Effect of Structural Modifications in the C7-C11 Region of the Retinoid Skeleton on Biological Activity in a Series of Aromatic Retinoids

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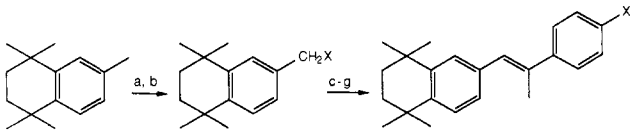
A series of conformationally restricted analogues of (*E*)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)propenyl]benzoic acid—(*E*)-4-[1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-propenyl]benzoic acid, (*E*)-4-[3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-buten-2-yl]benzoic acid, *trans*-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)cyclopropyl]benzoic acid, 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)benzoic acid, 6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-naphthalenecarboxylic acid, 6-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-2-naphthalenecarboxylic acid, and 6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-5-methyl-2-naphthalenecarboxylic acid—were synthesized and screened for retinoid biological activity. Comparison of the conformers of these analogues generated by molecular mechanics calculations with the biological activity profiles of these compounds indicates that geometric constraints required for high biological activity are imposed on the bridge joining the two aromatic ring systems by the retinoid receptor.

In 1980 Loeliger et al.[1] reported the synthesis and biological activity of retinoid **2** (Table I), an analogue of retinoic acid (**1**) in which the β-cyclogeranylidene ring and 7-double bond, and the 11,13-double bond system and C20-methyl group, were replaced by aromatic ring systems. Because of the high biological activity of **2** in controlling cell differentiation and reversing the process of preneoplastic transformation[2] and our own interests in conformationally restricted retinoids,[3] we undertook the syntheses and biological evaluation of analogues of **2** having modification in the region corresponding to the C8-C11 bonds of the retinoic acid skeleton to correlate the biological activity of retinoids **1-9** with their lowest energy conformations.[4,5] This study was initiated to establish the conformation that the retinoids adopt on binding to their various binding proteins and receptors.[6-9]

Synthetic Methodology. Retinoid **3** is an analogue of **2** in which the methyl group is shifted to the adjacent vinylic carbon (C10-retinoid position). A structure–activity study predicted that **3** would have high biological activity in the hamster tracheal organ culture reversal of keratinization (TOC) assay for retinoid activity.[10] As in the preparation of **2**,[1] the synthesis of **3** used a Wittig reaction to introduce the *E* double bond (Scheme I). The ylide generated from **12** was allowed to react with 4-acetylbenzonitrile (**13**) to afford a mixture of nitriles in which the *Z* isomer predominated (*E*/*Z* 1:3). The mixture of double bond isomers was hydrolyzed to the acids, which were esterified. Photoisomerization of the ester mixture (*E*/*Z* 1:4) gave the equilibrium mixture of isomers (*E*/*Z* 7:3), from which **15** and its *Z* isomer were isolated by crystallization. Hydrolysis under mild conditions afforded **3**.

The stereochemistries of **3**, **14**, and **15** were established from the ^{1}H NMR spectra. In each case, the spectrum of the *Z* isomer displayed characteristic upfield shifts[1,3d] for the allylic methyl group (0.11-0.14 ppm) and the vinylic proton (0.37-0.43 ppm). In addition, the signals for the geminal methyl groups at the C5- and C8-positions of the tetrahydronaphthalene rings of the *Z* isomers were nonequivalent (1.20 and 0.96 ppm, respectively), whereas those

Scheme I[a]



[a] (a) NBS, $(C_6H_5CO_2)_2$, CCl_4. (b) X = Br: $(C_6H_5)_3P$, CH_2Cl_2. (c) $NaCH_2SOCH_3$, Me_2SO; 4-$CH_3COC_6H_4CN$ (**13**), Me_2SO. (d) X = CN (*E*/*Z*): KOH, EtOH, H_2O. (e) X = CO_2H (*E*/*Z*): CH_3CHN_2, CH_2Cl_2, Et_2O. (f) X = CO_2Et (*E*/*Z*): *hν*, hexane. (g) X = CO_2Et: aqueous NaOH, $MeOCH_2CH_2OH$, Et_2O; 2 N HCl.

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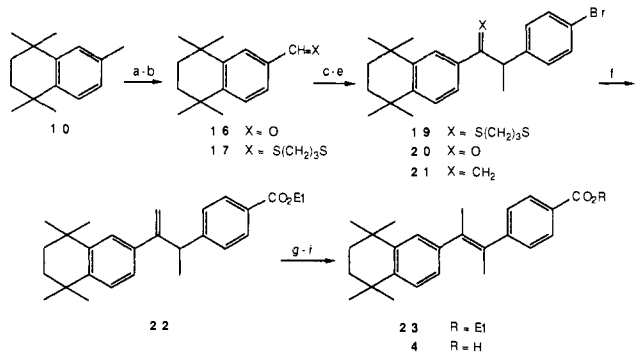
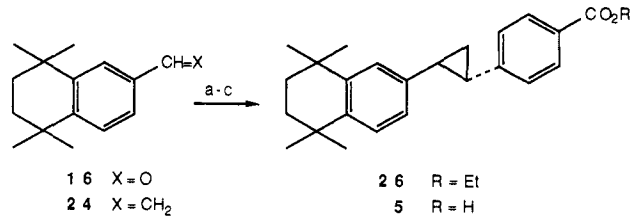
Scheme II[a]



[a] (a) $Ce(NH_4)_2(NO_3)_6$, 50% aqueous HOAc. (b) X = O: $HS(CH_2)_3SH$, HCl, $CHCl_3$. (c) X = $S(CH_2)_3S$: *n*-BuLi, THF; 4-$BrC_6H_4CH(Cl)CH_3$ (**18**). (d) X = $S(CH_2)_3S$: $CuCl_2$, CuO, acetone, H_2O. (e) X = O: $[CH_3P(C_6H_5)_2Br$, *n*-BuLi], THF. (f) X = CH_2: Mg, EtBr, THF; $ClCO_2Et$. (g) *p*-TsOH·H_2O, C_6H_6. (h) R = Et: *hν*. (i) R = Et: aqueous NaOH, $MeOCH_2CH_2OH$, Et_2O.

Scheme III[a]

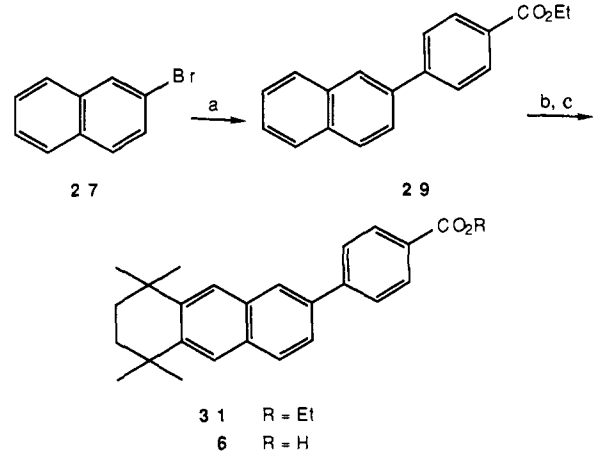


[a] (a) X = O: $[CH_3P(C_6H_5)_3Br$, *n*-BuLi], THF. (b) X = CH_2: 4-$N_2HCC_6H_4CO_2Et$ (**25**). (c) R = Et: aqueous KOH, EtOH.

for the *E* isomers were equivalent.

In retinoid **4**, which is a homologue of both **2** and **3**, steric interactions between the methyl groups on the double bond and the ortho protons on the adjacent aromatic rings were expected to force one of the rings out of the plane of the double bond, as in the case of the dimethylstilbenes.[11] The synthesis of **4** is presented in Scheme II. Because Wittig reactions to afford tetrasubstituted double bonds proceed in poor yield, the double bond was introduced in an indirect fashion by alkylation of the 1,3-dithiane **17**. 1,3-Dithianes of this type can be alkylated with secondary bromides in good yield.[12] The masked carbonyl group of the alkylation product (**19**) was then used to introduce the methyl group and the double bond. Dithiane **19** was contaminated by the 2-aryl-2-butyl-1,3-dithiane arising from alkylation by the butyl halide produced by metal–halogen exchange between unreacted *n*-butyllithium and the alkylating agent. This impurity and its subsequent reaction products were removed after the conversion of the carbonyl to the methylene group, giving **21**. Alkylative cleavage (MeI, acetone, H_2O, reflux)[13] of the dithianes to the ketones did not occur, and oxidative cleavage [$CuCl_2$, CuO, H_2O[14] and $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O[15]] proceeded in only moderate yield. After introduction of the carbethoxy group onto the phenyl ring to afford **22**, acid-catalyzed isomerization produced the tetrasubstituted

Scheme IV[a]



[a] (a) Mg, THF; $ZnCl_2$, THF; $[(C_6H_5)_3P]_4Ni$, 4-$BrC_6H_4CO_2Et_2$ (**28**), THF. (b) $ClMe_2C(CH_2)_2CMe_2Cl$ (**30**), $AlCl_3$, CS_2. (c) Aqueous KOH, MeOH.

double bond, which was photoisomerized to the *E* isomer.

The stereochemistry of the double bonds of **4** and its *Z* isomer was assigned from the ^1H NMR and UV spectra. The geminal methyl groups of **4** and its ethyl ester were equivalent (1.31 ppm), whereas in the *Z* isomers they were nonequivalent and shifted upfield (0.87 and 1.20 ppm). Most of the aromatic protons in the *Z* isomer were shifted upfield of those of the *E* isomer. The methyl groups on the double bond of **4** appeared at higher field than those of the *Z* isomer and were nonequivalent. Similar shifts are found in other tetrasubstituted stilbenes.[16] The decreased conjugation of the aromatic rings of **4** was also evident from the UV spectrum (λ_{max} 257 nm, ϵ 1.7×10^4) compared with that of the *Z* isomer (λ_{max} 296 nm, ϵ 2.7×10^4).

The cyclopropane **5** is an analogue of **2** and **3** in which a trans-substituted cyclopropane ring replaced the propenyl group. We had previously demonstrated that the 5- and 7-double bonds of the retinoid skeleton could be replaced by a cyclopropane ring without loss of retinoid activity. Because of low activity in the series of benzonorbornyl analogues of **2**, a similar effect on activity was not established in the case of the 9-double bond.[3d]

The route used for the preparation of **5** was the same as that used for *trans*-1-(4-carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthalenyl)cyclopropane.[3d] Although only a moderate yield was expected for the cyclopropanation step, this route had merit because it was simple and the starting materials were readily available. Reaction of the olefin **24** with ethyl 4-(diazomethyl)-benzoate afforded a mixture of cis and trans cyclopropane esters (24:76). The structures of the ester **26** and the carboxylic acid **5** were established by comparison of their ^1H NMR spectra with those of the cis isomers. The cis ester showed upfield shifts for almost all the signals compared with those of the trans isomer, indicating interaction of the aromatic rings of the former. The signals for the methyl groups at the C5 and C8 tetrahydronaphthalene ring positions were equivalent in **26** (1.30 ppm) but were nonequivalent in the cis isomer (0.96, 1.00, 1.15, and 1.16 ppm). The cyclopropane ring protons were also dramatically affected by the change in the substitution pattern of the ring. The geminal methylene protons of **26** were nearly equivalent (1.46 ppm), whereas they were nonequivalent (1.33 and 1.49 ppm) in the cis isomer. The

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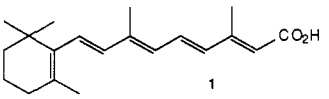
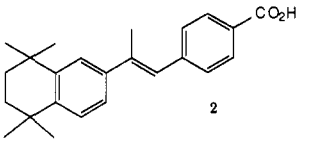
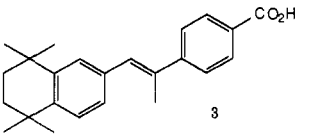
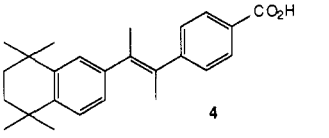
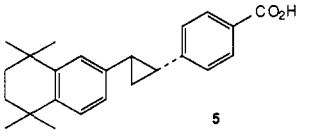
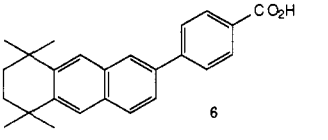
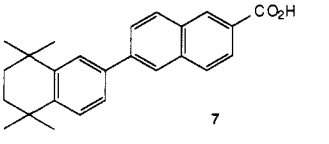
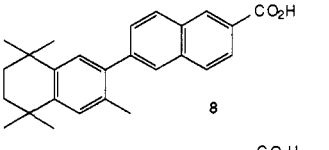
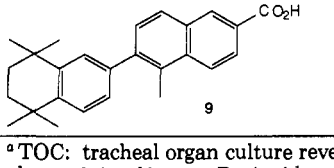
Table I. Biological Activity of Retinoids 1–9

retinoid	assay											
		TGase[b] inhibn, % cntrl		$CholSO_4$[d] inhibn, % cntrl			F9			CRABP Binding	
	TOC[a] ID_{50}, nM	0.1 nM	10 nM[c]	0.1 nM	10 nM[c]	cross-linked envelope inhibn,[e] % cntrl	laminin release ED_{50}, nM	plasminogen activator release ED_{50}, nM	ODC ID_{50}, nmol	rat,[f] % cntrl	chick ID_{50},[g] μM
 1	0.01		15	100	5	<1	1.5	0.1	0.04	91	1.0
 2	0.002		1	6	1	<1	1.5	0.08	0.03	100	0.8
 3	0.007	10	5	2	1	0	1.5	0.7	0.03	27	1.0
 4	>10[h]		68	73	33	100	>100[h]	>10[h]	142		1.0
 5	>0.1[h]	130	23	73	2	<1	90	2.0	3.2		4.8
 6	0.01	12	14	13	2	<1	0.2	0.3	0.07		0.8
 7	0.003		9	15	2	<1	31	1.0	2.2	91	1.6
 8	0.02	37	11	12	2	<1	>100[h]	0.5	0.4		4.8
 9	0.08	114	47	187	14	5	>5000[h]	3.0	66		15.0

[a] TOC: tracheal organ culture reversal of keratinization. [b] TGase: type I transglutaminase. [c] Concentration of retinoid tested. [d] $CholSO_4$: cholesterol 3-sulfate. [e] Retinoids screened at 10 nM. [f] Competition for binding using 3 μM retinoid and [^{3}H]-*all-trans*-retinoic acid. [g] Concentration of retinoid required to inhibit binding of 2.5 μM [^{3}H]-*all-trans*-retinoic acid by 50%. [h] Highest concentration of retinoid screened.

benzylic methine protons of **26** were also equivalent (2.21 ppm) but appeared as two complex multiplets in the cis isomer (2.44 and 2.49 ppm).

Strickland et al.[17] reported the high biological activity of the 3-methyltetrahydronaphthalene analogue of **2** in several assays used to assess the effects of retinoids on cell differentiation. The tetrahydroanthracene **6** could be regarded as an analogue of **2** and **3** in both of which the methyl groups are replaced by the benzo ring system. In **6** the only degree of rotational freedom is about the bond joining the two aromatic ring systems and corresponding to the C11–C12 bond of the retinoic acid side chain. The synthesis of **6** is outlined in Scheme IV. In intermediate **29** one of the rings of the naphthalene ring system is deactivated by the carbethoxyphenyl substituent; therefore, Friedel–Crafts cycli-alkylation[18] proceeded selectively in high yield. Intermediate **29** was prepared by the biaryl coupling method of Negishi.[19]

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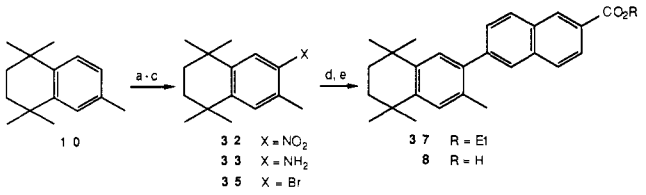
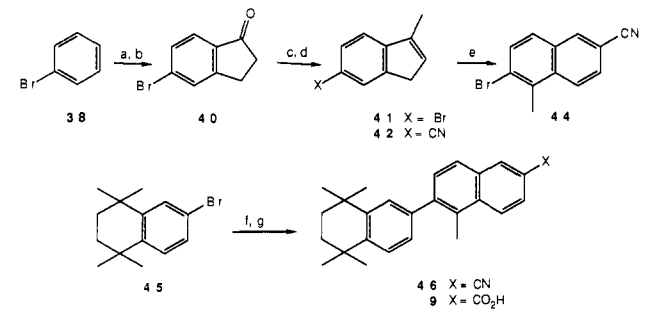
Scheme V[a]



[a] (a) HNO_3, Ac_2O. (b) X = NO_2: H_2, 5% Pd/C, EtOH, dioxane. (c) X = NH_2: $CH_3(CH_2)_5ONO$ (**34**), $CHBr_3$. (d) X = Br: Li (1% Na), Et_2O; $ZnCl_2$, THF; 6-$BrC_{10}H_6$-2-CO_2Et (**36**), $[(C_6H_5)_3P]_4Ni$, THF. (e) R = Et: aqueous KOH, EtOH.

Scheme VI[a]



[a] (a) $Cl(CH_2)_2COCl$ (**39**), $AlCl_3$, CH_2Cl_2. (b) $AlCl_3$, NaCl. (c) MeMgBr, Et_2O; 1.35 N H_2SO_4. (d) X = Br: CuCN, DMF; $FeCl_3 \cdot 6H_2O$, aqueous HCl. (e) $C_6H_5HgCBr_3$ (**43**), C_6H_6. (f) Mg, THF; $ZnCl_2$, THF; 44, $[(C_6H_5)_3P]_4Ni$, THF. (g) X = CN: aqueous NaOH, EtOH.

The naphthalenecarboxylic acids **7–9** were also prepared by using the Negishi coupling. In these compounds, the propenyl group of **2** has been replaced by the benzo ring of naphthalene and the only degree of rotational freedom is about the bond joining the two ring systems that corresponds to the C8–C9 single bond of the retinoic acid side chain. The synthesis of the parent naphthalenecarboxylic acid **7** was previously reported by us.[3b] The syntheses of the methyl-substituted analogues **8** and **9**, in which rotation about the C7–C8 bond was restricted by steric interaction of the methyl groups with the ortho biaryl protons, are shown in Schemes V and VI, respectively.

Bromotetrahydropentamethylnaphthalene intermediate **35** in the synthesis of **8** could be prepared by bromination of **10**[20] or by cycli-alkylation of *o*-bromotoluene with dichloride **30**. However, because aromatic amine **33** was an available intermediate, it was transformed into **35** by nonaqueous diazotization and reaction with hexyl nitrite and bromoform.[21] Negishi coupling of the arylzinc reagent derived from **35** with bromonaphthalene **36** afforded ester **37**, in low yield because of steric hindrance by the 3-methyl group on the naphthalene ring. Retinoid **9** was prepared in an analogous fashion, but in this case the yield of the biaryl coupling step was higher, indicating less steric hindrance. Functionality at the 2,6-positions of the naphthalene ring was introduced by a dihalocarbene ring expansion[22,23] of cyanoindene **42**, which was prepared by treatment of 5-bromo-1-indanone (**40**)[24] with MeMgBr and dehydration of the tertiary alcohol product using aqueous acid,[25] followed by reaction of the aryl bromide with CuCN in DMF. The attempted dehydration of the tertiary alcohol using anhydrous $CuSO_4$ in refluxing xylene gave a mixture of **42** and higher molecular weight material. 2-Bromonaphthalenes have been prepared from indenes by using either $CHBr_3$–KO-*t*-Bu[22] or $C_6H_5HgCBr_3$ in benzene at reflux.[23] We found that both methods on **41** gave 2,6-dibromo-1-methylnaphthalene and no 3,6-dibromo-1-methylnaphthalene. The bromo groups of this product did not exhibit any selectivity in reaction with CuCN in refluxing DMF,[26,27] and the isomeric bromonitrile products were separable only with difficulty. Therefore, the bromo group of the precursor **41** was transformed to the nitrile to give **42**. In this reaction an oxidative workup ($FeCl_3$, aqueous HCl)[26,27] was found to be a more convenient method for decomposing the Cu(I)–nitrile complexes formed than complexation with 1,2-diaminoethane,[27] which produced emulsions. Ring expansion afforded **44**, the ^1H NMR spectrum of which exhibited the expected ortho and meta coupling patterns. The proton signals of **9** were unambiguously assigned by proton-decoupling experiments despite the similarity in chemical shifts for the signals.

Biological Activity. In the absence of retinoids, the mucociliary epithelium of the trachea loses its normal pattern of differentiation and is replaced by a squamous metaplastic epithelium characterized by excessive cellular proliferation and the presence of several characteristic markers.[28–30] In the presence of retinoids in vivo and in organ and cell cultures, these markers—type I transglutaminase (Tgase inhibition assay), increases in cholesterol 3-sulfate ($CholSO_4$ inhibition assay) and keratin (TOC assay), and formation of cross-linked envelope (cross-linked envelope inhibition assay)—associated with the expression of the squamous phenotype are decreased or inhibited and the normal cellular phenotype is restored.[31]

In the presence of retinoid, F9 embryonal carcinoma cells differentiate to parietal endoderm, are no longer tumorigenic, and synthesize laminin (F9 laminin release assay) and plasminogen (F9 plasminogen activator release assay), which are secreted into the medium.[32–34] In epithelial cells undergoing neoplastic transformation upon treatment with a tumor promoter, the marker ornithine decarboxylase is induced. The induction of this enzyme is inhibited by retinoids (ODC assay).[35]

Retinoids **1–9** were screened in these assays (Table I) to assess their ability to regulate cell differentiation. Retinoic acid (**1**), the methylstilbenes **2** and **3**, the tetrahydroanthracene **6**, and the naphthalenecarboxylic acids **7** and **8** showed moderate to high activity, whereas the

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dimethylstilbene **4**, the cyclopropane **5**, and the 5-methyl-2-naphthalenecarboxylic acid **9** had low activity.

Linear regression analysis of the data in Table I indicated a high correlation between retinoid activities in these assays. For example, the ID_{50} values for these retinoids in the TOC and ODC assays correlated ($r = 0.974$, $P < 0.001$, $n = 7$), and the correlation between the activities in the TOC and the other assays ranged from $r = 0.917$ to $r = 0.962$ ($P < 0.001$ to $P < 0.005$, $n = 7$), except for the laminin release assay, which had a very small sample size ($n = 5$). However, a high correlation ($r = 0.950$, $P < 0.005$, $n = 6$) was found between the effects that these retinoids had on laminin and plasminogen activator release in F9 cells, as expected for assays performed on the same cell line. The difference between the two assays was the demonstration with the laminin release assay that retinoids **2** and **6** produced maximum responses that were 30% greater than that of **1** ($P < 0.05$). The ODC assay also showed a high correlation ($r = 0.826$ to $r = 0.991$, $P < 0.001$ to $P < 0.02$, $n = 8$ to $n = 9$) with the other assays. These results indicate that retinoid activity in one assay can be predictive of activity in another and that in vivo and in vitro assay results can be compared in a similar set of retinoids in this series of assays.

Cellular retinoic acid binding protein (CRABP) is present in the cell cytosol[6,7] and has been shown to translocate **1** to the nucleus,[36-39] where a nuclear retinoic acid receptor has been identified.[8,9] Therefore, it appears that, in those cell systems containing CRABP, this protein has some influence on retinoid activity. However, linear regression analysis of the ID_{50} values of these retinoids in the TOC and ODC assays compared with those for binding to CRABP from chick skin afforded variable results. When the ID_{50} values of those retinoids that were active in the TOC assay were compared with those for CRABP binding, the correlation was high ($r = 0.987$, $P < 0.001$, $n = 7$). In contrast, no correlation was found between the ID_{50} values in the ODC assay and those for binding to CRABP. In addition, **4**, which had low activity in both assays, bound to CRABP with an affinity equal to that of **1**. These results support the findings of Jetten et al.[40] on the lack of correlation between retinoid cell differentiation activity and CRABP binding activity.

Conformational Analysis. Molecular mechanics calculations were performed on **2–9** by use of the program MOLMEC.[4] The structures shown in Figure 1 were the result of complete geometry optimizations for all bond lengths, bond angles, and torsion angles, starting with randomly chosen α_1 and α_2 values. The conformational minima were found by varying the initial values at intervals of 30°. In order to estimate rotational barriers, constrained optimizations were conducted for **2–9** by keeping a selected torsion angle at a fixed value. The partial charges for the Coulomb term were taken from MNDO[5] calculations using geometries that were optimized by MOLMEC without the charge term. The predictive reliability of this procedure for the geometries and relative energies of molecular conformations has been demonstrated.[41] It was found that the geometries and relative energies of the conformational isomers changed very little by including the Coulomb term. The saturated portion of the tetrahydronaphthalene ring system was optimized as a cyclohexene ring with a twist conformation. The overlapping structures shown in Figure 2 were calculated by root-mean-square minimization of the six aromatic carbons of the tetrahydronaphthalene ring, the deviation of which in all cases was lower than 0.01 Å. The results of our conformational studies are summarized in Table II.

Table II. Optimized Torsion Angles α_1 and α_2 and Relative Energies ΔE of the Low-Lying Conformations of Structures **2–9**[a]

no.	α_1	α_2	ΔE (kcal/mol)
2a	31	40	0.0
2b	31	128	1.4
2c	148	41	0.1
2d	147	127	1.5
2e	213	42	0.2
2f	213	125	1.4
2g	326	41	0.2
2h	326	127	1.4
3a	40	31	0.0
3b	39	118	1.7
3c	138	31	0.2
3d	137	117	1.6
3e	221	32	0.4
3f	223	115	1.8
3g	315	31	0.2
3h	316	117	1.5
4a	50	52	0.0
4b	52	148	2.2
4c	126	51	0.1
4d	128	149	2.1
4e	232	55	0.2
4f	233	145	2.3
4g	302	51	0.2
4h	306	146	2.0
5a	132	65	0.0
5b	52	67	0.2
6a	180	32	0.0
6b	180	148	0.1
6c	180	213	0.1
6d	180	326	0.1
7a	39	180	0.0
7b	142	180	0.1
7c	218	180	0.0
7d	324	180	0.1
8a	54	180	0.0
8b	125	180	0.1
8c	231	180	0.2
8d	304	180	0.1
9a	56	180	0.0
9b	123	180	0.2
9c	235	180	0.2
9d	303	180	0.1

[a] α_1 = C7–C8–C9–C10; α_2 = C9–C10–C11–C12.

Discussion and Conclusions

Shudo[42] designed a series of novel analogues of **2** having

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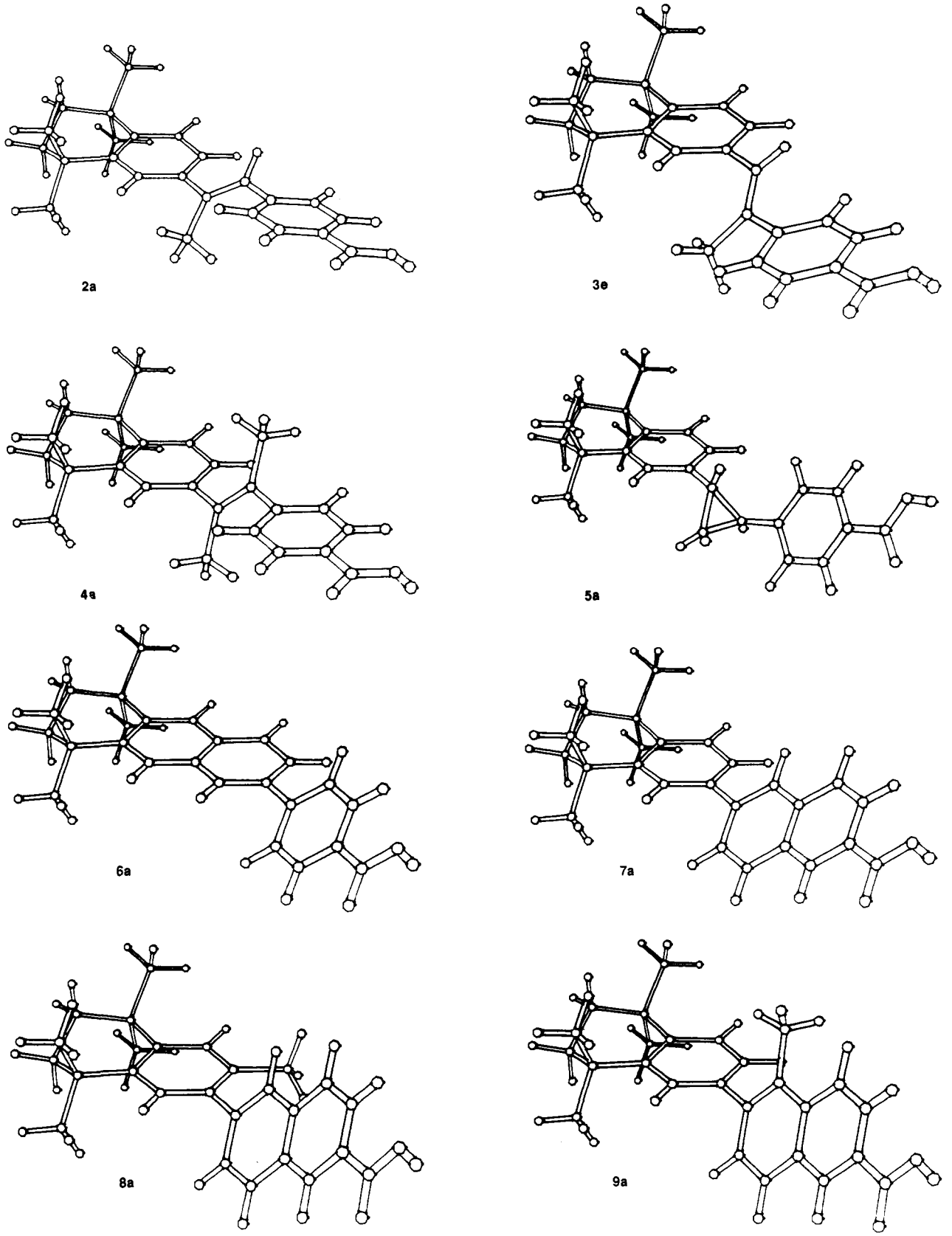

Figure 1. Selected energy-minimized conformers of retinoids 2–9 (Table II).

the propenyl group replaced by such heterofunctional groups as CONH, NHCO, and N=N. From the activities of these compounds in the HL-60 cell differentiation assay and other assays,[40] he concluded that the requirements for retinoid activity were a hydrophobic group having sufficient steric bulk joined by a bridge "X" to a benzoic acid group.[42] However, from the testing results there did not appear to be rigid spatial requirements for this spacer. In contrast, the results of the biological testing of **2–9** indicate that the receptor imposes spatial requirements on this bridge.

The conformational flexibility of **2** and its analogues is given mainly by the rotation around the C8–C9 (retinoic acid numbering) bond (i.e., the torsion angle α_1 defined

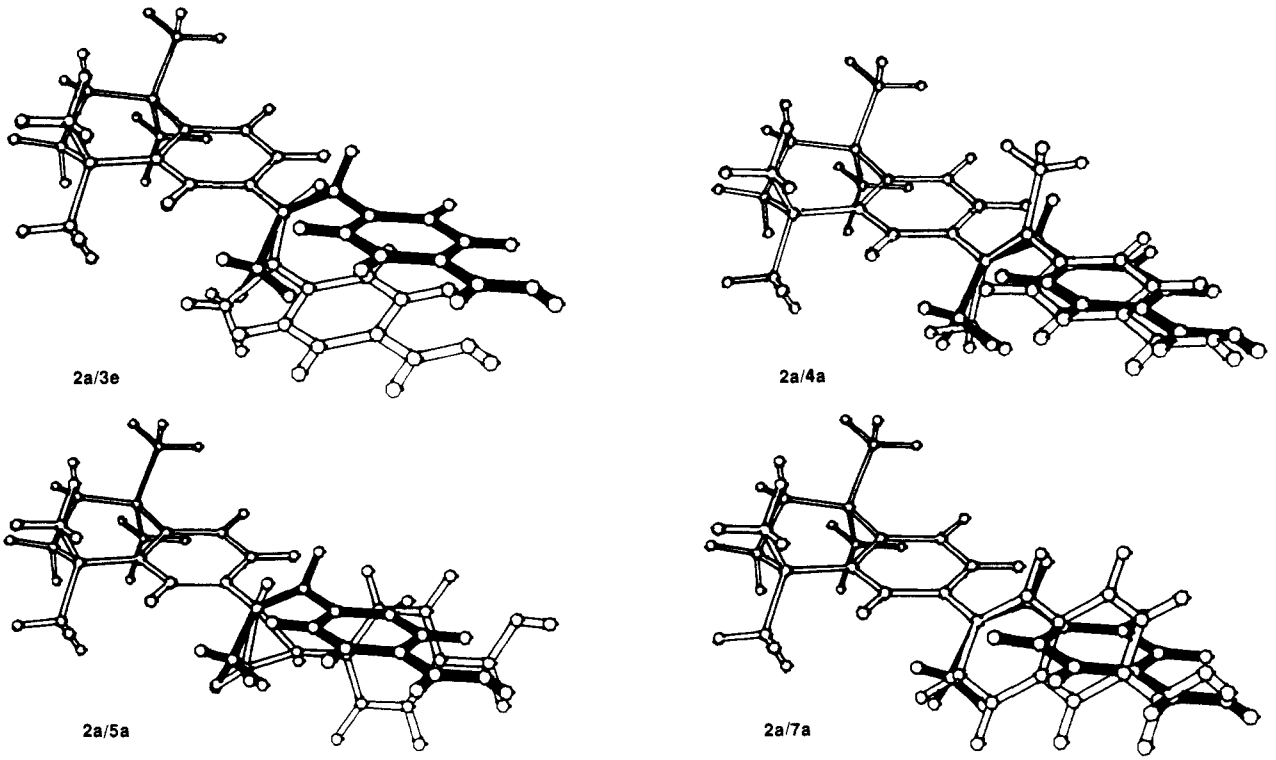

Figure 2. Overlapped conformer **2a** with related conformers **3e**, **4a**, **5a**, and **7a**.

by the atoms C7–C8–C9–C10) and/or the rotation α_2 around the C10–C11 bond (α_2 = C9–C10–C11–C12). Rotation about α_1 yielded four different energy minima. For two rotamers, the methyl group on the double bond was "below" the plane of the tetrahydronaphthalene ring, whereas for the other two it was "above" the plane. These rotational forms, although close in energy, were not degenerate because rotation around α_1 is not a symmetry element of the molecule. For each rotamer of **2**, two minima caused by rotation of the phenyl ring around α_2 had the aromatic ring systems nearly planar or perpendicular. All conformational minima were within 2 kcal/mol. The barriers for rotation were always less than 4 kcal/mol, indicating the flexible rotational profile of **2**. For the rotamer of **2a** shown in Figure 1, α_1 was calculated as 31° and α_2 was 40°, which agreed with the angle of 34.5° for *trans*-α-methylstilbene caculated by Suzuki[43] from the UV spectrum taken in *n*-heptane. The interplanar twisting angle of 77° of the aromatic rings calculated for the perpendicular forms agreed with the X-ray, which gave a displacement angle of 71°.[1]

The data in Table II show that the calculated conformational profile of **3** was comparable with that of **2**. For example, the corresponding rotamer **3a** had twisting angles α_1 = 40° and α_2 = 31°. Steric interactions of the two methyl groups on the double bond in **4a** led to larger twisting angles (α_1 = α_2 = 58°), which agreed with the reported[43] value of 58° for α,α'-dimethylstilbene in solution.

Compounds **2–4** had substantial differences in activity. Whereas **2** and **3** had high potency, **4** was essentially inactive. Because the rotational profiles of these compounds were not very different, we do not think that the lower potency of **4** was caused by the slightly different twisting angles because **4** could adopt a conformation similar to that of **2** that permitted overlapping of the benzoic acid ring with that of **2**. The only distinct difference between **2** and **4** was the second methyl group on the double bond that was above the planes of the aromatic rings. It is possible that steric interactions at the receptor site permit one methyl group on one side of the plane through the aromatic ring systems but not two on opposite sides of the planes through the aromatic ring systems. Although **2** and **3** have their methyl groups on adjacent carbons, **3** could adopt conformations in which its methyl group was on the same side of the molecular plane as that of **2**. An example of this is **3e**, which is shown in Figure 1.

The cyclopropane **5** could also adopt conformations (two minima differing by 0.2 kcal/mol) in which the cyclopropane methylene could overlap the C9-methyl group of **2**; however, in doing so, the plane of the benzoic acid group of **5** was perpendicular to that of **2**. This shift may explain the lower activity found with **5**. The tetrahydroanthracene **6a** had α_2 = 32°, resembling **3a**, and the tetrahydronaphthalene **7a** had α_1 = 39°, which was higher than that of **2a**. Suzuki calculated a twisting angle of 40–43° for biphenyl.[44] Rotation around α_2 of **6** yielded two minima having energies within 1 kcal/mol, and rotation around α_1 of **7** yielded two minima within 2 kcal/mol. Loss of rotational freedom about α_1 did not affect potency for **6**, which had activity comparable with that of **3**, whereas the reduced rotational freedom in **7** may be the cause of its potency being lower than that of **2**. Overlapping the rotamer **2a** shown in Figure 1 with the lowest lying rotational isomer of **7a** brought the carboxyl groups in close proximity, but the adjacent aromatic rings did not overlap. Rotation about α_1 in **7** would achieve more overlap of these rings but, although energetically permissible, would not permit sufficient overlap of the naphthalene ring with the olefinic bond of **2**.

The activity of retinoid **8** was comparable with that of **7** although the torsional angle between the rings for the energetically lowest lying conformer **8a** increased from 39° to 54°, still less than the calculated value of 58° for α-

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methylbiphenyl.[45] Evidently, the methyl group at the 3-position of the tetrahydronaphthalene ring system did not interfere with binding to the retinoid receptor in the naphthalenecarboxylic acid series, as was the case in the benzoic acid series.[17] In contrast, shifting the methyl group to the corresponding ortho position on the naphthalene ring appreciably reduced activity. In **9a**, the torsional angle α_1 was 56°, but the methyl group assumed a position above the planes of the aromatic rings comparable with that of the C10-methyl group of **4**.

Therefore, there appear to be steric constraints on the bridge joining the two aromatic systems that affect activity. These calculations did not indicate the optimal orientation of the benzoic acid ring with respect to the tetrahydronaphthalene ring system because the planar and perpendicular rotamers were so close together in energy. New retinoid structures will have to be screened to answer this question.

Experimental Section

Synthetic Methods. When required, reactions were conducted with deoxygenated solvents under inert gas (argon). Solvents were dried or distilled before use. Melting points were uncorrected. TLC analyses were performed on Analtech analytical silica gel plates. Merck silica gel 60 was used for preparative chromatography. IR spectra were recorded with a Perkin-Elmer 710B infrared spectrophotometer, and NMR spectra with a JEOL FX90Q or 400-MHz Varian spectrometer. UV spectra were taken on a Perkin-Elmer 575 spectrometer. High-resolution mass spectral analyses were conducted with a CEC-21-110B high-resolution mass spectrometer equipped with facilities for combination GC–MS.

[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-methyl]triphenylphosphonium Bromide (12). A mixture of 12.14 g (60.0 mmol) of 1,1,4,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (**10**),[20] 11.21 g (63.0 mmol) of NBS, and 0.436 g (1.80 mmol) of $(C_6H_5CO_2)_2$ in 120 mL of CCl_4 was heated at reflux with stirring for 30 min [TLC(5% Et_2O/hexane) R_f 0.14, 0.59 (**11**), and no 0.67 (**10**)]. The mixture was cooled, diluted with petroleum ether (120 mL), filtered, and concentrated to give 28.7 g of a colorless oil; LC (Radialpak B, hexane, 2 mL/min, 260 nm) t_R 3.3 (4%, **10**), 4.4 (26%, dibrominated), 5.1 min (70%, **11**). Distillation (128–134 °C, 1.2 mmHg) afforded 11.98 g (71%) of crude **11** as a colorless oil, consisting of **10** (7%), **11** (89%), and dibromide (4%) by ^1H NMR.

The oil was stirred with 13.4 g (51.1 mmol) of $(C_6H_5)_3P$ in 50 mL of CH_2Cl_2 for 18 h and then slowly diluted with Et_2O (200 mL). The precipitated solid was washed with Et_2O and dissolved in CH_2Cl_2 (60 mL). The Et_2O precipitation was repeated to give 19.4 g (59%) of **12** as colorless crystals: mp 264–266 °C (60 °C, 0.05 mmHg, 24 h); IR ($CHCl_3$) 2955, 2930, 1490, 1470 cm^{-1}; ^1H NMR (20% Me_2SO-d_6/$CDCl_3$) δ 0.95 and 1.23 (2 s, 12, 5,8-CH_3), 1.61 (s, 4, 6,7-CH_2), 4.90 (d, J = 14 Hz, 2, CH_2P), 6.72 (m, 1, 3-ArH), 6.90 (m, 1, 1-ArH), 7.13 (d, J = 8 Hz, 1, 4-ArH), 7.4–8.0 [m, 15, $(C_6H_5)_3P$]. Anal. ($C_{33}H_{36}BrP$) C, H, Br, P.

(*E*)-4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-propenyl]benzenecarbonitrile (14). A mixture of 12.50 g (23.0 mmol) of **12** and 0.840 g (21.0 mmol of NaH) of a 60% NaH–mineral oil dispersion in 70 mL of Me_2SO was stirred under argon for 20 min before a solution of 2.90 g (20.0 mmol) of 4-acetylbenzonitrile (**13**) in 30 mL of Me_2SO was added. The mixture was stirred for 6 h [TLC (10% acetone/hexane) R_f 0.19 (**13**), 0.47 (**14**), and 0.53 [(*Z*)-**14**]], poured onto ice (300 g), and extracted with Et_2O (250 mL, 3 × 50 mL). The extracts were washed with H_2O (30 mL) and saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2 (15 mL) and precipitated with petroleum ether (100 mL). This procedure was repeated twice to give 12.9 g of an almost colorless solid containing (*Z*)-**14** (48%), **14** (41%), **10** (5%), and **13** (5%), as well as $(C_6H_5)_3PO$ by ^1H NMR. Chromatography (200 g of silica gel, 10% acetone/petroleum ether) gave 6.42 g (97%) of a 54:46 mixture of (*Z*)-**14** and **14** by ^1H NMR; LC (Radialpak B, 4% EtOAc/hexane, 2 mL/min, 260 nm) t_R 3.4 [43%, (*Z*)-**14**], 3.8 min (57%, **14**). Repeated chromatography (silica gel, 5% acetone/hexane) and crystallization (5% acetone/hexane) gave analytically pure **14** as colorless needles: mp 160–162 °C; LC (Radialpak A, MeCN, 1 mL/min, 260 nm) t_R 3.7 min (100%), (Radialpak B, 4% EtOAc/hexane, 2 mL/min, 260 nm) t_R 3.7 min (100%); IR (CCl_4) 2225, 1605, 1505, 835 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.30 (s, 12, 5,8-CH_3), 1.71 (s, 4, 6,7-CH_2), 2.30 (d, J = 1 Hz, 3, C=CCH_3), 6.87 (br s, 1, HC=C), 7.14 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 7.29 (m, 1, 1-NapH), 7.33 (d, J = 8 Hz, 1, 4-NapH), 7.62 (s, 4, ArH ortho and meta to CN). Anal. ($C_{24}H_{27}N$) C, H, N.

Chromatography also afforded (*Z*)-**14** as colorless crystals: mp 95–97 °C (hexane); LC t_R 3.5 (3%, **14**), 3.7 min [97%, (*Z*)-**14**]; IR (CCl_4) 2225, 1505, 1490 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 0.96 and 1.20 (2 s, 12, 5,8-CH_3), 1.58 (s, 4, 6,7-CH_2), 2.17 (d, J = 1 Hz, 3, C=CCH_3), 6.51 (br s, 1, HC=C), 6.72 (m, 1, 3-ArH), 6.76 (s, 1, 1-ArH), 7.09 (d, J = 9 Hz, 1, 4-ArH), 7.29 (d, J = 8 Hz, 2, ArH meta to CN), 7.57 (d, J = 8 Hz, 2, ArH ortho to CN); MS calcd for $C_{24}H_{27}N$ 329.214, found 329.215.

Ethyl (*E*)-4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-propenyl]benzoate (15). A suspension of 756 mg (2.29 mmol) of **14** and (*Z*)-**14** (21:79 *E*:*Z*) in a solution of 1.46 g (22.9 mmol) of 88% KOH in 4.9 mL of EtOH and 0.82 mL of H_2O was heated at reflux with stirring for 18 h [TLC (20% acetone/hexane) R_f 0.0 and no 0.68 (**14**)]. The mixture was cooled, poured onto ice (100 g), and washed with Et_2O (3 × 100 mL). The aqueous phase was acidified at 0 °C with 2 N HCl and extracted with Et_2O (2 × 100 mL). The extracts were washed with brine (4 × 10 mL), dried (Na_2SO_4), and concentrated to give 714 mg (89%) of crude **3** as a tan residue; TLC (25% MeOH/$CHCl_3$) R_f 0.45 (**3**), 0.54 [(*Z*)-**3**].

The 714 mg of crude acid mixture was esterified with CH_3CHN_2 in 50% CH_2Cl_2/Et_2O, filtered through a 2-cm pad of silica gel (10% EtOAc/hexane), and concentrated to give 751 mg (87%) of esters as a yellow gum; LC (Radialpak B, 5% EtOAc/hexane, 2 mL/min, 260 nm) t_R 3.1 [71%, (*Z*)-**15**], 3.4 min (29%, **15**). The gum was dissolved in 350 mL of hexane and irradiated for 15 min from a distance of 2 cm with a Pyrex-jacketed, medium-pressure mercury lamp (Hanovia, 550 w) to give a 30:70 mixture of (*Z*)-**15** and **15** (LC). Concentration and crystallization (−20 °C EtOH) gave 339 mg (39%) of **15** as colorless plates. The photoisomerization and crystallization process was repeated to give two more crops of **15** for a total of 576 mg (67%). Recrystallization (EtOH) gave 488 mg (57%) of **15** as shiny, colorless plates: mp 95–96 °C; LC (Radialpak A, MeCN, 1 mL/min, 260 nm) t_R 10.4 min (100%), (Radialpak B, 3% EtOAc/hexane, 1 mL/min, 260 nm) t_R 4.6 min (100%); IR (CCl_4) 1720, 1610, 850, 700 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.30 and 1.31 (s, 12, 5,8-CH_3), 1.41 (t, J = 7 Hz, 3, CH_2CH_3), 1.71 (s, 4, 6,7-CH_2), 2.32 (d, J = 1 Hz, 3, C=CCH_3), 4.39 (q, J = 7 Hz, 2, CH_2CH_3), 6.89 (br s, 1, HC=C), 7.17 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 7.31 (s, 1, 1-NapH), 7.32 (d, J = 8 Hz, 1, 4-NapH), 7.57 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 8.03 (d, J = 8 Hz, 2, ArH ortho to CO_2Et). Anal. ($C_{26}H_{32}O_2$) C, H.

The mother liquors were purified by LC (4% EtOAc/hexane) using the recycle technique to give 169 mg (20%) of (*Z*)-**15** as a colorless gum: LC (Radialpak A, MeCN, 1 mL/min, 260 nm) t_R 8.2 min (100%), (Radialpak B, 4% EtOAc/hexane, 2 mL/min, 260 nm) t_R 3.0 min (100%); IR (CCl_4) 1720, 1605, 865 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 0.96 and 1.19 (2 s, 12, 5,8-CH_3), 1.38 (t, J = 8 Hz, 3, CH_2CH_3), 1.57 (s, 4, 6,7-CH_2), 2.19 (d, J = 1 Hz, 3, C=CCH_3), 4.37 (q, J = 7 Hz, 2, CH_2CH_3), 6.46 (br s, 1, HC=C), 6.72 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 6.80 (m, 1, 1-ArH), 7.05 (d, J = 8 Hz, 1, 4-ArH), 7.27 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.97 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); MS calcd for $C_{26}H_{32}O_2$ 376.240, found 376.241.

(*E*)-4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-propenyl]benzoic Acid (3). A solution of 419 mg (1.11 mmol) of **15** in 20 mL of $MeOCH_2CH_2OH$, 5 mL of Et_2O, and 4.45 mL (22.2 mmol) of 5 N aqueous NaOH was stirred under argon for 2 h [TLC (10% acetone/hexane) R_f 0.0 and no 0.60 (**15**)]. The mixture was diluted with a −10 °C solution of H_2O (150 mL), MeOH (100 mL), and 2 N HCl (30 mL) to give a white, microcrystalline solid, which was washed with 30% MeOH/H_2O (until wash pH 5) and dried (0.5 mmHg, 16 h) to afford 381 mg (98%)

(45) Suzuki, H. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 1350–1356.

of **3** as a colorless, microcrystalline powder: mp 214–216 °C; LC (Radialpak A, 35% H_2O/MeOH, 2 mL/min, 260 nm) t_R 17.2 min (100%); IR (Nujol) 1685, 1605, 1560 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.31 and 1.32 (2 s, 12, 5,8-CH_3), 1.71 (s, 4, 6,7-CH_2), 2.34 (d, J = 1 Hz, 3, C=CCH_3), 5.5 (br s, 1, CO_2H), 6.93 (s, 1, HC=C), 7.18 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 7.32 (s, 1, 1-NapH), 7.33 (d, J = 8 Hz, 1, 4-NapH), 7.62 (d, J = 9 Hz, 2, ArH meta to CO_2H), 8.11 (d, J = 9 Hz, 2, ArH ortho to CO_2H); ^{13}C NMR ($CDCl_3$) 17.4, 31.9, 34.2, 35.2, 126.0, 126.4, 127.6, 130.3, 134.8, 135.4, 143.8, 144.7, 149.7, 171.8 ppm; UV (EtOH) λ_{max} 228 (sh, ϵ 1.2 × 10^4), 296 nm (ϵ 2.7 × 10^4). Anal. ($C_{24}H_{28}O_2$) C, H.

(*Z*)-4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-propenyl]benzoic Acid [(*Z*)-3]. A solution of 136 mg (0.362 mmol) of (*Z*)-**15** in 6.5 mL of $MeOCH_2CH_2OH$, 1.65 mL of Et_2O, and 1.45 mL (7.24 mmol) of 5 N aqueous NaOH was stirred under argon for 2 h [TLC (20% acetone/hexane) R_f 0.0 and no 0.67 [(*Z*)-**15**]]. The mixture was poured into H_2O (50 mL) and 2 N HCl (10 mL) and extracted with Et_2O (5 × 50 mL). The extracts were washed with brine (3 × 30 mL, until wash pH 5), dried (Na_2SO_4), and concentrated. Crystallization (hexane) afforded 77 mg (61%) of (*Z*)-**3** as pale yellow crystals: mp 148–149 °C; LC (Radialpak A, 35% H_2O/MeOH, 1 mL/min, 260 nm) t_R 6.6 min (100%); IR (CCl_4) 2200–3500, 1690, 1605, 1560, 865 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 0.96 and 1.20 (2 s, 12, 5,8-CH_3), 1.58 (s, 4, 6,7-CH_2), 2.20 (d, J = 1 Hz, 3, C=CCH_3), 4.5 (br s, 1, CO_2H), 6.49 (br s, 1, HC=C), 6.75 (m, 1, 3-NapH), 6.79 (m, 1, 1-NapH), 7.07 (d, J = 8 Hz, 1, 4-NapH), 7.32 (d, J = 8 Hz, 2, ArH meta to CO_2H), 8.05 (d, J = 8 Hz, 2, ArH ortho to CO_2H); ^{13}C NMR ($CDCl_3$) 26.7, 31.4, 31.7, 33.9, 34.0, 35.0, 126.2, 127.4, 128.1, 128.6, 130.5, 133.8, 136.4, 143.3, 144.3, 148.9, 171.6 ppm; UV (EtOH) λ_{max} 237 (ϵ 2.5 × 10^4), 270 nm (sh, ϵ 1.2 × 10^4). Anal. ($C_{24}H_{28}O_2$) C, H.

5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenecarboxaldehyde (16). Method A. To a stirred slurry of 91.56 g (0.500 mol) of 2,5-dichloro-2,5-dimethylhexane (**30**)[18] in 157 g (1.00 mol) of bromobenzene at 5 °C was added 40.0 g (0.3 mol) of $AlCl_3$ in small portions over a 15-min period. The dark brown mixture was stirred at 5–10 °C for 20 min [GC (0.125 in. × 6 ft, 3% OV-17, 150 °C, 2 min, 16 °C/min to 200 °C) t_R 3.8 (82%, **45**), 5.0 (11%), 6.4 (7%), and no 0.8 min (**30**)]. The mixture was poured onto ice (300 g) and concentrated HCl (50 mL) and extracted with petroleum ether (300 mL, 2 × 100 mL). The extracts were washed with 2 N HCl (25 mL) and saturated $NaHCO_3$ (2 × 25 mL), dried ($MgSO_4$), and concentrated to a pale yellow oil from which excess bromobenzene was removed by distillation (bp 70–73 °C, 480 mmHg). The residue was distilled to give 79.4 g (59%) of **45**[46] as a colorless oil: bp 110–114 °C, 0.8 mmHg; TLC (10% acetone/hexane) R_f 0.76; GC t_R 3.8 (90%, **45**), 5.0 (7.5%), 6.4 min (2.5%); ^1H NMR ($CDCl_3$) δ 1.25 and 1.26 (2 s, 12, 5,8-CH_3), 1.66 (s, 4, 6,7-CH_2), 7.08–7.25 (m, 2, 3,4-ArH), 7.39 (m, 1, 1-ArH).

A procedure of Olah[47] was used. To a vigorously stirred suspension of 4.89 g (0.201 mol) of Mg turnings in 5 mL of THF containing 0.1 mL of MeI at 50 °C under argon was added a solution of 44.8 g (0.168 mol) of **45** (90% by GC) in 160 mL of THF over a 1-h period. To the resultant dark solution, which was heated at 50–55 °C for 30 min and then cooled to −20 °C, was added 24.7 g (0.218 mol) of piperidine-1-carboxaldehyde in 100 mL of THF over a 20-min period. The mixture was stirred at −20 to 0 °C for 1 h, poured onto ice (500 g) and concentrated HCl (50 mL), and extracted with petroleum ether (300 mL, 3 × 100 mL). The extracts were washed with 2 N HCl (25 mL) and saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), and concentrated to give 38.4 g of a pale yellow oil [TLC (10% acetone/hexane) R_f 0.49 (**16**), 0.76]. Chromatography (300 g of silica gel, 5% acetone/hexane) afforded 36.7 g of **16** as a colorless semisolid; GC (3% OV-17, 150 °C, 2 min, 16 °C/min to 200 °C) t_R 1.1 (6%), 4.2 (88%, **16**), 5.0 min (6%).

Method B. The method of Syper[48] was used. To a vigorously stirred, 100 °C mixture of 20.23 g (0.100 mol) of 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (**10**)[20] and 20 mL of HOAc was added a solution of 239.6 g (0.437 mol) of $(NH_4)_2Ce(NO_3)_6$ in 800 mL of 50% aqueous HOAc over a 2-h period. The mixture was stirred 15 min, cooled, poured onto ice (500 g), and extracted with petroleum ether (3 × 300 mL). The extracts were washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated to give 21.7 g of a yellow solid [TLC (10% acetone/hexane) R_f 0.13, 0.49 (**16**), and no 0.75 (**10**)]. Chromatography (300 g of silica gel, 10% Et_2O/hexane) and crystallization (hexane) gave 16.83 g (78%) of **16** as colorless crystals: mp 51–53 °C (lit.[49] 53–54 °C); IR (CCl_4) 2805, 1700, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 and 1.32 (2 s, 12, 5,8-CH_3), 1.72 (s, 4, 6,7-CH_2), 7.45 (d, J = 8 Hz, 1, 4-ArH), 7.63 (dd, J = 8 Hz, J = 2 Hz, 1, 3-ArH), 7.83 (d, J = 2 Hz, 1, 1-ArH), 9.94 (s, 1, CHO). Further elution of the column (15% acetone/hexane) and crystallization (hexane) gave 3.28 g (14%) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-carboxylic acid as colorless needles: mp 190–193 °C (lit.[20] 198–199.5 °C); IR (CCl_4) 2300–3400, 1695, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 and 1.32 (2 s, 12, 5,8-CH_3), 1.71 (s, 4, 6,7-CH_2), 7.39 (d, J = 8 Hz, 1, 4-ArH), 7.85 (dd, J = 8 Hz, J = 2 Hz, 1, 3-ArH), 8.08 (d, J = 2 Hz, 1, 1-ArH), 10.8 (br s, 1, CO_2H).

2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dithiane (17). A procedure by Seebach and co-workers[12] was used. Anhydrous HCl was bubbled into a −20 °C, stirred solution of 4.33 g (20.0 mmol) of **16** and 2.38 g (22.0 mmol) of 1,3-propanedithiol in 20 mL of $CHCl_3$ for 15 min. The reaction mixture was stirred at 20 °C for 16 h [TLC (20% EtOAc/hexane) R_f 0.59 (**17**) and no 0.63 (**16**)]. The mixture was diluted with $CHCl_3$ (100 mL) and ice (100 g). The organic layer was washed with H_2O (50 mL), 10% NaOH (3 × 20 mL), and saturated $NaHCO_3$ (20 mL), dried (Na_2SO_4), and concentrated to 6.22 g (100% of crystalline residue, which was recrystallized from hexane (50 mL, −50 °C) to give 5.95 g (97%) of **17** as shiny, colorless crystals: mp 103–105 °C; IR (CCl_4) 1490, 1460, 1425, 1410, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 and 1.28 (2 s, 12, 5,8-CH_3), 1.66 (s, 4, 6,7-CH_2), 1.75–2.30 (m, 2, CH_2CH_2S), 3.0 (m, 4, CH_2S), 5.12 (s, 1, SCHS), 7.23 (m, 2, 3,4-NapH), 7.35 (br s, 1, 1-NapH); MS calcd for $C_{18}H_{26}S_2$ 306.148, found 306.148.

2-[3-(4-Bromophenyl)buten-2-yl]-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (21). To a solution of 3.50 g (11.4 mmol) of dithiane **17** in 56 mL of THF at −78 °C under argon was added 8.7 mL (12 mmol) of 1.37 M *n*-BuLi in hexane over a 5-min period. After 1 h at −78 °C, a solution of 12.8 g (12.5 mmol) of 4-(1-chloroethyl)bromobenzene (**18**)[50] in 10 mL of THF was added over a 5-min period, and the reaction mixture was stirred at −78 °C for 3 h [TLC (10% Et_2O/hexane) R_f 0.64 (**19**) and no 0.45 (**17**)]. The mixture was diluted with ice (50 g) and saturated $NaHCO_3$ (20 mL) and extracted with petroleum ether (200 mL, 3 × 100 mL). The extracts were washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated to give 6.75 g of a yellow gum, which was chromatographed (200 g silica gel, 2% Et_2O/hexane) to give 5.13 g of impure **19** as a colorless gum: TLC (5% Et_2O/hexane) R_f 0.35 (**19**) and 0.40; LC (Radialpak B, 2% Et_2O/hexane, 2 mL/min, 260 nm) t_R 2.0 (24%) and 2.6 min (76%, **19**); IR (CCl_4) 1490, 1460, 1390, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (m, impur), 1.12 and 1.16 (2 s, impur), 1.28 (s, 12, 5,8-CH_3), 1.38 (d, J = 7 Hz, 3, $CHCH_3$), 1.67 (s, 4, 6,7-CH_2), 1.9 (m, 2, CH_2CH_2S), 2.6 (m, 4, CH_2S), 3.27 (q, J = 7 Hz, 1, $CHCH_3$), 6.66 (d, J = 9 Hz, 2, ArH meta to Br), 7.21 (d, J = 9 Hz, 2, ArH ortho to Br), 7.35 (m, 3, NapH).

A procedure of Mukaiyama and co-workers[14] was used. A mixture of 2.16 g (approximately 4.2 mmol) of crude **19**, 1.13 g (8.4 mmol) of anhydrous $CuCl_2$, 1.34 g (16.8 mmol) of CuO, 40 mL of acetone, and 0.4 mL of H_2O was heated at reflux for 50 min [TLC (10% Et_2O/hexane) R_f 0.53 (**20**)]. After cooling, the reaction mixture was diluted with Et_2O (40 mL), filtered, dried ($MgSO_4$), and concentrated to give 2.18 g of a dark yellow oil, which was chromatographed (90 g of silica gel, 10% Et_2O/hexane) to give 0.58 g (35%) of **20** as a colorless gum: LC (Radialpak B, 1% Et_2O/hexane, 2 mL/min, 260 nm) t_R 4.6 (18%) and 7.2 min (82%, **20**); IR (CCl_4) 1690, 1680, 1640, 1605, 1490 cm^{-1}; ^1H NMR

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($CDCl_3$) δ (**20**) 1.25 (s, 3.6, CCH_3), 1.29 and 1.32 (2 s, 3.6, CCH_3), 1.50 (d, J = 7 Hz, 1.8, $CHCH_3$), 1.66 (s, 2.4, 6,7-CH_2), 4.63 (q, J = 7 Hz, 0.6, $CHCH_3$), 7.3 (m, 5, ArH and 4-NapH), 7.69 (m, 1, 3-NapH), 7.93 (m, 1, 1-NapH); and (aryl butyl ketone) 0.95 (m, 1.2, CH_2CH_3), 1.21 and 1.28 (2 s, 4.8, CCH_3), 1.70 (s, 1.6, 6,7-CH_2), 2.93 (t, J = 7 Hz, 0.8, $COCH_2$).

To a −40 °C stirred suspension of 1.73 g (4.84 mmol) of $CH_3P(C_6H_5)_3Br$ in 50 mL of THF was added 3.4 mL (4.6 mmol) of 1.37 M n-BuLi in hexane over a 5-min period. The reaction mixture was stirred at −40 to −10 °C for 0.5 h and at −10 °C for 0.5 h. The clear orange solution was cooled to −40 °C while a solution of 1.61 g (4.0 mmol) of crude **20** in 10 mL of THF was added over a 5-min period. The mixture was stirred at −40 to −20 °C for 0.5 h, at which time the reaction was complete [TLC (2% Et_2O/hexane) R_f 0.11 (trace, **20**), 0.42 (**21**), 0.60]. It was diluted with ice (50 g) and saturated $NaHCO_3$ (20 mL) and extracted with 50% Et_2O/petroleum ether (200 mL, 2 × 50 mL). The extracts were washed with saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated to a semisolid, which was triturated with hexane (20 mL) to afford 1.60 g of a colorless oil. Chromatography (90 g of silica gel, 2% Et_2O/hexane) afforded 0.38 g (35%) of arylhexene (MS calcd for $C_{20}H_{30}$ 270.235, found 270.235) and 0.62 g (39%) of **21** as a colorless oil: LC (Radialpak B, hexane, 2 mL/min, 260 nm) t_R 2.5 (2%) and 3.7 min (98%); IR (film) 1630, 1575, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 and 1.20 (2 s, 6, 8-CH_3), 1.23 (s, 6, 5-CH_3), 1.43 (d, J = 7 Hz, 3, $CHCH_3$), 1.63 (s, 4, 6,7-CH_2), 3.96 (q, J = 7 Hz, 1, $CHCH_3$), 5.11 [br s, 1, (*E*)-HC=CAr], 5.44 [br s, 1, (*Z*)-HC=CAr], 7.02 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 7.12 (s, 1, 1-NapH), 7.13 (d, J = 8 Hz, 2, ArH meta to Br), 7.19 (d, J = 8 Hz, 1, 4-NapH), 7.38 (d, J = 8 Hz, 2, ArH ortho to Br); MS calcd for $C_{24}H_{29}Br$ 396.145, found 396.144.

Ethyl 4-[2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)buten-3-yl]benzoate (22). To a stirred suspension of 190 mg (7.83 mmol) of Mg powder in a solution of 300 mg (0.783 mmol) of **21** in 5 mL of THF was added at 45–50 °C 512 mg (4.70 mmol) of EtBr in 5 mL of THF over a 30-min period. Heating was continued for 3 h. The Grignard reagent was cooled to room temperature and then added to a solution of 765 mg (7.05 mmol) of $ClCO_2Et$ in 10 mL of THF at −60 °C over a 15-min period. After an additional 15 min at −60 °C, the reaction mixture was warmed to 0 °C, poured into ice (20 g) and saturated $NaHCO_3$ (20 mL), and extracted with Et_2O (50 mL, 2 × 20 mL). The extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give 315 mg of a colorless oil: TLC (5% Et_2O/hexane) R_f 0.35 (**22**) and 0.67 (**21**); LC (Radialpak B, 4% Et_2O/hexane, 2 mL/min, 260 nm) t_R 2.0 (42%, **21**) and 3.0 min (58%, **22**). ^1H NMR indicated that 53% of the oil was **22**, on the basis of integration of the vinylic and ester ethyl group protons. Chromatography (200 g of silica gel, 5% Et_2O/hexane) afforded 81 mg (27%) of **21** and 161 mg (53%) of **22** as a colorless gum: LC (Radialpak B, 4% Et_2O/hexane, 2 mL/min, 260 nm) t_R 2.6 (3%), 3.0 (95%, **22**), and 3.7 min (2%); IR (CCl_4) 1720, 1630, 1605, 1495, 1460, 1420, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 and 1.19 (2 s, 6, 8-CH_3), 1.22 (s, 6, 5-CH_3), 1.43 (t, J = 7 Hz, 3, CH_2CH_3), 1.47 (d, J = 7 Hz, 3, $CHCH_3$), 1.62 (s, 4, 6,7-CH_2), 4.06 (q, J = 7 Hz, 1, $CHCH_3$), 4.34 (q, J = 7 Hz, 2, CH_2CH_3), 5.14 [br s, 1, (*E*)-HC=CNap], 5.47 [br s, 1, (*Z*)-HC=CNap], 7.02 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 7.11 (s, 1, 1-NapH), 7.20 (d, J = 8 Hz, 1, 4-NapH), 7.33 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.94 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); MS calcd for $C_{27}H_{34}O_2$ 390.255, found 390.256.

(*E*)-4-[3-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-buten-2-yl]benzoic Acid (4). A mixture of 134 mg (0.343 mmol) of **22**, 68 mg (0.36 mmol) of p-TsOH·H_2O, and 13 mL of C_6H_6 was heated at reflux with stirring for 15 min [TLC (5% Et_2O/hexane) R_f 0.31 (trace, **22**) and 0.34 (**23**)]. The mixture was cooled, diluted with hexane (200 mL), filtered through a 1-cm silica gel pad (200 mL of 5% Et_2O/hexane), and concentrated to give 133 mg (100%) of **23** as a colorless gum: LC (Radialpak B, 2% Et_2O/hexane, 2 mL/min, 260 nm) t_R 7.6 min (99%); ^1H NMR ($CDCl_3$) δ [(*Z*)-**23**] 0.87 (s, 3.5, 8-CH_3), 1.20 (s, 3.5, 5-CH_3), 1.34 (t, J = 7 Hz, 1.7, CH_2CH_3), 1.54 (s, 2.3, 6,7-CH_2), 2.17 (s, 3.5, $H_3CC{=}CCH_3$), 4.31 (q, J = 7 Hz, 1.2, CH_2CH_3), 6.68 (d, J = 2 Hz, 0.6, 1-NapH), 6.85 (dd, J = 8 Hz, J = 2 Hz, 0.6, 3-NapH), 7.00 (d, J = 8 Hz, 1.2, ArH meta to CO_2Et), 6.80–7.40 (m, NapH), 7.75 (d, J = 8 Hz, 1.2, ArH ortho to CO_2Et); and (**23**) 1.31 (s, 5, 5,8-CH_3), 1.41 (t, J = 7 Hz, 1.3, CH_2CH_3), 1.71 (s, 1.7, 6,7-CH_2), 1.90 (m, 2.5, $H_3CC{=}CCH_3$), 4.39 (q, J = 7 Hz, 0.8, CH_2CH_3), 8.05 (d, J = 8 Hz, 0.8, ArH ortho to CO_2Et). This gum was heated at reflux with 87 mg (0.46 mmol) of p-TsOH·H_2O in 13 mL of C_6H_6 for 6 h. Workup as described above afforded 131 mg (98%) of a colorless oil in which the *Z*:*E* ratio by ^1H NMR was changed from 58:42 to 46:54.

The oil in 200 mL of hexane at 0 °C was irradiated with a 550-W Pyrex-jacketed Hanovia lamp at a distance of 2 cm for 30 min. The solution was filtered through a 2-cm silica gel pad (200 mL of 10% EtOAc/hexane) to give 131 mg (98%) of **23** and (*Z*)-**23** (82:18 by ^1H NMR) as a colorless gum: LC (Radialpak A, MeCN, 1 mL/min, 260 nm) t_R 9.3 [14%, (*Z*)-**23**], 10.3 min (86%, **23**); IR (CCl_4) 1720, 1610, 1500, 1465, 1405, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) signals at δ 7.01 (dd, J = 8 Hz, J = 2 Hz, 0.8, 3-NapH), 7.18 (d, J = 2 Hz, 0.8, 1-NapH), 7.28 (d, J = 8 Hz, 0.8, 4-NapH), and 7.34 (d, J = 8 Hz, 1.6, ArH meta to CO_2Et) were evident, as were the other signals listed above. Attempted crystallization (−80 °C hexane) of the mixture failed.

A mixture of 130 mg (0.333 mmol) of *Z*/*E* esters in 1.33 mL (6.7 mmol) of 5 N aqueous NaOH, 6.0 mL of $MeOCH_2CH_2OH$, and 2.0 mL of Et_2O was stirred under argon for 2 h [TLC (5% Et_2O/hexane) R_f 0.0–0.04 and no 0.36 (**23**)]. The reaction mixture was poured into ice (30 g) and 2 N HCl (12 mL) and extracted with Et_2O (3 × 50 mL). The extracts were washed with brine (3 × 15 mL, pH 5), dried (Na_2SO_4), and concentrated to give 108 mg of a gum, which was dissolved in 10 mL of 50% CH_2Cl_2/hexane. The CH_2Cl_2 was removed by evaporation, and the residue was cooled (−20 °C) to give 42 mg (35%) of 4. The mother liquors were concentrated to a gum, which was dissolved in 5 mL of hexane and irradiated for 15 min. Filtration and crystallization afforded 17 mg (14%) of 4. The total yield was 59 mg (49%) of 4 as fine colorless crystals: mp 204–206 °C; LC (Radialpak A, 35% H_2O/MeOH, 1 mL/min, 260 nm) t_R 29.6 min (100%); IR (CCl_4) 2400–3400, 1690, 1610, 1420, 1315 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (2 s, 12, 5,8-CH_3), 1.71 (s, 4, 6,7-CH_2), 1.89 and 1.93 (2 m, 6, $H_3CC{=}CCH_3$), 7.03 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 7.19 (d, J = 2 Hz, 1, 1-NapH), 7.30 (d, J = 8 Hz, 1, 4-NapH), 7.40 (d, J = 9 Hz, 2, ArH meta to CO_2H), 8.13 (d, J = 9 Hz, 2, ArH ortho to CO_2H); ^{13}C NMR ($CDCl_3$) 22.3, 22.4, 31.9, 34.1, 34.3, 35.3, 125.3, 126.2, 126.4, 127.1, 128.7, 130.2, 131.8, 134.5, 140.6, 143.0, 144.4, 150.9, 171.6 ppm; UV (EtOH) λ_{max} 257 nm (ε 1.7 × 10^4). Anal. ($C_{25}H_{30}O_2$) C, H.

6-Ethenyl-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (24). To a stirred suspension of 23.2 g (65.0 mmol) of $CH_3P(C_6H_5)_3Br$ in 300 mL of THF at −30 °C was added 41 mL (65 mmol) of 1.6 M n-BuLi in hexane over a 15-min period. The orange reaction mixture was warmed slowly to −5 °C over a 30-min period and stirred at −5 °C for 30 min before being cooled to −40 °C. A solution of 10.8 g (50.0 mmol) of **16** in 50 mL of THF was added over a 15-min period. After 1 h at −40 to 0 °C the reaction was complete [TLC (5% Et_2O/5% CH_2Cl_2/hexane) R_f 0.74 (**24**) and no 0.36 (**16**)]. The reaction mixture was poured into ice (200 g) and H_2O (200 mL) and extracted with 10% CH_2Cl_2 (4 × 100 mL). The extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated to give 27 g of a yellow solid, which was dissolved in warm CH_2Cl_2 (80 mL) and diluted with petroleum ether (420 mL). The solid was removed by filtration, and the filtrate was concentrated to 16.7 g of a semisolid, which was chromatographed (200 g of silica gel, 5% Et_2O/hexane) to give 9.6 g (90%) of **24** as a colorless oil; IR (film) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 and 1.29 (2 s, 12, 1,4-CH_3), 1.68 (s, 4, 2,3-CH_2), 5.17 [dd, J = 11 Hz, J = 1 Hz, 1, (*E*)-ArC=CH], 5.68 [dd, J = 18 Hz, J = 1 Hz, 1, (*Z*)-ArC=CH], 6.69 (dd, J = 18 Hz, J = 11 Hz, 1, ArHC=C), 7.10–7.35 (m, 3, 5,7,8-ArH). Anal. ($C_{16}H_{22}$) C, H.

Ethyl *cis*- and *trans*-4-[2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)cyclopropyl]benzoate [26 and (*Z*)-26]. A solution of 17.8 g (100 mmol) of 4-carbethoxybenzaldehyde in 40 mL of EtOH was added to an ice-cooled solution of 6.01 g (0.12 mol) of $(NH_2)_2{\cdot}H_2O$ in 70 mL of EtOH. The reaction mixture was stirred at 0–20 °C for 2.5 h [TLC (50% Et_2O/hexane) R_f 0.26 (hydrazone)] and then diluted with Et_2O (120 mL), dried (Na_2SO_4, cold), and concentrated to an oil, which was diluted with 10% hexane/Et_2O (100 mL). The solution was filtered and then cooled to give 17.8 g (93%) of the hydrazone.

A solution of 17.3 g (90.0 mmol) of the hydrazone in 180 mL of Et_2O was added at −5 °C to a stirred mixture of 23.8 g (110 mmol) of HgO (yellow) and 50 mL of 0.10 M KOH in EtOH. The reaction mixture was stirred at 0 °C for 15 min, warmed slowly to 25 °C, and stirred at 25 °C for 1 h. A gray solid slowly formed. Filtration (2 × 50 mL Et_2O rinse) afforded a red solution, which was concentrated to give a suspension. The suspension was mixed with a solution of 10.7 g (49.7 mmol) of olefin **24** in 50 mL of hexane. The solvents were removed below 50 °C at reduced pressure. The red residue was heated under argon at 80–100 °C for 20 min. Within 10 min of heating, the mixture became brown and the reaction appeared to be complete [TLC (5% Et_2O/5% CH_2Cl_2/hexane) R_f 0.42 (**26**), 0.45 (*cis*-**26**), and 0.80]. The mixture was cooled, diluted with 5% Et_2O/petroleum ether (200 mL), filtered (3-cm pad of silica gel), and concentrated to 17.2 g of a yellow gum. Chromatography (200 g of silica gel, 5% Et_2O/5% CH_2Cl_2/hexane) afforded 0.96 g (9%) of recovered **24**, 0.09 g (0.5%) of *cis*-**26**, and 5.87 g (32%) of a cis/trans mixture of the cyclopropanes. Repeated crystallizations from 5% CH_2Cl_2 followed by recrystallization from 80 mL of hexane (−30 °C) afforded 3.77 g (20%) of **26** as shiny, colorless needles: mp 115–117 °C; IR (CCl_4) 1720, 1610, 1500, 1460, 1365, 1275, 1180, 1110, 1020, 920, 855 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.30 (s, 9, 5,5,8-CH_3), 1.31 (s, 3, 8-CH_3), 1.41 (t, J = 7 Hz, 3, CH_2CH_3), 1.43–1.49 (m, 2, 3-cyclopropyl-H), 1.70 (s, 4, 6,7-CH_2), 2.21 (t, J = 7 Hz, 2, 1,2-cyclopropyl-H), 4.39 (q, J = 7 Hz, 2, CH_2CH_3), 6.89 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 7.13 (d, J = 2 Hz, 1, 1-NapH), 7.19 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.27 (d, J = 8 Hz, 1, 4-NapH), 7.98 (d, J = 8 Hz, 2, ArH ortho to CO_2Et). Anal. ($C_{26}H_{32}O_2$) C, H.

The 0.97 g of residual mother liquors obtained from the purification of **26** was repeatedly preparatively chromatographed (silica gel, 2.5% Et_2O/2.5% CH_2Cl_2/hexane) to give 0.60 g of material enriched in *cis*-**26**, which was crystallized from 5 mL of pentane (−50 °C) to give 0.43 g (2%) of *cis*-**26** as colorless crystals: mp 47–49 °C; IR (CCl_4) 1720, 1615, 1500, 1460, 1365, 1275, 1180, 1110, 1020, 945, 865, 855 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 0.96 and 1.00 (2 s, 6, 8,8-CH_3), 1.15 and 1.16 (2 s, 6, 5,5-CH_3), 1.32 (t, J = 7 Hz, 3, CH_2CH_3), 1.33 (m, 1, 2-cyclopropyl-H cis to Ar, Nap), 1.49 (dt, J = 9 Hz, J = 5 Hz, 1, 2-cyclopropyl-H trans to Ar, Nap), 1.54 (2 s, 4, 6,7-CH_2), 2.44 and 2.49 (2 dt, J = 9 Hz, J = 6 Hz, 2, 1,3-cyclopropyl-H), 6.66 (d, J = 2 Hz, 1, 1-NapH), 6.78 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 6.94 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.03 (d, J = 8 Hz, 1, 4-NapH), 7.73 (d, J = 8 Hz, 2, ArH ortho to CO_2Et). Anal. ($C_{26}H_{32}O_2$) C, H.

***trans*-4-[2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)cyclopropyl]benzoic Acid (5).** A mixture of 3.31 g (8.79 mmol) of **26** and a solution of 11.3 g (176 mmol) of 87% KOH in 90 mL of EtOH and 9 mL of H_2O was stirred under argon at 80 °C for 5 min, at which time hydrolysis was complete [TLC (5% MeOH/$CHCl_3$) R_f 0.0-0.12 and no 0.83 (**26**)]. The mixture was cooled, diluted with ice (200 g) and HOAc (15 mL), and extracted with Et_2O (200 mL, 2 × 50 mL). The extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated to 200 mL before dilution with 100 mL of hexane and reconcentration to 100 mL. Crystallization was completed by cooling to −30 °C (−50 °C hexane rinse) to give 2.97 g (97%) of **5** as a microcrystalline powder: mp 179–181 °C; TLC (25% MeOH/$CHCl_3$) R_f 0.55; LC (Radialpak A, 35% H_2O/MeOH, 2 mL/min, 260 nm) t_R 9.8 min (100%); IR ($CHCl_3$) 2400–3600, 2950, 2925, 2855, 1690, 1610, 1575, 1495, 1460, 1420, 1365, 1315, 1285, 1180, 1110, 1015, 940, 910, 860 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.25 (s, 6, 5,5-CH_3), 1.26 and 1.27 (2 s, 6, 8,8-CH_3), 1.48 and 1.52 (2 dt, J = 7 Hz, J = 5 Hz, 2, 3-cyclopropyl-H), 1.66 (s, 4, 6,7-CH_2), 2.19 (t, J = 7 Hz, 2, 1,2-cyclopropyl-H), 6.86 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 7.10 (d, J = 2 Hz, 1, 1-NapH), 7.18 (d, J = 8 Hz, 2, ArH meta to CO_2H), 7.24 (d, J = 8 Hz, 1, 4-NapH), 8.00 (d, J = 8 Hz, 2, ArH ortho to CO_2H); ^{13}C NMR ($CDCl_3$) 19.0, 28.1, 29.1, 31.9, 34.0, 34.2, 35.2, 122.4, 124.4, 125.5, 126.6, 126.7, 130.4, 138.6, 142.8, 144.9, 149.7, 172.1 ppm; UV (EtOH) λ_{max} 251 nm (ϵ 2.4 × 10^4). Anal. ($C_{24}H_{28}O_2$) C, H.

Ethyl 4-(2-Naphthalenyl)benzoate (29). The Grignard reagent was prepared by the dropwise addition of 5.18 g (25.0 mmol) of 2-bromonaphthalene (**27**) in 40 mL of THF to a stirred suspension of 730 mg (30.0 mmol) of Mg powder in 10 mL of THF at 35–40 °C over a 1-h period followed by heating for 2 h. The reagent was added dropwise to 3.58 g (26.2 mmol) of fused $ZnCl_2$ in 25 mL of THF at −10 °C over a 20-min period followed by stirring at −10 to 0 °C for 3 h. A Ni(0) catalyst solution, prepared by the reduction of 275 mg (0.42 mmol) of $[(C_6H_5)_3P]_2NiCl_2$ and 221 mg (0.84 mmol) of $(C_6H_5)_3P$ in 10 mL of THF with 0.84 mL (0.84 mmol) of 1.0 M DIBAL in hexane at 10 °C for 5 min, was added to the organozinc reagent at 0 °C. Next, 4.58 g (20.0 mmol) of ethyl 4-bromobenzoate (**28**) in 15 mL of THF was added, and the mixture was stirred for 16 h at 20 °C. The reaction mixture was poured onto ice (300 g) and 2 N HCl (30 mL) and extracted with Et_2O (200 mL, 2 × 50 mL). The extracts were washed with brine (2 × 10 mL) and saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated to 7.89 g of a solid [TLC (10% Et_2O/hexane) R_f 0.34 (**29**), 0.46 (**28**), 0.56, 0.62, and no 0.65 (**27**)]. Chromatography (200 g of silica gel, 10% Et_2O/petroleum ether) and crystallization (2% CH_2Cl_2/hexane) afforded 4.66 g (84%) of **29** as fine, colorless crystals: mp 85–87 °C; IR (CCl_4) 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, J = 7 Hz, 3, CH_2CH_3), 4.41 (q, J = 7 Hz, 2, CH_2CH_3), 7.4–8.0 (m, 6, ArH meta to CO_2Et, 5,6,7,8-NapH), 8.06 (br s, 1, 1-NapH), 8.14 (d, J = 8 Hz, 2, ArH ortho to CO_2Et). Anal. ($C_{19}H_{16}O_2$) C, H.

Ethyl 4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)benzoate (31). To a stirred, 10 °C solution of 4.15 g (15.0 mmol) of **29** and 3.30 g (18.0 mmol) of 2,5-dichloro-2,5-dimethylhexane (**30**) in 100 mL of CS_2 was added 4.00 g (30.0 mmol) of $AlCl_3$ in portions over a 10-min period. The reaction mixture was stirred at ambient temperature for 30 min [TLC (5% Et_2O/5% CH_2Cl_2/hexane) R_f 0.28 (**29**), 0.32 (**31**), 0.39, 0.54, and no 0.63 (**30**)]. The mixture was poured onto ice (200 g) and 2 N HCl (20 mL) and extracted with Et_2O (200 mL, 2 × 100 mL). The extracts were washed with brine (20 mL) and saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated to 7.10 g of a pink solid, which after chromatography (200 g of silica gel, 5% Et_2O/5% CH_2Cl_2/hexane) and crystallization (25% hexane/EtOH) afforded 4.34 g (75%) of **31** as shiny, colorless plates: mp 120–122 °C; IR (CCl_4) 1720, 1610 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.43 (s, 12, 5,8-CH_3), 1.44 (t, J = 7 Hz, 3, CH_2CH_3), 1.81 (s, 4, 6,7-CH_2), 4.43 (q, J = 7 Hz, 2, CH_2CH_3), 7.66 (dd, J = 9 Hz, J = 2 Hz, 1, 3-AnthH), 7.79 (d, J = 9 Hz, 2, ArH meta to CO_2Et), 7.83 (s, 1, 9-AnthH), 7.84 (d, J = 9 Hz, 1, 4-AnthH), 7.87 (s, 1, 10-AnthH), 8.02 (br s, 1, 1-AnthH), 8.15 (d, J = 9 Hz, 2, ArH ortho to CO_2Et). Anal. ($C_{27}H_{30}O_2$) C, H.

4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)benzoic Acid (6). A suspension of 2.41 g (6.24 mmol) of **31** in 70 mL of MeOH to which was added 3.60 g (56.0 mmol) of 87% KOH in 6 mL of H_2O and 14 mL of MeOH was heated at reflux (70 °C) with stirring for 0.5 h [TLC (5% MeOH/$CHCl_3$) R_f 0.0, 0.13, and no 0.85 (**31**)]. The resultant clear solution was cooled and poured onto ice (200 g) and 2 N HCl (50 mL) and extracted with Et_2O (400 mL, 2 × 50 mL). The extracts were washed with brine (3 × 20 mL), dried (Na_2SO_4), diluted with hexane (200 mL), and then concentrated to 100 mL to initiate crystallization of 1.95 g (87%) of **6**, which was isolated as shiny, colorless needles: mp 270–272 °C; LC (Radialpak A, 35% H_2O/MeOH, 1 mL/min, 260 nm) t_R 10.8 min (100%); IR (mull) 1680, 1610, 1425 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$/5% Me_2SO-d_6) δ 1.28 (s, 12, 5,8-CH_3), 1.66 (s, 4, 6,7-CH_2), 7.52 (dd, J = 8 Hz, J = 2 Hz, 1, 3-AnthH), 7.65 (d, J = 8 Hz, 2, ArH meta to CO_2H), 7.68 (s, 1, 9-AnthH), 7.69 (d, J = 8 Hz, 1, 4-AnthH), 7.73 (s, 1, 10-AnthH), 7.88 (br s, 1, 1-AnthH), 8.02 (d, J = 8 Hz, 2, ArH ortho to CO_2H); ^{13}C NMR ($CDCl_3$/5% Me_2SO-d_6) 32.5, 34.6, 35.0, 124.3, 124.7, 125.4, 125.5, 126.9, 127.8, 129.4, 130.3, 131.3, 131.9, 136.4, 145.0, 145.5, 168.4 ppm; UV (EtOH) λ_{max} 224 (ϵ 3.6 × 10^4), 267 (ϵ 5.1 × 10^4), 303 nm (ϵ 1.8 × 10^4). Anal. ($C_{25}H_{26}O_2$) C, H.

1,2,3,4-Tetrahydro-1,1,4,4,7-pentamethyl-6-nitronaphthalene (32). To 60 mL of stirred concentrated HNO_3 at −5 to −10 °C (internal) was added over a 20-min period a solution of 12.0 g (59 mmol) of **10**, prepared by the method of Myhre and Schubert,[20] in 60 mL of Ac_2O (10-mL rinse). The yellow suspension was stirred in an ice bath for 20 min [TLC (pentane) R_f 0.14 (**32**) and no 0.74 (**10**)], poured onto ice (300 g), and extracted with C_6H_6 (2 × 200 mL). The extracts were washed with H_2O (3 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), and concentrated to afford 13.5 g of a yellow solid, from which polar material was removed by LC (4% EtOAc/hexane, sample loaded in C_6H_6), giving 8.8 g of yellow crystals. Washing (hexane) the

crystals gave 6.0 g (41%) of **32** as an off-white solid: mp 152–154 °C; LC (3% EtOAC/hexane, 2 mL/min, 260 nm) t_R 1.0 (99%), 1.2 min (1%); IR ($CHCl_3$) 1620, 1560, 1510, 1460, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 12, 1,4-CH_3), 1.70 (s, 4, 2,3-CH_2) 2.57 (s, 3, 7-CH_3), 7.25 (s, 1, 8-ArH), 8.00 (s, 1, 5-ArH); MS calcd for $C_{15}H_{21}NO_2$ 247.157, found 247.158.

6-Amino-1,2,3,4-tetrahydro-1,1,4,4,7-pentamethylnaphthalene (33). A solution of 4.2 g (17 mmol) of **32** in 175 mL of EtOH and 90 mL of *p*-dioxane containing 1.0 g of 5% Pd/C was hydrogenated (25–30 psi) at room temperature for 20 h before 2 g of Celite was added, and the mixture was filtered through a pad of Celite and concentrated to give 3.7 g of green crystals. Chromatography (450 g of silica gel, 25% Et_2O/hexane) and recrystallization (hexane) gave 2.26 g (61%) of **33** as yellow crystals: mp 96–97 °C; LC (Radialpak B, 25% Et_2O/hexane, 2 mL/min, 260 nm) t_R 4.2 min (100%); IR ($CHCl_3$) 3380, 2960, 1630, 1500, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (s, 12, 1,4-CH_3), 1.6 (s, 4, 2,3-CH_2), 2.15 (s, 3, 7-CH_3), 3.4 (br s, 2, NH_2), 6.6 (s, 1, 5-ArH), 7.0 (s, 1, 8-ArH); MS calcd for $C_{15}H_{23}N$ 217.183, found 217.182.

6-Bromo-1,2,3,4-tetrahydro-1,1,4,4,7-pentamethylnaphthalene (35). A literature method[21] was modified. To a solution of 7.90 g (60.2 mmol) of hexyl nitrite (**34**) in 125 mL of $CHBr_3$ at 95 °C was added over a 15-min period 10.9 g (50.2 mmol) of **33** in 25 mL of $CHBr_3$. The reaction mixture was stirred at 95 °C for 1.5 h and cooled to room temperature. Most of the $CHBr_3$ was removed at reduced pressure, and the residue was chromatographed (750 g of silica gel, hexane) to give 10.1 g of a solid, which was evaporatively distilled (110 °C, 0.05 mmHg), affording 9.0 g of white solid. This solid was crystallized (hexane) to give 3.65 g (26%) of **35** as a white solid: mp 92–93.5 °C; TLC (hexane) R_f 0.55; IR ($CHCl_3$) 2960, 1480, 1390, 1365, 1080, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 12, 1,4-CH_3), 1.65 (s, 4, 2,3-CH_2), 2.35 (s, 3, 7-CH_3), 7.15 (s, 1, 8-ArH), 7.45 (s, 1, 5-ArH); MS calcd for $C_{15}H_{21}{}^{79}Br$ 280.083, found 280.081.

Ethyl 6-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-2-naphthalenecarboxylate (37). A solution of 3.65 g (14.5 mmol) of **35** in 8 mL of Et_2O was added to a 0 °C, stirred mixture of 0.553 g (79.7 mmol) of Li (1% Na) wire (prewashed with Et_2O, MeI, and Et_2O) in 5 mL of Et_2O. The mixture was stirred 2 h at 0 °C, cooled to −10 °C, and added to 2.00 g (15.2 mmol) of fused $ZnCl_2$ in 25 mL of THF at −5 °C. The zincate was stirred for 1 h at −5 °C and then added to a solution of 3.2 g (11 mmol) of ethyl 2-bromo-6-naphthalenecarboxylate (**36**) and 0.18 g (0.16 mmol) of $[(C_6H_5)_3P]_4Ni$ in 20 mL of THF at 5 °C. After 3 h, GC (3% OV-1, 200 °C, 1 min, 16 °C/min to 330 °C) indicated that the coupling reaction had stopped (40% of **36** remained). The mixture was poured onto ice (100 g) and cold 10% HCl (20 mL) and extracted with Et_2O (3 × 70 mL). The extracts were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give 5.1 g of a yellow oil, which was chromatographed (silica gel, 9% EtOAc/6% C_6H_6/hexane) to give 1.1 g (24%) of **37** as white crystals: mp 120–122 °C; TLC (9% EtOAc/6% C_6H_6/hexane) R_f 0.58; LC (Radialpak A, MeCN, 2 mL/min, 260 nm) t_R 4.0 min (100%), (Radialpak B, 2% EtOAc/hexane, 1 mL/min, 260 nm) t_R 4.0 min (100%); IR ($CHCl_3$) 2950, 1710, 1635, 1480, 1370, 1290, 1140, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 and 1.35 (2 s, 12, 5,8-CH_3), 1.46 (t, J = 7 Hz, 3, CH_2CH_3), 1.72 (s, 4, 6,7-CH_2), 2.29 (s, 3, 3-CH_3), 4.46 (q, J = 7 Hz, 2, CH_2CH_3), 7.23 and 7.25 (2 s, 2, 1,4-ArH), 7.56 (dd, J = 8 Hz, J = 2 Hz, 1, 7-NapH), 7.82 (br s, 1, 5-NapH), 7.82 (br s, 1, 5-NapH), 7.88 (d, J = 9 Hz, 1, 4-NapH), 7.97 (d, J = 8 Hz, 1, 8-NapH), 8.09 (dd, J = 9 Hz, J = 2 Hz, 1, 3-NapH), 8.64 (br s, 1, 1-NapH). Anal. ($C_{28}H_{32}O_2$) C, H.

6-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-2-naphthalenecarboxylic Acid (8). A mixture of 1.50 g (3.74 mmol) of **37** in a solution of 2.3 g (41 mmol) of 85% KOH in 4 mL of H_2O and 36 mL of EtOH was heated at reflux for 15 min, cooled to room temperature, diluted with cold H_2O (20 mL), and acidified with HOAc. The milky suspension was extracted with Et_2O (500 mL); the extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 1.5 g of a white solid, which was crystallized (EtOAc) to afford 1.2 g (86%) of **8** as a fluffy white solid: mp 263–265 °C; LC (Radialpak A, MeOH, 1 mL/min, 260 nm) t_R 8.6 min (100%); IR ($CHCl_3$) 2400–3300, 1695, 1630, 1480, 1285, 1140 cm^{-1}; 300-MHz ^1H NMR (Me_2SO-d_6) δ 1.24 and 1.27 (2 s, 12, 5,8-CH_3), 1.64 (s, 4, 6,7-CH_2), 2.21 (s, 3, 3-CH_3), 7.20 and 7.25 (2 s, 2, 1,4-ArH), 7.58 (dd, J = 8 Hz, J = 1 Hz, 1, 7-NapH), 7.91 (br s, 1, 5-NapH), 7.98 (d, J = 9 Hz, 1, 4-NapH), 8.02 (d, J = 8 Hz, 1, 8-NapH), 8.13 (d, J = 9 Hz, 1, 3-NapH), 8.63 (br s, 1, 1-NapH); ^{13}C NMR (Me_2SO-d_6) 19.9, 31.6, 33.5, 34.7, 125.4, 127.3, 127.5, 127.9, 128.2, 128.9, 130.2, 130.9, 131.8, 134.9, 138.2, 141.6, 142.0, 143.7, 167.4 ppm; UV (EtOH) λ_{max} 233 (ϵ 5.0 × 10^4), 291 nm (ϵ 1.3 × 10^4). Anal. ($C_{26}H_{28}O_2$) C, H.

6-Bromo-3-methyl-1*H*-indene (41). To a stirred solution of 0.34 mol of MeMgBr in 400 mL of Et_2O was added over a 40-min period by cannula under argon pressure a solution of 26.0 g (0.123 mol) of **40**[24] in 1.2 L of Et_2O. The solution was then heated at reflux for 1 h, cooled, poured into ice (1.5 kg) and saturated NH_4Cl (500 mL), and shaken until the precipitate dissolved. The aqueous phase was extracted with Et_2O (2 × 500 mL). The combined extracts were washed with brine (3 × 200 mL), dried (Na_2SO_4), and concentrated to give 29.5 g of 5-bromo-1-methyl-1-indanol as a dark semisolid. The analytical sample was obtained by crystallization (hexane) as large, pale yellow crystals: mp 69–70.5 °C; TLC (35% EtOAc/hexane) R_f 0.57; IR ($CHCl_3$) 3550, 1600, 1305, 1185 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (s, 3, CH_3), 1.83 (s, 1, OH), 2.19 (m, 2, $ArCH_2CH_2$), 2.90 (m, 2, $ArCH_2$), 7.25 (m, 3, ArH). Anal. ($C_{10}H_{11}BrO$) C, H, Br.

A suspension of 29.1 g of the crude alcohol in 370 mL of 1.35 N H_2SO_4 was heated in a 120 °C oil bath for 40 min and then cooled. The oily suspension was extracted with CH_2Cl_2 (2 × 150 mL). The extract was washed with H_2O (50 mL), 5% NaOH (50 mL), and H_2O (2 × 50 mL), dried (Na_2SO_4), and concentrated to give 26.4 g of a dark oil, which was chromatographed (silica gel, 5% CH_2Cl_2/hexane) to give 21.2 g (83% from **40**) of **41** as very pale yellow needles. The analytical sample was obtained by two recrystallizations (hexane) as white needles: mp 31–32 °C; TLC (hexane) R_f 0.66; IR ($CHCl_3$) 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (m, 3, C=CCH_3), 3.27 (m, 2, $ArCH_2$), 6.17 (m, 1, C=CH), 7.16 (d, J = 8 Hz, 1, 4-ArH), 7.41 (d, J = 8 Hz, 1, 5-ArH), 7.53 (s, 1, 7-ArH); UV (EtOH) λ_{max} 259 nm (ϵ 1.5 × 10^4). Anal. ($C_{10}H_9Br$) C, H, Br.

3-Methyl-1*H*-indene-6-carbonitrile (42). A mixture of 1.05 g (5.02 mmol) of **41** and 0.605 g (6.75 mmol) of CuCN in 2.5 mL of DMF was heated at reflux under argon for 22 h and cooled. The dark suspension was then stirred with a solution of 3.0 g (11 mmol) of $FeCl_3 \cdot 6H_2O$ in 5 mL of H_2O and 0.75 mL (9 mmol) of concentrated HCl with heating in a 70–75 °C oil bath for 25 min. The mixture was diluted with H_2O (30 mL) and toluene (30 mL) and filtered to remove copper salts (2 × 30 mL of toluene rinse). The toluene rinses were used to reextract the aqueous phase. The combined red organic extracts were washed with 10-mL portions of 1 N HCl, 5% NaOH, and brine, dried (Na_2SO_4), and concentrated. Chromatography (silica gel, 50% CH_2Cl_2/hexane) and crystallization (hexane) afforded 0.51 g (65%) of **42** as a yellow solid: mp 35.5–36.5 °C; TLC (10% EtOAc/hexane) R_f 0.47, (50% CH_2Cl_2/hexane) R_f 0.49; IR ($CHCl_3$) 2200, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (m, 3, C=CCH_3), 3.36 (m, 2, $ArCH_2$), 6.43 (m, 1, C=CH), 7.37 (d, J = 8 Hz, 1, 4-ArH), 7.62 (d, J = 8 Hz, 1, 5-ArH), 7.68 (s, 1, 7-ArH); UV (EtOH) λ_{max} 224 (ϵ 1.1 × 10^4), 274 nm (ϵ 1.8 × 10^4). Anal. ($C_{11}H_9N$) C, H, N.

6-Bromo-5-methylnaphthalene-2-carbonitrile (44). A solution of 5.20 g (33.5 mmol) of **42** and 35.5 g (67.1 mmol) of $C_6H_5HgCBr_3$ (**43**)[23] in 150 mL of C_6H_6 was heated at reflux under argon for 16 h and cooled. The light brown suspension was filtered to remove white, solid C_6H_5HgBr (100 mL of C_6H_6 rinse). The filtrate was concentrated to a solid, which was extracted with 33% CH_2Cl_2/hexane (100 mL). The extract was concentrated, and the residue was chromatographed (silica gel, 35% CH_2Cl_2/hexane) to give 7.52 g of a white solid, which was crystallized (180 mL of MeOH) to give 6.59 g (80%) of **44** as very pale yellow crystals, mp 130–132 °C. Analytically pure material was obtained by two recrystallizations (EtOH): mp 133–134 °C; TLC (15% EtOAc/hexane) R_f 0.47, (50% CH_2Cl_2/hexane) R_f 0.53; IR ($CHCl_3$) 2200, 1610, 1570, 1300, 1110 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 2.78 (s, 3, CH_3), 7.57 (d, J = 9 Hz, 1, 7-ArH), 7.64 (dd, J = 9 Hz, J = 2 Hz, 1, 3-ArH), 7.71 (d, J = 8 Hz, 1, 8-ArH), 8.09 (d, J = 9 Hz, 1, 4-ArH), 8.16 (d, J = 2 Hz, 1, 1-ArH); UV (EtOH) λ_{max} 245 (ϵ 8.2 × 10^4), 291 nm (ϵ 8.0 × 10^3). Anal. ($C_{12}H_8BrN$) C, H, N, Br.

6-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-5-methyl-2-naphthalenecarbonitrile (46). To 0.36 g (15

mmol) of granular Mg was added over a 5-min period under argon with stirring in a 50 °C oil bath a solution of 3.21 g (12.0 mmol) of **45** in 18 mL of THF. The reaction was initiated with 15 μL of MeI after 0.33 mL of **45** had been added. The mixture was maintained at 50 °C for 15 min, cooled to room temperature, and then added under argon to a stirred solution of 1.80 g (13.2 mmol) of fused $ZnCl_2$ in 15 mL of THF. The zincate was stirred for 35 min. A solution of 2.00 g (8.13 mmol) of **44** in 8 mL of THF was added, followed at 15-min intervals by three 5-mL aliquots of a Ni(0) catalyst solution, prepared by reduction at room temperature under argon of a solution of 0.82 g (1.25 mmol) of $[(C_6H_5)_3P]_2NiCl_2$ and 0.66 g (2.5 mmol) of $(C_6H_5)_3P$ in 3.5 mL of THF by 2.5 mL (2.5 mmol) of 1 M DIBAL in hexane. The brown suspension was stirred at room temperature for 20 h, treated with 40 mL of 1 N HCl with stirring for 1 h, and extracted with EtOAc (100 mL). The extract was washed with H_2O (30 mL). The aqueous phases were extracted with EtOAc (30 mL). The yellow extracts were washed with 10-mL portions of 1 N HCl, H_2O, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated to a yellow gum, which was chromatographed (silica gel, 35% CH_2Cl_2/hexane) to give 1.61 g (56%) of **46** as a white solid. Crystallization (CH_2Cl_2/hexane) gave analytical material as white crystals: mp 176–176.5 °C; TLC (10% EtOAc/hexane) R_f 0.56, (50% CH_2Cl_2/hexane) R_f 0.52; LC (Radialpak B, 5% Et_2O/hexane, 1 mL/min, 260 nm) t_R 9.0 min (100%); IR ($CHCl_3$) 2225, 1610, 1190 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.30 and 1.34 (2 s, 12, 5,8-CH_3), 1.73 (s, 4, 6,7-CH_2), 2.63 (s, 3, NapCH_3), 7.12 (dd, J = 8 Hz, J = 2 Hz, 1, 3-ArH), 7.27 (d, J = 2 Hz, 1, 1-ArH), 7.38 (d, J = 8 Hz, 1, 4-ArH), 7.53 (d, J = 8 Hz, 1, 7-NapH), 7.66 (dd, J = 9 Hz, J = 2 Hz, 1, 3-NapH), 7.76 (d, J = 8 Hz, 1, 8-NapH), 8.16 (d, J = 9 Hz, 1, 4-NapH), 8.22 (d, J = 2 Hz, 1, 1-ArH); UV (EtOH) λ_{max} 233 (ε 4.7 × 10^4), 246 (ε 5.2 × 10^4), 304 nm (ε 1.2 × 10^4). Anal. ($C_{26}H_{27}N$) C, H, N.

6-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-5-methyl-2-naphthalenecarboxylic Acid (9). A suspension of 1.61 g (4.55 mmol) of **46** in 60 mL of EtOH and 6 mL of 40% aqueous NaOH was heated at reflux under argon for 24 h. The nitrile dissolved at reflux temperature, and then a white solid formed. The white suspension was cooled, diluted with 300 mL of H_2O containing 12 mL of concentrated HCl, stirred for 45 min, and filtered. The white solid was washed with H_2O (200 mL), dried, and dissolved in hot acetone (250 mL). Filtration, concentration to 100 mL, and cooling (−20 °C) afforded 1.41 g (83%) of **9** as white crystals: mp 267.5–269 °C; TLC (5% MeOH/CH_2Cl_2) R_f 0.44; LC (Radialpak A, 20% H_2O/MeOH, 1 mL/min, 260 nm) t_R 10.2 min (100%); IR (Nujol) 2300–3200, 1680, 1620 cm^{-1}; 400-MHz ^1H NMR (Me_2SO-d_6) δ 1.30 and 1.32 (2 s, 12, 5,8-CH_3), 1.71 (s, 4, 6,7-CH_2), 2.61 (s, 3, NapCH_3), 7.16 (dd, J = 8 Hz, J = 2 Hz, 1, 3-ArH), 7.32 (d, J = 2 Hz, 1, 1-ArH), 7.41 (d, J = 8 Hz, 1, 4-ArH), 7.46 (d, J = 8 Hz, 1, 7-NapH), 7.96 (d, J = 8 Hz, 1, 8-NapH), 8.06 (dd, J = 8 Hz, J = 2 Hz, 1, 3-NapH), 8.17 (d, J = 9 Hz, 1, 4-NapH), 8.59 (d, J = 2 Hz, 1, 1-NapH); ^{13}C NMR (Me_2SO-d_6) 16.1, 31.6, 31.6, 33.8, 34.0, 34.7, 34.7, 124.8, 125.6, 126.2, 126.7, 127.2, 127.6, 127.6, 128.9, 130.3, 130.8, 131.4, 134.6, 138.5, 140.8, 143.1, 144.2, 167.4 ppm; UV (95% aqueous EtOH) λ_{max} 249 (ε 5.8 × 10^4), 294 nm (ε 1.2 × 10^4). Anal. ($C_{26}H_{28}O_2$) C, H.

Pharmacology. Hamster TOC Assay. The protocol for the assay of the reversal by retinoids of keratinization of retinoid-deficient hamster tracheal epithelial cells in organ culture was essentially that described by Newton et al.[29] and was conducted as described. At least six cultures were assayed at each retinoid concentration. The ID_{50} values were calculated by polynomial interpolation of the data.

Isolation and Culture of Rabbit Tracheal Epithelial Cells. Tracheal epithelial cells were isolated from tracheas of male New Zealand White rabbits (Hazelton, Denver, PA) as described.[51] Approximately 5 × 10^4 cells were plated in 60-mm dishes that were pretreated for 2 h with a solution of 10 μg/mL fibronectin, 10 μg/mL BSA, and 30 μg/mL vitrogen (Collagen Corp., Palo Alto, CA). Cells were grown in Ham's F12 medium supplemented with 10 μg/mL insulin, 5 μg/mL transferrin, 25 ng/mL epidermal growth factor, and 0.5% hypothalamic extract. Cells were treated with various retinoids in Me_2SO at day 5 of culture (approximately 1.5 × 10^6 cells/dish) for 5 days before transglutaminase activity and cholesterol 3-sulfate levels were determined.

Type I Transglutaminase Inhibition Assay. Rabbit tracheal epithelial cells grown to confluency in 60-mm dishes were washed twice with phosphate-buffered saline (PBS) and stored at −70 °C until the assay was performed. After thawing, the cells were scraped into 200 μL of PBS containing 10 mM dithiothreitol and briefly sonicated. Transglutaminase activity was determined in triplicate by measuring the incorporation of [^3H]putrescine into casein as described.[51]

Cholesterol 3-Sulfate Inhibition Assay. Rabbit tracheal epithelial cells in 60-mm dishes were metabolically radiolabeled by incubation for 22 h with 25 μCi of carrier-free $Na_2{}^{35}SO_4$/mL. Cells were harvested after digestion with 2 mL of trypsin/EDTA solution and pelleted by centrifugation. Cell pellets were extracted by the addition of 4 mL of $CHCl_3$/MeOH (92:1), followed by sonication for 10 s. The inhibition of $^{35}SO_4$ incorporation into cholesterol 3-sulfate was determined as described.[52] Retinoids were assayed at 0.1 and 10 nM. Approximately a 15% variation in the amount of cholesterol 3-sulfate inhibition relative to the control was found when the retinoids were assayed.

Cross-Linked Envelope Formation. At day 6 of culture, rabbit tracheal epithelial cells were incubated with 1 × 10^{-8} M retinoid, and cross-linked envelope formation was determined as described[52] on day 12. Measurements were performed in triplicate.

ODC Assay. The procedure for the assay of the inhibitory effect of retinoids on the induction of ornithine decarboxylase in CD-1 mouse dorsal epidermis treated with the tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate was that described by the group of Verma and Boutwell.[53] This assay was performed in triplicate on three groups of three mice each.

F9 Laminin Release Assay.[54] F9 embryonal carcinoma cells growing on nongelatinized plates were treated for 96 h with 1 mM dibutyryl-cAMP and graded concentrations of the retinoids in 5 μL ethanol, ethane, with medium changes every 24 h. Each compound was assayed in triplicate. Compounds for which ED_{50} values are given in Table I were assayed over the concentration range of 1 pM–1 μM (**1–3**) or 10 pM–5 μM (**5–7**). Testing of three of the compounds (**4**, **8**, and **9**) was limited by their low solubility in the ethanol vehicle. The amount of laminin secreted into the medium in the final 24 h was measured in triplicate by a nonequilibrium ELISA,[55] modified for use with medium from cultured cells. Data were analyzed statistically and fitted to dose–response curves by the Allfit program,[56,57] rewritten for use with an IBM PC. Compounds **4–9** had ED_{50} values that were significantly different from that of retinoic acid (P <0.01).

F9 Plasminogen Activator Release Assay.[33,58] F9 cells were plated at a density of 1 × 10^5 cells/mL on 85-mm tissue culture dishes in Dulbecco's modified essential medium containing 15% fetal bovine serum. The cells were allowed to attach to the culture dishes for 24 h at 37 °C in 5% CO_2 atmosphere. Retinoids (10^{-11}–10^{-7} M) were added in Me_2SO. After 4 days, 20 μL of harvest fluid was mixed with 0.13 M plasminogen, 0.3 mM H-D-Val-Leu-Lys-*p*-NA, 24 μg of fibrinogen fragments, and 0.1% Tween-80. Absorbance at 405 nm at 2, 4, and 6 h at 25 °C was plotted against concentration. Assays were performed in triplicate. The midpoint between the maximal and minimal absorbance values of a retinoid corresponded to its ED_{50} value.

Retinoid Binding to Rat Testis CRABP. CRABP was partially purified from rat testis according to Ong and Chytil.[59]

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CRABP was purified through the DEAE-cellulose step at pH 8.3 and incubated with 3×10^{-6} M [^{3}H] *all-trans*-retinoic acid alone (control) or in the presence of retinoids. The competition for binding was determined by Sephadex G-25 gel filtration on 2-mL columns as described.[60] Binding measurements were performed in triplicate.

Retinoid Binding to Chick Embryo CRABP. CRABP from 12- to 13-day-old chick skins was used.[61] Affi-Gel Blue column chromatography was used to remove albumin, which also binds retinoids. Portions of the protein eluates (1 mg of protein/0.4 mL) were incubated with saturable amounts of [^{3}H]-*all-trans*-retinoic acid in the presence or absence of 1-, 5-, 10-, and 25-fold molar excess of unlabeled retinoid. Free retinoids were removed by adsorption on dextran-coated charcoal, the solution was filtered (0.65-μm membrane), and the amount of radioactivity bound was determined. The specific binding of [^{3}H]-*all-trans*-retinoic acid to CRABP was calculated as the difference between the totally bound radioactivity at a particular concentration of 1 and the total nonspecifically bound radioactivity after competition with a 25-fold molar excess of unlabeled **1**. ID_{50} values were calculated from the semilog plots of the molar concentration of the retinoid against the percent inhibition of labeled retinoic acid by the retinoid. Binding measurements were performed in triplicate.

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Registry No. **2**, 71441-28-6; **3**, 119999-05-2; (*Z*)-**3**, 119999-31-4; **4**, 119999-06-3; (±)-**5**, 119999-07-4; **6**, 107430-51-3; **7**, 86471-16-1; **8**, 119999-08-5; **10**, 6683-48-3; **11**, 119435-90-4; **11** (dibromide), 119999-29-0; **12**, 119436-52-1; **13**, 1443-80-7; **14**, 119999-10-9; (*Z*)-**14**, 119999-30-3; **15**, 119999-11-0; (*Z*)-**15**, 119999-32-5; **16**, 92654-79-0; **16** (acid), 103031-30-7; **17**, 119999-12-1; (±)-**18**, 119999-13-2; (±)-**19**, 119999-14-3; (±)-**20**, 119999-15-4; (±)-**21**, 119999-16-5; (±)-**22**, 119999-17-6; **23**, 119999-18-7; (*Z*)-**23**, 119999-34-7; **24**, 119999-19-8; (±)-**26**, 120022-39-1; (±)-*cis*-**26**, 119999-33-6; **27**, 580-13-2; **28**, 5798-75-4; **29**, 119999-21-2; **30**, 13275-18-8; **31**, 107430-52-4; **32**, 116233-16-0; **33**, 116233-17-1; **34**, 638-51-7; **35**, 119999-22-3; **36**, 86471-14-9; **37**, 119999-23-4; **38**, 108-86-1; **40**, 34598-49-7; **41**, 119999-25-6; **42**, 119999-26-7; **43**, 3294-60-8; **44**, 119999-27-8; **45**, 27452-17-1; **46**, 119999-28-9; 4-$OHC_6H_4CO_2Et$, 6287-86-1; 4-$H_2NN{=}CHC_6H_4CO_2Et$, 119999-20-1; (±)-5-bromo-1-methyl-1-indanol, 119999-24-5.

Supplementary Material Available: Complete biological data for the tracheal organ culture, transglutaminase inhibition, cross-linked envelope formation, ornithine decarboxylase inhibition, F9 plasminogen activator release assays, and rat testis and chick embryo CRABP binding studies (5 pages). Ordering information is given on any current masthead page.

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Synthesis and Antitumor Activity of 5-Deaza-5,6,7,8-tetrahydrofolic Acid and Its N^{10}-Substituted Analogues

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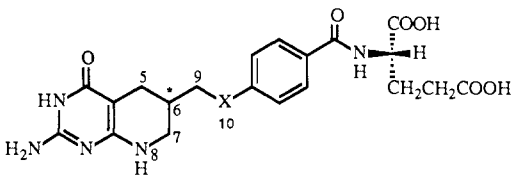
Syntheses of 5-deaza-5,6,7,8-tetrahydrofolic acid (**7a**) and its 10-formyl (**7b**), 10-acetyl (**7c**), and 10-methyl (**7d**) derivatives are described. These compounds, prepared as analogues of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF), the lead compound of a new class of folate antimetabolites, exhibit potent growth inhibition against leukemic cells in culture as well as substantial antitumor activity against transplantable murine solid tumors in vivo.

Recently we reported the synthesis and biological activity of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (**1**) (DDATHF), the lead compound of a new class of folate



1, X = CH_2

7a, X = NH

antimetabolites possessing unique biochemical properties and potent antitumor activity in experimental animals.[1-5] DDATHF has a novel mode of action as compared to conventional antifolates such as methotrexate [which inhibits dihydrofolate reductase (DHFR)] or 10-propargyl-5,8-dideazafolic acid (CB3717) [which inhibits thymidylate synthase (TS)].[6] DDATHF inhibits purine biosynthesis in cultured mouse (L1210) and human (CCRF-CEM)

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