Conformational Effects on Retinoid Receptor Selectivity. 2. Effects of Retinoid Bridging Group on Retinoid X Receptor Activity and Selectivity

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The natural retinoid 9-*cis*-retinoic acid is an activating ligand for both the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs), which are members of the retinoid/thyroid hormone/steroid hormone family of nuclear receptor proteins that activate gene transcription through specific response elements. The pharmacophoric groups necessary to confer RXR selectivity were established by evaluating the ability of 21 conformationally restricted retinoids to activate the TREpal retinoic acid receptor response element for gene transcription in the presence of one of the three RAR subtypes or RXRα. In contrast to those retinoids selective for the RARs, these RXR-selective retinoids have one less atom in the bridge linking the hydrophobic and carboxylic acid termini of the retinoid skeleton. Therefore, a one-carbon bridge replaces the 19-methyl group and 9*E*-double bond of 9-*cis*-retinoic acid and is further functionalized by inclusion in an isopropylidene group, a dioxolane ring, or a cyclopropane ring for optimal RXRα activity and selectivity. In addition, the β-geranylidene and 20-methyl-(11*E*,13*E*)-dienoic acid groups of 9-*cis*-retinoic acid are replaced by a 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl ring and a 4-carboxylphenyl ring, respectively, for optimal activation and selectivity. RXRα selectivity is reduced on replacement of the 4-carboxylphenyl group by a 2-carboxyl-5-thienyl group or the 9-*cis*-retinoic acid methylpentadienoic acid terminus.

Introduction

To exert their effects on cell differentiation and proliferation, the retinoid *all-trans*-retinoic acid (*trans*-RA, **2**) binds to the retinoic acid receptors (RARs) and its 9-*cis* isomer (9-*cis*-RA, 1) binds to both the RARs and the retinoid X receptors (RXRs). These two subclasses of retinoid receptors are members of the steroid/thyroid hormone family of nuclear receptors, and each class has three subtypes (α, β, and γ), of which there are several isoforms (reviewed in refs 1–6). The RARs and RXRs can regulate retinoid-dependent gene function by two major pathways: (1) binding to specific DNA sequences in the promoter regions of genes, which are called retinoid responsive elements, or (2) interacting with other regulatory proteins. In the first pathway, in which the RAR/RXR heterodimers or RXR homodimers interact directly with their response elements (RAREs or RXREs, respectively),[4,6,7] these receptors may impart either low constitutive or repressor activity to the response elements in the absence of retinoids. After binding retinoids, the receptors evidently undergo conformational changes that activate the response elements to induce gene transcription. The RXRs also form heterodimeric complexes with the thyroid hormone, vitamin D_3, peroxisome proliferator-activated, and several orphan receptors that activate other gene response elements. Therefore, the RXRs have a central role in the regulation of several hormone signals. In the second pathway, the RARs and RXRs affect the activity of the transcription factor AP-1 (Jun/Fos) complex by protein–protein interaction to regulate transcription from AP-1 sites in the promoter region of genes.[8–10] In the presence of retinoids, gene transcription from these sites is repressed or inhibited.

To probe the mechanism of retinoid receptor action so that the effects of retinoids on such cellular processes as differentiation and apoptosis are more clearly understood, and, subsequently, to identify retinoids having specific cancer chemoprotective and chemotherapeutic activities without concomitant unfavorable side effects, we[11–13] and other groups[14–18] have sought retinoid receptor class- and subtype-selective retinoids. These studies have led to the identification of RAR class-selective retinoids,[11,19] such as (*E*)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)propenyl]benzoic acid (TTNPB),[20] 6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)naphthalene-2-carboxylic acid (TTNN),[21] and 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)benzoic acid (TTAB).[22] Here, we report the syntheses and RXRα activation activity of a series of RXR-selective retinoids. Members of this subclass were previously identified[13] by their ability to induce the formation and activation of the RXRα/RXRα homodimer, which binds to and activates specific retinoid REs for gene transcription, including that for the cytoplasmic retinol-binding protein II (CRBPII–RXRE). This response element is activated by RXR homodimers but not by RAR/RAR homodimers or RXR/RAR heterodimers in the presence of 9-*cis*-RA. *trans*-RA has no effect. These compounds showed appreciably less ability to activate RXR/RAR heterodimers or RAR/RAR homodimers on the TRE-pal RARE.[13,23] Using transcriptional activation assays, we identify here the structural requirements for retinoids that allow their selective activation of the RXR homodimer response pathway. In the presence of 9-*cis*-RA, the TRE-pal RARE is activated

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by both RAR/RAR and RXR/RXR homodimers and RXR/RAR heterodimers.

Results

Chemistry. The RAR-selective retinoids TTNPB, TTNN, and TTAB are conformationally restricted analogs of *trans*-RA characterized by tetrahydrotetramethylnaphthalene and benzoic acid rings in place of the β-cyclogeranylidene and 3-methyl-(2*E*,4*E*)-pentadienoic acid groups, respectively, of *trans*-RA. These ring systems are linked by two-carbon spacers that replace the 19-methyl group and the 9*E*-double bond of *trans*-RA. The RXR-selective retinoids presented here differ from the RAR-selective retinoids in their bridging group, which is decreased by one carbon. This one-carbon spacer replaces the 19-methyl group and the 9*Z*-double bond of 9-*cis*-RA, decreases the distance between the two ring systems, and modifies their spatial orientation relative to the RAR-selective retinoids.

The syntheses of the majority of these RXR-selective retinoids can be most readily accomplished by straightforward methods involving modification of the one-carbon carbonyl unit of the known methyl ester (**26**)[24] of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalene)carbonyl]benzoic acid (SR11004, **3**) followed by ester hydrolysis, as shown in Scheme 1. Diaryl ketone **26** was readily prepared by Friedel–Crafts acylation of 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (**47**)[20] by 4-carbomethoxybenzoyl chloride.[25] Reductions were used to convert diaryl ketone **26** to the esters **28** and **29** of diarylmethanol SR11202 (**4**) and diarylmethane SR11224 (**6**), respectively. Wittig reactions were used to construct the esters of the 1,1-diarylethylenes SR11201 (**9**), SR11332 (**10**), SR11331 (11), and SR11217 (**12**), whereas ketalization and thioketalization methodologies were employed in generating the 1,3-diheterosubstituted 5- and 6-membered rings of SR11237 (**14**), SR11235 (**15**), SR11234 (**16**), SR11236 (**17**), and SR11203 (**18**). The ammonium salts of SR11237 (**14**) and SR11236 (**17**) were prepared for biological evaluation to ensure the stability of the ketal group during storage. Hydrogenation was used to transform the 1,1-diarylethylene SR11201 (**9**) to the 1,1-diarylethane SR11223 (**7**), whereas the Simmons–Smith cyclopropanation reaction on the ester (**30**) of SR11201 (**9**) produced the ester (**35**) of the 1,1-diarylcyclopropane SR11246 (**13**).

The diaryl ether SR11215 (**5**) and the diaryldimethylmethane SR11255 (**8**) were prepared by sequences that are also shown in Scheme 1. Friedel–Crafts cycloalkylation of phenol (**41**) with 2,5-dichloro-2,5-dimethylhexane afforded tetrahydrotetramethylnaphthalenol **42**, which underwent a copper-catalyzed arylation[26] with 4-bromobenzoic acid to afford the ester (**43**) of diaryl ether SR11215 (**5**), after esterification to facilitate purification. Friedel–Crafts alkylation of tetrahydrotetramethylnaphthalene **47** with the α,α-dimethylbenzyl bromide **46** introduced the aryl- and *gem*-dimethyl-substituted carbon of aryl bromide **48**, whose bromo group was then transformed in four steps to the carboxyl group of the diaryldimethylmethane SR11255 (**8**).

The observation that the 3,5,5,8,8-pentamethyltetrahydronaphthalene analog of TTNPB was more active than TTNPB itself in effecting the differentiation of HL-60 leukemia cells but not as active in differentiating F9 teratocarcinoma cells,[27] and the subsequent report that this analog also bound to and activated RXR,[16] indicated to us that addition of a similar methyl group to the above RXR-selective compounds might further enhance their RXR selectivity and activity. As shown in Scheme 1, the tetrahydropentamethylnaphthalenyl 4-carbomethoxyphenyl ketone **27**, which was prepared from **54** by the same route[24] used to produce **26**, was the precursor in the synthesis of the diaryl ketone SR11225 (**19**) and the diarylethylene SR11247 (**20**). Syntheses of SR11225 (**19**) and SR11247 (**20**) have been reported by Boehm *et al.*[18]

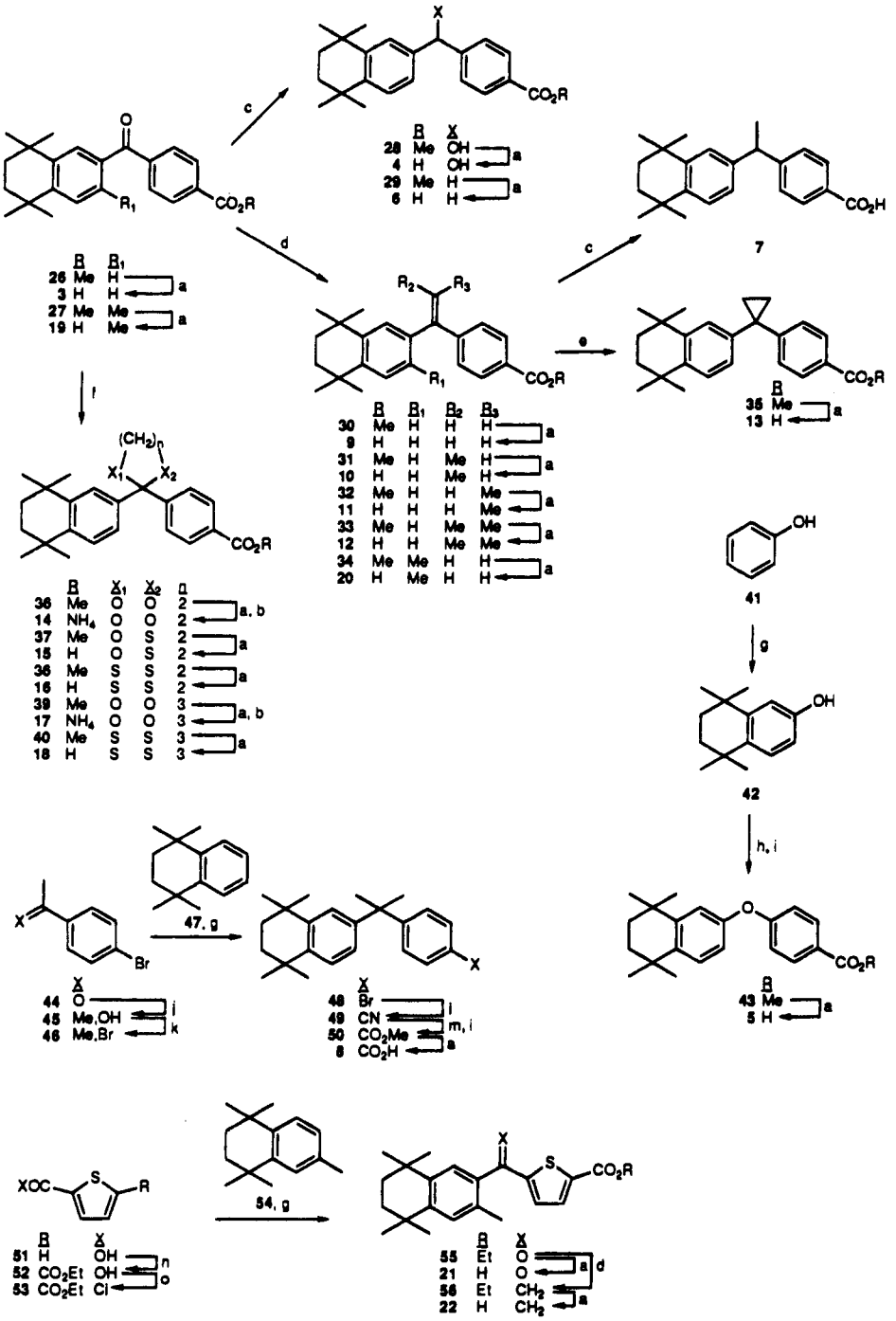
We had demonstrated previously that a thiophenecarboxylic acid group could be used in place of a benzoic acid group with retention of retinoid activity in the tracheal organ culture reversal of keratinization assay.[28] Therefore, the thiophenecarboxylic acids SR11245 (**21**) and SR11251 (**22**) were also synthesized.

To determine the effect on RXR activity of increasing the distance between the carboxyl and lipophilic termini, the benzoic acid ring was replaced by 3-methyl-(2*E*,4*E*)-pentadienoic acid groups in SR11269 (**23**), SR11268 (**24**), and SR11249 (**25**), which were prepared by the routes outlined in Scheme 2. The isopropylidene groups of SR11269 (**23**) and SR11268 (**24**) were introduced by a Pd(0)-catalyzed coupling of the tetrahydronaphthalene-2-boronic acids **58** and **60** with ethyl 2-bromo-3-methylbutenoate followed by conversion of the carbethoxy groups to the aldehyde groups of **64** and **67** and Horner–Emmons–Wadsworth olefination of the aldehyde groups with the anion of triethyl 3-methyl-4-phosphono-2-butenoate to produce ethyl dienoates **68** and **69**, respectively. Aldol condensation of aryl methyl ketone **61**, which was prepared by Friedel–Crafts acetylation of **54**, with ethyl (*E*)-3-formyl-2-butenoate, β-elimination of the hydroxyl group of the product **70**, ketalization, and ester hydrolysis afforded 2-(4-carboxy-3-methyl-(1*E*,3*E*)-butadienyl)-2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-1,3-dioxolane (SR11249, **25**).

Biological Activity. These compounds were evaluated for their ability to induce expression of the chloramphenicol acetyltransferase (CAT) reporter with the TRE-pal RARE after transfection of this synthetic construct along with either a RAR or RXRα expression vector into CV-1 cells. In this assay, the relative level of retinoid response depends on both the RARE (or RXRE) and the receptor transfected and the levels of endogenous retinoid receptors naturally present in CV-1 cells. We used the synthetic TRE-pal RARE because this response element can be activated by both RXR/RXR homodimers and RXR/RAR heterodimers. It has been previously established that RXR-selective retinoids activate this RARE.[18,23] The amount of CAT produced, as measured by the transfer of radiolabeled acetate, is proportional to the ability of a retinoid to interact with its receptor to activate gene transcription. Dose–response curves of the relative activities of 9-*cis*-RA and *trans*-RA in activating RXRα, RARα, RARβ, and RARγ are given in Figure 1, and those for retinoids **3**–**25** are shown in Figure 2.

For comparison of retinoid structure with biological activity, the retinoids were classified into groups depending on the modification of the bridge group: (1) polar and acyclic alkyl substituents (Figure 2a), (2) substituents that cause the bridging carbon to be sp^2-hybridized (Figure 2b), (3) heterocyclic modifications

Scheme 1. Syntheses of RXR-Selective Retinoids **3**–**22** Having a Terminal Benzoic or Thiophenecarboxylic Acid Group[a]

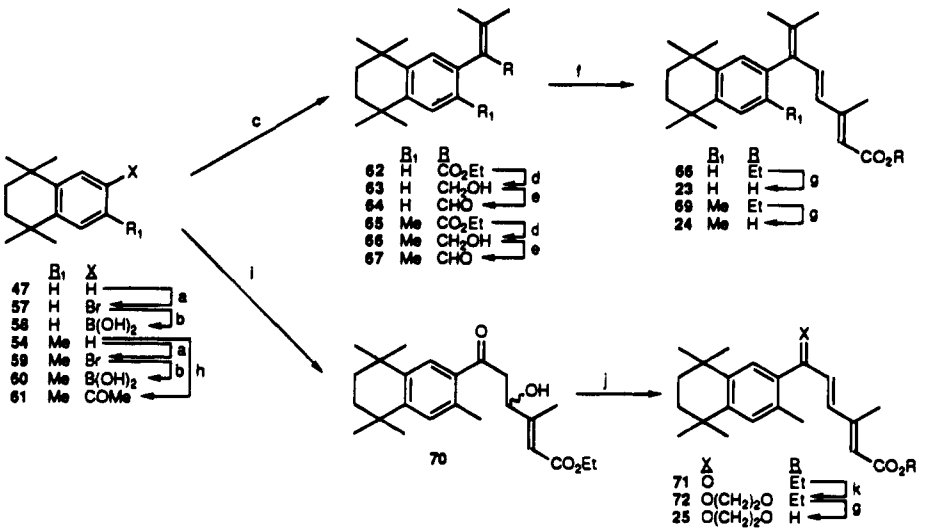


[a] (a) KOH (aq), MeOH, 60–70 °C; H_3O^+; (b) NH_3 (liq), CH_2Cl_2; (c) reduction (**26** to **28**) $NaBH_4$; (**3** to **29**) Zn, HOAc, HCl; K_2CO_3, MeI; (**9** to **7**) H_2, Pd(C), EtOH; (d) Wittig reaction (**26** to **30**, **27** to **34**, and **55** to **56**) [$MeP(C_6H_5)_3Br$, $KN(TMS)_2$, C_6H_5Me], C_6H_6; (**26** to **31** and **32**) [$EtP(C_6H_5)_3Br$, $KN(TMS)_2$, C_6H_5Me], THF; (**26** to **33**) [$Me_2CHP(C_6H_5)_3I$, $KN(TMS)_2$, C_6H_5Me], C_6H_6, reflux; (e) (**30** to **35**) Et_2Zn, CH_2I_2, C_6H_6, 60 °C; O_2; (f) ketalization and thioketalization (**26** to **36**) $(CH_2OTMS)_2$, $(CH_2OH)_2$, *p*-TsOH, C_6H_6, reflux; (**26** to **37**) $HO(CH_2)_2SH$, *p*-TsOH, C_6H_6, reflux; [**26** to **38** ($n = 2$) or **40** ($n = 3$)] $HS(CH_2)_nSH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (**26** to **39**) $HO(CH_2)_3OH$, *p*-TsOH, C_6H_6, reflux; (g) Friedel–Crafts (**41** to **42**) $ClMe_2C(CH_2)_2CMe_2Cl$, $AlCl_3$, $(CH_2Cl)_2$; (**46** to **48**) **47**, $AlCl_3$ $(CH_2Cl)_2$, 0 °C; (**53** to **55**) **54**, $(CH_2Cl)_2$, $AlCl_3$; (h) 4-$BrC_6H_4CO_2H$, Cu, KOH, 200 °C; (i) MeI, K_2CO_3, DMF; (j) MeMgBr, THF, C_6H_6, 0 °C; (k) $C_5H_5NHBr_3$, $HN(TMS)_2$, $CHCl_3$; (l) CuCN, NMP, 190–200 °C; (m) NaOH, $(CH_2OH)_2$, 180–185 °C; (n) LDA (2 equiv), THF, −78 °C; $ClCO_2Et$; (o) $(COCl)_2$, DMF (cat.), CH_2Cl_2.

(Figure 2c), and (4) examples of the first three groups having (a) a 3-methyltetrahydronaphthalene ring (Figure 2d), (b) a thiophenecarboxylic acid terminus (Figure 2d), or (c) a 3-methyl-(2*E*,4*E*)-pentadienoic acid terminus (Figure 2e). In Table 1 are presented the concentrations of retinoids required to obtain 50% of the maximal response (EC_{50} values) and the relative activation responses at 10^{-6} M for these retinoids. The retinoid responses were compared to those of 10^{-6} M 9-*cis*-RA for RXRα and 10^{-6} M *trans*-RA for the RARs, which were taken as 100% response values. EC_{50} values were used to compare the relative sensitivities of the receptor responses.

At concentrations as low as 10^{-8} M, none of the conformationally restricted retinoids was as active as 9-*cis*-RA in activating RXRα for inducing gene transcription with the TRE-pal RARE. However, at 10^{-7} M, **8**–**10**, **12**–**17**, **19**, **20**, and **23**–**25** showed retinoid X receptor activities comparable to at least 50% of that of 9-*cis*-RA. These compounds had far higher RXR selec-

Scheme 2. Syntheses of RXR-Selective Retinoids **23**–**25** Having a Terminal 3-Methyl-(2*E*,4*E*)-pentadienoic Acid Group[a]



[a] (a) Br_2, $CHCl_3$; (b) *n*-BuLi, THF; $B(OMe)_3$; H_3O^+; (c) (**58** to **62** and **60** to **65**) $EtO_2C(Br)C{=}CMe_2$, $Pd[P(C_6H_5)_3]_4$, Na_2CO_3 (aq), DME, EtOH; (d) DIBAL, CH_2Cl_2; MeOH; (e) $(C_5H_5N)_2CrO_3$, CH_2Cl_2; (f) $[(EtO)_2P(O)CH_2(Me)C{=}CHCO_2Et$, $KN(TMS)_2$, THF, −78 °C], −78 → 0 °C; (g) KOH (aq), EtOH, 60–70 °C; H_3O^+; (h) AcCl, $AlCl_3$, $(CH_2Cl)_2$; (i) (**61** to **70**) LDA, THF, −78 °C, (*E*)-OHC(Me)C=CHCO$_2$Et; (j) MsCl, Et_3N, CH_2Cl_2, 0 °C; (k) $(CH_2OH)_2$, $(CH_2OTMS)_2$, *p*-TsOH, C_6H_6, reflux.

tivity with the TRE-pal RARE promoter element than did 9-*cis*-RA. The lack of selectivity was most evident with RARβ in the presence of **7**, **9**–**11**, **14**, and the retinoids having thiophenecarboxylic and 3-methyl-(2*E*,4*E*)-pentadienoic acid termini. For example, although the 1,1-diarylethane SR11223 (**7**) demonstrated higher RXRα activity at 10^{-6} M than 9-*cis*-RA did, it also activated RARβ to 41% of the level obtained with 9-*cis*-RA, and there was no activation of either RARα or RARγ. The 1,1-diarylethylene SR11201 (**9**) also showed high RXRα activation but also activated RARβ by 35% at 10^{-6} M. The RXR selectivity we found for SR11201 (**9**) was lower than that previously reported by Boehm *et al.*,[18] who also reported higher RXR selectivities for SR11004 (**3**), SR11225 (**19**), and SR11247 (**20**). The differences in selectivities (demonstrated by a comparison of the EC_{50} values) may be caused by differences in the promoter constructs used in the bioassays by the two groups. Our efforts in improving selectivity focused on modifying the substituents on the one-carbon spacer and resulted in the 1,1-diaryl-2,2-dimethylethylene SR11217 (**12**). The RXRα selectivity of SR11217 (**12**) was enhanced by the increase in lipophilic volume caused by the two methyl groups on the double bond. One of the most active and RXR-selective retinoids in this series was found to be the 1,1-diarylcyclopropane SR11246 (**13**). Although its activity was only 6% of that of 9-*cis*-RA at 10^{-8} M, at 10^{-7} M its relative activity increased to 72%. The ketal SR11237 (**14**) also proved to be very active. Its RXRα activity was 99% of that of 9-*cis*-RA at 10^{-7} M, and the only RAR activated was RARβ.

The following parameters appear to be required for enhanced RXR activity: (1) reduced polarity on the one-carbon spacer (*e.g.*, C=CH$_2$ > C=O), (2) lipophilic bulk on the spacer (*e.g.*, C=CMe$_2$ > C=CH$_2$), (3) addition of a 3-methyl group on the tetrahydronaphthalene ring, and (4) use of a benzoic acid or dienoic acid terminus. RXR selectivity was enhanced by (1) increasing the lipophilic volume in the region of the one-carbon spacer and (2) using a benzoic acid terminus. The number of 3-methyltetrahydronaphthalene analogs we evaluated was too small to determine the overall effect of the 3-methyl substitutent on receptor selectivity in this series of analogs, although comparison of SR11201 (**9**) and SR11269 (**23**) with SR11247 (**20**) and SR11268 (**24**), respectively, indicated that the trend was to enhance selectivity.

Computational Studies. Conformational analyses were conducted on these retinoids as described in the Experimental Methods section. Low-energy conformations of these retinoids were obtained and compared. On correlation of these results with the retinoid receptor transcriptional activation profiles, we found that activity and selectivity were strongly dependent on the distances between the carbons corresponding to the C4 and C15 carbons in 9-*cis*-RA. Activity was also dependent on the geometry of the retinoid skeleton between these two points in that the backbone of those compounds having RXR selectivity assumed a bent conformation, whereas the backbone of those having RAR selectivity was more linear.

Discussion

The flexibility of their tetraene side chains permits 9-*cis*-RA and *trans*-RA to assume many different conformations. Our first goal was to identify those conformations most similar to the low-energy conformation of TTAB, which is one of the most potent retinoids for inducing gene transcription with the RARs but not with RXRα. Moreover, TTAB is an excellent candidate for structural comparison purposes because it's bonds corresponding to the double bonds of the tetraene side chains are locked by inclusion in aromatic rings so that only the bond corresponding to the C10–C11 bond of *trans*-RA is capable of rotation. Conformational analysis produced two energetically equivalent low-energy conformers for *trans*-RA that differed only in their geometry about the 11*E*,13*E*-double bond system, with conformer **2A** being s-transoid and conformer **2B** being s-cisoid. The C1–C15 distances were 12.3 and 11.6 Å, respectively, whereas the corresponding distance between C8 of the tetrahydroanthracene ring and the carboxyl carbon in a low-energy conformer of TTAB was 11.4 Å. Overlapping conformers **2A**,**B** of *trans*-RA with that of TTAB indicated that conformer **2B** of *trans*-RA

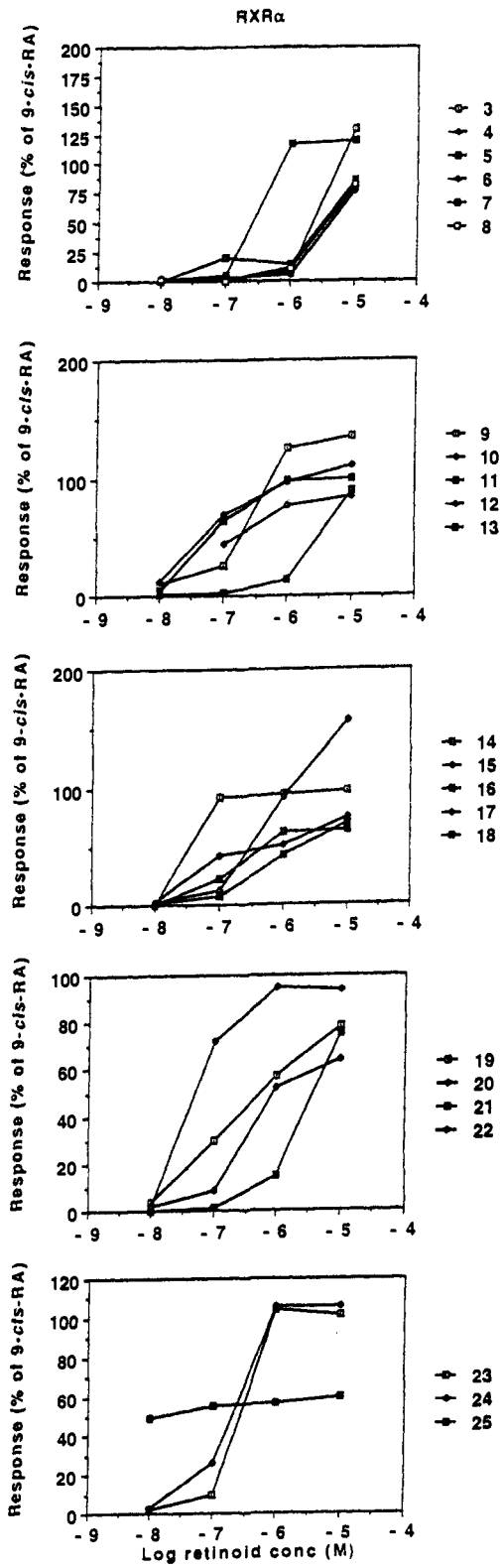


Figure 1. Dose–response curves for 9-*cis*-RA and *trans*-RA for activating RXRα, RARα, RARβ, and RARγ on the construct TRE-pal-*tk*-CAT relative to 100% response at 10^{-6} M 9-*cis*-RA for RXRα and 10^{-6} M *trans*-RA for RARα.

was the closer match to TTAB because of its lower interatomic distances (Figure 3A). Therefore, conformer **2B** was selected for use in overlap studies with the other retinoids as the more appropriate conformer to represent the general *trans*-RA conformation taken in the activation of the RARs.

The low-energy conformer of 9-*cis*-RA that was to be used for overlap studies was identified in a similar manner by comparison to the low-energy conformers of the RAR-selective retinoid TTAB and the RXR-selective retinoids 1,1-diaryl-2,2-dimethylethylene SR11217 (**12**) and dioxolane SR11237 (**14**) because 9-*cis*-RA binds to and activates both RXRα and the RARs.[29] The s-transoid 11*E*,13*E*-double bond conformer (**1A**) and the s-cisoid conformer (**1B**) of 9-*cis*-RA were energetically equivalent and had C1–C15 distances of 10.7 and 8.9 Å and C4–C15 distances of 9.6 and 7.7 Å, respectively. Only conformer **1A** provided a suitable overlap with the low-energy conformers of the RXR-selective retinoids SR11217 (**12**) and SR11237 (**14**) (Figure 3B).[12] These two conformers have C5–CO_2H distances of 9.9 and 9.8 Å, respectively, which are 2.7 Å shorter than the C4–C15 distance of conformer **2B** of *trans*-RA. Their shorter intramolecular distances indicate why SR11217 (**12**) and SR11237 (**14**) interact poorly with the RARs. Therefore, conformer **1A** was selected to represent the RXRα-selective conformation of 9-*cis*-RA necessary for activation of RXRα. Conformer **1A** also overlapped with conformer **2B** of *trans*-RA and the low-energy conformer of TTAB when **1A** was flipped so that C1 and C4 of **1A** were superimposed on C4 and C1 of **2B** and on C5 and C8 of TTAB. These overlapped conformers, which are shown in Figure 3C, illustrate why 9-*cis*-RA can also bind to and activate the RARs. In contrast, conformer **1B** of 9-*cis*-RA overlapped poorly with the low-energy conformers of SR11217 (**12**), SR11237 (**14**), and TTAB.[12] Therefore, to fit in the binding pockets of both RXRα and the RARs, 9-*cis*-RA assumes conformation **1A**.

Computational analysis indicated that optimal activation of the RXRα occurred with those retinoids having a distance of 9.5–10.5 Å between the C5 of the tetrahydronaphthalene ring and the carboxylic acid carbon in their active conformers. This intramolecular distance was not the sole determinant for receptor subclass selectivity. For example, although the C5–CO_2H distance in both the diaryl ether SR11215 (**5**) and the oxathiolane SR11235 (**15**) was 9.6 Å, the latter was 34-fold more active than the former. The angle defined by C2 of the tetrahydronaphthalene ring, the carbon bridge, and the C4 of the benzoic acid ring was considered as another factor that might affect RXR selectivity. However, our studies indicated that in the most active RXRα-selective retinoids the size of this angle ranged from 108° to 120°, but the difference between these angles was only 1° (115° and 116°, repectively) in the potent RXRα-selective SR11217 (**12**) and the much less active SR11215 (**5**), which had 3% of the activity for RXRα shown by SR11217 and low selectivity. Therefore, the structural elements that confer RXR selectivity and biological activity to these compounds are not solely dependent on the distance between the lipophilic and carboxyl termini and the angle between the two ring systems. Our studies indicate that substituents in the central region of the molecule are also involved. Sufficient lipophilic steric volume on the central atom joining the two ring systems is important for both receptor selectivity and activation potency. As shown in Figure 4, the groups on the one-carbon bridges of the most active RXRα-selective retinoids in this series—SR11217 (**12**), SR11246 (**13**), and SR11237 (**14**)—provide lipophilic volume that substitutes for the 19-methyl group and 9-double bond of 9-*cis*-RA (Figure 4). Overlap studies indicated that the interatomic distances between the low-energy conformer of SR11237 (**14**) and conformer **1A** of 9-*cis*-RA were shorter than those between

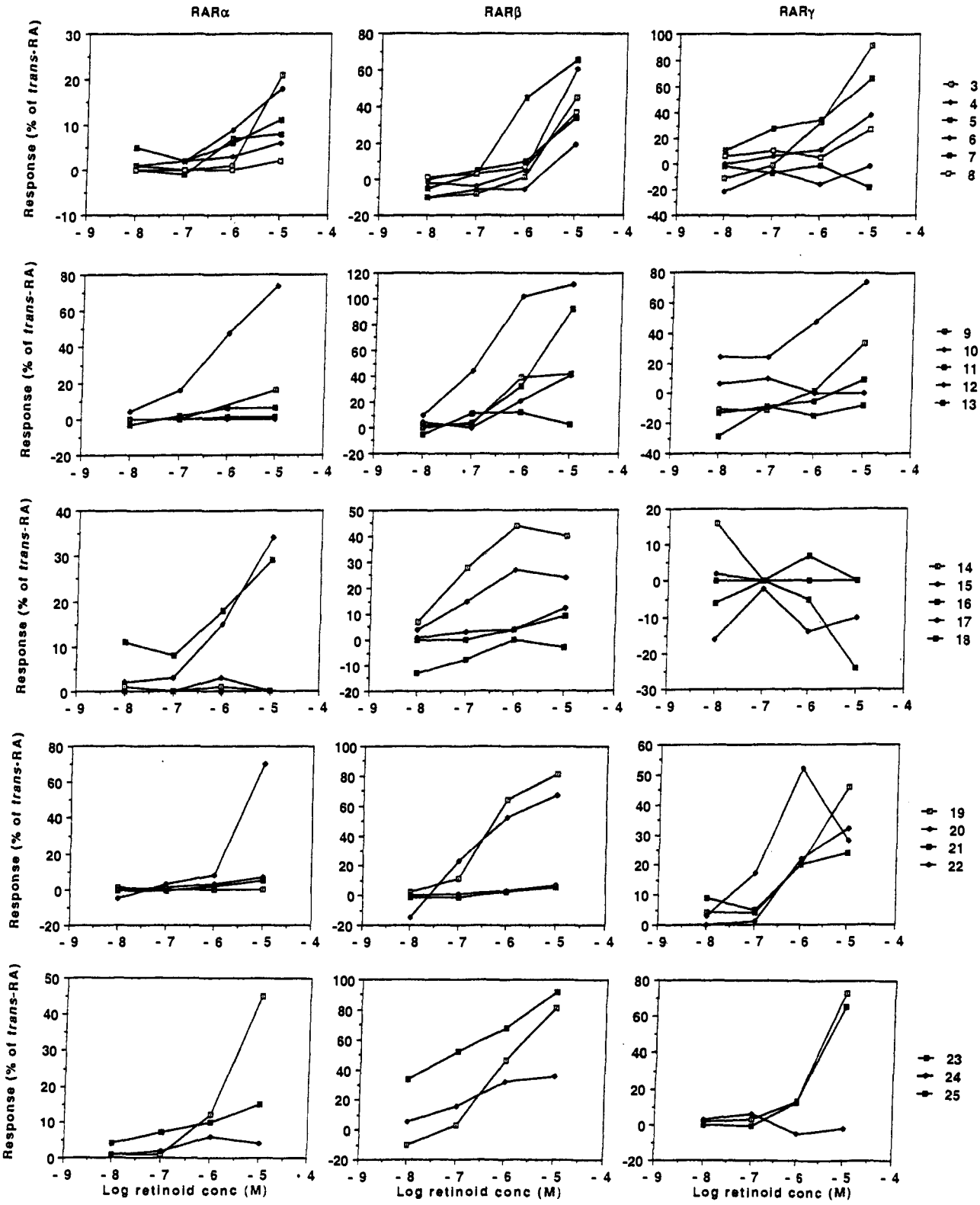


Figure 2. Dose–response curves for retinoids **3**–**25** for activating RXRα, RARα, RARβ, and RARγ on TRE-pal-*tk*-CAT relative to 100% response at 10^{-6} M 9-*cis*-RA for RXRα and 10^{-6} M *trans*-RA for RARα.

the low-energy conformers of the other two retinoids and **1A**, which may partially explain the lower EC_{50} value of the former, although the more polar substituents on its bridging carbon may also be involved.

We extended these studies to determine the effect on RXRα activation activity of varying the distance between the lipophilic terminus and the carboxyl group. Replacement of the phenyl ring of **20** by the thiophene ring of **22** decreased the distance and also decreased RXRα activity. Replacement of the phenyl ring of SR11217 (**12**) by a *E,E*-diene increased this distance in SR11269 (**23**) and SR11268 (**24**) but decreased receptor subclass selectivity because RAR activation was increased also. An explanation for the decrease in RXR receptor class selectivity in this case may be that both SR11269 (**23**) and SR11268 (**24**) have two energetically similar low-energy conformers, which are within 2 kcal/mol of the low-energy minimum and are conformationally similar to the low-energy conformers **1A** and **2B**. For example, the C5–CO_2H distance in the low-energy

Table 1. Retinoid Receptor Relative Transcriptional Activation Activities and EC_{50} Values for 9-*cis*-Retinoic Acid, *trans*-Retinoic Acid, and 23 Retinoids

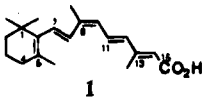
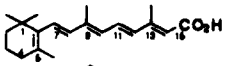
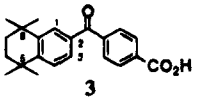
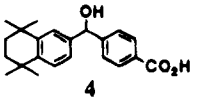
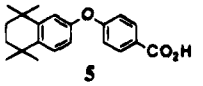
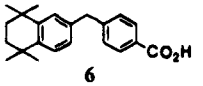
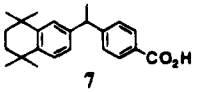
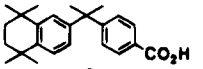
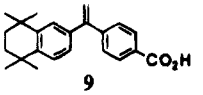
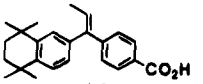
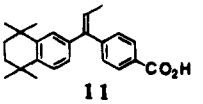
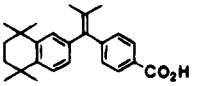
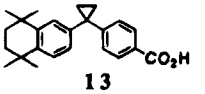
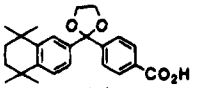
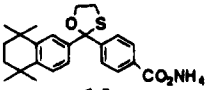
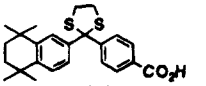
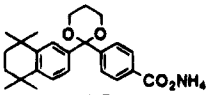
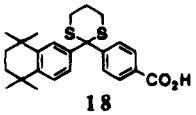
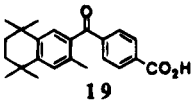
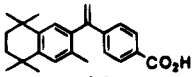
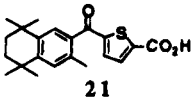
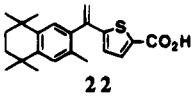
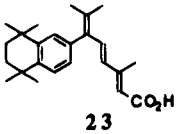
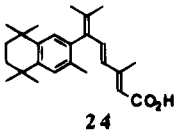
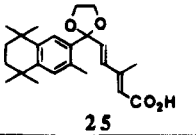
Retinoid	Code Number or Name	RXRα		RARα		RARβ		RARγ	
		Rel. Act.[a] (%)	EC_{50}[b] (nM)	Rel. Act.[c] (%)	EC_{50}[b] (nM)	Rel. Act.[c] (%)	EC_{50}[b] (nM)	Rel. Act.[c] (%)	EC_{50}[b] (nM)
 1	9-*cis*-RA[d]	100	6	100	23	100	2.6	100	4.3
 2	*trans*-RA	53	530	82	54	78	4.5	73	2.0
 3	SR11004	7	3000	1	4500	1	3200	33	1700
 4	SR11202	5	2900	3	—[e]	-6	—	-16	—
 5	SR11215	14	2500	7	—	10	1900	35	530
 6	SR11224	11	2500	9	—	5	2700	11	2000
 7	SR11223	117	300	6	—	45	500	-1	—
 8	SR11255	10	3100	0	—	7	2200	5	2300
 9	SR11201	125	270	3	2300	39	320	2	3000
 10	SR11332	97	55	48	470	102	160	48	370
 11	SR11331	14	2500	1	—	32	1600	-15	—
 12	SR11217	77	86	0	—	21	980	0	—
 13	SR11246	98	55	6	—	12	—	9	—
 14	SR11237	95	34	1	—	44	55	0	—
 15	SR11235	51	74	3	—	27	180	0	—
 16	SR11234	62	170	0	—	4	—	7	—
 17	SR11236	92	750	15	1200	4	—	-14	—

Table 1 (Continued)

Retinoid	Code Number or Name	RXRα Rel. Act.[a] (%)	RXRα EC_{50}[b] (nM)	RARα Rel. Act.[c] (%)	RARα EC_{50}[b] (nM)	RARβ Rel. Act.[c] (%)	RARβ EC_{50}[b] (nM)	RARγ Rel. Act.[c] (%)	RARγ EC_{50}[b] (nM)
 **18**	SR11203	42	630	18	540	0	—	-5	—
 **19**	SR11225	57	210	0	—	64	360	20	1200
 **20**	SR11247	95	42	17	—	67	112	9	122
 **21**	SR11245	15	2200	2	—	26	1000	20	300
 **22**	SR11251	52	330	3	—	74	33	22	520
 **23**	SR11269	104	380	12	2500	46	850	13	650
 **24**	SR11268	106	200	6	—	32	140	-5	—
 **25**	SR11249	57	21	10	—	68	47	12	2300

[a] Activity at 10^{-6} M retinoid relative to 10^{-6} M 9-*cis*-RA (100%). [b] Retinoid concentration giving half-maximal activity or activity at 10^{-6} M, whichever is greater. [c] Activity at 10^{-6} M retinoid relative to 10^{-6} M *trans*-RA (100%). [d] Activity compared at 10^{-6} M 9-*cis*-RA for RARα (100%) is 95% for RXRα, 110% for RARβ, and 120% for RARγ. [e] Activity at 10^{-5} M retinoid below 20% of that of 9-*cis*-RA or *trans*-RA positive control.

conformer (**23A**) of SR11269 (**23**), which has s-cisoid geometry about the dienoic acid terminus, is 9.6 Å, whereas in the s-transoid conformer **23B** this distance is increased to 11.2 Å. Conformer **23A** overlapped as closely to conformer **1A** of 9-*cis*-RA (Figure 5A) as did the low-energy conformer of SR11217 (**12**). The C5–CO_2H distances of both **23A** and SR11217 (**12**) were very similar (≤0.2 Å) to that of conformer **1A**, but the diene side chain of SR11269 was sterically smaller than the phenyl ring of SR11217 (**12**), which may account for the higher RXRα activation activity of SR11269 at 10^{-6} M. Unfortunately, its enhanced potency was accompanied by a loss of selectivity, with RARβ moderately activated and RARα and RARγ slightly activated at concentrations ≥ 10^{-6} M. The s-transoid conformer **23B** was readily superimposed onto the low-energy conformer **2B** of *trans*-RA (Figure 5B), thereby accounting for the decreased receptor selectivity found when the phenyl ring of SR11217 (**12**) was replaced by the *E,E*-diene of SR11269 (**23**).

The effects on receptor activation potency and selectivity caused by introduction of a methyl group on the tetrahydronaphthalene ring adjacent to the one-atom spacer were explored by modeling, which indicated that this group should have negligible effects on the geometry of the low-energy conformer as compared to conformer **1A** of 9-*cis*-RA. This conclusion was supported by the biological results, which showed that the maximal relative activities at 10^{-6} M for SR11201 (**9**) and SR11269 (**23**) were 125% and 104%, respectively, whereas those for their tetrahydropentamethylnaphthalene analogs SR11247 (**20**) and SR11268 (**24**) were 95% and 106%, respectively; however, incorporating this methyl group decreased the EC_{50} values for receptor activation and increased receptor selectivity. SR11268 (**24**) was far more RXR-selective than SR11269 (**23**) but not as selective as SR11217 (**12**) because RARβ was activated more. The methyl group did not overly affect the geometry of the dienoic acid side chain or its position relative to that of the tetrahydronaphthalene ring system in the low-energy conformers (**24A,B**) of SR11268 (**24**) as compared to the respective conformers (**23A,B**) of SR11269 (**23**) (Figure 5), an observation suggesting that the major effect of this methyl substituent was steric interference with the groups in the RAR binding pocket. In addition, they should be more suitable for

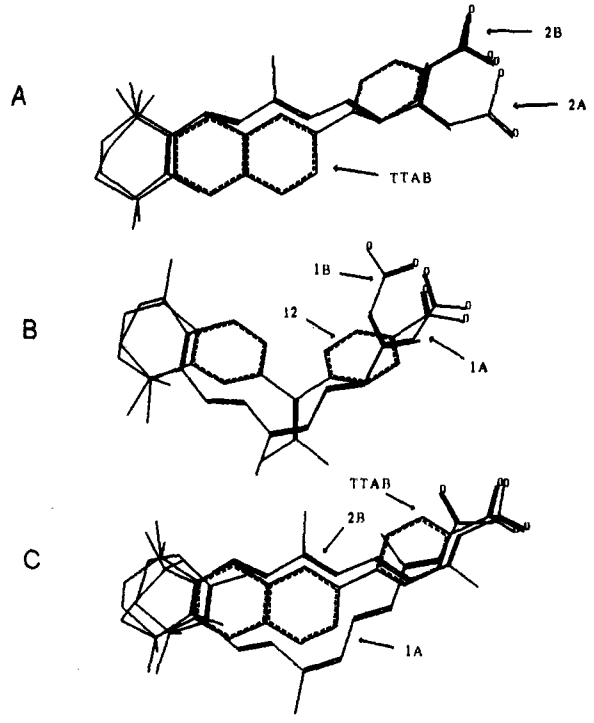


Figure 3. Overlapped low-energy conformers: (A) **2A,B** of *trans*-RA and that of TTAB, (B) **1A,B** of 9-*cis*-RA and that of SR11217 (**12**), and (C) **1A** of 9-*cis*-RA, **2B** of *trans*-RA, and that of TTAB.

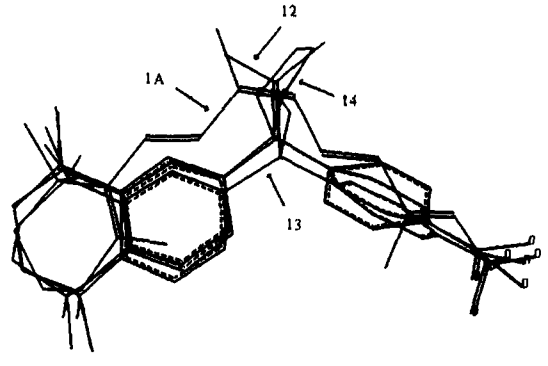


Figure 4. Overlapped low-energy conformers: **1A** of 9-*cis*-RA and those of SR11217 (**12**), SR11246 (**13**), and SR11237 (**14**).

therapeutic use because their targeted activity reduces the potential for side effects.

The strategy of incorporating an *o*-methyl group was not as effective in the case of the dioxolane analog SR11249 (**25**), which showed poorer activation of and lower selectivity for RXRα. Retinoid SR11249 (**25**) demonstrated moderate activation of RARβ and low activation of RARα and RARγ. Conformational analysis indicated three low-energy conformers (**25A–C**) for SR11249 (**25**). Steric hindrance between the hydrogens on the 3-methyl group and the 1-hydrogen on the aromatic ring and the hydrogens on the dioxolane ring favored the low-energy s-cisoid conformer **25A** and s-transoid conformer **25B**, in which the aromatic ring systems were essentially orthogonal to those of the low-energy conformer of SR11237 (**14**) and the RAR- and RXR-selective conformer **1A** of 9-*cis*-RA (Figure 6), an indication that conformers **25A,B** would not easily fit in the RXR or RAR binding pocket. Conformer **25C**, which has its aromatic ring system in an orientation similar and planar to that of SR11237 (**14**) and a s-cisoid dienoic acid group, was 1.9 kcal/mol higher in energy

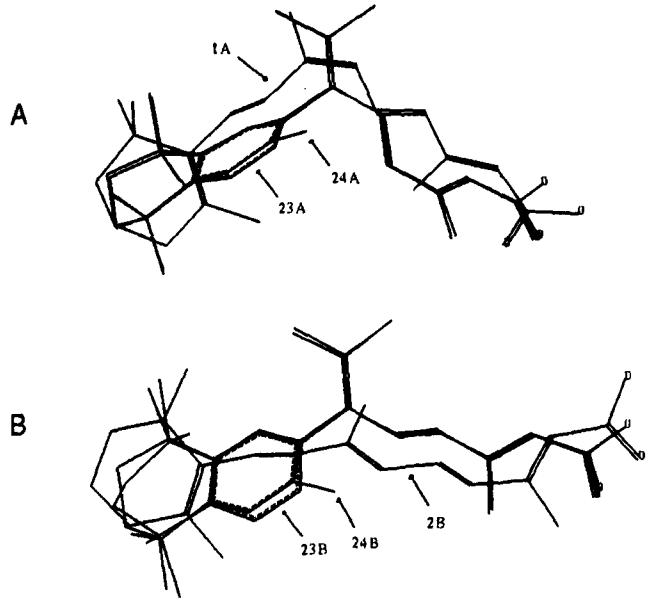


Figure 5. Overlapped low-energy conformers: (A) **1A** of 9-*cis*-RA, **23A** of SR11269 (**23**), and **24A** of SR11268 (**24**) and (B) **2B** of *trans*-RA, **23B** of SR11269 (**23**), and **24B** of SR11268 (**24**).

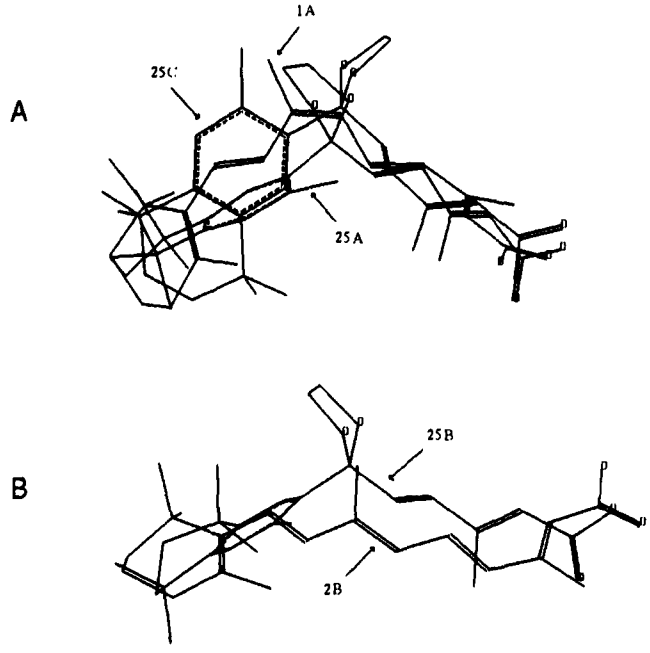


Figure 6. Overlapped low-energy conformers: (A) **25A,C** of SR11249 (**25**) and **1A** of 9-*cis*-RA and (B) **25B** of SR11249 (**25**) and **2B** of *trans*-RA.

than **25A** and 2.2 Å shorter in its C5–CO_2H distance than conformer **1A** of 9-*cis*-RA, features indicating that it is unfavored for interaction with RXRα. The energetic equivalance of conformers **25A,B** indicates that SR11249 (**25**) could readily adopt either conformation and therefore bind to both RXRα and the RARs but not with as high affinity because of the different geometry about the aromatic rings.

These studies demonstrate that replacing the 9*Z*-double bond of 9-*cis*-RA by suitably functionalized one-carbon spacers produced RXR-selective retinoids. RXR selectivity was enhanced by introducing suitable functional groups on this spacer and replacing the 20-methyl-(11*E*,13*E*)-dienyl group of 9-*cis*-RA by a phenyl ring. Retinoid receptor class-selective compounds should be useful probes of the mechanism of retinoid action.

Experimental Methods

Synthetic Methods. When required, reactions were conducted with deoxygenated solvents under inert gas (Ar). Solvents were dried or distilled before use. Merck silica gel 60 was used for preparative chromatography. Melting points are uncorrected. TLC analyses were performed on Analtech analytical silica gel plates. IR spectra were recorded with a Perkin-Elmer 1600 FTIR spectrophotometer. NMR spectra were run on a Gemini 300 or XL 400 Varian spectrometer with chemical shifts expressed in ppm relative to tetramethylsilane. High-resolution mass spectral analyses were conducted at the University of Minnesota (Minneapolis, MN), and elemental analyses were carried out by Atlantic Microlab, Inc. (Norcross, GA).

General Procedures. Presented below are the general methods used for the syntheses of retinoids 3–**25**. Specific methods follow in numerical order.

(a) Ester Hydrolysis. To a suspension of the ester (0.199 mmol) in 75% aqueous MeOH (3 mL) was added 1 pellet of KOH (0.11 g), and the mixture was stirred at 70 °C for 1 h during which time the compound dissolved. The solution was cooled to room temperature, acidified with 1 N HCl, and extracted (80% EtOAc/hexane). The combined organic layers were dried ($MgSO_4$) and concentrated to afford a solid.

(b) Friedel–Crafts Acylation. To a suspension of $AlCl_3$ (8.5 mmol) in $Cl(CH_2)_2Cl$ (1.5 mL) at 0 °C under Ar was added a solution of 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (7.7 mmol) and the appropriate 4-substituted benzoyl chloride (7.9 mmol) in $Cl(CH_2)_2Cl$ (6 mL). The resulting solution was brought to room temperature and stirred for 16 h. The reaction mixture was poured into ice water and extracted (40% EtOAc/hexane). The combined organic layers were washed (saturated $NaHCO_3$ and brine), dried ($MgSO_4$), and concentrated to afford a solid.

(c) Horner–Emmons Olefination. To a solution of $(EtO)_2P(O)CH_2C(CH_3)=CHCO_2Et$ (6.07 mmol) in THF (15 mL) under Ar was added 0.5 M $KN(TMS)_2$ (6.07 mmol) in toluene (12 mL), and stirring was continued for 10 min at −78 °C. Next, a solution of the aldehyde (6.00 mmol) in THF (4 mL) was added, and the reaction mixture was stirred at 0 °C for 30 min. The orange solution was diluted (20% EtOAc/hexane), filtered (silica gel), and concentrated to afford a solid.

(d) Ketalization. To a solution of keto ester (0.228 mmol) in C_6H_6 (1 mL) were added the diol or mercaptoethanol and *p*-TsOH·H_2O (catalytic amt). The reaction mixture was heated at reflux for 4 h and then cooled to room temperature. The solution was poured into saturated aqueous $NaHCO_3$ and extracted (40% EtOAc/hexane). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford a solid.

(e) Palladium(0)-Catalyzed Biaryl Coupling. A mixture of aryl bromide (0.443 mmol) in anhydrous DME (3 mL) and $Pd[P(C_6H_5)_3]_4$ (0.044 mmol) was stirred for 15 min under Ar. A solution of arylboronic acid (0.526 mmol) in EtOH (0.3 mL) was added to the yellow solution followed by 2 M aqueous Na_2CO_3 (1.10 mmol). The reaction mixture was heated at reflux to completion (1–3 h), and the reaction was quenched by pouring into brine. The aqueous layer was extracted twice (40% EtOAc/hexane). The extract was dried ($MgSO_4$) and concentrated to afford a solid.

(f) Thioketalization. To a solution of the keto ester (0.228 mmol) in CH_2Cl_2 (2 mL) at 0 °C under Ar was added a solution of the dithiol (0.27 mmol) in CH_2Cl_2 (0.5 mL) followed by BF_3·Et_2O (0.3 mmol). The resulting mixture was stirred at 0 °C for 1 h and then warmed to room temperature overnight. The reaction was quenched by pouring the mixture into saturated Na_2CO_3, and the mixture was extracted (CH_2Cl_2). The combined organic layers were dried ($MgSO_4$) and concentrated to afford a solid. Flash chromatography (50% CH_2Cl_2/hexane) yielded a white solid.

(g) Wittig Olefination. To a suspension of alkyltriphenylphosphonium halide (2.18 mmol) in C_6H_6 (5 mL) under Ar at room temperature was added 0.5 M potassium bis(trimethylsilyl)amide (2.2 mmol) in toluene (4.4 mL). The yellow solution of the ylide was stirred for 5 min before a solution of the keto ester (1.455 mmol) in C_6H_6 (7 mL) was added. The orange solution was stirred for 1 h at room temperature, diluted (20% EtOAc/hexane), filtered (silica gel), and concentrated to afford a solid.

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbonyl]benzoic Acid (3). Ester **26** (0.59 g, 1.68 mmol) was hydrolyzed at 70 °C for 1 h using the general procedure. Crystallization (Et_2O/hexane) afforded **3** as a white crystalline solid (0.435 g, 77%): mp 188–190 °C; IR (KBr) 3600–2500, 1697, 1659, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 6, $C(CH_3)_2$), 1.33 (s, 6, $C(CH_3)_2$), 1.73 (s, 4, CH_2CH_2), 7.42 (d, J = 8 Hz, 1, ArH), 7.55 (dd, J = 2, 8 Hz, 1, ArH), 7.81 (d, J = 2 Hz, 1, ArH), 7.87 (d, J = 8.0 Hz, 2, ArH), 8.22 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{22}H_{24}O_3$) C, H.

4-[Hydroxy(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methyl]benzoic Acid (4). Ester **28** (0.106 g, 0.30 mmol) was hydrolyzed using the general procedure. Crystallization (C_6H_6/hexane) afforded **4** as a white crystalline powder (0.099 g, 97%): mp 183–184 °C; IR (KBr) 3600–2400, 1694, 1281 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 6, $C(CH_3)_2$), 1.27 (s, 6, $C(CH_3)_2$), 1.68 (s, 4, CH_2CH_2), 5.86 (s, 1, Ar_2CH), 7.08 (dd, J = 2.0, 8.0 Hz, 1, ArH), 7.27 (d, J = 8.0 Hz, 1, ArH), 7.32 (d, J = 2.0 Hz, 1, ArH), 7.53 (d, J = 8.0 Hz, 2, ArH), 8.08 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{22}H_{26}O_3$) C, H.

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)oxy]benzoic Acid (5). Ester **43** (58 mg, 0.17 mmol) was hydrolyzed using the general procedure to provide a white solid (0.059 g). Crystallization (C_6H_6/hexane) afforded **5** as a white crystalline solid (0.049 g, 89%): mp 243–245 °C; IR (KBr) 3600–2500, 1686, 1292, 1245, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6, $C(CH_3)_2$), 1.30 (s, 6, $C(CH_3)_2$), 1.70 (s, 4, CH_2CH_2), 6.83 (dd, J = 2.0, 8.0 Hz, 1, ArH), 7.00 (d, J = 8.0 Hz, 2, ArH), 7.01 (d, J = 2.0 Hz, 1, ArH), 7.31 (d, J = 8.0 Hz, 1, ArH), 8.05 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{21}H_{24}O_3$) C, H.

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methyl]benzoic Acid (6). Ester **29** (28 mg, 0.083 mmol) was hydrolyzed using the general procedure. Crystallization (C_6H_6/hexane) afforded **6** as a white crystalline solid (0.019 g, 71%): mp 186–188 °C; IR (KBr) 3600–2500, 1686, 1284 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 6, $C(CH_3)_2$), 1.26 (s, 6, $C(CH_3)_2$), 1.67 (s, 4, CH_2CH_2), 4.00 (s, 2, Ar_2CH_2), 6.90 (dd, J = 2.0, 8.0 Hz, 1, ArH), 7.11 (d, J = 2.0 Hz, 1, ArH), 7.22 (d, J = 8.0 Hz, 1, ArH), 7.30 (d, J = 8.0 Hz, 2, ArH), 8.01 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{22}H_{26}O_2$) C, H.

4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)ethyl]benzoic Acid (7). 1,1-Diarylethene **9** (0.011 g, 0.031 mmol) was hydrogenated over 5% Pd(C) (1 mg) in EtOH (0.5 mL). After 1 equiv of H_2 was taken up (0.7 mL), the catalyst was removed by filtration (Celite), and the solvent was removed at reduced pressure to give the crude acid as a white solid (0.019 g). Crystallization (C_6H_6/hexane) afforded **7** as a white crystalline solid (0.008 g, 74%): mp 186–188 °C; IR (KBr) 3600–2500, 1688, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3, CH_3), 1.24 (s, 3, CH_3), 1.25 (s, 6, $C(CH_3)_2$), 1.64 (d, J = 7.0 Hz, 3, Ar_2CHCH_3), 1.66 (s, 4, CH_2CH_2), 4.15 (q, 1, J = 7.0 Hz, Ar_2CHCH_3), 6.93 (dd, J = 2.0, 8.0 Hz, 1, ArH), 7.13 (d, J = 2.0 Hz, 1, ArH), 7.20 (d, J = 8.0 Hz, 1, ArH), 7.32 (d, J = 8.0 Hz, 2, ArH), 8.01 (d, J = 8.0 Hz, 2, ArH); HRMS for $C_{23}H_{28}O_2$ (M^+) calcd 336.2089, found 336.2104.

4-[2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-propyl]benzoic Acid (8). To a solution of $C_5H_5NHBr_3$ (1.73 g, 5.4 mmol) in $CHCl_3$ (3 mL) under Ar was added 1,1,1,3,3,3-hexamethyldisilazane (1.14 mL, 5.4 mmol) followed by the benzyl alcohol **45** (0.90 g, 4.19 mmol) in $CHCl_3$ (3 mL). After being stirred for 30 min, the reaction mixture was filtered through silica gel with 5% EtOAc/hexane and concentrated to afford the benzyl bromide **46** as a colorless oil (1.07 g, 92%): R_f 0.44 (hexane); IR (KBr) 2978, 1485, 1253, 1174, 1097, 1039, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 6, CH_3), 7.31 (d, J = 8.7 Hz, 2, ArH), 7.42 (d, J = 8.7 Hz, 2, ArH). This bromide was used without futher purification for the Friedel–Crafts alkylation.

To $AlCl_3$ (0.09 g, 0.7 mmol) in $(CH_2Cl)_2$ (1 mL) under Ar at 0 °C was added a mixture of 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (**47**; 0.132 g, 0.7 mmol) and **46** (0.167 g, 0.6 mmol) in $(CH_2Cl)_2$ (4 mL). After being stirred for 10 min, the reaction mixture was poured into ice–water and extracted (40% EtOAc/hexane). The extract was washed

(saturated $NaHCO_3$ and brine), dried ($MgSO_4$), and concentrated to afford **48** as an oil (0.19 g). A mixture of the aryl bromide **48** (0.19 g, 0.46 mmol) and CuCN (0.8 g, 8.9 mmol) in NMP (4 mL) under Ar was heated (190–200 °C) overnight. The black homogenous solution was cooled before NaCN (0.5 g) in water (25 mL) was added, and stirring was continued for 15 min. The mixture was extracted twice (40% EtOAc/hexane). The extract was dried ($MgSO_4$), filtered (silica gel), and concentrated to afford **49** as a solid (0.17 g): R_f 0.23 (50% CH_2Cl_2/hexane); IR (KBr) 2957, 1684, 1628, 1476, 1419, 1292 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6, $C(CH_3)_2$), 1.26 (s, 6, $C(CH_3)_2$), 1.66 (s, 10, $C(CH_3)_2$, CH_2CH_2), 6.88 (dd, J = 2.2, 8.4 Hz, 1, ArH), 7.08 (d, J = 2.2 Hz, 1, ArH), 7.18 (d, J = 8.4 Hz, 1, ArH), 7.33 (d, J = 8.3 Hz, 2, ArH), 7.55 (d, J = 8.3 Hz, 2, ArH).

A solution of the benzyl cyanide **49** in $(CH_2OH)_2$ (3 mL), NaOH (0.1 g, 2.5 mmol), and water (2 drops) was heated (180–185 °C) for 1.5 h. After cooling, the solution was diluted with water, acidified (1 N HCl), and extracted (80% EtOAc/hexane). The combined organic layers were dried ($MgSO_4$) and concentrated to afford a pale-yellow solid (0.16 g). The crude product was treated with excess K_2CO_3 and MeI in DMF (5 mL) for 3 h. The methylated product was diluted with water and extracted (40% EtOAc/hexane). The extract was washed (water and brine), dried ($MgSO_4$), and concentrated to afford a solid, which on flash chromatography (50% CH_2Cl_2/hexane) yielded the methyl benzoate **50** as a white solid (0.12 g, 55% from **46**): mp 82–85 °C; IR (KBr) 2958, 1722, 1276, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 6, $C(CH_3)_2$), 1.25 (s, 6, $C(CH_3)_2$), 1.65 (s, 4, CH_2CH_2), 1.67 (s, 6, $C(CH_3)_2$), 3.89 (s, 3, CO_2CH_3), 6.91 (dd, J = 2.1, 8.3 Hz, 1, ArH), 7.10 (d, J = 2.1 Hz, 1, ArH), 7.16 (d, J = 8.3 Hz, 1, ArH), 7.31 (d, J = 8.7 Hz, 2, ArH), 7.93 (d, J = 8.7 Hz, 2, ArH).

The methyl ester **50** (0.12 g, 0.33 mmol) was hydrolyzed using the general procedure. Crystallization (CH_2Cl_2/hexane) afforded **8** as a white powder (0.102 g, 88%): mp 223–225 °C; IR (KBr) 2959, 1687, 1608, 1422, 1289 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6, $C(CH_3)_2$), 1.26 (s, 6, $C(CH_3)_2$), 1.66 (s, 4, CH_2CH_2), 1.69 (s, 6, $C(CH_3)_2$), 6.92 (dd, J = 2.1, 8.4 Hz, 1, ArH), 7.12 (d, J = 2.1 Hz, 1, ArH), 7.17 (d, J = 8.4 Hz, 1, ArH), 7.34 (d, J = 8.3 Hz, 2, ArH), 8.01 (d, J = 8.3 Hz, 2, ArH); HRMS for $C_{24}H_{30}O_2$ (M^+) calcd 350.2246, found 350.2275. Anal. ($C_{24}H_{30}O_2 \cdot 0.35H_2O$) C, H.

4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)ethenyl]benzoic Acid (9). Diaryl ketone **26** (0.51 g, 1.455 mmol) was allowed to react with the ylide of $Me(C_6H_5)_3PBr$ (0.78 g, 2.18 mmol), using the general procedure, to give a solid. Flash chromatography (30% CH_2Cl_2/hexane) yielded methyl 4-[1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)ethenyl]benzoate (**30**) as a white solid (0.405 g, 80%): mp 117–118 °C; R_f 0.2 (25% CH_2Cl_2/hexane); IR (KBr) 2958, 1714, 1610, 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 6, $C(CH_3)_2$), 1.29 (s, 6, $C(CH_3)_2$), 1.69 (s, 4, CH_2CH_2), 3.92 (s, 3, CO_2CH_3), 5.47 (s, 1, C=CH), 5.53 (s, 1, C=CH), 7.08 (dd, J = 1.9, 8.2 Hz, 1, ArH), 7.22 (d, J = 1.9 Hz, 1, ArH), 7.28 (d, J = 8.2 Hz, 1, ArH), 7.43 (d, J = 8.7 Hz, 2, ArH), 8.01 (d, J = 8.7 Hz, 2, ArH).

Ester **30** (94 mg, 0.27 mmol) was hydrolyzed using the general procedure. Crystallization (CH_2Cl_2/hexane) afforded **9** as a white crystalline solid (0.074 g, 82%): mp 201–204 °C; IR (KBr) 3600–2400, 1690, 1609, 1283 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 6, $C(CH_3)_2$), 1.31 (s, 6, $C(CH_3)_2$), 1.70 (s, 4, CH_2CH_2), 5.09 (s, 1, C=CH), 5.56 (s, 1, C=CH), 7.09 (dd, J = 2.0, 8.0 Hz, 1, ArH), 7.24 (d, J = 2.0 Hz, 1, ArH), 7.28 (d, J = 8.0 Hz, 1, ArH), 7.48 (d, J = 8.0 Hz, 2, ArH), 8.09 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{23}H_{26}O_2$) C, H.

(Z)- and (E)-4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)propen-1-yl]benzoic Acids (10 and 11). Diaryl ketone **26** (100 mg, 0.28 mmol) was allowed to react with the ylide of $Et(C_6H_5)_3PBr$ (160 mg, 0.43 mmol) at room temperature for 3 h using the general Wittig olefination procedure to afford a yellow gum. Chromatography (38% CH_2Cl_2/hexane) yielded the isomeric mixture as a pale-yellow gum (51 mg, 50%): R_f 0.43, 0.47 (40% CH_2Cl_2/hexane). Preparative HPLC (Waters Radialpak Novapak silica gel, 8 mm × 10 cm, 2% Et_2O/hexane, 1.0 mL/min, 260 nm) gave the white solid **31** (25 mg, t_R = 10.8 min) and the colorless gum **32** (20 mg, t_R = 9.8 min).

The *Z*-ester **31** (25 mg) in EtOH (0.5 mL) and 40% aqueous KOH (0.2 g) was stirred at 70 °C under argon for 2 h. The solution was concentrated under an argon stream at 70 °C. The residue was cooled to room temperature, acidified to pH 2–3 (1 N H_2SO_4), and filtered. The precipitate was repeatedly washed with water (6 × 1 mL) and dried to a pale-yellow solid, which was recrystallized (EtOAc) to afford **10** as a pale-yellow solid (21 mg, 20% overall yield): mp 229 °C; IR (KBr) 2300–3400, 1687, 1600, 1544, 1462, 1380, 1271, 836, 780 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.21 (s, 6, $C(CH_3)_2$), 1.27 (s, 6, $C(CH_3)_2$), 1.66 (s, 4, CH_2CH_2), 1.73 (d, J = 7.0 Hz, 3, C=CCH_3), 6.21 (q, J = 7.0 Hz, 1, C=CH), 6.84 (dd, J = 1.6, 8.0 Hz, 1, ArH), 7.08 (d, J = 1.6 Hz, 1, ArH), 7.16 (d, J = 8.2 Hz, 2, ArH), 7.33 (d, J = 8.0 Hz, 1, ArH), 7.78 (d, J = 8.2 Hz, 2, ArH). The *Z*-regiochemistry of **10** was confirmed by ^1H NOE NMR spectroscopy. Irradiation of the vinylic proton at δ 6.21 gave a NOE enhancement of the aryl protons *meta* to CO_2H at δ 7.16 (H-3,5); HRMS for $C_{24}H_{28}O_2$ (M^+) calcd 348.2185, found 348.2114.

The *E*-ester **32** was hydrolyzed as above to give 20 mg of a white powder. Crystallization (EtOAc/hexane) afforded 11 as a white powder (16 mg, 16% overall yield): mp 212 °C; IR (KBr) 2300–3400, 2961, 1687, 1605, 1400, 1283, 821 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.14 (s, 6, $C(CH_3)_2$), 1.20 (s, 6, $C(CH_3)_2$), 1.60 (s, 4, CH_2CH_2), 1.68 (d, J = 7.1 Hz, 3, C=CCH_3), 6.18 (q, J = 7.1 Hz, 1, C=CH), 6.85 (dd, J = 1.7, 8.2 Hz, 1, ArH), 7.08 (d, J = 1.7 Hz, 1, ArH), 7.19 (m, 3, ArH), 7.94 (d, J = 7.7 Hz, 2, ArH). The *E*-regiochemistry of 11 was confirmed by ^1H NOE NMR spectroscopy. Irradiation of the vinylic proton at δ 6.18 gave a NOE enhancement of the naphthalenyl protons at δ 7.08 and 6.85 (H-1,3); HRMS for $C_{24}H_{29}O_2$ (MH^+) calcd 349.2167, found 349.2159.

4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-methyl-1-propenyl]benzoic Acid (12). Ester **33** (0.115 g, 0.304 mmol) was hydrolyzed using the general procedure to afford **12** as a white powder (0.11 g, 99%): mp 204–206 °C; IR (KBr) 2923, 1686, 1291 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 6, $C(CH_3)_2$), 1.25 (s, 6, $C(CH_3)_2$), 1.66 (s, 4, CH_2CH_2), 1.79 (s, 3, C=CCH_3), 1.84 (s, 3, C=CCH_3), 6.77 (dd, J = 1.8, 8.1 Hz, 1, ArH), 7.07 (d, J = 1.8 Hz, 1, ArH), 7.16 (d, J = 8.1 Hz, 1, ArH), 7.24 (d, J = 8.1 Hz, 2, ArH), 8.01 (d, J = 8.1 Hz, 2, ArH). Anal. ($C_{25}H_{30}O_2$) C, H.

4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)cyclopropyl]benzoic Acid (13). Ester **35** (60 mg, 0.166 mmol) was hydrolyzed using the general procedure. Crystallization (CH_2Cl_2/hexane) afforded **13** as a white powder (0.055 g, 95%): mp 333–335 °C; IR (KBr) 2959, 1686, 1287 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 6, $C(CH_3)_2$), 1.27 (s, 6, $C(CH_3)_2$), 1.35 (m, 4, cyclopropyl H), 1.67 (s, 4, CH_2CH_2), 6.99 (dd, J = 2.1, 8.2 Hz, 1, ArH), 7.17 (d, J = 2.1 Hz, 1, ArH), 7.23 (d, J = 8.2 Hz, 1, ArH), 7.25 (d, J = 8.6 Hz, 2, ArH), 7.99 (d, J = 8.6 Hz, 2, ArH). Anal. ($C_{24}H_{28}O_2$) C, H.

2-(4-Carboxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dioxolane Ammonium Salt (14). Ester **36** (50 mg, 0.127 mmol) was hydrolyzed using the general procedure to afford the acid as a white solid, which was dissolved in CH_2Cl_2 (4 mL) under Ar. NH_3 (g) was condensed at 0 °C into this solution of the acid, which was stirred for 5 min and then warmed to room temperature for 20 min to evaporate the ammonia before concentration to provide the ammonium salt **14** as a white powder (47 mg, 93%): mp 259–261 °C; IR (KBr) 2956, 1693, 1282, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 12, $C(CH_3)_2$), 1.65 (s, 4, CH_2CH_2), 4.01–4.11 (m, 4, OCH_2CH_2O), 7.17 (dd, J = 1.9, 8.7 Hz, 1, ArH), 7.23 (d, J = 8.7 Hz, 1, ArH), 7.43 (d, J = 1.9 Hz, 1, ArH), 7.69 (br s, 2, ArH), 8.05 (br s, 2, ArH). Anal. ($C_{24}H_{28}O_4$) C, H.

2-(4-Carboxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-oxathiolane (15). Ester **37** (64 mg, 0.156 mmol) was hydrolyzed using the general procedure. Crystallization (CH_2Cl_2/hexane) afforded **15** as a white powder (0.06 g, 97%): mp 216–217.5 °C; IR (KBr) 2943, 1690, 1420, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 6, $C(CH_3)_2$), 1.24 (s, 6, $C(CH_3)_2$), 1.65 (s, 4, CH_2CH_2), 3.24 (m,

2, SCH_2CH_2O), 4.24 (m, 2, SCH_2CH_2O), 7.19 (dd, J = 1.7, 8.0 Hz, 1, ArH), 7.21 (d, J = 8.0 Hz, 1, ArH), 7.42 (d, J = 1.7 Hz, 1, ArH), 7.62 (d, J = 8.7 Hz, 2, ArH), 8.03 (d, J = 8.7 Hz, 2, ArH). Anal. ($C_{24}H_{28}O_3S$) C, H, S.

2-(4-Carboxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dithiolane (16). Ester **38** (85 mg, 0.199 mmol) was hydrolyzed at 70 °C for 1 h using the general procedure. Crystallization (CH_2Cl_2/hexane) afforded **16** as a white powder (0.064 g, 79%): mp 218–221 °C; IR (KBr) 2958, 1685, 1415, 1281, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 6, $C(CH_3)_2$), 1.25 (s, 6, $C(CH_3)_2$), 1.66 (s, 4, CH_2CH_2), 3.30–3.51 (m, 4, SCH_2), 7.19 (d, J = 8.4 Hz, 1, ArH), 7.21 (dd, J = 2.0, 8.4 Hz, 1, ArH), 7.46 (d, J = 2.0 Hz, 1, ArH), 7.76 (d, J = 8.4 Hz, 2, ArH), 8.02 (d, J = 8.4 Hz, 2, ArH). Anal. ($C_{24}H_{28}O_2S_2$) C, H, S.

2-(4-Carboxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dioxane Ammonium Salt (17). Ester **39** (0.1 g, 0.245 mmol) was hydrolyzed using the general procedure at 80 °C for 30 min to afford the acid as a white solid. NH_3 (g) was condensed at 0 °C under Ar into a solution of the acid in CH_2Cl_2 (4 mL) with stirring for 10 min. Workup as described above afforded the ammonium salt **17** as a white powder (0.238 g, 97%): mp 228–230 °C; IR (KBr) 2961, 1689, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 6, $C(CH_3)_2$), 1.25 (s, 6, $C(CH_3)_2$), 1.64 (s, 4, CH_2CH_2), 1.8–2.0 (m, 2, OCH_2CH_2), 4.03 (m, 4, OCH_2CH_2), 7.21 (dd, J = 1.2, 8.0 Hz, 1, ArH), 7.24 (d, J = 8.0 Hz, 1, ArH), 7.43 (d, J = 1.2 Hz, 1, ArH), 7.65 (d, J = 8.7 Hz, 2, ArH), 8.04 (d, J = 8.7 Hz, 2, ArH). Anal. ($C_{25}H_{33}O_4N$) C, H.

2-(4-Carboxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dithiane (18). The general thioketalization procedure was used to prepared **40** from **26** (97 mg, 0.277 mmol), 1,3-propanedithiol (33 μL, 36 mg, 0.332 mmol), and $BF_3{\cdot}Et_2O$ (17 μL, 0.140 mmol). Crystallization (EtOAc/hexane) afforded 2-(4-carbomethoxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dithiane (**40**) as a white crystalline solid (0.087 g, 71%): mp 195–197 °C; R_f 0.32 (50% CH_2Cl_2/hexane); IR (KBr) 1722, 1279 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6, $C(CH_3)_2$), 1.25 (s, 6, $C(CH_3)_2$), 1.66 (s, 4, CH_2CH_2), 1.98–2.04 (m, 2, SCH_2CH_2), 2.75–2.80 (m, 4, SCH_2CH_2), 3.93 (s, 3, CO_2CH_3), 7.21 (m, 2, ArH), 7.54 (s, 1, ArH), 7.89 (d, J = 8.0 Hz, 2, ArH), 8.03 (d, J = 8.0 Hz, 2, ArH).

Ester **40** (85 mg, 0.193 mmol) was hydrolyzed at 50 °C for 2 h using the general procedure. Crystallization (C_6H_6/hexane) afforded **18** as a white powder (0.076 g, 92%): mp 229–231 °C; IR (KBr) 2400–3600, 1693, 1277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 6, $C(CH_3)_2$), 1.26 (s, 6, $C(CH_3)_2$), 1.67 (s, 4, CH_2CH_2), 1.98–2.04 (m, 2, SCH_2CH_2), 2.74–2.81 (m, 4, SCH_2CH_2), 7.22 (m, 2, ArH), 7.56 (br s, 1, ArH), 7.93 (d, J = 8.0 Hz, 2, ArH), 8.11 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{25}H_{30}O_2S_2$) C, H, S.

4-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)carbonyl]benzoic Acid (19). Ester **27** (0.120 g, 0.329 mmol) was hydrolyzed at 60 °C for 1 h using the general procedure to afford a white solid. Crystallization (C_6H_6/hexane) afforded **19** as a white crystalline solid (0.102 g, 89%): mp 209–212 °C; IR (KBr) 3448, 2961, 1701, 1656, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 6, $C(CH_3)_2$), 1.32 (s, 6, $C(CH_3)_2$), 1.70 (s, 4, CH_2CH_2), 2.36 (s, 3, $ArCH_3$), 7.22 (s, 1, ArH), 7.27 (s, 1, ArH), 7.89 (d, J = 8.1 Hz, 2, ArH), 8.19 (d, J = 8.1 Hz, 2, ArH). Anal. ($C_{23}H_{26}O_3$) C, H.

4-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]benzoic Acid (20). Ester **34** (0.058 g, 0.156 mmol) was hydrolyzed using the general procedure. Crystallization (CH_2Cl_2) afforded **20** as a white solid (42 mg, 91%): mp 230–231 °C; IR (KBr) 2959, 1677, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 6, $C(CH_3)_2$), 1.31 (s, 6, $C(CH_3)_2$), 1.71 (s, 4, CH_2CH_2), 1.96 (s, 3, $ArCH_3$), 5.35 (s, 1, C=CH), 5.84 (s, 1, C=CH), 7.09 (s, 1, ArH), 7.14 (s, 1, ArH), 7.38 (d, J = 8.3 Hz, 2, ArH), 8.03 (d, J = 8.3 Hz, 2, ArH). Anal. ($C_{24}H_{28}O_2$) C, H.

5-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)carbonyl]thiophene-2-carboxylic Acid (21). Ester **55** (50 mg, 0.13 mmol) was hydrolyzed using the general procedure to give a white solid (46 mg). Crystallization (MeOH) afforded **21** as a white crystalline solid (42 mg, 91%): mp 214–215 °C; IR (KBr) 2954, 1679, 1643, 1292, 1258 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.27 (s, 6, $C(CH_3)_2$), 1.31 (s, 6, $C(CH_3)_2$), 1.71 (s, 4, CH_2CH_2), 2.38 (s, 3, $ArCH_3$), 7.22 (s, 1, ArH), 7.45 (s, 1, ArH), 7.48 (d, J = 4.0 Hz, 1, ArH), 7.86 (d, J = 4.0 Hz, 1, ArH). Anal. ($C_{21}H_{24}O_3S$) C, H, S.

5-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]thiophene-2-carboxylic Acid (22). Ketone **55** (0.10 g, 0.26 mmol) was allowed to react with the ylide of $Me(C_6H_5)_3PBr$ (0.143 g, 0.4 mmol) at room temperature for 30 min according to the general Wittig olefination procedure to afford a yellow solid. Flash chromatography (25% CH_2Cl_2/hexane) yielded ethyl 5-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]thiophene-2-carboxylate (**56**) as a white solid (0.079 g, 80%): R_f 0.4 (50% CH_2Cl_2/hexane); IR (KBr) 2959, 1685, 1426, 1288, 1229, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6, $C(CH_3)_2$), 1.30 (s, 6, $C(CH_3)_2$), 1.36 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 1.69 (s, 4, CH_2CH_2), 2.10 (s, 3, $ArCH_3$), 4.33 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 5.17 (s, 1, C=CH), 5.84 (s, 1, C=CH), 6.69 (d, J = 3.9 Hz, 1, ArH), 7.10 (s, 1, ArH), 7.11 (s, 1, ArH), 7.60 (d, J = 3.9 Hz, 1, ArH).

Ester **56** (0.058 g, 0.152 mmol) was hydrolyzed using the general procedure. Crystallization (CH_2Cl_2/hexane) afforded **22** as a white crystalline solid (0.053 g, 98%): mp 208–211 °C; IR (KBr) 2954, 1657, 1456, 1294 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6, $C(CH_3)_2$), 1.30 (s, 6, $C(CH_3)_2$), 1.69 (s, 4, CH_2CH_2), 2.10 (s, 3, $ArCH_3$), 5.21 (s, 1, C=CH), 5.88 (s, 1, C=CH), 6.75 (d, J = 4.0 Hz, 1, ArH), 7.11 (s, 2, ArH), 7.69 (d, J = 4.0 Hz, 1, ArH). Anal. ($C_{22}H_{26}O_2S$) C, H, S.

(2*E*,4*E*)-6-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-3,7-dimethyl-2,4,6-octatrienoic Acid (23). To CrO_3 (0.36 g, 3.7 mmol) in CH_2Cl_2 (7 mL) was added C_5H_5N (0.6 mL, 7.4 mmol) with stirring under Ar. After 5 min, the allylic alcohol **63** (0.10 g, 0.37 mmol) in CH_2Cl_2 (2 mL) was added, and stirring was continued for 5 min more. The solution was decanted and concentrated. The residue was diluted with Et_2O and filtered. The filtrate was washed (aqueous $CuSO_4$ and brine), dried ($MgSO_4$), and concentrated to afford 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-3-methyl-2-butenal (**64**) as a colorless oil (0.10 g): ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6, $C(CH_3)_2$), 1.28 (s, 6, $C(CH_3)_2$), 1.68 (s, 4, CH_2CH_2), 1.87 (s, 3, CH_3), 2.33 (s, 3, CH_3), Hz, 6.81 (dd, J = 1.9, 8.1 Hz, 1, ArH), 6.95 (d, J = 1.9 Hz, 1, ArH), 7.27 (d, J = 8.1 Hz, 1, ArH), 10.24 (s, 1, CHO). Aldehyde **64** was then subjected to the Horner–Emmons olefination without further purification.

Reaction of the crude aldehyde **64** with the anion of $(EtO)_2P(O)CH_2C(CH_3)=CHCO_2Et$ (0.127 g, 0.48 mmol) at 0 °C for 30 min using the olefination procedure and flash chromatography (3% EtOAc/hexane) yielded ethyl (2*E*,4*E*)-6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-3,7-dimethyl-2,4,6-octatrienoate (**68**) as a colorless oil (0.099 g, 70% from **63**): ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 1.25 (s, 6, $C(CH_3)_2$), 1.30 (s, 6, $C(CH_3)_2$), 1.64 (s, 3, CH_3), 1.70 (s, 4, CH_2CH_2), 2.03 (s, 3, CH_3), 2.35 (s, 3, CH_3), 4.12 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 5.55 (s, 1, C=C(H)CO_2), 5.68 (d, J = 15.6 Hz, 1, C=CH), 6.75 (dd, J = 1.8, 8.0 Hz, 1, ArH), 6.93 (d, J = 1.8 Hz, 1, ArH), 7.23 (d, J = 15.6 Hz, 1, HC=C), 7.24 (d, J = 8.0 Hz, 1, ArH).

Ester **68** (80 mg, 0.21 mmol) was hydrolyzed using the general procedure. Crystallization (CH_2Cl_2/hexane) afforded **23** as a pale-yellow solid (70 mg, 95%): mp 161–164 °C; IR (KBr) 3423, 2961, 1678, 1585, 1253, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6, $C(CH_3)_2$), 1.30 (s, 6, $C(CH_3)_2$), 1.65 (s, 3, CH_3), 1.70 (s, 4, CH_2CH_2), 2.04 (s, 3, CH_3), 2.35 (s, 3, CH_3), 5.57 (s, 1, C=C(H)CO_2), 5.71 (d, J = 15.6 Hz, 1, C=CH), 6.75 (dd, J = 1.8, 8.0 Hz, 1, ArH), 6.93 (d, J = 1.8 Hz, 1, ArH), 7.25 (d, J = 8.0 Hz, 1, ArH), 7.27 (d, J = 15.6 Hz, 1, HC=C); HRMS for $C_{24}H_{32}O_2$ (M^+) calcd 352.2402, found 352.2416.

(2*E*,4*E*)-6-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-3,7-dimethyl-2,4,6-octatrienoic Acid (24). Allylic alcohol **66** (0.203 g, 0.709 mmol) was oxidized by CrO_3 (0.7 g, 7.0 mmol) and C_5H_5N (1.13 mL, 14.0 mmol) in CH_2Cl_2 (15 mL) using the procedure described above to afford 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-3-methyl-2-butenal (**67**) as a colorless oil (0.2 g), which was then subjected to the Horner–Emmons olefination without further purification. Reaction of the crude aldehyde **67** with the anion of

$(EtO)_2P(O)CH_2C(CH_3)$=$CHCO_2Et$ (0.28 g, 1.06 mmol) at 0 °C for 30 min and flash chromatography (3% EtOAc/hexane) yielded ethyl (2*E*,4*E*)-6-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-3,7-dimethyl-2,4,6-octatrienoate (**69**) as a colorless oil (0.09 g, 32% from **66**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3, CH_3), 1.22 (s, 3, CH_3), 1.24 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 1.28 (s, 3, CH_3), 1.30 (s, 3, CH_3), 1.54 (s, 3, CH_3), 1.68 (s, 4, CH_2CH_2), 1.96 (s, 3, CH_3), 2.04 (s, 3, CH_3), 2.35 (s, 3, CH_3), 4.11 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 5.50 (d, J = 15.4 Hz, 1, C=CH), 5.52 (s, 1, C=C(H)CO_2), 6.78 (s, 1, ArH), 7.06 (s, 1, ArH), 7.22 (d, J = 15.4 Hz, 1, HC=C).

Ester **69** (0.065 g, 0.171 mmol) was hydrolyzed using the general procedure. Crystallization (CH_2Cl_2/hexane) afforded **24** as a pale-yellow solid (55 mg, 88%): mp 161–164 °C; IR (KBr) 3425, 2960, 1679, 1587, 1252, 1185 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3, CH_3), 1.22 (s, 3, CH_3), 1.28 (s, 3, CH_3), 1.30 (s, 3, CH_3), 1.54 (s, 3, CH_3), 1.67 (s, 4, CH_2CH_2), 1.96 (s, 3, CH_3), 2.05 (s, 3, CH_3), 2.35 (s, 3, CH_3), 5.53 (d, J = 15.3 Hz, 1, C=CH), 5.53 (s, 1, C=C(H)CO_2), 6.78 (s, 1, ArH), 7.07 (s, 1, ArH), 7.26 (d, J = 15.3 Hz, 1, C=CH); HRMS for $C_{25}H_{34}O_2$ (M^+) calcd 366.2559, found 366.2578.

2-(4-Carboxy-(1*E*,3*E*)-3-methylbutadienyl)-2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-1,3-dioxolane (25). The general ketalization procedure was used to prepare dioxolane **72** from **71** (0.12 g, 0.33 mmol), 1,2-bis-[(trimethylsilyl)oxy]ethane (2 mL), and *p*-TsOH·H_2O (catalytic). Flash chromatography (5% EtOAc/hexane) yielded 2-(4-carbethoxy-3-methyl-(1*E*,3*E*)-butadienyl)-2-(5,6,7,8-tetrahydro--3,5,5,8,8-pentamethyl-2-naphthalenyl)-1,3-dioxolane (**72**) as a colorless oil (0.109 g, 80%): R_f 0.43 (10% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 1.27 (s, 12, $C(CH_3)_2$), 1.67 (s, 4, CH_2CH_2), 2.26 (s, 3, CH_3), 2.31 (s, 3, CH_3), 3.93 (m, 2, OCH_2), 4.04 (m, 2, OCH_2), 4.15 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 5.79 (s, 1, C=C(*H*)CO_2Et), 6.18 (d, J = 15.7 Hz, 1, C=CH), 6.34 (d, J = 15.7 Hz, 1, HC=C), 7.04 (s, 1, ArH), 7.52 (s, 1, ArH).

Ester **72** (30 mg, 0.073 mmol) was hydrolyzed using the general procedure at 60 °C for 0.5 h. Recrystallization (CH_2Cl_2/hexane) afforded **25** as a white, crystalline solid (27 mg, 96%): mp 189–190 °C; IR (KBr) 2958, 1693, 1612, 1262, 1191 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 12, $(CH_3)_2$), 1.68 (s, 4, CH_2CH_2), 2.28 (s, 3, CH_3), 2.33 (s, 3, CH_3), 3.96 (m, 2, OCH_2), 4.07 (m, 2, OCH_2), 5.84 (s, 1, C=C(*H*)CO_2H), 6.25 (d, J = 15.7 Hz, 1, C=CH), 6.41 (d, J = 15.7 Hz, 1, HC=C), 7.06 (s, 1, ArH), 7.54 (s, 1, ArH); HRMS for $C_{24}H_{33}O_4$ (MH^+) calcd 385.2379, found 385.2369.

Methyl 4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbonyl]benzoate (26). Benzoate **26** was prepared from 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (1.45 g, 7.7 mmol) and 4-carbomethoxybenzoyl chloride (1.56 g, 7.9 mmol) according to the above procedure for Friedel–Crafts acylation. Flash chromatography (50% CH_2Cl_2/hexane) yielded **26** as a pale-yellow solid (2.07 g). Recrystallization (CH_2Cl_2/hexane) gave **26** as a white crystalline solid (1.96 g, 50%): mp 146–148 °C; R_f 0.14 (50% CH_2Cl_2/hexane); IR (KBr) 1717, 1656, 1282 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 6, $C(CH_3)_2$), 1.34 (s, 6, $C(CH_3)_2$), 1.74 (s, 4, CH_2CH_2), 3.99 (s, 3, CO_2CH_3), 7.43 (d, J = 8 Hz, 1, ArH), 7.55 (dd, J = 2, 8 Hz, 1, ArH), 7.80 (d, J = 2 Hz, 1, ArH), 7.85 (d, J = 8.0 Hz, 2, ArH), 8.16 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{23}H_{26}O_3$·0.25H_2O) C, H.

Methyl 4-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)carbonyl]benzoate (27). Ester **27** was prepared from 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (1.52 g, 7.5 mmol) and 4-carbomethoxybenzoyl chloride (1.57 g, 7.87 mmol) using the general Friedel–Crafts acylation procedure. Flash chromatography (60% CH_2Cl_2) yielded **27** as a white crystalline solid (1.733 g, 64%): mp 146–149 °C; R_f 0.11 (50% CH_2Cl_2/hexane); IR (KBr) 2959, 1719, 1672, 1280, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 6, $C(CH_3)_2$), 1.33 (s, 6, $C(CH_3)_2$), 1.71 (s, 4, CH_2CH_2), 2.36 (s, 3, $ArCH_3$), 3.97 (s, 3, CO_2CH_3), 7.22 (s, 1, ArH), 7.27 (s, 1, ArH), 7.87 (d, J = 8.1 Hz, 2, ArH), 8.13 (d, J = 8.1 Hz, 2, ArH). Anal. ($C_{24}H_{28}O_3$) C, H.

Methyl 4-[Hydroxy(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methyl]benzoate (28). To a solution of **26** (0.146 g, 0.417 mmol) in EtOH (7.5 mL) and Et_2O (1 mL) under Ar was added $NaBH_4$ (25 mg, 0.65 mmol). After being stirred for 2 h at room temperature, the reaction mixture was diluted with Et_2O, washed (water and brine), dried ($MgSO_4$), and concentrated to afford a white solid, which on crystallization (EtOAc/hexane) afforded **28** as a white crystalline solid (0.125 g, 85%): mp 136–138 °C; IR (KBr) 3550–3100, 1720, 1279 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (br s, 12, $C(CH_3)_2$), 1.66 (s, 4, CH_2CH_2), 2.19 (d, J = 3.0 Hz, 1, OH), 3.90 (s, 3, CO_2CH_3), 5.83 (d, J = 3.0 Hz, 1, Ar_2CH), 7.05 (dd, J = 2.0, 8.0 Hz, 1, ArH), 7.26 (d, J = 8.0 Hz, 1, ArH), 7.30 (d, J = 2.0 Hz, 1, ArH), 7.49 (d, J = 8.0 Hz, 2, ArH), 8.01 (d, J = 8.0 Hz, 2, ArH); HRMS for $C_{23}H_{28}O_3$ (M^+) calcd 352.2038, found 352.2038.

Methyl 4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)methyl]benzoate (29). A suspension of **3** (0.065 g, 0.193 mmol) and zinc dust (0.145 g, 2.22 mmol) in glacial HOAc (2 mL) was heated at reflux under Ar for 1 h. Concentrated HCl (0.2 mL) was added, and the reaction mixture was heated at reflux for another 1 h. After cooling, the reaction mixture was diluted with 1 N HCl (10 mL) and extracted (CH_2Cl_2). The combined organic layers were washed (H_2O and brine), dried ($MgSO_4$), and concentrated to afford a yellow solid. The crude acid (0.062 g, 0.192 mmol) was treated with K_2CO_3 (0.133 g, 0.965 mmol) and MeI (60 mL, 0.965 mmol) in DMF (2 mL) for 14 h. The methylated product was diluted with water and extracted (Et_2O). The extract was washed (water and brine), dried ($MgSO_4$), and concentrated to afford a yellow solid. Flash chromatography (25% CH_2Cl_2/hexane) yielded **29** as a white solid (0.045 g). Crystallization (pentane at −78 °C) afforded **29** as a white crystalline solid (0.032 g, 49%): mp 90–91 °C; IR (KBr) 1715, 1280 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 6, $C(CH_3)_2$), 1.26 (s, 6, $C(CH_3)_2$), 1.66 (s, 4, CH_2CH_2), 3.90 (s, 3, CO_2CH_3), 3.98 (s, 2, Ar_2CH_2), 6.89 (dd, J = 2.0, 8.0 Hz, 1, ArH), 7.10 (d, J = 2.0 Hz, 1, ArH), 7.21 (d, J = 8.0 Hz, 1, ArH), 7.27 (d, J = 8.0 Hz, 2, ArH), 7.96 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{23}H_{28}O_2$) C, H.

Methyl 4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-methyl-1-propenyl]benzoate (33). Ketone **26** (0.169 g, 0.481 mmol) was allowed to react with the ylide of $Me_2CH(C_6H_5)_3PI$ (0.35 g, 0.807 mmol) by using the general Wittig olefination procedure. When the reaction was complete, C_6H_6 (*ca.* 4 mL) was removed by distillation at 110 °C. After 1 h, the reaction mixture was cooled, diluted (40% EtOAc/hexane), washed (saturated $NaHCO_3$ and brine), dried ($MgSO_4$), filtered (silica gel), and concentrated to afford an oil, which on flash chromatography (40% CH_2Cl_2/hexane) yielded **33** as a colorless oil (0.128 g, 71%): R_f 0.44 (50% CH_2Cl_2/hexane); IR (KBr) 2958, 1725, 1276 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 6, $C(CH_3)_2$), 1.25 (s, 6, $C(CH_3)_2$), 1.66 (s, 4, CH_2CH_2), 1.78 (s, 3, C=CCH_3), 1.84 (s, 3, C=CCH_3), 3.90 (s, 3, CO_2Me), 6.77 (dd, J = 1.8, 8.1 Hz, 1, ArH), 7.06 (d, J = 1.8 Hz, 1, ArH), 7.15 (d, J = 8.1 Hz, 1, ArH), 7.21 (d, J = 8.6 Hz, 2, ArH), 7.95 (d, J = 8.6 Hz, 2, ArH); HRMS for $C_{26}H_{32}O_2$ (M^+) calcd 376.2402, found 376.2399.

Methyl 4-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]benzoate (34). Diaryl ketone **27** (0.1 g, 0.274 mmol) was allowed to react with the ylide of $Me(C_6H_5)_3PBr$ (0.196 g, 0.55 mmol) at room temperature for 3 h according to the general procedure of Wittig olefination. Flash chromatography (30%; 40% CH_2Cl_2/hexane) yielded **34** as a white solid (0.077 g, 78%): mp 167–168 °C; R_f 0.4 (50% CH_2Cl_2/hexane); IR (KBr) 2958, 1719, 1280, 1111 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 6, $C(CH_3)_2$), 1.31 (s, 6, $C(CH_3)_2$), 1.71 (s, 4, CH_2CH_2), 1.95 (s, 3, $ArCH_3$), 3.92 (s, 3, CO_2CH_3), 5.33 (s, 1, C=CH), 5.81 (s, 1, C=CH), 7.08 (s, 1, ArH), 7.13 (s, 1, ArH), 7.36 (d, J = 8.3 Hz, 2, ArH), 7.96 (d, J = 8.3 Hz, 2, ArH). Anal. ($C_{25}H_{30}O_2$·0.33H_2O) C, H.

Methyl 4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)cyclopropyl]benzoate (35). To a solution of **30** (0.130 g, 0.373 mmol) in C_6H_6 (10 mL) under Ar at room temperature was added 1 M Et_2Zn (5.6 mmol) in hexane (5.6 mL). The reaction mixture was heated to 60 °C before CH_2I_2 (0.48 mL, 6.0 mmol) in C_6H_6 (2 mL) was added dropwise over a period of 5 min. The reaction mixture was cooled to room temperature, and oxygen was bubbled through for 3 h. The cloudy solution was diluted (40% EtOAc/hexane) and washed (HCl, H_2O, and saturated $NaHCO_3$). The organic layer was

dried ($MgSO_4$) and concentrated to afford a solid, which on flash chromatography (30% and then 40% CH_2Cl_2/hexane) yielded **35** as a white solid (0.08 g, 59%): mp 100–102 °C; R_f 0.36 (50% CH_2Cl_2/hexane); IR (KBr) 2956, 1715, 1284, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 6, $C(CH_3)_2$), 1.26 (s, 6, $C(CH_3)_2$), 1.33 (m, 4, cyclopropyl H), 1.66 (s, 4, CH_2CH_2), 3.89 (s, 3, CO_2CH_3), 6.96 (dd, J = 2.1, 8.2 Hz, 1, ArH), 7.14 (d, J = 2.1 Hz, 1, ArH), 7.20 (d, J = 8.0 Hz, 2, ArH), 7.23 (d, J = 8.2 Hz, 1, ArH), 7.92 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{25}H_{30}O_2 \cdot 0.4H_2O$) C, H.

2-(4-Carbomethoxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dioxolane (36). The general ketalization procedure was modified to prepare **36** from **26** (80 mg, 0.228 mmol), $(CH_2OH)_2$ (1 mL), 1,2-bis[(trimethylsilyl)oxy]ethane (2 mL), and *p*-TsOH·H_2O (catalytic). Flash chromatography (50% CH_2Cl_2/hexane) yielded **36** as a white solid (0.082 g, 91%): mp 145–147 °C; R_f 0.16 (50% CH_2Cl_2/hexane); IR (KBr) 2953, 1721, 1275, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 12, $C(CH_3)_2$), 1.65 (s, 4, CH_2CH_2), 3.90 (s, 3, CO_2CH_3), 3.98–4.12 (m, 4, OCH_2), 7.17 (dd, J = 1.9, 8.0 Hz, 1, ArH), 7.23 (d, J = 8.0 Hz, 1, ArH), 7.42 (d, J = 1.9 Hz, 1, ArH), 7.61 (d, J = 8.6 Hz, 2, ArH), 8.0 (d, J = 8.6 Hz, 2, ArH). Anal. ($C_{25}H_{30}O_4$) C, H.

2-(4-Carbomethoxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-oxathiolane (37). The general ketalization procedure was modified to prepare **37** from **26** (88 mg, 0.251 mmol), 2-mercaptoethanol (1 mL), and *p*-TsOH·H_2O (catalytic). Flash chromatography (50% CH_2Cl_2/hexane) yielded **37** as a white solid (0.09 g, 87%): mp 122–124 °C; R_f 0.24 (50% CH_2Cl_2/hexane); IR (KBr) 2943, 1713, 1279, 1102, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 6, $C(CH_3)_2$), 1.24 (s, 6, $C(CH_3)_2$), 1.65 (s, 4, CH_2CH_2), 3.24 (m, 2, SCH_2CH_2O), 3.90 (s, 3, CO_2CH_3), 4.23 (m, 2, SCH_2CH_2O), 7.17 (dd, J = 1.6, 8.0 Hz, 1, ArH), 7.2 (d, J = 8.0 Hz, 1, ArH), 7.41 (d, J = 1.6 Hz, 1, ArH), 7.58 (d, J = 8.3 Hz, 2, ArH), 7.97 (d, J = 8.3 Hz, 2, ArH); HRMS for $C_{25}H_{30}O_3S$ (M^+) calcd 410.1916, found 410.1915. Anal. ($C_{25}H_{30}O_3S \cdot 0.2H_2O$) C, H.

2-(4-Carbomethoxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dithiolane (38). The above general procedure was used to prepared **38** from **26** (80 mg, 0.228 mmol), $(CH_2SH)_2$ (26 mg, 0.27 mmol), and $BF_3 \cdot Et_2O$ (0.04 mL, 0.3 mmol). Flash chromatography (30%, 40% CH_2Cl_2/hexane) yielded **38** as a white solid (0.088 g, 90%): mp 105–107 °C; R_f 0.33 (50% CH_2Cl_2/hexane); IR (KBr) 2954, 1718, 1441, 1277, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6, $C(CH_3)_2$), 1.25 (s, 6, $C(CH_3)_2$), 1.65 (s, 4, CH_2CH_2), 3.3–3.45 (m, 4, SCH_2), 3.91 (s, 3, CO_2CH_3), 7.17 (d, J = 8.4 Hz, 1, ArH), 7.2 (dd, J = 2.1, 8.4 Hz, 1, ArH), 7.45 (d, J = 2.1 Hz, 1, ArH), 7.72 (d, J = 8.3 Hz, 2, ArH), 7.95 (d, J = 8.3 Hz, 2, ArH). Anal. ($C_{25}H_{30}O_2S_2$) C, H.

2-(4-Carbomethoxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dioxane (39). The general ketalization procedure was modified to prepare **39** from **26** (150 mg, 0.428 mmol), 1,3-propanediol (1.5 mL), and *p*-TsOH·H_2O (catalytic). Flash chromatography (50% CH_2Cl_2/hexane) yielded **39** as a white solid (0.164 g, 94%): mp 157–159 °C; R_f 0.24 (5% EtOAc/hexane); IR (KBr) 2956, 1716, 1278, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 6, $C(CH_3)_2$), 1.24 (s, 6, $C(CH_3)_2$), 1.64 (s, 4, CH_2CH_2), 1.7–1.9 (m, 2, OCH_2CH_2), 3.89 (s, 3, CO_2CH_3), 4.03 (m, 4, OCH_2CH_2), 7.20 (dd, J = 1.7, 8.0 Hz, 1, ArH), 7.24 (d, J = 8.0 Hz, 1, ArH), 7.42 (d, J = 1.7 Hz, 1, ArH), 7.61 (d, J = 8.3 Hz, 2, ArH), 7.99 (d, J = 8.3 Hz, 2, ArH). Anal. ($C_{26}H_{32}O_4$) C, H.

Methyl 4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)oxy]benzoate (43). Using phenol (**41**; 55.05 g, 0.585 mol), 2,5-dichloro-2,5-dimethylhexane (89.55 g, 0.5 mol), and $AlCl_3$ (6.00 g, 0.045 mol) in the general Friedel–Crafts alkylation procedure yielded 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenol (**42**) as a light-brown solid (73.1 g, 72%): mp 141–143 °C; R_f 0.37 (CH_2Cl_2); IR (KBr) 3600–3100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6, $C(CH_3)_2$), 1.27 (s, 6, $C(CH_3)_2$), 1.67 (s, 4, CH_2CH_2), 6.62 (dd, J = 2.0, 8.0 Hz, 1, ArH), 6.74 (d, J = 2.0 Hz, 1, ArH), 7.17 (d, J = 8.0 Hz, 1, ArH).

A mixture of **42** (1.103 g, 5.4 mmol), 4-bromobenzoic acid (0.201 g, 1.0 mmol), powdered KOH (0.163 g, 2.9 mmol), and Cu powder (0.025 g, 0.39 mol) was slowly heated to 200 °C under argon with stirring for 6 h. After cooling, the solid mass was partitioned between CH_2Cl_2 (50 mL) and 2 N HCl (50 mL). Once solution was complete, the layers were separated and the aqueous phase was extracted (CH_2Cl_2). The organic layer was washed (water, saturated $NaHCO_3$, 2 N NaOH, water, and brine), dried ($MgSO_4$), and concentrated to afford 0.4 g of recovered **42** as a brown solid. The basic aqueous extract was acidified (concentrated HCl) to give a precipitate, which was extracted (CH_2Cl_2). The organic extract was washed (water and brine), dried ($MgSO_4$), and concentrated to afford a solid foam (0.444 g). To facilitate purification, the crude product was methylated using K_2CO_3 (0.946 g, 6.8 mmol) and MeI (0.43 mL, 6.8 mmol) in DMF (5 mL) for 18 h. The reaction mixture was diluted with water and extracted (Et_2O). The organic extract was washed (water and brine), dried ($MgSO_4$), and concentrated to afford a brown solid. Flash chromatography (25% CH_2Cl_2/hexane) yielded a white solid (0.082 g). Crystallization (hexane) afforded **43** as white needles (0.065 g, 19%): mp 115–116 °C; R_f 0.25 (50% CH_2Cl_2/hexane); IR (KBr) 1716, 1282, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 6, $C(CH_3)_2$), 1.29 (s, 6, $C(CH_3)_2$), 1.70 (s, 4, CH_2CH_2), 3.90 (s, 3, CO_2CH_3), 6.81 (dd, J = 2.0, 8.0 Hz, 1, ArH), 7.98 (d, J = 8.0 Hz, 2, ArH), 7.00 (d, J = 2.0 Hz, 1, ArH), 7.29 (d, J = 8.0 Hz, 1, ArH), 7.99 (d, J = 8.0 Hz, 2, ArH). Anal. ($C_{22}H_{26}O_3$) C, H.

2-(4-Bromophenyl)-2-propanol (45).[30] To a solution of 4-bromoacetophenone (**44**; 4.02 g, 20.2 mmol) in C_6H_6 (20 mL) under Ar at 0 °C was added 3 M MeMgBr (27 mmol) in THF (9.0 mL). After being stirred for 10 min, the reaction was quenched with aqueous NH_4Cl and the mixture was extracted twice (40% EtOAc/hexane). The organic extracts were dried ($MgSO_4$) and concentrated to afford a colorless oil. Flash chromatography (15% EtOAc/hexane) yielded **45** as a white solid (3.95 g, 91%): mp 44–45 °C; R_f 0.21 (10% EtOAc/hexane); IR (KBr) 3385, 2976, 1484, 1396, 1365, 1254, 1169, 1094, 1008, 956, 861, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 6, CH_3), 7.36 (d, J = 8.9 Hz, 2, ArH), 7.46 (d, J = 8.9 Hz, 2, ArH); HRMS for $C_9H_{10}Br$ ($M - OH$)$^+$ calcd 196.9966, found 196.9978.

5-Carbethoxythiophene-2-carboxylic Acid (52).[31] To a solution of *i*-Pr_2NH (3.6 mL, 25.75 mmol) in THF (10 mL) at −78 °C under Ar was added 1.6 M *n*-BuLi (25.8 mmol) in hexane (16.1 mL), and stirring was continued for 15 min. 2-Thiophenecarboxylic acid (**51**; 1.5 g, 11.705 mmol) in THF (5 mL) was added slowly, and stirring was continued for 15 min before $ClCO_2Et$ (2.7 mL, 28.33 mmol) was added. The mixture was stirred for 30 min at −78 °C and at 0 °C for 30 min. The reaction mixture was poured into saturated $NaHCO_3$ and washed (80% EtOAc/hexane). The aqueous layer was acidified (HOAc) and extracted (80% EtOAc/hexane). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford a yellow solid. Flash chromatography (25% MeOH/CH_2Cl_2) yielded the acid **52** as a white solid (1.76 g, 75%): mp >300 °C; IR (KBr) 3383, 1708, 1556, 1529, 1251 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.29 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 4.26 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 7.35 (d, J = 3.8 Hz, 1, ArH), 7.60 (d, J = 3.8 Hz, 1, ArH); HRMS for $C_8H_9O_4S$ (MH^+) calcd 201.0222, found 201.0212.

Ethyl 5-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)carbonyl]thiophene-2-carboxylate (55). To a suspension of acid **52** (0.64 g, 3.2 mmol) in CH_2Cl_2 (20 mL) under Ar was added 2.0 M $(COCl)_2$ (4.8 mmol) in CH_2Cl_2 (2.4 mL) and DMF (*ca.* 2 drops). After overnight stirring, the excess $(COCl)_2$ and CH_2Cl_2 were removed at reduced pressure, and the viscous, light-yellow residue was dried overnight to afford 5-carbethoxythiophene-2-carbonyl chloride (**53**) as a yellow solid (0.7 g, 100%): IR (KBr) 1763, 1717, 1277, 1249, 1185 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.31 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 4.32 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 7.73 (d, J = 3.9 Hz, 1, ArH), 7.79 (d, J = 3.9 Hz, 1, ArH).

Diaryl ketone **55** was prepared from 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (**54**; 0.712 g, 3.52 mmol) and **53** (0.7 g, 3.2 mmol) by using the general Friedel–Crafts acylation procedure. Flash chromatography (50% CH_2Cl_2/hexane) yielded a light-yellow solid. Crystallization (CH_2Cl_2/hexane) afforded **55** as a white crystalline solid (0.62 g, 50%): mp 111–112 °C; R_f 0.2 (50% CH_2Cl_2/hexane); IR (KBr) 2956, 1718, 1643, 1249 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.26 (s, 6, $C(CH_3)_2$), 1.31 (s, 6, $C(CH_3)_2$), 1.39 (t, J = 7.1 Hz, 3, CO_2-

CH_2CH_3), 1.70 (s, 4, CH_2CH_2), 2.37 (s, 3, $ArCH_3$), 4.39 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 7.20 (s, 1, ArH), 7.43 (s, 1, ArH), 7.44 (d, J = 4 Hz, 1, ArH), 7.76 (d, J = 4 Hz, 1, ArH). Anal. ($C_{23}H_{28}O_3S$) C, H, S.

5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthaleneboronic Acid (58). The arylboronic acid **58**, which was prepared from 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (**47**) by the same method used to synthesize arylboronic acid **60** that is described below, was obtained as a white powder: mp 190–192 °C; IR (KBr) 3375, 2960, 1609, 1461, 1399, 1345, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 6, $C(CH_3)_2$), 1.39 (s, 6, $C(CH_3)_2$), 1.75 (s, 4, CH_2CH_2), 7.46 (d, J = 8.0 Hz, 1, ArH), 7.96 (dd, J = 1.3, 8.0 Hz, 1, ArH), 8.21 (d, J = 1.3 Hz, 1, ArH); HRMS for $C_{42}H_{57}B_3O_3$ (trimeric anhydride M^+) calcd 642.4587, found 642.4598.

5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthaleneboronic Acid (60). To a solution of 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (**54**; 1.23 g, 6.08 mmol) in CCl_4 (6 mL) was added Br_2 until the red color persisted. After being stirred for 15 min at room temperature, the reaction mixture was diluted (40% EtOAc/hexane) and washed (aqueous $Na_2S_2O_3$). The combined organic layers were dried ($MgSO_4$) and concentrated to afford a solid. Flash chromatography yielded 2-bromo-5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene (**59**) as a white solid (1.71 g, 80%): mp 92–93 °C; R_f 0.57 (hexane); IR (KBr) 2957, 1480, 1361, 1077, 884 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 12, $C(CH_3)_2$), 1.65 (s, 4, CH_2CH_2), 2.33 (s, 3, $ArCH_3$), 7.14 (s, 1, ArH), 7.42 (s, 1, ArH).

To a solution of aryl bromide **59** (1.60 g, 5.68 mmol) in THF (20 mL) under Ar at −78 °C was added 2.0 M n-BuLi (6.40 mmol) in hexane (3.20 mL), and stirring was continued for 10 min. $B(OMe)_3$ (2.0 mL, 17.61 mmol) was added, and the reaction mixture was stirred at room temperature for 5 h. The solution was cooled to 0 °C, acidified (1 N HCl) to pH 3, and extracted (90% EtOAc/hexane). The extract was dried ($MgSO_4$) and concentrated to afford a solid, which was dissolved ($CHCl_3$) and filtered to remove the inorganic salts. The filtrate was concentrated to give a white solid, which on crystallization (CH_2Cl_2/hexane) afforded **60** as a white powder (1.20 g, 86%): mp 203–206 °C; IR (KBr) 3219, 2560, 1604, 1458, 1393, 1331, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 6, $C(CH_3)_2$), 1.34 (s, 6, $C(CH_3)_2$), 1.72 (s, 4, CH_2CH_2), 2.81 (s, 3, $ArCH_3$), 7.21 (s, 1, ArH), 8.28 (s, 1, ArH); HRMS for $C_{45}H_{63}B_3O_3$ (trimeric anhydride M^+) calcd 684.5056, found 684.5068.

1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalenyl)ethanone (61). Reaction of 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (**54**; 1.2 g, 5.93 mmol) and AcCl (0.51 g, 6.52 mmol) at room temperature for 1 h using the general Friedel–Crafts acylation procedure afforded **61** as a white solid (1.45 g, 99%): mp 54–57 °C; R_f 0.62 (10% ethyl acetate/hexane); IR (KBr) 2924, 1676, 1359, 1254, 636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 6, $C(CH_3)_2$), 1.3 (s, 6, $C(CH_3)_2$), 1.69 (m, 2, CH_2CH_2), 2.49 (s, 3, $ArCH_3$), 2.60 (s, 3, $COCH_3$), 7.14 (s, 1, ArH), 7.66 (s, 1, ArH); HRMS for $C_{17}H_{24}O$ (M^+) calcd 244.1827, found 244.1834.

Ethyl 2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-3-methyl-2-butenoate (62). Ester **62** was prepared from ethyl 2-bromo-3-methylcrotonate (0.11 g, 0.53 mmol) and the boronic acid **58** (0.1352 g, 0.5825 mmol) by using the general Pd(0)-coupling procedure to afford an oil. Flash chromatography (5% EtOAc/hexane) yielded **62** as a colorless oil (0.152 g, 92%): R_f 0.26 (5% EtOAc/hexane); IR (film) 2960, 1714, 1456, 1219, 1090, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 1.25 (s, 6, $C(CH_3)_2$), 1.27 (s, 6, $C(CH_3)_2$), 1.67 (s, 4, CH_2CH_2), 1.72 (s, 3, CH_3), 2.04 (s, 3, CH_3), 4.18 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 6.95 (dd, J = 1.9, 8.1 Hz, 1, ArH), 7.11 (d, J = 1.9 Hz, 1, ArH), 7.23 (d, J = 8.1 Hz, 1, ArH); HRMS for $C_{21}H_{30}O_2$ (M^+) calcd 314.2246, found 314.2239.

2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-3-methyl-2-buten-1-ol (63). To a solution of ester **62** (0.13 g, 0.41 mmol) in CH_2Cl_2 (5 mL) was added 1.0 M DIBAL (1.0 mmol) in CH_2Cl_2 (1.0 mL). The solution was stirred for 1 h at −78 °C under Ar and warmed to 0 °C, the reaction was quenched with MeOH, and the mixture was extracted twice (40% EtOAc/hexane). The extract was dried ($MgSO_4$) and concentrated to afford an oil. Flash chromatography (10% EtOAc/hexane) yielded **63** as a white solid (0.11 g, 98%): mp 75–76 °C; R_f 0.12 (5% EtOAc/hexane); IR (KBr) 3333, 2923, 1492, 1456, 1385, 1362, 989, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6, $C(CH_3)_2$), 1.28 (s, 6, $C(CH_3)_2$), 1.64 (s, 3, CH_3), 1.68 (s, 4, CH_2CH_2), 1.91 (s, 3, CH_3), 4.41 (s, 2, $C{=}CCH_2$), 4.42 (d, J = 12.0 Hz, 1, $C{=}CCH$), 6.93 (dd, J = 1.9, 8.0 Hz, 1, ArH), 7.08 (d, J = 1.9 Hz, 1, ArH), 7.24 (d, J = 8.0 Hz, 1, ArH). Anal. ($C_{19}H_{28}O$) C, H.

Ethyl 2-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-3-methyl-2-butenoate (65). Ester **65** was prepared from ethyl 2-bromo-3-methylcrotonate (0.15 g, 0.7 mmol) and the boronic acid **60** (0.190 g, 0.772 mmol) by using the general Pd(0)-coupling procedure to afford an oil. Flash chromatography (5% EtOAc/hexane) yielded **65** as a colorless oil (0.17 g, 75%): R_f 0.27 (5% EtOAc/hexane); IR (KBr) 2960, 1712, 1458, 1217, 1091, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 1.27 (s, 6, $C(CH_3)_2$), 1.31 (s, 6, $C(CH_3)_2$), 1.60 (s, 3, CH_3), 1.70 (s, 4, CH_2CH_2), 2.15 (s, 3, CH_3), 2.17 (s, 3, CH_3), 4.18 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 7.00 (s, 1, ArH), 7.09 (s, 1, ArH); HRMS for $C_{22}H_{32}O_2$ (M^+) calcd 328.2402, found 328.2404.

2-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-3-methyl-2-buten-1-ol (66). Ester **65** (0.24 g, 0.73 mmol) was reduced by DIBAL (1.6 mmol) using the procedure described above to afford **66** as an oil (0.203 g, 97%): R_f 0.04 (5% EtOAc/hexane); IR (film) 3353, 2922, 1496, 1456, 1389, 1362, 1004, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3, CH_3), 1.25 (s, 3, CH_3), 1.26 (s, 3, CH_3), 1.27 (s, 3, CH_3), 1.46 (s, 3, CH_3), 1.66 (s, 4, CH_2CH_2), 1.90 (s, 3, CH_3), 2.11 (s, 3, CH_3), 4.23 (d, J = 12.0 Hz, 1, $C{=}CCH_2$), 4.42 (d, J = 12.0 Hz, 1, $C{=}CCH_2$), 6.91 (s, 1, ArH), 7.08 (s, 1, ArH); HRMS for $C_{20}H_{30}O$ (M^+) calcd 286.2297, found 286.2287.

Ethyl (*E*)-4-Hydroxy-3-methyl-6-oxo-6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-2-hexenoate (70). To a solution of i-Pr_2NH (0.5 mL, 3.52 mmol) in THF (7 mL) at −78 °C under Ar was added 1.6 M n-BuLi (3.5 mmol) in hexane (2.2 mL). The LDA solution was stirred for 25 min before ketone **61** (0.78 g, 3.2 mmol) in THF (4 mL) was added slowly with stirring. After 20 min, ethyl (*E*)-3-formyl-2-butenoate (0.45 g, 3.2 mmol) in THF (3 mL) was added slowly, and stirring was continued for 35 min at −78 °C. The reaction mixture was poured into saturated NH_4Cl and extracted (40% EtOAc/hexane). The combined organic layers were dried ($MgSO_4$) and concentrated to afford a light-yellow solid. Flash chromatography (20% EtOAc/hexane) yielded **70** as a white crystalline solid (0.98 g, 80%): mp 126–128 °C; R_f 0.13 (10% EtOAc/hexane); IR (KBr) 3430, 2959, 1712, 1678, 1213, 1138 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 12, $C(CH_3)_2$), 1.29 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 1.69 (s, 4, CH_2CH_2), 2.18 (d, J = 1.3 Hz, 3, $C{=}CCH_3$), 2.49 (s, 3, $ArCH_3$), 3.05 (dd, J = 9.2, 17.3 Hz, 1, $COCH_2$), 3.20 (dd, J = 2.6, 17.3 Hz, 1, $COCH_2$), 3.52 (br s, 1, OH), 4.18 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 4.67 (m, 1, $CHOH$), 6.10 (q, J = 1.3 Hz, 1, $C{=}C(H)CO_2Et$), 7.16 (s, 1, ArH), 7.6 (s, 1, ArH). Anal. ($C_{24}H_{34}O_4$) C, H.

Ethyl (2*E*,4*E*)-3-Methyl-6-oxo-6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-2,4-hexadienoate (71). To **70** (0.33 g, 0.85 mmol) in THF (8 mL) at 0 °C was added Et_3N (0.5 mL, 4 mmol) followed by MsCl (0.106 g, 0.93 mmol) in THF (2 mL) slowly. The mixture was stirred for 1 h at 0 °C, warmed to room temperature for 30 min, and filtered through silica gel (10% EtOAc/hexane). Concentration gave **71** as a light-yellow solid. Crystallization (CH_2Cl_2/hexane) afforded **71** as a yellow powder (0.3 g, 95%): mp 101–102 °C; R_f 0.42 (10% EtOAc/hexane); IR (KBr) 2958, 1716, 1642, 1225, 1161, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 6, $C(CH_3)_2$), 1.29 (s, 6, $C(CH_3)_2$), 1.30 (t, J = 7.1 Hz, 3, $CO_2CH_2CH_3$), 1.70 (s, 4, CH_2CH_2), 2.36 (s, 3, $C{=}CCH_3$), 2.40 (s, 3, $ArCH_3$), 4.21 (q, J = 7.1 Hz, 2, $CO_2CH_2CH_3$), 6.05 (s, 1, $C{=}C(H)CO_2$), 6.92 (d, J = 15.8 Hz, 1, $CO(H)C{=}CH$), 7.14 (d, J = 15.8 Hz, 1, $COHC{=}CH$), 7.17 (s, 1, ArH), 7.43 (s, 1, ArH). Anal. ($C_{24}H_{32}O_3$) C, H.

Computational Analysis. Computational analysis was performed using SYBYL 6.03 software from Tripos Assoc.[32] Retinoids were built within SYBYL, and bond angles and lengths were optimized with the MAXIMIN2 program. Atomic point charges were computed by using the Gasteiger–Hückel

method. Conformational analyses were performed using the RANDOMSEARCH command in SYBYL. Rotatable bonds were identified, and default parameters were used. The various energy minima available to each molecule were located with RANDOMSEARCH by randomly perturbing torsions, minimizing, and eliminating duplicates. Low-energy conformers were overlapped with the FIT command. Hydrogen atoms were included during optimization but were omitted for display in the figures. Conformers within 2 kcal/mol of the global energy minimum were considered energetically acceptable.

Retinoid Receptor Activation Activity. Transfections were performed in CV-1 cells as previously described.[12,33] Briefly, CV-1 cells were transiently transfected using the calcium phosphate method with the TRE-pal-*tk*-CAT reporter plasmid, the pECE expression plasmid for RARα, -β, or -γ or RXRα, and the β-galactosidase expression vector as an internal standard. Cells were incubated with added retinoids for 24 h, and then CAT and β-galactosidase activities were determined by counting transferred radiolabeled acetate and by colorimetric assay, respectively. CAT activity was normalized to that of β-galactosidase to correct for variations in transfection and harvesting efficiencies. Percent activation activity represents the mean percent activation from assays performed in triplicate and is represented relative to that of 10^{-6} M 9-*cis*-RA for RXRα activation and to that of 10^{-6} M *trans*-RA for RAR activation, which are represented as 100%. The standard error was 5–15%. EC_{50} values were determined graphically and represent the concentrations of retinoids producing receptor activation that was half-maximal of the activation at 10^{-6} or 10^{-5} M retinoid, whichever was higher.

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