure for 3 days. After chromatography, **(*S*)-20** was isolated in 43% yield with 95% ee. The purity of the enantiomeric esters could be enhanced by recrystallization from EtOAc−hexane to give >99.8% ee and 97% ee for **(*R*)-20** and **(*S*)-20**, respectively. Interestingly, a small amount of ketone **23** (<5%) resulting from oxidation of alcohol **20** was isolated during the enzyme reaction. Replacement of DME with isopropyl ether as a cosolvent was found to significantly slow the reaction rate. We also noted that under the same acetylation conditions with PS-30, alcohol **(*R,S*)-20** is completely inert toward *Mucor japanicus* lipase (MAP-10, Amano), porcine pancrease, and *Candida cylindracea* lipase (Sigma), indicating the specificity of lipase PS-30 for the diaryl alcohol. Saponification of the individual enantiomers afforded the corresponding acids. The enantiomeric purity of each acid was confirmed by proton nuclear magnetic resonance using the chiral solvating agent (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[18] In addition, acid **(*R*)-1** was esterified with diazomethane, and the ester obtained was subjected to HPLC analysis on a Chiralcel OD column. The results showed no trace of **(*S*)-20**, indicating that no racemization occurred during the saponification reaction. The absolute configuration of the enantiomers was determined by X-ray crystallographic analysis of the *p*-bromobenzoate ester of **(*R*)-20**.[19]

The synthesis of racemic alcohol **(*R,S*)-1**, amine **3**, and ketone **2**, along with olefin **11** and the *E*−*Z* mixture of oxime **12**, has been reported by Shroot et al.[16] For the remainder of the retinoids shown in Chart 1, the group 1 compounds were prepared using standard methodologies depicted in Scheme 2. Excluding cyclopropane **6** and difluoro derivative **9** which do not have a chiral center, the retinoids were prepared as racemic mixtures.

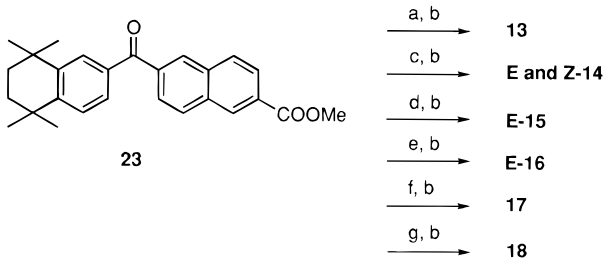
Scheme 3 illustrates the preparation of the group 2 derivatives. *O*-Methyl oxime **13** and hydrazone derivatives **14**−**16** were prepared by reacting ketone **23** with *O*-methylhydroxylamine or hydrazines in the presence of concentrated sulfuric acid or hydrochloric acid. In the case of oximes **12** and **13**, the *E*- and *Z*-geometric isomers were produced in a 1:1 and 3:2 ratio, respectively, and were inseparable by flash chromatography. The mixture of the *E*/*Z* isomers of oxime **12** was therefore derivatized as pivaloy esters, and the isomers were separated by chromatography. Saponification of the individual oxime gave **(*E*)-12** and **(*Z*)-12**, respectively. However, some of the oxime acid (15% and 5% for the *Z* and *E* isomers, respectively) isomerized in the hydrolysis process due to the chemical instability of the oxime functionality. For hydrazones **14**−**16**, the resulting *E* and *Z* isomers, ranging from 1:1 to 9:1 ratio, were separated by flash chromatography. However, only the *E* isomers of acids **15** and **16** were obtained, since **(*Z*)-15** isomerized in the saponification conditions and a very low yield of the methyl ester of **(*Z*)-16** was obtained in the formation of the hydrazone. The stereochemistry

Scheme 2[a]



[a] (a) NaH, MeI; (b) NaOH, H_3O^+; (c) H_2, Pd/C; (d) CH_2N_2, $Pd(OAc)_2$; (e) BH_3, H_2O_2−NaOH; (f) DMSO−trifluoroacetic acid anhydride, Et_3N; (g) $NaClO_2$, H_2NSO_3H; (h) DAST; (i) $TMSCF_3$, catalytic TBAF, TBAF.

Scheme 3[a]



[a] (a) NH_2OMe, H_2SO_4−Et_3N; (b) NaOH; (c) NH_2NH_2, H_2SO_4−Et_3N; (d) $TsNHNH_2$, HCl; (e) $MsNHNH_2$, H_2SO_4; (f) $(EtO)_2POCH_2CN$, *t*-BuOK; (g) $(EtO)_2POCH_2COOEt$, *n*-BuLi.

of **12** and **14** was determined by NOE experiments on the pivaloyl and acetyl derivatives of the oxime and hydrazone derivatives, respectively. For **15** and **16** the stereochemistry was easily confirmed by NOE experiments on the methyl esters of (***E***)**-15**, (***Z***)**-15**, and (***E***)**-16**. Preparation of nitrile **17** and carboxylic acid **18** was achieved by Horner−Emmons reaction of ketone **23** with the corresponding phosphonates. The resulting *E*/*Z* isomers could not be separated; therefore, acids **17** and **18** were obtained as *E*/*Z* mixtures (1:1 and 3:2, respectively). Early attempts to synthesize difluoro derivative **19** by treating ketone **23** with Ph_2POCF_2H and *n*-BuLi were unsuccessful.[20]

In an alternative route, lithiation of 6-bromo-2-naphthol silyl ether **24** followed by the addition of difluoromethyl ketone **25** afforded alcohol **26** (Scheme 4). The silyl protecting group on the naphthol was removed, and the resulting alcohol was dehydrated using pyridine hydrochloride at 220 °C to provide difluoro olefin **28** in 70% yield. The naphthol was then transformed into a carboxylic acid methyl ester (**30**) through a palladium-catalyzed carbonylation of triflate **29**.[21] Saponification of **30** gave a mixture of several products. Milder deprotection conditions using Bu_2SnO[22] cleanly afforded **19** in 64% yield.

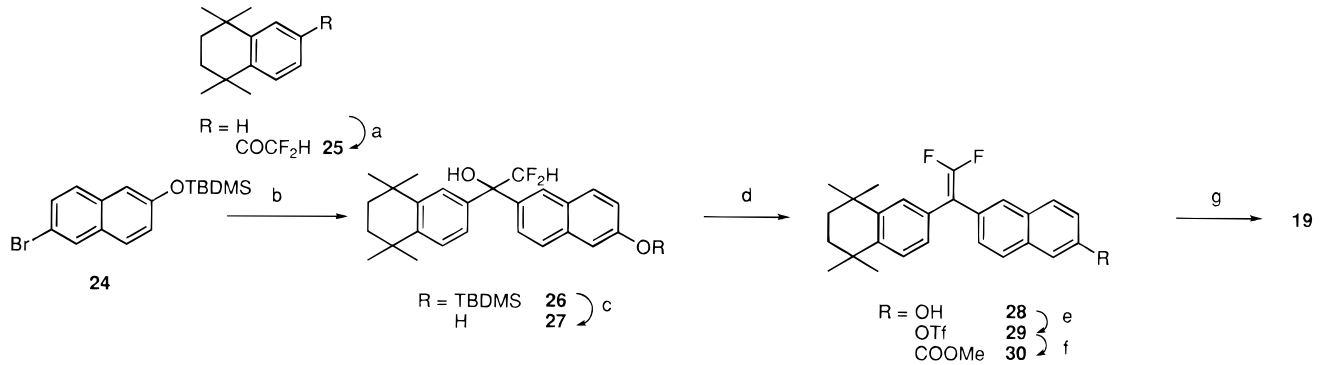
Results and Discussion

The naphthoic acid derivatives prepared were evaluated in the RAR transactivation assays to determine their ability to transactivate a reporter gene after their interaction with RAR α, β, or γ, respectively.[23] The assay was performed in HeLa cells transfected with Gal-4 RAR (DEF) α, β, or γ chimera, along with a receptor plasmid containing the Gal 4 response element and a CAT reporter gene. The β-galactosidase gene was included as a control for transfection efficiency. The tested compounds were evaluated at concentrations ranging from 10^{-10} to 10^{-6} M. The results of group 1 and 2 derivatives are shown in Figures 1 and 2, respectively.

Figure 1 clearly indicates that the group 1 derivatives which have an sp^3 center in the linker region show extremely weak or no RAR α activity and are therefore RAR β,γ selective. As previously noted, the transactivation activity of alcohol **1** depended upon the chirality of the alcohol in the linker. Although both **(*R*)-1** and **(*S*)-1** are RAR γ selective, the *S*-isomer is about 10 times more potent than the corresponding *R*-isomer for both RAR β and γ. The influence of chirality on the transactivation activity of alcohol **1** implies stereospecific interactions of the retinoids with the RARs. Conversion of the hydroxyl group of **1** to an amino functionality (**3**) or a methyl ether (**4**) or introduction of CF_3 group in the linker (**10**) maintains RAR β activity and decreases RAR γ activity, thus reducing the RAR γ selectivity of **1**. Replacement of the polar hydroxyl group of **1** with a methyl group (**5**), a cyclopropyl group (**6**), or a geminal difluoro group (**9**) only slightly increases RAR γ activity. However, the modifications significantly increase RAR β activity and thus reduce the RAR γ selectivity. Extension of the hydroxyl group of **1** by one carbon to give alcohol **7** retains RAR β activity, but the RAR γ activity is considerably reduced. Oxidation of alcohol **7** to carboxylic acid **8** further reduces RAR β and γ activity. Results from the group 1 derivatives indicate that the polar functional groups in the linker are critical for their RAR γ selectivity.

The group 2 retinoids differ from the group 1 retinoids by virtue of an sp^2 center in the linker instead of an sp^3 center. In general, the group 2 retinoids are more potent than the group 1 retinoids, although they are less RAR selective (Figure 2). In agreement with Pfahl's results, ketone **2** is potent and RAR β,γ selective.[11] Replacement of the oxygen of the ketone with a methylene group afforded olefin **11** which is more potent than retinoic acid and yet retains RAR β,γ selectivity. Exchange of the ketone functionality of **2** with an oxime resulted in **12** which is a potent RAR γ-selective retinoid. Oxime **12** has comparable RAR γ activity to that of retinoic acid but only transactivates the RAR β at very high concentrations (10^{-6} M). Interestingly, unlike the enantiomers of **1**, the *E* and *Z* isomers of **12** were not found to be significantly different from the *E*/*Z* mixture (data not shown), possibly due to the isomerization of the *E* and *Z* isomers in the assay. Figure 2 also clearly shows that *O*-methylation of the oxime (**13**) or replacement of the oxime with a basic hydrazone ((***E***)**-14** and (***Z***)**-14**) reduces the RAR γ activity. Tosylated and mesylated hydrazones ((***E***)**-15** and (***E***)**-16**), which have acidic N-H protons, are weak RAR γ retinoids, suggesting that the acidity of the oxime does not

Scheme 4[a]



[a] (a) CF_2HCOCl, $AlCl_3$; (b) *t*-BuLi, **25**; (c) TBAF; (d) pyridine·HCl, 220 °C; (e) Tf_2O, DMAP; (f) CO, MeOH, $Pd(OAc)_2$, dppp, Et_3N; (g) Bu_2SnO, aqueous HCl.

contribute to the RAR γ activity of **12**. These results imply that the oxime possesses unique properties for RAR γ selectivity and potency. In comparison with olefin **11**, difluoro olefin **19** and nitrile **17** showed significantly reduced RAR α and γ activity. Carboxylic acid **18** is RAR β,γ selective, although its potency is weak.

Several of the retinoids which showed significant transactivation activity have been tested in a competition binding assay[24,25] using tritiated retinoic acid (Table 1). Previously, Shroot[26] reported that the ability of retinoids to induce differentiation in F9 cells correlates with their binding affinity to the RARs. In our study, we found that a general correlation exists between the binding affinity of the ligands to the receptors and their transactivation activity; however, the binding affinity does not always precisely correlate with their transactivation activity.

In summary, the SAR study described above indicates that (1) all the 2-substituted naphthoic acid retinoids prepared in this study are RAR β,γ selective; (2) the naphthalenecarboxylic acids with an sp^2 center in the linker region are in general more potent than those with an sp^3 center; and (3) the RAR selectivity of these retinoids is attributed to the specific polar interactions of the linker, such as alcohol or oxime groups, although the polar linkers in general decrease RAR activity. From this study we have also identified oxime **12** as a selective and potent ligand for RAR γ. Since RAR γ is the predominant receptor in skin, it has been speculated that the dermatological activity of retinoic acid is mediated through RAR γ. Therefore, this compound will be useful as a tool to study this hypothesis.[27]

Experimental Section

Melting points were determined on an electrothermal apparatus and are not corrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AM-300 or a Varian Gemini 300 spectrometer. All spectra were determined in $CDCl_3$ or DMSO-d_6, and chemical shifts are reported in δ units relative to tetramethylsilane (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad peak; dd, doublet of doublets. Mass spectra were recorded on a Kratos MS-50 or a Finnegan 4500 instrument utilizing direct chemical ionization (DCI, isobutene). Preparative chromatography was performed with flash chromatography on silica gel from Universal Scientific. *Pseudomonas* lipase (PS-30) and *M. japanicus* lipase (MAP-10) were purchased from Amano (Troy, VA); porcine pancrease and *C. cylindracea* lipase were from Sigma.

(*R*)- and (*S*)-Methyl 6-[Hydroxy(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)methyl]naphthalene-2-carboxylate [(*R*)-20 and (*S*)-20]. Alcohol **(*R*,*S*)-20**[16] (1.40 g, 3.48 mmol) and 7.0 g of PS-30 in 24 mL of vinyl acetate and 12 mL of ethylene glycol dimethyl ether (DME) were stirred at 40−55 °C for 2 days. The enzyme was removed by filtration, and the filtrate was evaporated. The residue was purified by flash chromatography on silica gel (EtOAc:hexane = 1:10−1:5) to give 605 mg of **(*R*)-21** and the unreacted alcohol (836 mg). **(*R*)-21**: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 12 H), 1.67 (s, 4 H), 2.20 (s, 3H), 3.98 (s, 3 H), 7.01 (s, 1 H), 7.10 (dd, J = 1.9, 8.2 Hz, 1 H), 7.27 (d, J = 8.2 Hz, 1 H), 7.32 (d, J = 1.9 Hz, 1 H), 7.50 (dd, J = 1.6, 8.6 Hz, 1 H), 7.88 (d, J = 8.6 Hz, 1 H), 7.88 (s, 1 H), 7.92 (d, J = 8.6 Hz, 1 H), 8.07 (dd, J = 1.5, 8.6 Hz, 1 H), 8.58 (s, 1 H).

(*R*)-21 (600 mg) was stirred with 1.0 g of K_2CO_3 in 20 mL of MeOH and 1 mL of water for 1 h and filtered. The filtrate was evaporated, and the residue was purified by flash chromatography on silica gel (hexane:EtOAc = 1:10−1:5) to give 506 mg of the product, which was recrystallized from EtOAc−hexane to afford 281 mg of the pure **(*R*)-20**: $[\alpha]^{20}_D$ 45.2° (*c* 0.31, THF). The product is >99.8% ee by HPLC analysis using Chiralcel OD (Diacel Chemical Co.) column eluted with hexane:2-propanol (9:1).

The nonreacting alcohol mixture was resubjected to the acetylation procedure described above for 3 days. Chromatography afforded 600 mg of nonreacting alcohol, which crystallized from EtOAc−hexane to provide 300 mg of **(*S*)-20** (97% ee): $[\alpha]^{20}_D$ −45.6° (*c* 0.34, THF).

(*R*)- and (*S*)-6-[Hydroxy(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)methyl]naphthalene-2-carboxylic Acid [(*R*)-1 and (*S*)-1]. (*R*)-20 (205 mg, 0.51 mmol) was stirred with 2 mL of 1 N NaOH in 10 mL of tetrahydrofuran and 5 mL of MeOH for 20 h. The mixture was concentrated under reduced pressure, acidified with ice-cold 1 N HCl, and extracted with EtOAc (20 mL × 3). The combined extracts were washed with water and brine (10 mL each), dried over magnesium sulfate, and evaporated. The residue was recrystallized from EtOAc−hexane to give 132 mg of **(*R*)-1**: $[\alpha]^{20}_D$ 42.6° (*c* 0.26, THF). Anal. ($C_{26}H_{28}O_3$) C, H.

The same procedure was applied to **(*S*)-20** (205 mg) to give **(*S*)-1** (130 mg): $[\alpha]^{20}_D$ −42.3° (*c* 0.25, THF). Anal. ($C_{26}H_{28}O_3$) C, H.

Methyl 6-[[(4-Bromobenzoyl)oxy](5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]naphthalene-2-carboxylate. To a solution of **(*R*)-20** (65 mg, 0.16 mmol), triethylamine (34 mg, 0.32 mmol), and (dimethylamino)-pyridine (5 mg) in 2 mL of CH_2Cl_2 was added *p*-bromobenzoyl chloride (52 mg, 0.24 mmol) at 0 °C, and the mixture was stirred for 3 h. The mixture was diluted with 20 mL of CH_2Cl_2 and 20 mL of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (20 mL). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 1:20−1:10) to give the product, which recrystallized from EtOAc to afford needle crystals of the title compound for X-ray analysis: ^{1}H NMR δ 1.21 (s, 3 H), 1.23 (s, 9 H), 1.65 (s, 4 H), 4.00 (s, 3 H), 7.15 (dd, J = 1.8, 8.2 Hz, 1 H), 7.20 (s, 1 H), 7.27 (d, J = 8.2 Hz, 1 H), 7.37 (d, J = 1.8 Hz, 1 H), 7.55 (dd, J = 1.5, 8.6

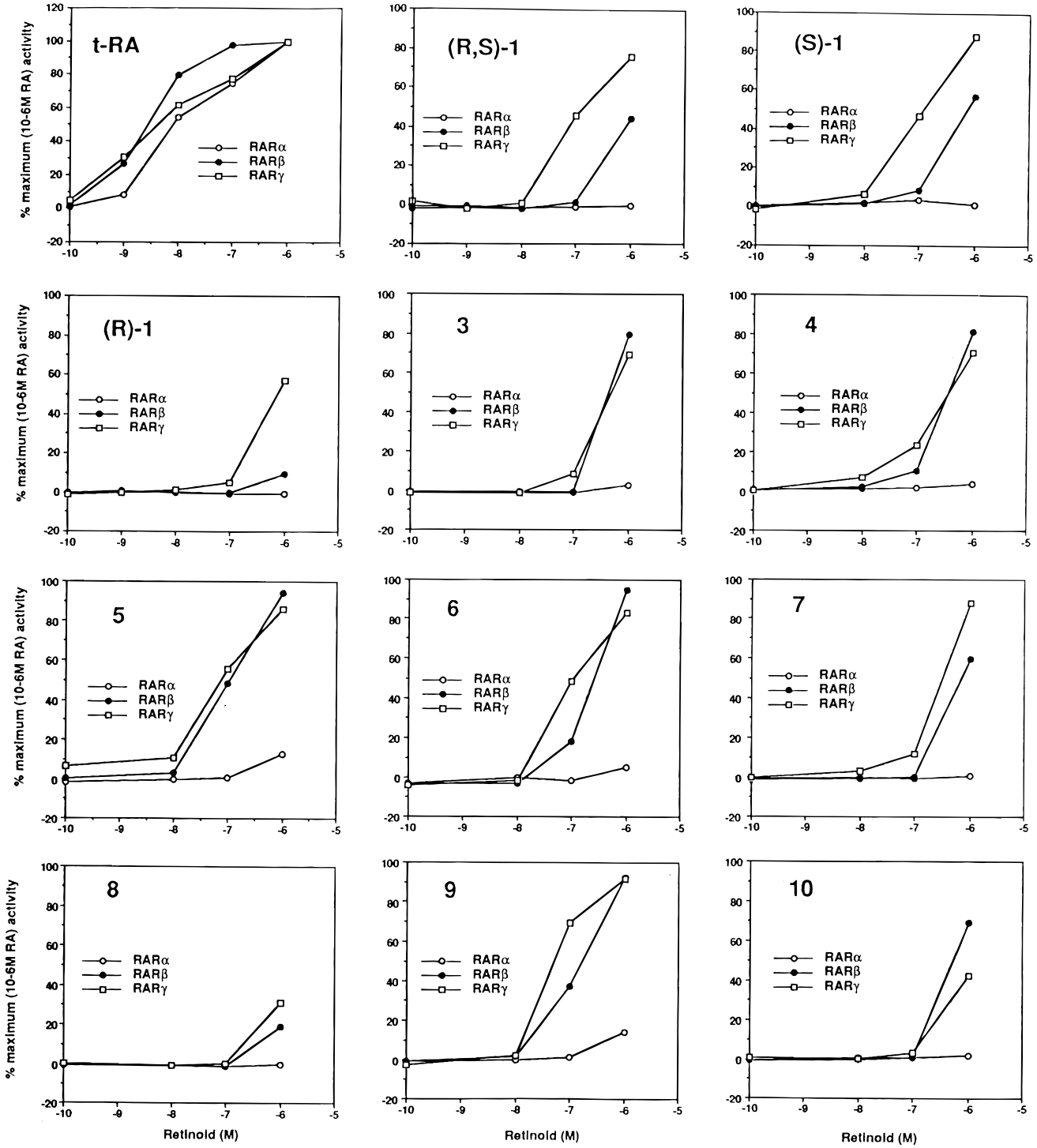


Figure 1.

Hz, 1 H), 7.60 (d, J = 8.6 Hz, 2 H), 7.86 (d, J = 8.6 Hz, 1 H), 7.90 and 7.92 (s over d, J = 8.6 Hz, 2 H), 8.00 (d, J = 8.6 Hz, 2 H), 8.05 (dd, J = 1.5, 8.6 Hz, 1 H), 8.56 (s, 1 H).

General Saponification Procedure for the Naphthalene-2-carboxylic Acid Esters. A solution of the ester (1 mmol) and 1 or 10 N NaOH (10 mmol) in a mixture of tetrahydrofuran (5 mL) and MeOH (5 mL) was stirred at room temperature for 1−2 days or at 60 °C for 2−4 h. The resulting solution was acidified with 1 N HCl and filtered or extracted with EtOAc. Generally, the product obtained was analytically pure; otherwise, the product was triturated with hexane−Et_2O or MeOH−water or recrystallized from EtOAc−hexane.

6-[Methoxy(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)methyl]naphthalene-2-carboxylic Acid (4). To a solution of alclohol **20**[16] (120 mg, 0.30 mmol) in 2 mL of anhydrous dimethylformamide was added sodium hydride (18 mg, 0.45 mmol) at 0 °C. After stirring for 30 min, methyl iodide (51 mg, 0.36 mmol) was added. The resulting mixture was stirred at room temperature for 4 h, diluted with water (40 mL), and extracted with Et_2O (20 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 1:20−1:10) to give 100 mg (80% yield) of methyl 6-[methoxy(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)methyl]naphthalene-2-carboxylate as an oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.28 (s, 6 H), 1.67 (s, 4 H), 3.44 (s, 3 H), 3.98 (s, 3 H), 5.38 (s, 1 H), 7.09 (dd, J = 1.6, 8.2 Hz, 1 H), 7.26 (d, J = 8.2 Hz, 1 H), 7.37 (d, J = 1.6 Hz, 1 H), 7.53 (d, J = 8.5 Hz, 1 H), 7.88−7.93 (m, 3 H), 8.08 (d, J = 8.6 Hz, 1 H), 8.59 (s, 1 H); MS (DCI) *m/e* 417 (MH^+).

The ester obtained above was saponified to give **4**: ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 6 H), 1.23 (s, 6 H), 1.63 (s, 4 H), 3.41 (s, 3

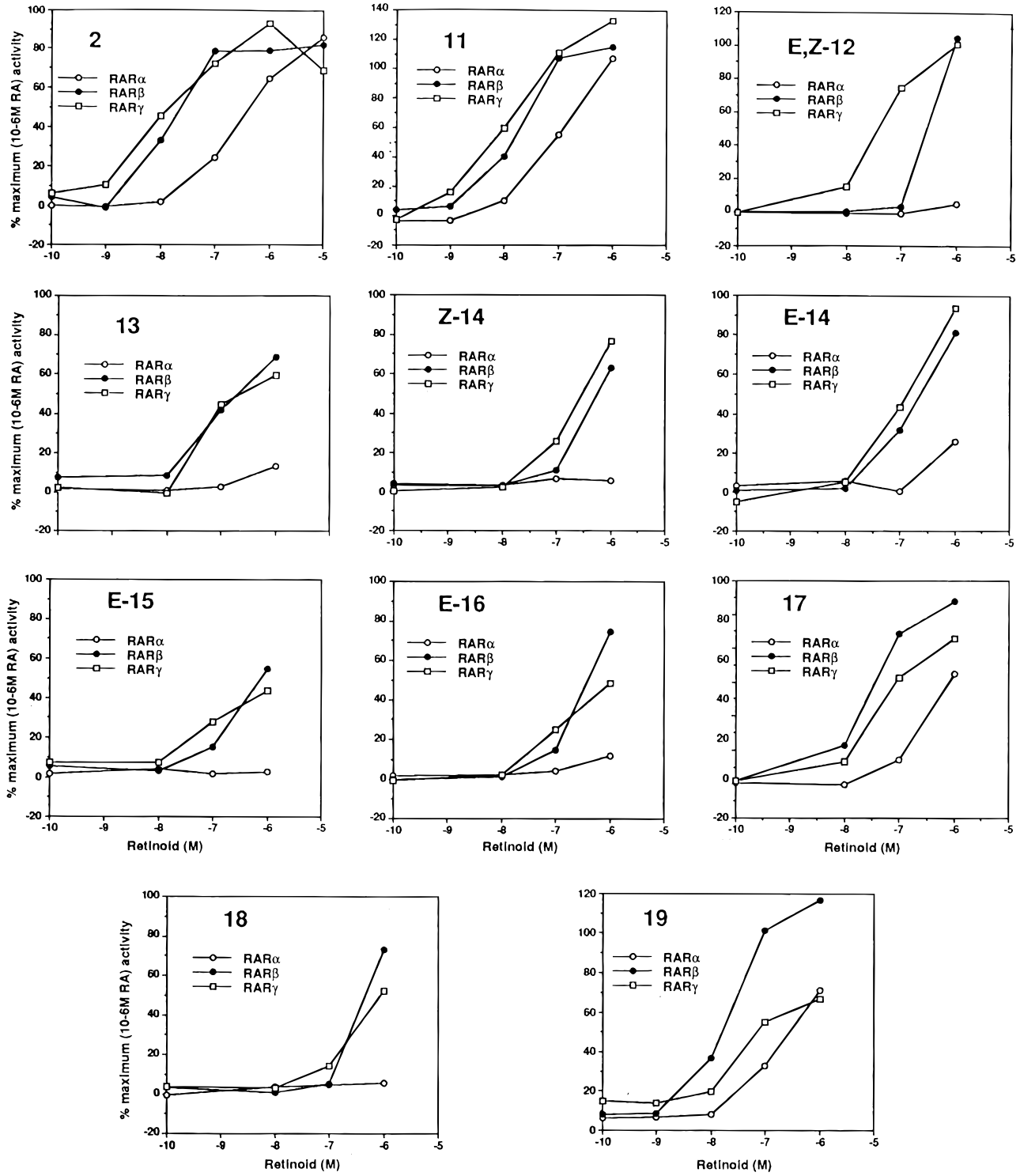


Figure 2.

H), 5.35 (s, 1 H), 7.05 (dd, J = 1.6, 8.2 Hz, 1 H), 7.22 (d, J = 8.2 Hz, 1 H), 7.32 (d, J = 1.6 Hz, 1 H), 7.53 (d, J = 8.4 Hz, 1 H), 7.90 (t, J = 8.5 Hz, 3 H), 8.08 (d, J = 1.4, 8.6 Hz, 1 H), 8.63 (s, 1 H); MS (DCI) *m/e* 403 (MH^+). Anal. ($C_{27}H_{30}O_3$) C, H.

6-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)ethyl]naphthalene-2-carboxylic Acid (5). A mixture of acid **11**[16] (66 mg, 0.17 mmol) and 10% palladium on carbon (7 mg) in EtOH (3 mL) and tetrahydrofuran (1 mL) was hydrogenated at 40 psi for 1 h at room temperature. The mixture was filtered through a pad of Celite, and the filtrate was evaporated. The residue was dissolved in EtOH (2 mL) and then diluted with water (50 mL). The resulting precipitate was filtered, and the solid collected was dried *in vacuo* to give 47 mg (71% yield) of a white powder: mp 215−218 °C; ^{1}H NMR (DMSO-d_6) δ 1.16 (s, 3 H), 1.17 (s, 3 H), 1.19 (s, 6 H), 1.58 (s, 4 H), 1.65 (d, J = 7.2 Hz, 3 H), 4.26 (q, J = 7.2 Hz, 1 H), 7.00 (dd, J = 1.8, 8.2 Hz, 1 H), 7.18 (d, J = 8.2 Hz, 1 H), 7.27 (d, J = 1.8 Hz, 1 H), 7.48 (dd, J = 1.6, 8.5 Hz, 1 H), 7.91 (d over s, J = 8.5 Hz, 3 H), 7.98 (d, J = 8.6, 1 H), 8.50 (bs, 1 H); MS (DCI) *m/e* 385 (MH^+). Anal. ($C_{27}H_{28}O_2$) C, H.

6-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)cyclopropyl]naphthalene-2-carboxylic Acid (6). To the mixture of ester **22**[16] (50 mg, 0.13 mmol) and palladium acetate (2 mg) in 2 mL of tetrahydrofuran was added an excess of diazomethane in ether. After evolution of nitrogen ceased, the solvent was evaporated. The same process was repeated three times. The crude product was purified by flash chromatography on silica gel (hexane:EtOAc = 20:1−10:1) to give 39 mg (75% yield) of methyl 6-[1-(5,6,7,8-tetrahydro-5,5,8,8-

Table 1. Apparent Binding Constants of the Retinoids to RARs α, *β*, and *γ*

retinoid	apparent K_d (nM)		
	RAR α	RAR *β*	RAR *γ*
all-trans-RA	2.3	0.4	0.3
(*R*,*S*)-1	7500	679	64
(*S*)-1	16 500	531	75
(*R*)-1	7500	4095	816
2	118	1.2	3
4	6500	250	400
11	68	1.1	1.3
12	700	50	3.3
(*E*)-14	2200	43	95
(*E*)-16	11 000	1275	4375
19	73	1.7	7.5

tetramethylnaphthalen-2-yl)cyclopropyl]naphthalene-2-carboxylate: ^{1}H NMR ($CDCl_3$) *δ* 1.24 (s, 6 H), 1.27 (s, 6 H), 1.40 (s, 2 H), 1.43 (s, 2 H), 3.98 (s, 3 H), 7.02 (d, *J* = 8.2 Hz, 1 H), 7.21, 7.22 (s over d, *J* = 8.2 Hz, 1 H), 7.46 (d, *J* = 8.5 Hz, 1 H), 7.70 (d, *J* = 8.5 Hz, 1 H), 7.80 (d, *J* = 8.5 Hz, 1 H), 7.86 (d, *J* = 8.5 Hz, 1 H), 8.03 (d, *J* = 8.6 Hz, 1 H), 8.57 (s, 1 H); MS (DCI) *m/e* 413 (MH^+).

The ester obtained above was saponified at 60 °C for 1 h to give 98% yield of **6** as a white powder: ^{1}H NMR ($CDCl_3$) *δ* 1.20 (s, 6 H), 1.24 (s, 6 H), 1.37 (s, 4 H), 6.98 (dd, *J* = 2.2, 8.4 Hz, 1 H), 7.17, 7.19 (d over d, *J* = 2.2, 8.4 Hz, 2 H), 7.44 (d, *J* = 1.8, 8.6 Hz, 1H), 7.67 (s, 1 H), 7.79 (d, *J* = 8.7 Hz, 1 H), 7.86 (d, *J* = 8.7 Hz, 1 H), 8.04 (dd, *J* = 1.6, 8.6 Hz, 1 H), 8.61 (s, 1 H); MS (DCI) *m/e* 399 (MH^+). Anal. ($C_{28}H_{30}O_2 \cdot 0.25H_2O$) C, H.

6-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-2-hydroxyethyl]naphthalene-2-carboxylic Acid (7). Olefin **22** (106 mg, 0.27 mmol) was added to a 1 M tetrahydrofuran solution of borane (5.0 mL, 5.0 mmol). After 18 h at room temperature, the mixture was oxidized with a solution of 3 N sodium hydroxide (7 mL) and 30% hydrogen peroxide (3.2 mL) for 30 min at room temperature. The mixture was extracted with ether (50 mL × 2), and the combined extracts were dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel (hexane:ethyl acetate = 4:1) to give 86 mg (78% yield) of methyl 6-[1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-2-hydroxyethyl]naphthalene-2-carboxylate as a white foam: mp 78−83 °C; ^{1}H NMR ($CDCl_3$) *δ* 1.24 (s, 12 H), 1.65 (s, 4 H), 3.96 (s, 3 H), 4.22−4.34 (m, 3 H), 7.00 (dd, *J* = 2.0, 8.1 Hz, 1 H), 7.21 (s, 2 H), 7.44 (dd, *J* = 1.7, 8.5 Hz, 1 H), 7.78 (s, 1 H), 7.83 (d, *J* = 8.7 Hz, 1 H), 7.88 (d, *J* = 8.5 Hz, 1 H), 8.03 (dd, *J* = 1.6, 8.7 Hz, 1 H), 8.55 (s, 1 H); MS (DCI) *m/e* 417 (MH^+). Anal. ($C_{28}H_{32}O_3 \cdot 0.25H_2O$) C, H.

The ester obtained was saponified to give **7** as a white powder: mp 146−150 °C; ^{1}H NMR (DMSO-d_6) *δ* 1.16 (s, 3 H), 1.17 (s, 3 H), 1.18 (s, 3 H), 1.19 (s, 3 H), 1.57 (s, 4 H), 3.96−4.21 (m, 3 H), 7.02 (dd, *J* = 1.7, 8.2 Hz, 1 H), 7.18 (d, *J* = 8.2 Hz, 1 H), 7.26 (d, *J* = 1.7 Hz, 1 H), 7.52 (dd, *J* = 1.5, 8.5 Hz, 1 H), 7.91, 7.92 (d over s, *J* = 8.5 Hz, 2 H), 7.99 (d, *J* = 8.6, 1 H), 8.51 (bs, 1 H); MS (DCI) *m/e* 403 (MH^+). Anal. ($C_{27}H_{30}O_3 \cdot 0.375H_2O$) C, H.

6-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)carboxymethyl]naphthalene-2-carboxylic Acid (8). To a solution of dimethyl sulfoxide (40 mL, 0.56 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added trifluoroacetic anhydride (83 mL, 0.59 mmol). After 10 min a solution of methyl 6-[1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-2-hydroxyethyl]naphthalene-2-carboxylate (0.111 g, 0.266 mmol) in CH_2Cl_2 (3 mL) was added. After 30 min at −78 °C, triethylamine (0.19 mL, 1.33 mmol) was added, and the mixture was slowly warmed to room temperature. After 1 h at room temperature, the mixture was diluted with CH_2Cl_2 (40 mL) and washed with 1 M hydrochloric acid (30 mL), saturated sodium bicarbonate (30 mL), and water (30 mL). The organic solution was dried over magnesium sulfate and evaporated, and the residue was used directly in the following procedure.

To a solution of the aldehyde obtained above in the tetrahydrofuran (4 mL) and water (3 mL) at 0 °C were added sulfamic acid (78 mg, 0.80 mmol) and sodium chlorite (90 mg, 0.80 mmol) in water (1 mL). After 15 min at room temperature, the solution was poured into brine (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2:MeOH = 97:3) to give 89 mg (78% yield) of methyl 6-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)carboxymethyl]naphthalene-2-carboxylate as a white solid: ^{1}H NMR ($CDCl_3$) *δ* 1.20 (s, 3 H), 1.21 (s, 3 H), 1.23 (s, 6 H), 1.64 (s, 4 H), 3.95 (s, 3 H), 5.14 (s, 1 H), 7.10 (dd, *J* = 1.8, 8.2 Hz, 1 H), 7.24 (d, *J* = 8.2 Hz, 1 H), 7.27 (d, *J* = 1.8 Hz, 1 H), 7.50 (dd, *J* = 1.4, 8.5 Hz, 1 H), 7.79−7.82 (m, 2 H), 7.87 (d, *J* = 8.6 Hz, 1 H), 8.02 (dd, *J* = 1.6, 8.6 Hz, 1 H), 8.54 (s, 1 H); MS (DCI) *m/e* 431 (MH^+).

The ester was saponified at room temperature for 36 h to give **8** as a white powder: mp 238−240 °C; ^{1}H NMR (DMSO-d_6) *δ* 1.18 (s, 3 H), 1.19 (s, 3 H), 1.20 (s, 6 H), 1.60 (s, 4 H), 5.19 (s, 1 H), 7.12 (d, *J* = 8.2 Hz, 1 H), 7.26 (d, *J* = 8.2 Hz, 1 H), 7.34 (d, *J* = 1.8 Hz, 1 H), 7.57 (d, *J* = 8.6 Hz, 1 H), 7.94, 7.95 (d over s, *J* = 8.6 Hz, 2 H), 8.04 (d, *J* = 8.7, 1 H), 8.54 (s, 1 H); MS (DCI) *m/e* 417 (MH^+). Anal. ($C_{27}H_{28}O_4 \cdot 0.5H_2O$) C, H.

6-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)difluoromethyl]naphthalene-2-carboxylic Acid (9). Ketone **23**[16] (196 mg, 0.49 mmol) was suspended in (diethylamino)sulfur trifluoride (2 mL)[28] and warmed to 70 °C. After stirring for 5 h, the solution was evaporated, and the residue was chromatographed on silica gel (hexane:EtOAc = 95:5) to give 51 mg (25% yield) of methyl 6-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)difluoromethyl]naphthalene-2-carboxylate as a yellow foam: mp 145−146 °C; ^{1}H NMR ($CDCl_3$) *δ* 1.25 (bs, 12 H), 1.67 (s, 4 H), 3.97 (s, 3 H), 7.18 (d, *J* = 8.3 Hz, 1 H), 7.31 (d, *J* = 8.3 Hz, 1 H), 7.50 (s, 1 H), 7.62 (dd, *J* = 1.7, 8.9 Hz, 1 H), 7.92 (d, *J* = 8.6 Hz, 1 H), 7.97 (d, *J* = 8.6 Hz, 1 H), 8.04 (s, 1 H), 8.09 (dd, *J* = 1.6, 8.6 Hz, 1 H), 8.61 (s, 1 H); MS (DCI) *m/e* 423 (MH^+).

The ester was saponified to give 72% yield of the title compound as a white powder: mp 199 °C; ^{1}H NMR (DMSO-d_6) *δ* 1.21 (s, 12 H), 1.62 (s, 4 H), 7.23 (d, *J* = n8.4 Hz, 1 H), 7.42 (d, *J* = 8.4 Hz, 1 H), 7.51 (s, 1 H), 7.66 (d, *J* = 8.6 Hz, 1 H), 8.03 (d, *J* = 8.6 Hz, 1 H), 8.15 (d, *J* = 8.7 Hz, 2 H), 8.21 (d, *J* = 8.7 Hz, 1 H), 8.26 (s, 1 H), 8.63 (s, 1 H); MS (DCI) *m/e* 409 (MH^+). Anal. ($C_{26}H_{26}O_2 \cdot 0.5H_2O$) C, H.

6-[1-Hydroxyl-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-2,2,2-trifluoroethyl]naphthalene-2-carboxylic Acid (10). A procedure described by Prakash et al. was followed.[29] To a solution of ketone **23** (205 mg, 0.51 mmol) and (trifluoromethyl)trimethylsilane (0.91 mL, 0.61 mmol) in tetrahydrofuran (5 mL) at 0 °C was added 1 M tetra-*n*-butylammonium fluoride in tetrahydrofuran (0.01 mL, 0.01 mmol). After 4 h at room temperature, 1 M tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.54 mL, 1.54 mmol) was added. After stirring for 16 h, the mixture was poured into saturated ammonium chloride (25 mL) and extracted with ether (30 mL × 2). The solution was dried over magnesium sulfate and evaporated, and the residue was chromatographed on silica gel (10% ethyl acetate in hexane) to give 160 mg (67% yield) of methyl 6-[1-hydroxy(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-2-trifluoroethyl]naphthalene-2-carboxylate as a white powder: ^{1}H NMR ($CDCl_3$) *δ* 1.20 (s, 3 H), 1.23 (s, 3 H), 1.26 (s, 6 H), 1.67 (s, 4 H), 3.49 (s, 1 H), 3.93 (s, 3 H), 7.19 (d, *J* = 8.4 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.50, 7.53 (s over d, *J* = 8.9 Hz, 1 H), 7.84 (d, *J* = 8.9 Hz, 1 H), 7.85 (d, *J* = 8.6 Hz, 1 H), 8.01 (dd, *J* = 1.6, 8.6 Hz, 1 H), 8.15 (bs, 1 H), 8.51 (bs, 1 H); MS (DCI) *m/e* 471 (MH^+).

The ester obtained was saponified to give the title compound as a white powder: mp 198−199 °C; ^{1}H NMR (DMSO-d_6) *δ* 1.15 (s, 6 H), 1.21 (s, 6 H), 1.62 (s, 4 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.43−7.44 (m, 1 H), 7.47 (s, 1 H), 7.99 (dd, *J* = 1.5, 8.5 Hz, 1 H), 8.09 (d over d, *J* = 8.1 Hz, 2 H), 8.19 (s, 1 H), 8.57 (s, 1 H); MS (DCI) *m/e* 457 (MH^+). Anal. ($C_{27}H_{27}O_3 \cdot H_2O$) C, H.

***(E)*- and *(Z)*-6-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)(hydroxyimino)methyl]-2-naphthalene-**

carboxylic Acid ((*E*)-12 and (*Z*)-12). A solution of a mixture of the *E*/*Z* oxime methyl ester of **12**[16] (575 mg, 1.39 mmol), trimethylacetyl chloride (168 mg, 1.39 mmol), and pyridine (110 mg, 1.39 mmol) in benzene (15 mL) was allowed to reflux for 16 h. The reaction mixture was then concentrated under reduced pressure and the residue chromatographed on silica gel (ethyl acetate:hexane = 4:96) to give 114 mg (17% yield) of the *E* isomer and 108 mg (16% yield) of the *Z* isomer of methyl 6-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)[(pivaloyloxy)imino]methyl]naphthalene-2-carboxylate.

***E* isomer**: ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.19 (s, 6 H), 1.25 (s, 6 H), 1.54 (s, 4 H), 3.99 (s, 3 H), 7.27 (m, 2 H), 7.46 (dd, J = 8.4, 1.6 Hz, 1 H), 7.59 (s, 1 H), 7.80 (s, 1 H), 7.87 (d, J = 8.7 Hz, 1 H), 8.00 (d, J = 8.6 Hz, 1 H), 8.10 (dd, J = 8.6, 1.7 Hz, 1 H), 8.66 (s, 1 H); MS (DCI) *m/e* 500 (MH^+).

***Z* isomer**: ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9 H), 1.23 (s, 6 H), 1.32 (s, 6 H), 1.48 (s, 4 H), 3.96 (s, 3 H), 7.07 (dd, J = 8.1, 1.8 Hz, 1 H), 7.21 (d, J = 1.8 Hz, 1 H), 7.38 (d, J = 8.2 Hz, 1 H), 7.84 (d, J = 8.7 Hz, 1 H), 7.94 (m, 3 H), 8.04 (dd, J = 8.6, 1.7 Hz, 1 H), 8.58 (s, 1 H); MS (DCI) *m/e* 500 (MH^+).

The pure *E* isomer ester was saponified at room temperature for 16 h to give 75% yield of (***E*)-12** (containing ~5% of *Z* isomer): ^{1}H NMR (DMSO-d_6) δ 1.15 (s, 6 H), 1.21 (s, 6 H), 1.62 (s, 4 H), 7.03 (dd, J = 8.2, 1.8 Hz, 1 H), 7.29 (d, J = 8.3 Hz, 1 H), 7.47 (d, J = 1.8 Hz, 1 H), 7.50 (d, J = 1.5 Hz, 1 H), 7.92 (s, 1 H), 7.98 (dd, J = 8.6, 1.6 Hz), 8.05 (d, J = 8.8 Hz, 1 H), 8.17 (d, J = 8.6 Hz, 1 H), 8.64 (s, 1 H), 11.38 (s, 1 H); MS (DCI) *m/e* 402 (MH^+); IR (KBr) 2960, 2926, 1692, 1416. Anal. ($C_{26}H_{27}N_1O_3 \cdot 0.75H_2O$) C, H, N.

The pure *Z* isomer ester was saponified at room temperature for 48 h to give 97% yield of (***Z*)-12** (containing 14% of *E* isomer): ^{1}H NMR (DMSO-d_6) δ 1.20 (s, 6 H), 1.29 (s, 6 H), 1.67 (s, 4 H), 7.13 (dd, J = 8.1, 1.7 Hz, 1 H), 7.27 (d, J = 1.7 Hz, 1 H), 7.42 (d, J = 8.16 Hz, 1 H), 7.74 (s, 1 H), 7.81 (dd, J = 8.6, 1.6 Hz, 1 H), 7.92 (s, 2 H), 8.09 (d, J = 8.8 Hz, 1 H), 8.57 (s, 1 H), 11.52 (s, 1 H), 13.07 (s, 1 H); MS (DCI) *m/e* 402 (MH^+); IR (KBr) 2960, 2926, 1692, 1388. Anal. ($C_{26}H_{27}N_1O_3 \cdot 1.0H_2O$) C, H, N.

(*E*,*Z*)-6-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)(methoxyimino)methyl]naphthalene-2-carboxylic Acid (13). To a solution of ketone **23** (179 mg, 0.44 mmol) in MeOH (20 mL) was added methoxylamine hydrochloride (75 mg, 0.90 mmol). The pH of the reaction mixture was adjusted to 4 by the dropwise addition of triethylamine. After heating at reflux for 16 h, the reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (30 mL), washed with water (30 mL), and evaporated, and the resulting residue was chromatographed on silica gel (hexane:EtOAc = 95:5) to give 144 mg (75% yield) of the methyl ester of **13** as an *E*/*Z* mixture (3:2) of isomers: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6 H, A), 1.25 (2, 6 H, B), 1.28 (s, 6 H, A), 1.33 (s, 6 H, B), 1.75 (s, 4 H, A), 1.78 (s, 4 H, B), 4.00 (s, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 7.60−7.08 (m, 8 H), 7.83−8.17 (m, 8 H), 8.59 (s, 1 H, B), 8.62 (s, 1 H, A); MS (DCI) *m/e* 430 (MH^+).

The mixture of the *E*/*Z* isomers of the ester was saponified to give 85% yield of the title product as a mixture of isomers *A*/*B* (3:2): ^{1}H NMR (DMSO-d_6) δ 1.13 (s, 6 H, A), 1.19 (s, 6 H, A), 1.21 (s, 6 H, B), 1.29 (s, 6 H, B), 1.61 (s, 4 H, A), 1.67 (s, 4 H, B), 3.87 (s, 3 H, A), 3.93 (s, 3 H, B), 7.07 (dd, J = 1.8, 8.1 Hz, 1 H, A), 7.12 (dd, J = 1.8, 8.1 Hz, B), 7.25−8.03 (m, 14 H), 8.10 (d, J = 8.6 Hz, 1 H, B), 8.17 (d, J = 8.6 Hz, 1 H, A), 8.57 (s, 1 H, B), 8.64 (s, 1 H, A); MS (DCI) *m/e* 416 (MH^+); IR (KBr) 2960, 2932, 1692, 1418 cm^{-1}. Anal. ($C_{27}H_{29}N_1O_3 \cdot 0.5H_2O$) C, H, N.

(*E*)- and (*Z*)-6-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)carbonyl]naphthalene-2-carboxylic Acid Hydrazone ((*E*)-14 and (*Z*)-14). A mixture of ketone **23** (1.00 g, 2.47 mmol), hydrazine (0.16 g, 4.90 mmol), triethylamine (0.68 g, 6.7 mmol), and concentrated sulfuric acid (0.18 g, 1.9 mmol) in 10 mL of MeOH was stirred at reflux for 1 day. The solvent was evaporated under reduced pressure, and to the residue was added 20 mL of water. This mixture was extracted with EtOAc (20 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 20:1−10:1) to give 420 mg of the *E* isomer and 200 mg of the *Z* isomer methyl ester. The esters were recrystallized from MeOH−EtOAc to afford 320 mg (31% yield) and 110 mg (11%) of pure *E* and *Z* isomers of the methyl ester of the title compounds, respectively.

(*E*)-14 methyl ester: ^{1}H NMR ($CDCl_3$) δ 1.29 (6 H), 1.37 (s, 6 H), 1.76 (s, 4 H), 3.97 (s, 3 H), 5.63 (bs, 2 H), 7.10 (dd, J = 1.6, 8.1 Hz, 1 H), 7.24 (s, 1 H), 7.48 (d, J = 8.1 Hz, 1 H), 7.62 (s, 1 H), 7.75 (d, J = 8.7 Hz, 1 H), 7.90 (d, J = 8.6 Hz, 1 H), 7.99 (dd, J = 1.6, 8.6 Hz, 1 H), 8.06 (dd, J = 1.6, 8.7 Hz, 1 H), 8.56 (s, 1 H); MS (DCI) *m/e* 415 (MH^+). Anal. ($C_{27}H_{30}N_2O_2$) C, H, N.

(*Z*)-14 methyl ester: ^{1}H NMR ($CDCl_3$) δ 1.23 (6 H), 1.26 (s, 6 H), 1.67 (s, 4 H), 4.02 (s, 3 H), 5.43 (bs, 2 H), 7.09 (dd, J = 1.9, 8.4 Hz, 1 H), 7.21 (d, J = 8.4 Hz, 1 H), 7.46 (dd, J = 1.4, 8.3 Hz, 1 H), 7.60 (d, J = 1.8 Hz, 1 H), 7.86 (s, 1 H), 7.92 (d, J = 8.7 Hz, 1 H), 8.11 (d, J = 8.3 Hz, 1 H), 8.11 (dd, J = 1.6, 8.3 Hz, 1 H), 8.68 (s, 1 H); MS (DCI) *m/e* 415 (H^+). Anal. ($C_{27}H_{30}N_2O_2$) C, H, N.

The esters were saponified separately to give the acids. (***E*)-14**: ^{1}H NMR (DMSO-d_6) δ 1.24 (6 H), 1.32 (s, 6 H), 1.70 (s, 4 H), 6.42 (s, 1 H), 6.48 (bs, 1 H), 7.05 (d, J = 8.1 Hz, 1 H), 7.21 (s, 1 H), 7.49 (s, 1 H), 7.54 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 8.9 Hz, 1 H), 7.87 (d, J = 8.6 Hz, 1 H), 7.93 (d, J = 8.9 Hz, 1 H), 8.01 (d, J = 8.6 Hz, 1 H), 8.50 (s, 1 H); MS (DCI) *m/e* 401 (MH^+). Anal. ($C_{26}H_{28}N_2O_2 \cdot 0.25H_2O$) C, H, N.

(*Z*)-14: ^{1}H NMR (DMSO-d_6) δ 1.14 (6 H), 1.19 (s, 6 H), 1.60 (s, 4 H), 6.25 (bs, 1 H), 6.30 (bs, 1 H), 6.91 (dd, J = 1.8, 8.3 Hz, 1 H), 7.19 (d, J = 8.3 Hz, 1 H), 7.39 (dd, J = 1.5, 8.2 Hz, 1 H), 7.45 (d, J = 1.8 Hz, 1 H), 7.90 (s, 1 H), 8.02 (d, J = 8.5 Hz, 1 H), 8.08 (d, J = 8.5 Hz, 1 H), 8.26 (d, J = 8.2 Hz, 1 H), 8.67 (s, 1 H); MS (DCI) *m/e* 401 (MH^+). Anal. ($C_{26}H_{28}N_2O_2 \cdot 0.125H_2O$) C, H, N.

6-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)carbonyl]naphthalene-2-carboxylic Acid Methyl Ester (*p*-Tolylsulfonyl)hydrazone (15). A solution of the ketone **23** (0.50 g, 1.24 mmol), *p*-toluenesulfonylhydrazide (0.46 g, 2.48 mmol), and 2 drops of concentrated HCl in 10 mL of MeOH was stirred at room temperature for 3 days. The solvent was evaporated, and the residue was diluted with 20 mL of water and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 15:1−5:1) to give 133 mg of higher R_f *E* isomer and 242 mg of the lower R_f *Z* isomer of the methyl ester of the title compound. The products were recrystallized from EtOAc−MeOH to afford 109 mg (15% yield) and 170 mg (24% yield) of the pure *Z* and *E* isomers, respectively.

(*E*)-15 methyl ester: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 1.35 (s, 6 H), 1.73 (s, 4 H), 2.41 (s, 3 H), 3.95 (s, 3 H), 6.88 (dd, J = 1.6, 8.2 Hz, 1 H), 7.01 (s, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.45 (d, J = 8.0 Hz, 1 H), 7.55 (s, 1 H), 7.72 (d, J = 8.6 Hz, 1 H), 7.76 (s, 1 H), 7.85−7.89 (m, 2 H), 7.97−8.02 (m, 2 H), 8.54 (s, 1 H); MS (DCI) *m/e* 569 (H^+). Anal. ($C_{34}H_{36}N_2O_4S$) C, H, N.

(*Z*)-5 methyl ester: ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 6 H), 1.22 (s, 6 H), 1.64 (s, 4 H), 2.42 (s, 3 H), 4.00 (s, 3 H), 7.06 (dd, J = 1.8, 8.3 Hz, 1 H), 7.18 (d, J = 8.4 Hz, 1 H), 7.24 (d, J = 8.4 Hz, 1 H), 7.33 (d, J = 8.2 Hz, 2 H), 7.47 (d, J = 1.8 Hz, 1 H), 7.68 (s, 1 H), 7.86 (d, J = 8.3 Hz, 3 H), 8.07 (d, J = 8.4 Hz, 1 H), 8.14 (dd, J = 1.4, 8.6 Hz, 1 H), 8.66 (s, 1 H); MS (DCI) *m/e* 569 (MH^+). Anal. ($C_{34}H_{36}N_2O_4S$) C, H, N.

The (***E*)-15** methyl ester was saponified to give the acid (***E*)-15**: ^{1}H NMR (DMSO-d_6) δ 1.11 (6 H), 1.18 (s, 6 H), 1.60 (s, 4 H), 2.39 (s, 3 H), 6.88 (dd, J = 1.8, 8.3 Hz, 1 H), 7.25 (d, J = 8.3 Hz, 1 H), 7.28 (d, J = 1.8 Hz, 1 H), 7.38 (dd, J = 1.5, 8.5 Hz, 1 H), 7.43 (d, J = 8.3 Hz, 2 H), 7.78 (d, J = 8.3 Hz, 2 H), 7.88 (s, 1 H), 8.00 (dd, J = 1.5, 8.6 Hz, 1 H), 8.09 (d, J = 8.6 Hz, 1 H), 8.21 (d, J = 8.5 Hz, 1 H), 8.67 (s, 1 H); MS (DCI) *m/e* 555 (MH^+). Anal. ($C_{33}H_{34}N_2O_4S$) C, H; N: calcd, 5.05; found, 4.59.

6-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)carbonyl]naphthalene-2-carboxylic Acid Methyl Ester (Methylsulfonyl)hydrazone (16). A solution of ketone **23** (400 mg, 0.99 mmol), methanesulfonylhydrazide (9.90

mmol), and 2 drops of concentrated sulfuric acid in 15 mL of MeOH was stirred at reflux for 20 h. The solvent was evaporated, and the residue was diluted with 20 mL of 1 N HCl and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2:EtOAc = 10:0−10:1) to give 420 mg of a mixture of *E* and *Z* isomers, which was recrystallized from tetrahydrofuran−MeOH to afford 367 mg (79% yield) of the pure *Z* isomer of the methyl ester of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.16 (6 H), 1.25 (s, 6 H), 1.65 (s, 4 H), 3.18 (s, 3 H), 4.01 (s, 3 H), 7.25 (d, J = 8.4 Hz, 1 H), 7.30 (dd, J = 1.6, 8.4 Hz, 1 H), 7.37, 7.38 (s over d, J = 8.4 Hz, 2 H), 7.49 (d, J = 1.6 Hz, 1 H), 7.82 (s, 1 H), 7.92 (d, J = 8.6 Hz, 1 H), 8.12 (d, J = 8.4 Hz, 1 H), 8.16 (dd, J = 1.6, 8.6 Hz, 1 H), 8.68 (s, 1 H); MS (DCI) *m/e* 493 (MH^+). Anal. ($C_{28}H_{32}N_2O_4S$) C, H, N.

The methyl ester was saponified to give the acid **16**: ^{1}H NMR (DMSO-d_6) δ 1.12 (6 H), 1.22 (s, 6 H), 1.61 (s, 4 H), 3.05 (s, 3 H), 7.20 (dd, J = 1.8, 8.4 Hz, 1 H), 7.33 (d, J = 8.4 Hz, 1 H), 7.40 (d, J = 1.8 Hz, 1 H), 7.45 (dd, J = 1.5, 8.4 Hz, 1 H), 7.96 (s, 1 H), 8.02 (dd, J = 1.5, 8.6 Hz, 1 H), 8.11 (d, J = 8.6 Hz, 1 H), 8.61 (d, J = 8.6 Hz, 1 H), 8.68 (s, 1 H); MS (DCI) *m/e* 479 (MH^+). Anal. ($C_{27}H_{30}N_2O_4S\cdot0.5H_2O$) C, H, N.

6-[2-Cyano-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)vinyl]naphthalene-2-carboxylic Acid (17). A solution of diethyl (cyanomethyl)phosphonate (220 mg, 1.24 mmol) and potassium *tert*-butoxide (121 mg, 0.99 mmol) in 5 mL of anhydrous tetrahydrofuran was stirred at 0 °C for 2 h. To the solution was added ketone **23** (200 mg, 0.49 mmol), and the mixture was stirred at 0 °C for 1 h and at room temperature for 4 h. The reaction was quenched with saturated NH_4Cl solution (20 mL) and the mixture extracted with EtOAc (20 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 30:1−10:1) to give 111 mg (53% yield) of the mixture of the *E*,*Z* isomers of the esters (1:1): ^{1}H NMR ($CDCl_3$) δ 1.21, 1.30, 1.33 (s, 12 H), 1.69, 1.73 (s, 4 H), 4.00, 4.01 (s, 3 H), 5.80, 5.84 (s, 1 H), 7.06, 7.15 (dd, J = 1.9, 8.3; 1.7, 8.2 Hz, 1 H), 7.25−7.53 (m, 3 H), 7.85−8.14 (m, 4 H), 8.62, 8.66 (s, 1 H); MS (DCI) *m/e* 424 (MH^+). Anal. ($C_{29}H_{29}NO_2$) C, H, N.

The mixture of the ester obtained was saponified to give the acids **17**: ^{1}H NMR (DMSO-d_6) δ 1.17, 1.22, 1.24, 1.29 (s, 12 H), 1.62, 1.69 (s, 4 H), 6.37, 6.49 (s, 1 H), 7.04, 7.09 (dd, J = 2.0, 8.4; 1.9, 8.2 Hz, 1 H), 7.35−7.56 (m, 3 H), 7.98−8.24 (m, 4 H), 8.62, 8.68 (s, 1 H), 13.18 (bs, 1 H); MS (DCI) *m/e* 410 (MH^+). Anal. ($C_{28}H_{27}NO_2\cdot0.625H_2O$) C, H, N.

6-[2-Carboxy-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)vinyl]naphthalene-2-carboxylic Acid (18). To a solution of triethyl phosphonoacetate (250 mg, 1.11 mmol) was slowly added *n*-butyllithium (1.7 M in hexane, 0.59 mL, 1.01 mmol) at −78 °C. After stirring for 1 h, ketone **23** (150 mg, 0.37 mmol) was added. The solution was stirred at −78 °C for 1 h and at room temperature for 2 h, the reaction was quenched with saturated NH_4Cl solution (20 mL), and the mixture was extracted with EtOAc (20 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 30:1−10:1) to give 95 mg (53%) of the mixture of the *E*,*Z* isomers of the esters (3:2), which was saponified to afford diacids **18**: ^{1}H NMR (DMSO-d_6) δ 1.37, 1.89, 1.20, 1.27 (s, 12 H), 1.61, 1.66 (s, 4 H), 6.43, 6.47 (s, 1 H), 6.89−6.70 (m, 1 H), 7.20−7.44 (m, 3 H), 7.78, 7.88 (s, 1 H), 7.97−8.10 (m, 4 H), 8.58, 8.62 (s, 1 H); MS (DCI) *m/e* 429 (MH^+). Anal. ($C_{28}H_{28}O_4\cdot0.15H_2O$) C, H.

2,2-Difluoro-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)ethanone (25). To difluoroacetic acid (10.0 g, 0.10 mol) in a 25 mL flask was added PCl_5 (22.7 g, 0.11 mmol) in several portions at −30 °C. The flask was then equipped with an ice−water condenser. The reaction temperature was raised to 80 °C, and difluoroacetic acid chloride (10.3 g, 87% yield) was collected in a receiver at −78 °C. Excess of the acid chloride was added in small portions to a mixture of aluminum chloride (1.47 g, 11.0 mmol) and 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (2.12 g, 9.99 mmol) in 5 mL of CH_2Cl_2 at 0 °C. After stirring at 0 °C for 4 h and at room temperature for 3 h, the mixture was diluted with 1 N HCL (30 mL) and extracted with CH_2Cl_2 (30 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 30:1−10:1) to give 2.35 g (88% yield) of **25**: ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 6 H), 1.30 (s, 6 H), 6.27 (t, J = 53.6 Hz, 1 H), 7.74 (d, J = 8.2 Hz, 1 H), 7.80 (d, J = 8.2 Hz, 1 H), 8.04 (s, 1 H).

[[6-[2,2-Difluoro-1-hydroxy-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)ethyl]naphthalen-2-yl]oxy]-dimethyl(1,1-dimethylethyl)silane (26). To a solution of **24**[30] (0.99 g, 2.93 mmol) in 10 mL of anhydrous tetrahydrofuran was added *tert*-butyllithium (1.7 M in hexane, 3.62 mL, 6.15 mmol) at −78 °C. After stirring for 10 min, the temperature was raised to −40 °C and ketone **25** (0.78 g, 2.93 mmol) in 2 mL of tetrahydrofuran was added. The reaction mixture was stirred for 30 min, then the reaction was quenched with saturated NH_4Cl solution (20 mL), and the mixture was extracted with EtOAc (30 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 20:1−10:1) to give 1.32 g (86% yield) of **26** as a thick oil: ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 6 H), 1.02 (s, 9 H), 1.23 (s, 3 H), 1.24 (s, 3 H), 1.26 (s, 6 H), 1.68 (s, 4 H), 2.76 (bs, 1 H), 6.27 (t, J = 55.3 Hz, 1 H), 7.09 (dd, J = 2.3, 8.7 Hz, 1 H), 7.14−7.17 (m, 2 H), 7.25 (d over $CHCl_3$, J = 6.4 Hz, 1 H), 7.40 (dd, J = 1.6, 8.6 Hz, 1 H), 7.48 (d, J = 1.6 Hz, 1 H), 7.65 (d, J = 8.7 Hz, 1 H), 7.74 (d, J = 8.7 Hz, 1 H), 7.96 (s, 1 H); MS (DCI) *m/e* 525 (MH^+).

6-[2,2-Difluoro-1-hydroxy-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)ethyl]naphthalen-2-ol (27). Silyl ether **26** (1.20 g, 2.29 mmol) in 2 mL of tetrahydrofurn was treated with tetra-*n*-butylammonium fluoride (1 M in tetrahydrofuran, 2.50 mL, 2.50 mmol). After stirring for 30 min, the mixture was evaporated, and the residue was purified by flash chromatography on silica gel (hexane:EtOAc = 20:1−5:1) to give 0.76 g (80%) of the product: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.23 (s, 3 H), 1.26 (s, 6 H), 1.68 (s, 4 H), 2.76 (bs, 1 H), 2.43 (bt, J = 8.4 Hz, 1 H), 6.27 (t, J = 55.4 Hz, 1 H), 7.10−7.18 (m, 3 H), 7.26 (d, J = 8.2 Hz, 1 H), 7.42 (dd, J = 1.6, 8.8 Hz, 1 H), 7.46 (d, J = 1.6 Hz, 1 H), 7.65 (d, J = 8.8 Hz, 1 H), 7.78 (d, J = 8.6 Hz, 1 H), 7.97 (s, 1 H); MS (DCI) *m/e* 411 (MH^+).

6-[2,2-Difluoro-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)vinyl]naphthalen-2-ol (28). The diol **27** (0.60 g, 1.46 mmol) and pyridine hydrochloride (5.0 g, 43.3 mmol) was stirred at 220 °C for 25 min. The mixture was cooled to room temperature, diluted with water (50 mL), and extracted with EtOAc (30 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 20:1−10:1) to give 0.40 g (70% yield) of the product: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 1.29 (s, 6 H), 1.69 (s, 4 H), 4.96 (s, 1 H), 7.02 (bd, J = 8.1 Hz, 1 H), 7.11 (dd, J = 2.4, 8.9 Hz, 1 H), 7.15 (d, J = 2.4 Hz, 1 H), 7.24−7.28 (m, 2 H), 7.33 (bd, J = 8.6 Hz, 1 H), 7.66 (d, J = 8.5 Hz, 1 H), 7.70 and 7.72 (s over d, J = 8.6 Hz, 2 H); MS (DCI) *m/e* 393 (MH^+).

6-[2,2-Difluoro-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)vinyl]naphthalen-2-ol (Trifluoromethyl)sulfonic Acid Ester (29). To a solution of the phenol **28** (0.39 g, 0.99 mmol) and 4-(dimethylamino)pyridine (0.24 g, 2.00 mmol) in 10 mL of CH_2Cl was added triflic anhydride (0.37 g, 1.30 mmol) at −78 °C. The reaction mixture was stirred at room temperature for 2 h, diluted with 1 N HCl (20 mL), and extracted with CH_2Cl_2 (20 mL × 2). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 30:1−10:1) to give 0.39 g (75% yield) of the product: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 6 H), 1.32 (s, 6 H) 1.72 (s, 4 H), 7.03 (bd, J = 8.2 Hz, 1 H), 7.25 (s, 1 H), 7.31 (d, J = 8.2 Hz, 1 H), 7.40 (dd, J = 2.2, 9.0 Hz, 1 H), 7.50 (d, J = 8.5 Hz, 1 H), 7.77 (d, J = 2.2 Hz, 1 H), 7.86 (s, 1 H), 7.86 (d, J = 8.5 Hz, 1 H), 7.90 (d, J = 9.0 Hz, 1 H); MS (DCI) *m/e* 525 (MH^+).

Methyl 6-[2,2-Difluoro-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)vinyl]naphthalene-2-carbox-

ylate (30). A solution of triflate **29** (0.38 g, 0.72 mmol), triethylamine (0.16 g, 1.59 mmol), palladium acetate (5 mg, 0.02 mmol), and 1,3-bis(diphenylphosphino)propane (9 mg, 0.02 mmol) in anhydrous dimethyl sulfoxide (4 mL) and MeOH (2.5 mL) was saturated with CO and stirred under a CO balloon at 60−70 °C for 6 h. The mixture was diluted with water (30 mL) and extracted with a mixture of EtOAc and Et_2O (1:1, 30 mL × 3). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (hexane:EtOAc = 20:1−10:1) to give 0.27 g (85% yield) of **30** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 6 H), 1.31 (s, 6 H), 1.70 (s, 4 H), 4.00 (s, 3 H), 7.02 (bd, J = 8.3 Hz, 1 H), 7.25 (s, 1 H), 7.29 (d, J = 8.3 Hz, 1 H), 7.45 (d, J = 8.6 Hz, 1 H), 7.83, 7.85 (s over d, J = 8.7 Hz, 2 H), 7.92 (d, J = 8.7 Hz, 1 H), 8.08 (dd, J = 1.5, 8.6 Hz, 1 H), 8.61 (s, 1 H); MS (DCI) *m/e* 435 (MH^+).

6-[2,2-Difluoro-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)vinyl]naphthalene-2-carboxylic Acid (19). A solution of the ester **30** (105 mg, 0.24 mmol) and di-*n*-butyltin oxide (180 mg, 0.72 mmol) in 5 mL of anhydrous toluene was stirred at reflux for 20 h. The solution was diluted with 1 N HCl (10 mL) and extracted with EtOAc (20 mL × 2). The combined extracts were washed with saturated NaCl solution (10 mL), dried over magnesium sulfate, and evaporated. The residue was dissolved in 20 mL of CH_2Cl and then stirred with 10 mL of 40% KF solution for 1 h. The aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2:MeOH = 30:1−10:1) to give the product which crystallized from hexane to afford 65 mg (64% yield) of **19**: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 1.30 (s, 6 H), 1.70 (s, 4 H), 7.02 (bd, J = 8.2 Hz, 1 H), 7.24 (s, 1 H), 7.29 (d, J = 8.2 Hz, 1 H), 7.47 (d, J = 8.6 Hz, 1 H), 7.84 (s, 1 H), 7.88 (d, J = 8.7 Hz, 1 H), 7.96 (d, J = 8.6 Hz, 1 H), 8.12 (dd, J = 1.6, 8.7 Hz, 1 H), 8.70 (s, 1 H); MS (DCI) *m/e* 421 (MH^+). Anal. ($C_{27}H_{26}F_2O_2 \cdot 0.125H_2O$) C, H.

Retinoid Transactivation Assay.[15] DNA-encoding chimeric receptor, CAT reporter vector, and pCH110 (ratio 1:20:20) at a final concentration of 20 μg/100 mm of plate was used to transfect HeLa cells following a standard calcium phosphate-mediated transfection protocol.[31,32] Cells with DNA precipitates were incubated at 37 °C with 5% CO_2 for 17−20 h. The cells were than washed with PBS and refed with DMEM supplemented with 5% delipidated serum. After several hours of recovery, cells were treated with different concentrations of retinoids and incubated at 37 °C for another 18 h. Retinoic acid and test compounds were routinely assayed at concentrations of 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, and 10^{-6} M. The cells were scraped into 1 mL of cold PBS and transferred to a 1.5 mL Eppendorf tube. From that point, samples were kept on ice. After all samples were collected, cells were pelleted by centrifugation at 3K rpm, 4 °C, for 5 min in a Beckman GPKR centrifuge. Supernatants were discarded, and pellets were drained for several minutes. Drained pellets were resuspended in 250 μL of cold 100 mM Tris-HCl, pH 7.5. Cell lysates were prepared by three consecutive freeze−thaw cycles consisting of 5 min on dry ice (−80 °C) followed by 5 min at 37 °C. Cellular debris was pelleted at 15K rpm in an Eppendorf microfuge for 10 min at 4 °C; 200 μL of cell extracts was transferred to a 96-well microtiter plate. Retinoid efficacy was measured by the concentration of induced CAT gene product in the extracts from transfected cells, using CAT ELISA kit (5-Prime-3-Prime, Inc., Boulder, CO). CAT activity was routinely normalized for transfection efficiency by the β-galactosidase activity.

Retinoid Competition Binding Assay. Recombinant RAR protein expressed in *Escherichia coli* was used in the direct binding assay. The apparent dissociation constants for the retinoids were determined by the charcoal absorption method.[24] Briefly, serial dilutions of the test retinoids (10^{-11}−10^{-5} M) were made in dimethyl sulfoxide in a volume of 100 μL. Twelve micrograms of crude cytosolic extract prepared from pET15b (Novagen, Madison, WI)/hRAR-α, -β, or -γ prepared protein was used for each data point. All reactions were carried out in binding buffer (60 mM Na imidazole, 500 mM NaCl, 20 mM Tris, pH 7.9) for 14−16 h at 4 °C in a final volume of 1 mL. Unbound [^{3}H]RA was removed by addition of 0.5 mL of equivalent-sized dextran-treated charcoal (final concentration 3% [wt/vol]) for 15 min at 4 °C.[25] To 12 mL of ReadySafe scintillation cocktail (Beckman) was added 0.5 mL of the supernatant, and it was then counted in an LS6500 scintillation counter (Beckman) using the auto-dpm program.

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References

(1) *The Retinoids, Biology, Chemistry, and Medicine*; Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven Press: New York, 1994.
(2) Lever, L.; Marks, R. Topical Retinoid Treatment For Skin Cancer: A Review. *Skin Pharmacol.* **1991**, *4*, 125−131.
(3) Smith, M. A.; Parkinson, D. R.; Cheson, B. D.; Friedman, M. A. Retinoids In Cancer Therapy. *J. Clin. Oncol.* **1992**, *10*, 839−864.
(4) Lippman, S. M.; Kessler, J. F.; Meyskens, F. L., Jr. Retinoids as Preventive and Therapeutic Anticancer Agents (Part I). *Cancer Treatment Rep.* **1987**, *71*, 391−405 (493−515).
(5) Leid, M.; Kastner, P.; Chambon, P. Multiplicity Generates Diversity in the Retinoic Acid Signalling Pathways. *Trends Biochem. Sci.* **1992**, *17*, 427−433.
(6) Mangelsdorf, D. J.; Ong, E. S.; Dyck, J. A.; Evans, R. M. Nuclear Receptor That Identifies A Novel Retinoic Acid Response Pathway. *Nature* **1990**, *345*, 224−229.
(7) Zelent, A.; Krust, A.; Petkovich, M.; Kastner, P.; Chambon, P. Cloning of Murine α and β Retinoic Acid Receptors and A Novel Receptor γ Predominantly Expressed in Skin. *Nature* **1989**, *339*, 714−717.
(8) Rees, J. L.; Daly, A. K.; Redfern, C. P. F. Differential Expression Of The α and β Retinoic Acid Receptors In Tissues of The Rat. *Biochem. J.* **1989**, *259*, 917−919.
(9) Elder, J. T.; Fisher, G. J.; Zhang, Q.-Y.; Eisen, D.; Krust, A.; Kastner, P.; Chambon, P.; Voorhees, J. J. Retinoic acid Receptor Gene Expression in Human Skin. *J. Invest. Dermatol.* **1991**, *96*, 425−433.
(10) 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.
(11) Graupner, G.; Malle, G.; Maignan, J.; Lang, G.; Prunieras, M.; Pfahl, M. 6′-Substituted Naphthalene-2-carboxylic Acid Analogs, A New Class Of Retinoic Acid Receptor Subtype-specific Ligands. *Biochem. Biophys. Res. Commun.* **1991**, *179*, 1554−1561.
(12) Lehmann, J. M.; Dawson, M. I.; Hobbs, P. D.; Husmann, M.; Pfahl, M. Identification of Retinoids With Nuclear Receptor Subtype-selective Activities. *Cancer Res.* **1991**, *51*, 4804−4809.
(13) Lehmann, J. M.; Jong, L.; Fanjul, A.; Cameron, J. F.; Lu, X. P.; Dawson, M. I.; Pfahl, M. Retinoids Selective for Retinoid X Receptor Response Pathway. *Science* **1992**, *258*, 1944−1946.
(14) 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.* **1992**, *40*, 556−562.
(15) Reczek, P. R.; Ostrowski, J.; Yu, K.-L.; Chen, S.; Hammer, L.; Roalsvig, T.; Starrett, J. E.; Driscoll, J.; Whiting, G.; Spinazze, P.; Tramposch, K. M.; Mansuri, M. M. The role of retinoic acid receptor gamma and the Rhino mouse and rabbit irritation models of retinoid activity. *Skin Pharmacol.* **1995**, *8*, 1−4.
(16) Maignan, J.; les Gonesse, T.; Lang, G.; Gratien, S.; Malle, G.; sur Morin, V.; Restle, S.; Boise, A. S.; Shroot, B. Bicyclic Naphthalenic Derivatives, A Process for Preparing The Same and Human or Veterinary Medicines and Cosmetic Compositions Containing Said Derivatives. U.S. Patent 4,826,969, 1989.
(17) Berkowitz, D. B.; Danishefsky, S. J. Enzymatic Resolution of Racemic Glycals: An Application of the Wong Acylation Method. *Tetrahedron Lett.* **1991**, *32*, 5497−5500.
(18) Pirkle, W.; Sikkenga, D. L. The Use of Chiral Solvating Agents for Nuclear Magnetic Resonance Determination of Enantiomeric Purity and Absolute Configuration of Lactones. Consequences of Three-Point Interactions. *J. Org. Chem.* **1977**, *42*, 1370−1374.
(19) Gao, Q.; Yu, K.-L.; Mansuri, M.; Kerns, E.; Starrett, J. E. Structure of Methyl 6-[(4-Bromobenzoyloxy)-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-methyl]-2-naphthalene-2-carboxylate. *Acta Crystallogr. C* **1995**, *C51*, 1672−1675.
(20) Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T.; Matthews, D. P.; McCarthy, J. R. Difluoromethyldiphenylphosphine Oxide. A New Reagent for Conversion of Carbonyl Compounds to 1,1-Difluoroolefins. *Tetrahedron Lett.* **1990**, *31*, 5571−5574.
(21) Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. Palladium Catalysed Alkoxycarbonylation of Phenols to Benzoate Esters. *J. Chem. Soc., Chem. Commun.* **1987**, 904−905.

(22) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. Bis(tributyltin) Oxide. A Mild Neutral and Selective Reagent for Cleavage of Esters. Scope and Limitation of the Reaction. *Tetrahedron Lett.* **1991**, *32*, 4239−4242.
(23) Brand, N.; Petkovich, M.; Krust, A.; Chambon, P.; de The, H.; Marchio, A.; Tiollais, P.; Dejean, A. Identification of A Second Human Retinoic Acid Receptor. *Nature* **1988**, *332*, 850−853.
(24) Yang, N.; Schule, R.; Mangelsdorf, D. J.; Evans, R. M. Characterization of DNA Binding and Retinoic Acid Binding Properties of Retinoic Acid Receptor. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 3559−3663.
(25) Dokoh, S.; Pike, J. W.; Chandler, J. S.; Mancini, J. M.; Haussler, M. R. An Improved Radioreceptor Assay for 1,25-Dihydroxyvitamin D in Human Plasma. *Anal. Biochem.* **1981**, *116*, 211−222.
(26) Darmon, M.; Rocher, M.; Cavey, M.-T.; Martin, B.; Rabilloud, T.; Delescluse, C.; Shroot, B. Biological Activity of Retinoid Correlates With Affinity For Nuclear Receptors But Not For Cytosolic Binding Protein. *Skin Pharmacol.* **1988**, *1*, 161−175.
(27) Chen, S.; Ostrowski, J.; Whiting, G.; Roalsvig, T.; Hammer, L.; Currier, S. J.; Honeyman, J.; Kwasniewski, B.; Yu, K.-L.; Sterzycki, R.; Kim, C. U.; Starrett, J. E., Jr.; Mansuri, M. M.; Reczek, P. R. Retinoic Acid Receptor Gamma Mediates Efficacy And Irritation In Animal Models. *J. Invest. Dermatol.* **1995**, *104*, 779−783.
(28) Middleton, W. J. New Fluorinating Reagents. Dialkylaminosulfur Fluorides. *J. Org. Chem.* **1975**, *40*, 574−578.
(29) Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S. Preparation of Trifluoromethyl And Other Perfluoroalkyl Compounds With (Perfluoroalkyl)trimethylsilanes. *J. Org. Chem.* **1991**, *56*, 984−989.
(30) Shroot, B.; Eustache, J.; Bouclier, M. 2,6-Disubstituted Naphthalene Derivatives, A Process For Preparing The Same And Pharmaceutical And Cosmetic Compositions Containing The Same. U.S. Patent 4,581,380, 1986.
(31) Vasios, G. W.; Gold, J. D.; Petkovich, M.; Chambon, P.; Gudas, L. J. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 9099−9103.
(32) Sambrook, J.; Fritsch, E. F.; Maniatis, T. *Molecular Cloning: A Laboratory Mannual*; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, 1989.

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