Conformationally Restricted Retinoids

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A series of conformationally restricted retinoids was synthesized and screened in two assays used to measure the ability of retinoids to control cell differentiation, namely, the reversal of keratinization in tracheal organ culture from vitamin A deficient hamsters and the inhibition of the induction of mouse epidermal ornithine decarboxylase by a tumor promoter. These compounds had bonds corresponding to selected bonds of the *E*-tetraene chain of retinoic acid (1) held in a planar cisoid conformation by inclusion in an aromatic ring. The meta-substituted analogue **3** of 4-[(*E*)-2-methyl-4-(2,6,6-trimethylcyclohexenyl)-1,3-butadienyl]benzoic acid (**2**) was far less active than **2** in both assays. In contrast, the vinyl homologue of **2** (**4**) and the 7,8-dihydro and 7,8-methano analogues (**5** and **6**) had activity comparable to that of **2**. Analogues of 4-[(*E*)-2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-6-naphthyl)propenyl]benzoic acid (**7**) were also screened. Replacement of the tetrahydronaphthalene ring of **7** by a benzonorbornenyl group (**9**) significantly reduced activity, as did removal of the vinylic methyl group from **9** (**10**). Replacement of the propenyl group of **9** by a cyclopropane ring (**12**) also reduced activity. Replacement of the tetrahydronaphthalene ring of **7** by 4,4-dimethyl-3,4-dihydro-2*H*-1-benzopyran and -benzothiopyran rings (**13** and **14**) also decreased activity. Inclusion of the 7,9 double bond system of **1** in an aromatic ring (**15** and **16**) reduced activity, whereas inclusion of the 5,7 double bond system in an aromatic ring enhanced activity (**7** and **19**). Inclusion of the 11,13 and 9,11,13 double bond systems in aromatic rings (**2** and **18**) also reduced activity below that of **1**. Retinoic acid, **7**, **13**, **14**, and **19** inhibited papilloma tumor formation in mice. Toxicity testing indicated that **7** was more toxic than **1**, **13**, **14**, and **19**, **19** was more toxic than **1**, and **13** and **14** were less toxic than **1**.

Because of their ability to regulate epithelial cell differentiation, the retinoids, such as retinoic acid, have therapeutic potential for the treatment of proliferative skin diseases, such as acne and psoriasis, and the chemoprevention of cancer.[1] Retinoic acid (**1**) is usually depicted in a conformation in which the *E* double bonds of the tetraene side chain are transoid, as shown in Table I. However, this conformation is not necessarily the one that **1** assumes in controlling differentiation. As part of a program to synthesize more active retinoids and study their structure–activity relationships, we have synthesized a series of conformationally restricted retinoids, the structures of which are shown in Table I. In these compounds certain bonds corresponding to those of the tetraene chain of **1** are held in a cisoid conformation by inclusion in an aromatic ring. In certain cases, the conformation is distorted by replacement of an *E* double bond by a cyclopropane ring. These compounds were screened in two bioassays used to measure the ability of retinoids to regulate cell differentiation, namely, (1) the reversal of keratinization in hamster tracheal organ culture (TOC assay) and (2) the inhibition of the induction of ornithine decarboxylase in mouse epidermis by the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (ODC assay).[2,3] We now report the syntheses and biological testing results for these compounds.

Synthesis. We have previously reported that the trienyl benzoic acid **2**, in which the bonds corresponding to the 11,13*E* double bond system of **1** are part of an aromatic ring, displayed high activity in both the TOC and ODC assays.[4] Analogues **3** and **4** were designed to assess the effect of shortening or lengthening, respectively, the distance between the polar terminus and the β-cyclogeranylidene ring of the retinoid skeleton. The syntheses of **3** and **4** are shown in Scheme I. Both compounds were prepared by stereoselective routes similar to that used to prepare **2**.[4] The stereochemistry of the side chains for these compounds was established from their ^{1}H NMR spectra that show the expected coupling constants for the vinylic protons on the 7_R- and 11_R-double bonds[5] and the positions of the signals for the vinylic protons on the 9_R-double bonds (δ 6.20 for **3** and 6.6 for **4**), which were all indicative of *E*-bond geometry.

Analogues **5** and **6** were designed to probe alterations in geometry about the $7,8_R$-bond. This bond is saturated in **5**, whereas it is replaced by a trans-substituted cyclopropane ring in **6**. Replacement of a double bond by a cyclopropane with retention of biological activity has precedent in the high biological activity displayed by ethyl 5,6-methanoretinoate in the TOC and ODC assays.[6] The syntheses of **5** and **6** are also shown in Scheme I. The starting material was β-ionone, which on reduction with 9-BBN afforded 7,8-dihydro-β-ionone (**28**) and β-ionol (**29**). Reduction with $LiAlH_4$ gave **28**, whereas reduction with $NaBH_4$ afforded **29**. Simmons–Smith cyclopropanation of **29** and Collins oxidation[7] afforded ketone **32**. Baker and

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(1) (a) Sporn, M. B.; Newton, D. L.; Roberts, A. B.; DeLarco, J. E.; Todaro, G. J. In "Molecular Actions and Targets for Cancer, Chemotherapeutic Agents"; Sartorelli, A. C., Bertino, J. R., Lazo, J. S., Eds.; Academic Press: New York, 1980. (b) Bollag, W.; Matter, A. *Ann. N.Y. Acad. Sci.* **1981**, *359*, 9–23. (c) Pawson, B. A.; Ehmann, C. W.; Itri, L. M.; Sherman, M. I. *J. Med. Chem.* **1982**, *25*, 1269–1277.

(2) (a) Sporn, M. B.; Newton, D. L.; Smith, J. M.; Acton, N.; Jacobson, A. E.; Brossi, A. In "Carcinogens: Identification and Mechanism of Action"; Annual Symposium on Fundamental Cancer Research, 31st, M. D. Anderson Hospital and Tumor Research Institute, Houston, 1978; Griffin, S. C., Shaw, C. R., Eds.; Raven Press: New York, 1979; pp 445–453. (b) Newton, D. L.; Henderson, W. R.; Sporn, M. B. *Cancer Res.* **1980**, *40*, 3413–3425.

(3) (a) Verma, A. K.; Shapas, B. G.; Rice, H. M.; Boutwell, R. K. *Cancer Res.* **1979**, *39*, 419–425. (b) Verma, A. K.; Rice, H. M.; Shapas, B. G.; Boutwell, R. K. *Ibid.* **1978**, *38*, 793–801. (c) Verma, A. K.; Boutwell, R. K. *Ibid.* **1977**, *37*, 2196–2201.

(4) Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W.-R.; Fung, V. A. *J. Med. Chem.* **1980**, *24*, 583–592.

(5) For structural comparisons, standard retinoid numbering has been used as shown in structure **1**. Similar proton and carbon atoms in the analogues have been denoted by the subscript R.

(6) Dawson, M. I.; Hobbs, P. D.; Chan, R. L.-S.; Chao, W. *J. Med. Chem.* **1981**, *24*, 1214–1223.

(7) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000–4002.

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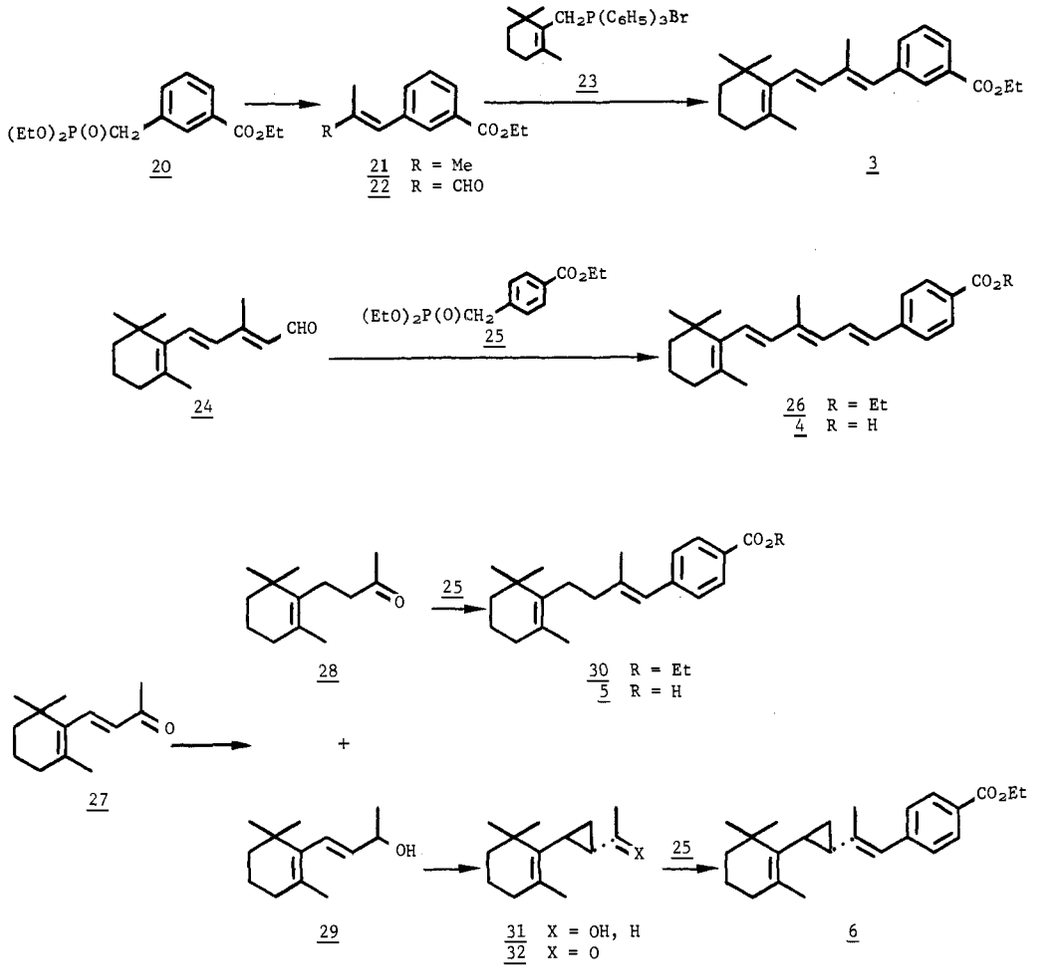
Scheme I



Sims have reported a modification of the Horner–Emmons reaction that affords a high yield of disubstituted *E* olefins.[8] Reaction of ketones **28** and **32** with phosphonate **25**[9] under these conditions yielded the trisubstituted *E* olefins as the major products. The ^{1}H NMR spectra were again used to assign *E*-bond geometry to the major isomers. For example, the vinylic methyl signal for the *Z* isomer of **6** was observed as a doublet (J = 1 Hz) because of allylic coupling to the vinylic proton; this signal for **6** was a singlet. Both the vinylic methyl and the β-cyclogeranylidene ring signals for the *Z* isomer were shifted upfield. Inspection of models indicates that the phenyl ring should cause these upfield shifts because of shielding effects.

The benzonorbornenes **9–12** have the bonds corresponding to the 5,7*E*- and 11,13*E* double bond systems of **1** in a cisoid conformation by inclusion in aromatic rings and were designed as analogues of **7** (Ro13-7410) because this compound is reported to show high activity in reversing the growth of papilloma tumors in mice.[10] These compounds are also analogues of the norbornenyl retinoid **8**,[11] which was too labile to display good activity in the TOC assay but did show significant activity in the ODC assay. The synthesis of these compounds is given in Scheme II. The starting material was benzonorbornene (**33**), which was prepared by Diels–Alder reaction of benzyne with cyclopentadiene[12] and hydrogenation. Friedel–Crafts acylation of **33** afforded ketone **34**. Horner–Emmons olefination of **34** with **25** using *n*-BuLi as the base afforded a 2:1 mixture of **36** and **35**, which on irradiation (Hanovia lamp)[10a] gave a 1:1 mixture of isomers. Hydrolysis of **35** gave **9**. Compounds **9** and **35** were assigned *E* double bond geometry by comparison of the UV and ^{1}H NMR spectra with those reported for **7** and its *Z* isomer.[10a] In **7** and its *Z* isomer, the vinylic proton signals appeared at δ 6.85 and 6.46, respectively, and in **35** and **36** they appeared at δ 6.81 and 6.42. The UV absorption maxima and the extinction coefficients were also greater in the *E* isomers.

Attempts to prepare aldehyde **38**, the starting material for the synthesis of compounds **10–12**, were not successful using **33** and DMF/$POCl_3$ or HCl/CO in the presence of $AlCl_3$/CuCl.[13] The former reagents gave only starting material and the latter several products, none of which showed a formyl proton by ^{1}H NMR. Therefore, aldehyde **38** was synthesized by haloform reaction of ketone **34** to the carboxylic acid **37**, followed by reduction and Collins oxidation. Horner–Emmons olefination of **38** with the anion of **25** gave **10**. The ^{1}H NMR coupling constant for the two vinylic protons of **10** was 16 Hz, which is indicative of *E* double bond geometry.

The double bond of **10** was deactivated to cyclo-

(8) Baker, R.; Sims, R. J. *Synthesis* **1981**, 117.
(9) Kreutzkamp, N.; Cordes, G. *Arch. Pharm. (Weinheim, Ger.)* **1961**, *294*, 49–56.
(10) (a) Loeliger, P.; Bollag, W.; Mayer, H. *Eur. J. Med. Chem.* **1980**, *15*, 9–15. (b) Bollag, W. *Cancer Chemother. Pharmacol.* **1981**, *7*, 27–29.
(11) Dawson, M. I.; Hobbs, P. D.; Kuhlmann, K.; Fung, V. A.; Helmes, C. T.; Chao, W.-R. *J. Med. Chem.* **1980**, *23*, 1013–1022.
(12) Wittig, G.; Knauss, E. *Chem. Ber.* **1958**, *91*, 895–907.
(13) Coleman, G. H.; Craig, D. In "Organic Syntheses"; Blatt, A. H., Ed.; Wiley: New York, 1963; Vol. 2, pp 583–586.

Table I. Activity of Retinoids in the TOC and ODC Assays

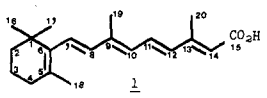
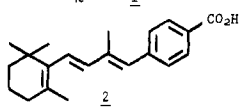
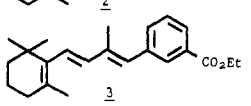
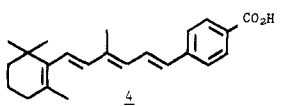
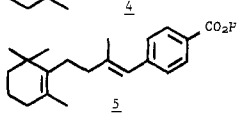
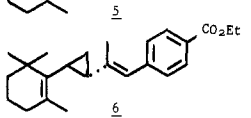
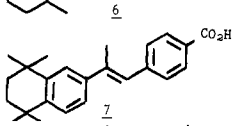
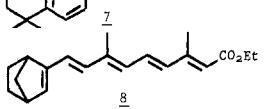
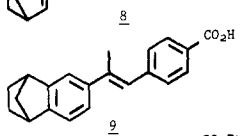
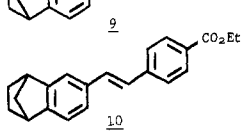
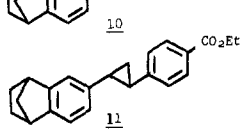
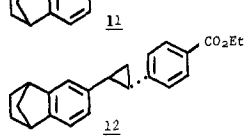
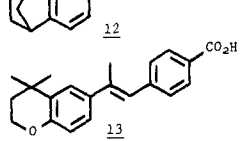
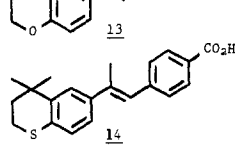
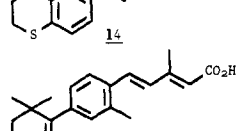
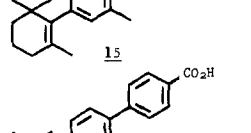
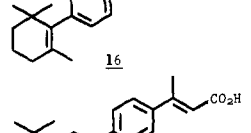
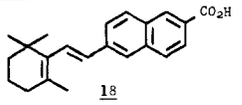
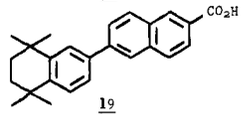
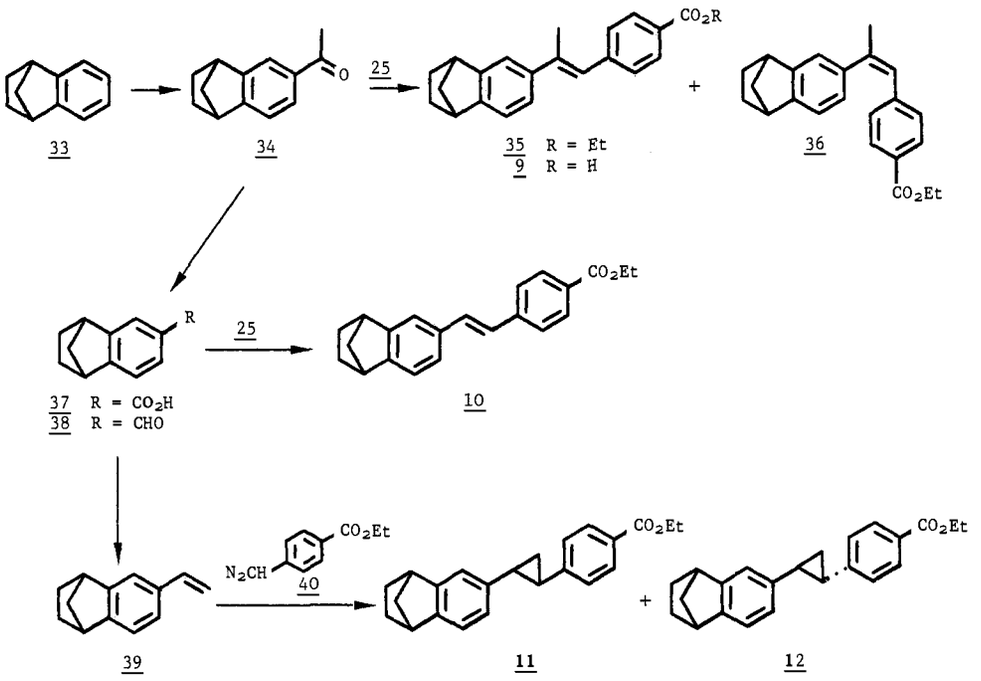
retinoid	TOC			ODC	
	concn, M	active/total cultures, %	ED_{50}[a]	dose, nmol	% inhibn of control
 1	10^{-10}	18/19 (95)	1×10^{-11}	1.7	88 ± 1[d]
	10^{-11}	10/20 (50)			
	10^{-12}	3/19 (16)			
 2			3×10^{-10}[c]	17	77 ± 6[d]
				1.7	34 ± 13[e]
 3	10^{-8}	1/7 (14)	$>10^{-8}$	17	6 ± 4[f]
	10^{-9}	1/6 (17)		1.7	13 ± 3[f]
	10^{-10}	2/7 (29)			
 4	10^{-8}	6/7 (86)	4×10^{-10}	17	56 ± 4[d]
	10^{-9}	4/7 (57)		1.7	33 ± 8[e]
	10^{-10}	3/7 (43)			
 5	10^{-8}	7/7 (100)	3×10^{-10}	17	83 ± 4[d]
	10^{-9}	14/15 (93)		1.7	45 ± 12[e]
	10^{-10}	4/15 (27)			
	10^{-11}	1/8 (13)			
 6	10^{-8}	7/7 (100)	3×10^{-10}	17	80 ± 1[d]
	10^{-9}	7/7 (100)		1.7	77 ± 0[d]
	10^{-10}	0/6 (0)			
 7	10^{-10}	15/15 (100)	1×10^{-12}	17	91 ± 1[d]
	10^{-11}	15/15 (100)		1.7	89 ± 2[d]
	10^{-12}	6/15 (40)			
 8	10^{-9}	5/19 (26)[b]	$>10^{-9}$	17	54 ± 10[e]
 9	10^{-8}	8/8 (100)	6×10^{-10}	17	69 ± 2[g]
	10^{-9}	8/14 (57)		1.7	33 ± 8[h]
	10^{-10}	3/14 (21)			
 10	10^{-8}	4/7 (57)	3×10^{-9}	17	39 ± 8[i]
	10^{-9}	3/7 (43)		1.7	15 ± 10[f]
	10^{-10}	1/6 (17)			
 11	10^{-8}	4/7 (57)	5×10^{-9}	17	0 ± 5[f]
	10^{-9}	2/6 (33)		1.7	12 ± 6[f]
	10^{-10}	1/7 (14)			
 12	10^{-8}	3/7 (43)	$>10^{-8}$	17	4 ± 5[f]
	10^{-9}	2/7 (29)		1.7	0 ± 3[f]
	10^{-10}	1/7 (14)			
 13	10^{-8}	7/7 (100)	2×10^{-10}	17	81 ± 2[d]
	10^{-9}	7/7 (100)		1.7	42 ± 6[d]
	10^{-10}	4/13 (31)			
	10^{-11}	1/7 (14)			
 14	10^{-8}	7/7 (100)	5×10^{-11}	17	85 ± 2[d]
	10^{-9}	7/7 (100)		1.7	68 ± 4[d]
	10^{-10}	12/14 (86)			
	10^{-11}	1/7 (14)			
 15	10^{-8}	2/7 (29)	$>10^{-8}$	17	23 ± 12[f]
	10^{-9}	1/7 (14)		1.7	9 ± 6[f]
	10^{-10}	1/7 (14)			
 16	10^{-8}	7/7 (100)	3×10^{-9}	17	55 ± 7[g]
	10^{-9}	2/12 (17)		1.7	34 ± 6[d]
	10^{-10}	2/12 (17)			
 17	10^{-8}	1/5 (20)[b]	$>10^{-8}$		
	10^{-9}	1/5 (20)			

Table I (Continued)

retinoid	TOC concn, M	TOC active/total cultures, %	TOC ED_{50}[a]	ODC dose, nmol	ODC % inhibn of control
 18	10^{-8}	7/7 (100)	1×10^{-10}	17	48 ± 1[d]
	10^{-9}	11/12 (92)		1.7	30 ± 2[d]
	10^{-10}	6/13 (46)			
	10^{-11}	1/5 (20)			
 19	10^{-10}	21/22 (95)	3×10^{-12}	17	80 ± 3[d]
	10^{-11}	17/22 (77)		1.7	56 ± 1[d]
	10^{-12}	4/15 (27)			

[a] ED_{50} is the molarity of retinoid required to effect reversal of keratinization in 50% of the cultures. [b] Reference 30. [c] Reference 2b. [d] $P \leq 0.001$. [e] $P < 0.05$. [f] Inhibition not significant, $P > 0.05$. [g] $P < 0.005$. [h] $P < 0.02$. [i] $P < 0.01$.

Scheme II



propanation with Simmons–Smith reagent or Pd-$(OAc)_2/CH_2N_2$.[14] Conversion of the electron-withdrawing carbethoxy group to the carbinol or its MEM ether did not improve the reactivity of the double bond. Cyclopropyl carboxylates have been prepared by reaction of styrene with diazoacetates.[15] Therefore, the related diazobenzyl carboxylate **40** was prepared and did react with the double bond of **39** to afford cyclopropanes **11** and **12**. Analysis of the ^1H NMR spectra indicated that the minor product was the cis-substituted cyclopropane **11** and the major product was its trans-substituted isomer **12**. The cyclopropane methylene protons and the aromatic protons of **11** were shifted upfield relative to those of **12** by the shielding effects of the aromatic rings, and the two ortho and two meta protons on the aromatic ring of **11** were nonequivalent.

The chroman **13** and thiochroman **14** are heterocyclic analogues of **7** in which the benzylic group at the 1-position of the tetrahydronaphthalene ring has been replaced by oxygen and sulfur, respectively. The placement of a heteroatom at this position is based on the work of Huisman,[16] who reported that, although (*E*)-4-thiaretinyl acetate had 5% of the growth potency of (*E*)-retinyl acetate in chickens, it had 18% of the liver storage capacity and was less toxic. Therefore, similarly substituted analogues of **7** may retain activity but have reduced toxicity. Synthetic routes to these analogues are shown in Scheme III.

The intermediates **46a** and **46b** for the synthesis of **13** and **14** were prepared by two routes that were based on literature procedures and began with phenol and thiophenol. The first route[17] used to prepare 4,4-dimethyl-3,4-dihydro-2*H*-1-benzopyran (**46a**) involved conversion of phenol to its dimethylacrylate ester **42a**, followed by an intramolecular Friedel–Crafts alkylation of this ester. The lactone product (**43a**) was reduced to the diol **44a**. The primary hydroxyl group of **44a** was selectively converted to the mesylate. Intramolecular displacement of the mesylate group[18] by phenoxide gave chroman **46a**. A more

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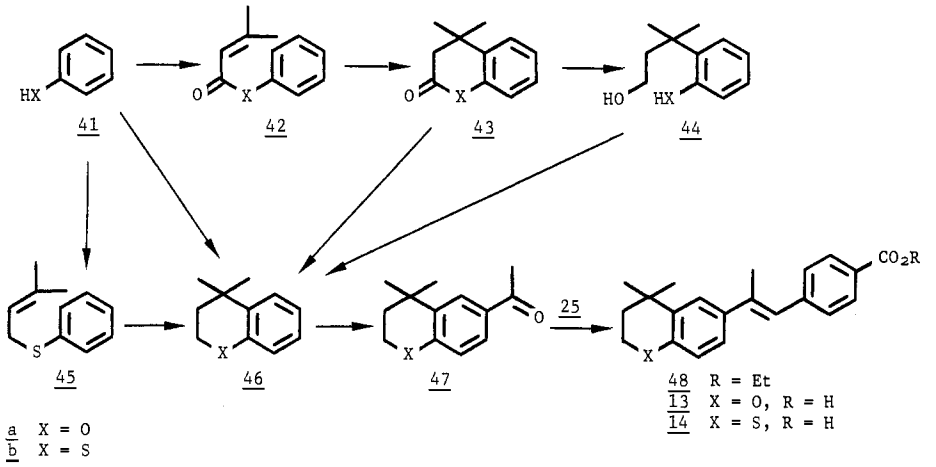
Scheme III



direct, lower yield route[19] to **46a** featured the Friedel–Crafts cycli-alkylation of phenol with diphenyl 3-methyl-3-buten-1-yl phosphate.

The allyl phenyl sulfide **45** was prepared by alkylation of sodium phenoxide with dimethylallyl bromide.[20] Intramolecular Friedel–Crafts alkylation of **45** gave thiochroman **46b**[21] and more polar material. It was necessary to conclusively establish the structure of **46b** because of a literature report[22] that **45** underwent a Lewis acid catalyzed reaction to 2,2-dimethyl-3,4-dihydro-2*H*-1-benzothiopyran and not **46b** and because the ^{1}H NMR spectrum of **46b** did not confirm the structure. Therefore a regiospecific synthesis, which was based on the first route used to prepare **46a**, was employed. Thiophenol was converted to thioester **42b**, which on treatment with $AlCl_3$ gave thiolactone **43b**. Reduction of **43b** with $LiAlH_4$ or $NaBH_4/BF_3{\cdot}Et_2O$ gave a mixture of thiophenol **44b** and thiochroman **46b**. The ^{1}H NMR spectra of the products prepared by the two routes were identical.

Chroman **46a** and thiochroman **46b** were acetylated at the 6-position[23,24] to give aryl methyl ketones **47a** and **47b**. Horner–Emmons reaction[8] of the anion of **25** with these ketones afforded the ethyl esters (**48a** and **48b**) of **13** and **14**, respectively, as the major products. The *E* geometry of the double bonds of **48a** and **48b** was verified by comparison of their ^{1}H NMR spectra, which were very similar with those of the *Z* isomer of **48a**, **7**, the *Z* isomer of **7**, **35**, and **36**. As expected, there were significant differences in the positions of the chemical shifts for the heterosubstituted aromatic ring, the *gem*-dimethyl, and the vinylic protons between the *E* and *Z* double bond isomers. In the *Z* isomers these signals were shifted upfield. For example, the vinylic proton signal for the *Z* isomer of **48a** was shifted upfield by 0.33 ppm. A similar shift was reported[25] for the vinylic protons of *cis*-stilbene relative to those of *trans*-stilbene. In addition, the extinction coefficients of the UV absorption maxima[26] also support the stereochemical assignments. Base hydrolysis of the ethyl esters **48a** and **48b** afforded the acids **13** and **14**.

The bonds corresponding to the 7,9*E* double bond system of **1** in analogues **15** and **16** are held in a planar cisoid conformation by the phenyl ring. The methyl group on the phenyl ring of **15** corresponds to the 19-methyl group of **1**. The syntheses of these compounds are shown in Scheme IV. Salient features are the reaction of aryllithium reagents prepared from bromides **50** and **57** with 2,2,6-trimethylcyclohexanone (**51**) to introduce the β-cyclogeranylidene ring system and elimination of the hindered tertiary benzylic hydroxyl group using $POCl_3$/pyridine at elevated temperatures. Elimination of the hydroxyl group of **59** failed at room temperature with $POCl_3$/pyridine and led to a 45:55 mixture of α- and β-cyclogeranylidene ring isomers with *p*-TsOH/C_6H_6 at reflux. The benzylic acetal group of **52** proved to be fairly stable to the elimination conditions but was readily hydrolyzed to afford benzaldehyde **53**. Horner–Emmons olefination of **53** with **54** gave a mixture of esters **55** and **56**. The assignment of the configuration of these esters was made by ^{1}H and ^{13}C NMR and UV spectral comparisons with spectra reported for the corresponding esters of **1** and its isomers.[27,28] Both isomers displayed a doublet (J = 16 Hz), indicating an 11_RE double bond. The ^{1}H NMR spectrum of the 13_RZ isomer (**56**) showed characteristic chemical shift differences from that of the *E* isomer, namely, upfield shifts for the 20_R-methyl and 14_R-vinylic protons and a downfield shift for the 12_R-vinylic proton. The ^{13}C NMR spectra showed the same shift differences as did ethyl (*E*)- and (13*Z*)-retinoates, namely, an upfield shift for the 12_R-carbon and a downfield shift for the 11_R-carbon of the 13_RZ isomer. The UV absorption maximum (322 nm) of **55** was lower than that (326 nm) of **56** as expected.[26]

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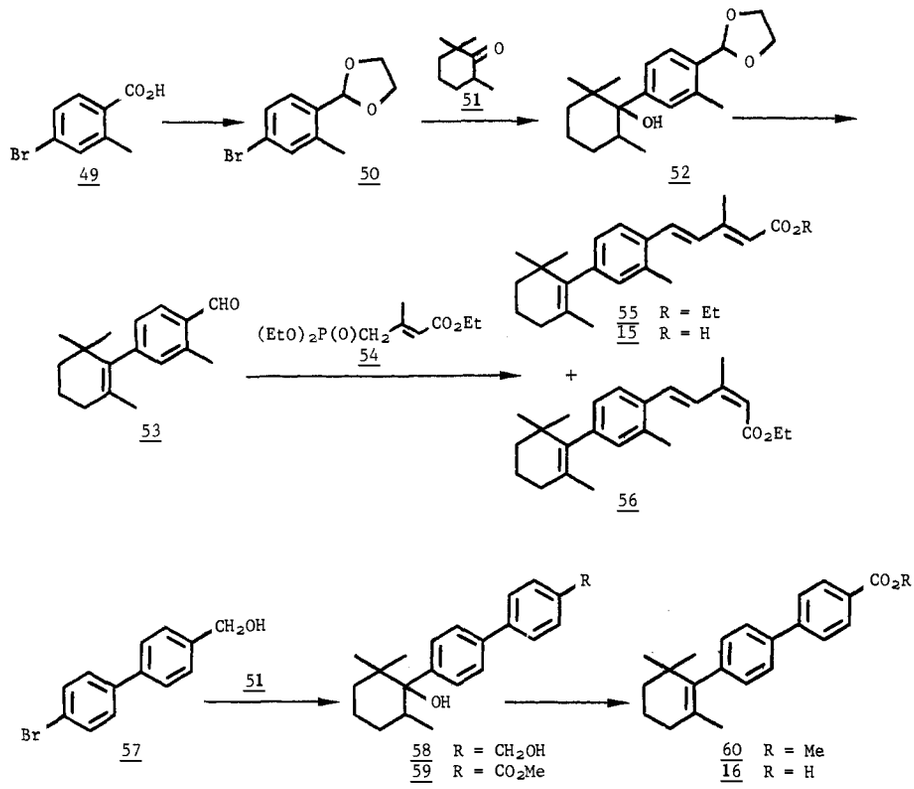
Scheme IV



Pharmacological Activity. TOC and ODC testing results for these compounds are presented in Table I. Because of the potential lability of the cyclopropane analogues when the terminal group was a carboxylic acid, the esters **6**, **11**, and **12** were used for screening. Use of the ethyl ester rather than the carboxylic acid in the TOC and ODC assays did not significantly affect the biological results in the series of retinoids we have synthesized. For example, we have found that the ED_{50} for retinoic acid in the TOC assay is 1×10^{-11} M and that for ethyl retinoate is 2×10^{-11} M. Both **2** and its ethyl ester and **9** and its ethyl ester (**35**) had comparable activities in these two assays.[29]

Trienyl benzoate **3**, in which the distance between the polar terminus and the β-cyclogeranylidene ring is shorter than that of its active analogue **2**, was inactive in both the TOC and ODC assays. However, the vinyl homologue of **2**, compound **4**, retained appreciable activity in both assays. Similar results are reported for **1** and its vinyl homologue in the TOC assay.[30] Both the $7,8_R$-dihydro and $7,8_R$-methano analogues (**5** and **6**) of **2** also had high activity. Evidently a $7,8_R$-double bond is not required nor is it necessary that the $6,7,8,9_R$-bond system be planar for activity to be retained.

The benzonorbornene **9** was more active in the TOC assay than norbornene **8** was, but it was far less active than the tetramethyltetrahydronaphthyl retinoid **7**. Activity was further decreased on removal of the vinylic methyl group (compound **10**). It appears that lipophilic bulk is required both in the ring and at the 9_R-position for activity to be retained. Replacement of the propenyl group of **9** by a cyclopropane ring also decreased activity (compounds **11** and **12**), suggesting that the $8,9,10,11_R$-bond system must be planar to maintain activity.

The heterocyclic analogues of **7** were less active than **1** and **7** in the TOC and ODC assays; however, both displayed significant activity. The thiochroman **14** was far more active than the more polar chroman **13** in the TOC assay. Evidently, introduction of a polar substituent at the 4_R-position of the retinoid skeleton decreases activity.

Compounds **15** and **16** showed very low activity in the TOC assay and, therefore, were not screened in the ODC assay. Analogue **17**, in which the bonds corresponding to the 9,11*E*-bond system of **1** are held in a cisoid conformation by the aromatic ring, was reported to have very low activity in the TOC assay.[30] In contrast, we have found that the naphthalenecarboxylic acids **18** and **19**, in which the bonds corresponding to the 9,11,13*E*-bond system of **1** are cisoid, were both active.[31] In fact, **19** had activity comparable to that of **1** and **7** in the TOC assay. These results suggest that **1** may assume an active conformation in which the 5,7*E* and 9,11,13*E* double bond systems are planar and cisoid.

The naphthalenecarboxylic acid **19**, the two heterocyclic analogues of **7** (**13** and **14**), **1**, and **7** were screened in the antipapilloma assay. This assay determines the effectiveness of retinoids in preventing papilloma tumor formation in mouse epidermis that has been pretreated with a tumor initiator and then treated twice weekly with a tumor promoter during the course of the experiment.[3a,b] The results of this 20-week experiment are presented in Table II. Although the relative activity that these retinoids had in this assay correlated with their activity in the ODC assay, all were able to inhibit tumor formation. The benzoic acid derivative **7** was the most active. A 1.7-nmol

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Table II. Twenty-Week Antipapilloma Experiment in Female CD-1 Mice

retinoid	dose, nmol	mice with papillomas, %	% decrease in av no. of papillomas/mouse ± SE[a]
control[b]	0	93	0
1	170	40	89.6 ± 0.4[f]
	17	47	74.1 ± 0.5[f]
	1.7	69	56.2 ± 9.9[g]
7	170[c]	*d*	
	17[c]	*e*	
	1.7[c]	50	92.3 ± 2.2[f]
	0.17	73	62.9 ± 8.9[h]
13	170	38	94.0 ± 0.3[f]
	17	53	75.0 ± 0.7[f]
14	170	33	93.6 ± 3.0[f]
	17	40	93.4 ± 2.1[f]
19	170[c]	28	95.2 ± 2.8[f]
	17	82	45.8 ± 11.6[i]

[a] Decrease in average number of papillomas/retinoid-treated mouse compared to control mouse at 20 weeks. [b] Average number of papillomas/mouse ± SE in control group was 17.3 ± 2.6. [c] Hypervitaminosis A toxic symptoms of skin redness and scaling and hair loss observed. [d] Animals died at 1–2 weeks. [e] Animals died at 3–7 weeks. [f] $P < 0.001$. [g] $P < 0.01$. [i] $P < 0.02$.

topical dose decreased the number of tumors formed by 92% relative to the control group; however, at this concentration the animals displayed significant symptoms of hypervitaminosis A toxicity, including skin redness and scaling, and hair loss. Both the 17- and 170-nmol doses of **7** caused death during the experiment. The naphthalenecarboxylic acid **19** was able to almost completely inhibit papilloma tumor formation at the 170-nmol dose and reduce the number of tumors by 46% at the 17-nmol dose. At the higher dose, however, skin scaling and redness and hair loss were observed. In contrast, **1** was able to decrease the number of tumors formed by 74% at the 17-nmol dose and by 90% at the 170-nmol dose without the appearance of toxic symptoms in the animals. Chroman **13** prevented tumor formation by 94% at the 170-nmol dose and reduced the number of tumors by 75% at the 17-nmol dose. Thiochroman **14** reduced the number of tumors formed by over 93% at the 17- and 170-nmol dose levels. No toxic symptoms in the animals were observed at these doses.

The retinoids tested in the antipapilloma experiment were screened for toxicity in mice (Table III). Compounds were administered by intraperitoneal injection over a period of 2 weeks. The toxicity of these compounds correlated with their activity in the TOC assay. Retinoid **7** was the most toxic retinoid, and **19**, which was less active in the TOC assay, had about one-tenth the toxicity of **7**. Both **7** and **19** were far more toxic than **1**. Interestingly, the heterocyclic analogues **13** and **14** were less toxic than **1** and therefore have potential value in the treatment of proliferative skin diseases. Work is now underway to synthesize less toxic variants of **13**, **14**, and **19**.

Experimental Section

Synthetic Methods. When required, reactions and purifications were conducted with deoxygenated solvents and under inert gas (argon) and subdued light. Solvents were dried or distilled before use. Melting points were uncorrected. TLC analyses were performed on Analtech silica gel analytical plates. Merck silica gel 60 was used for chromatography LC analyses were done on a Waters Associates ALC 210 equipped with a RCM-100 module containing a Radialpak A or B cartridge. Detection was by a Schoeffel Instrument Model 770 variable-wavelength UV monitor. Analyses were performed at ambient temperature. Preparative work was done on a Waters Associates Prep/LC System 500 instrument using Prep Pak 500/silica cartridges at a flow rate of 0.2 L/min. IR spectra were recorded with a Perkin-Elmer 710B infrared spectrophotometer. NMR spectra were obtained with a Varian EM360A, a JEOL FX90Q, or a 300-MHz Nicolet spectrometer, using Me_4Si as an internal standard (δ 0) and $CDCl_3$ as solvent. UV spectra were taken on a Perkin-Elmer 575 spectrometer. Spectral signal designations were based on the retinoid numbering system.[5] ^1H NMR signals were assigned by comparison with those reported for other retinoids[27,28] and other compounds.[10a,32] Unstable retinoids or those obtained as viscous oils were submitted for high-resolution mass spectral analysis rather than elemental analysis, which was conducted with a CEC-21-110B high-resolution mass spectrometer equipped with facilities for combination GC–MS.

Table III. Toxicity in Female Swiss Mice

retinoid	dose,[a] μmol/(kg day)	% survivors day 8	% survivors day 15	mortality range, days	total animals
control	0	100	100		30
1	600	95	0	7–13	20
	300	100	0	10–14	20
	200	100	63	14–15	30
	100	100	100		30
	67	100	100		20
	33	100	100		10
7	30	50	0	6–8	20
	10	87	0	7–10	30
	3.3	97	0	7–11	30
	1.0	100	30	10–15	30
13	600	70	0	7–10	10
	300	100	50	12–15	10
	200	100	90	14	10
	100	100	100		10
	30	100	100		10
14	600	100	0	9–10	10
	300	100	80	14–15	10
	100	100	100		10
	30	100	100		10
19	100	100	0	8	10
	30	100	0	9–12	10
	10	100	68	10–15	30
	3.3	100	100		10

[a] Retinoid administered by ip injection on weekdays over a period of 2 weeks.

Diethyl (3-Carbethoxybenzyl)phosphonate (20). To 93 mL (0.54 mol) of $(EtO)_3P$ heated in a 150 °C oil bath was added over a 0.5-h period 109.4 g (0.45 mol) of ethyl 3-(bromomethyl)benzoate under a stream of argon to remove the ethyl bromide formed. The oil bath temperature was raised to 200 °C over a 15-min period and maintained there for 1 h. The deep orange reaction mixture was cooled to room temperature and submitted to fractional distillation to afford 86.7 g (64%) of **20**, as a colorless, viscous liquid: bp 152–167 °C (0.06–0.15 mm); IR (film) 1720, 1610, 1590, 1280, 1250, 1190, 1100, 1040, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 6, $POCH_2CH_3$), 1.40 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 3.20 (d, J = 21 Hz, 2, PCH_2), 4.00 (q, J = 7 Hz, 4, $POCH_2CH_3$), 4.40 (q, J = 7 Hz, 2, $CO_2CH_2CH_3$), 7.3–7.6 (m, 2, 4,5-ArH), 7.75–8.15 (m, 2, 2,6-ArH); MS calcd for $C_{14}H_{21}O_5P$ 300.1127, found 300.1107.

Ethyl 3-(2-Methyl-1-propen-1-yl)benzoate (21). NaH (0.03 mol), isolated from 1.24 g of a 60% dispersion in mineral oil by washing with pentane (3 × 2 mL), was suspended in 25 mL of DMF. A solution of 8.6 g (0.03 mol) of **20** in 15 mL of DMF (15-mL rinse) was added dropwise with mechanical stirring over a period of 20 min. The reaction mixture became deep brown and hydrogen evolution ceased after 3.5 h, when 11.5 mL (0.16 mol) of acetone was added. After stirring at room temperature for 19 h, the reaction mixture was diluted with 300 mL of water and extracted with Et_2O (2 × 225 mL). The extract was washed with water (3 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), and concentrated at reduced pressure to an orange oil, which was chromatographed on silica gel (10% Et_2O/hexane) to afford 1.8

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g of a colorless oil containing the product and acetone polycondensation products. This oil was rechromatographed on silica gel (5% Et_2O/hexane) to give 1.47 g (25%) of **21** as a colorless oil (R_f 0.89): IR (film) 1720, 1680, 1660, 1605, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 7 Hz, 3, CH_2CH_3), 1.90 and 1.93 (2 d, J = 2 Hz, 6, HC=C(CH_3)$_2$), 4.40 (q, J = 7 Hz, 2, CH_2CH_3), 6.33 (br s, 1, C=CH), 7.35–7.50 (m, 2, 4,5-ArH), 7.85–8.10 (m, 2, 2,6-ArH); MS calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1156.

(*E*)-3-(3-Carbethoxyphenyl)-2-methylpropenal (22). To a solution of 1.47 g (7.2 mmol) of dimethyl olefin **21** in 50 mL of dioxane was added 1.20 g (10.8 mmol) of SeO_2. After degassing (argon), the reaction mixture was heated with mechanical stirring in a 110 °C oil bath for 2 h. The yellow solution and black precipitate were cooled and filtered. The filtrate was concentrated to give 2.2 g of a brown gum: LC (Radialpak B, 10% EtOAc/hexane, 2.0 mL/min, 260 nm) t_R 2.2 (1%), 4.2 (1%), 4.6 (2%, *Z* isomer), 6.4 min (96%, *E* isomer **22**). The gum was chromatographed on silica gel (10% EtOAc/hexane) to give 0.04 g (3%) of a 3:2 mixture of *Z*/*E* isomers by ^1H NMR and 0.87 g (56%) of **22** as a pale-yellow oil: LC t_R 6.4 min (99.5%); IR (film) 2820, 2700, 1720, 1680, 1630, 1600, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 7 Hz, 3, CH_2CH_3), 2.10 (d, J = 1 Hz, 3, CH_3C=C), 4.43 (q, J = 7 Hz, 2, CH_2CH_3), 7.33 (br s, 1, C=CH), 7.55–7.9 (m, 2, 4,5-ArH), 7.9–8.3 (m, 2, 2,6-ArH), 9.67 (s, 1, CHO); MS calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0938.

Ethyl 3-[(*E*)-2-Methyl-4-(2,6,6-trimethylcyclohexenyl)-1,3-butadienyl]benzoate (3). To a stirred suspension of 2.90 g (6.05 mmol) of β-cyclogeranyltriphenylphosphonium bromide (**23**) in 15 mL of THF, which was cooled in a dry ice–CCl_4 bath and degassed (argon), was added dropwise 3.6 mL (5.54 mmol) of 1.54 M *n*-BuLi in hexane. The resulting red reaction mixture was stirred for 30 min before the bath temperature was raised to 0 to 5 °C, at which point 0.847 g (3.88 mmol) of aldehyde **22** in 3 mL of THF (2 × 1-mL rinse) was added. After stirring for 2 h at room temperature, the reaction mixture was diluted with 20 mL of H_2O containing two drops of HOAc and extracted with Et_2O (2 × 150 mL). The extracts were washed with water (2 × 20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), and concentrated to 2.7 g of a semisolid, which was chromatographed on silica gel (10% EtOAc/hexane) to give 1.34 g of a pale-yellow oil, which was purified by preparative LC (2% Et_2O/hexane) to afford 0.99 g (76%) of **3** as a colorless, slightly viscous oil: LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 6.2 min (100%); LC (Radialpak A, 10% H_2O/MeCN, 2.0 mL/min, 260 nm) t_R 14.4 (0.6%), 16.3 min (99.4%); IR (film) 1720, 1690 (sh), 1600, 1580 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.05 (s, 6, 16,17$_R$-CH_3), 1.40 (t, J = 7 Hz, 3, CH_2CH_3), 1.48 and 1.63 (2 m, 4, 2,3$_R$-CH_2), 1.75 (s, 3, 18$_R$-CH_3), 2.05 (m, 2, 4$_R$-CH_2), 2.06 (s, 3, 19$_R$-CH_3), 4.38 (q, J = 7 Hz, 2, CH_2CH_3), 6.20 (d, J = 16 Hz, 1, 8$_R$-HC=C*H*), 6.27 (d, J = 16 Hz, 1, 7$_R$-*H*C=CH), 6.48 (s, 1, 10$_R$-C=CH), 7.40 (2 d, J = 8 Hz, J = 8 Hz, 1, 5-ArH), 7.48 (d, J = 8 Hz, 1, 4-ArH), 7.89 (d, J = 8 Hz, 1, 6-ArH), 7.99 (s, 1, 2-ArH); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.3, 19.2, 21.7, 28.9, 32.9, 34.2, 39.5, 60.9, 127.3, 127.7, 128.1, 128.7, 129.2, 130.2, 130.3, 133.4, 137.2, 137.6, 137.8, 138.3, 166.6 ppm; UV (EtOH) λ_{max} 229 nm (ϵ 1.4 × 10^4), 250 (sh, 1.3 × 10^4), 287 (2.1 × 10^4); MS calcd for $C_{23}H_{30}O_2$ 338.2246, found 338.2264.

4-[(*E*)-4-Methyl-6-(2,6,6-trimethylcyclohexenyl)-1,3,5-hexatrienyl]benzoic Acid (4). To 1.41 mL (10.1 mmol) of (*i*-Pr)$_2$NH in 5 mL of THF, which was cooled in a dry ice–acetone bath, was added with stirring 6.54 mL (10.1 mmol) of 1.54 M *n*-BuLi in hexane. After 20 min, a solution of 3.03 g (10.1 mmol) of **25**[9] in 5 mL of THF (1-mL rinse) was added. The anion came out of solution as a brown gum. After 15 min, 2.0 g (9.2 mmol) of **24**[33] in 5 mL of THF (1-mL rinse) was added. The reaction mixture was degassed (argon) and stirred at ambient temperature overnight. As the temperature of the reaction mixture rose, the anion dissolved and reaction occurred. The resultant orange solution was diluted with H_2O (50 mL) containing two drops of HOAc and extracted with 10% Et_2O/hexane (2 × 75 mL). The extracts were washed with water and brine (2 × 20 mL), dried ($MgSO_4$), and concentrated to 4.0 g of an orange oil: TLC (10% Et_2O/hexane) R_f 0.54 (bright yellow, phosphonate condensation products), 0.71 (yellow, 4), and 0.79 (yellow). Chromatography on silica gel (10% Et_2O/hexane) afforded 2.7 g of a yellow solid that was greater than 90% one component by analytical LC. Preparative LC (2% Et_2O/hexane) using the recycle technique afforded 1.24 g (37% yield) of benzoate **26** as yellow crystals: mp 96–96.5 °C (hexane); LC (Radialpak A, MeOH, 1.0 mL/min, 260 nm) t_R 3.4 (0.1%), 4.0 (0.2%), 10 min (99.7%); LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 254 nm) t_R 5.2 (0.1%), 5.4 (0.1%), 6.2 min (99.8%); IR ($CHCl_3$) 1710, 1595 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.03 (s, 6, 16,17$_R$-CH_3), 1.39 (t, J = 6.5 Hz, 3, CH_2CH_3), 1.47 and 1.64 (2 m, 4, 2,3$_R$-CH_2), 1.73 (s, 3, 18$_R$-CH_3), 2.03 (m, 2, 4$_R$-CH_2), 2.05 (s, 3, 19$_R$-CH_3), 4.37 (q, = 6.5 Hz, 2, CH_2CH_3), 6.16 (d, J = 14 Hz, 1, 8$_R$-HC=C*H*), 6.22 (d, J = 10 Hz, 1, 10$_R$-C=CH), 6.27 (d, J = 14 Hz, 1, 7$_R$-*H*C=CH), 6.57 (d, J = 14 Hz, 1, 12$_R$-HC=C*H*), 7.27 (dd, J = 10 Hz, J = 14 Hz, 1, 11$_R$-*H*C=CH), 7.46 (d, J = 8 Hz, 2, 3,5-ArH), 7.97 (d, J = 8 Hz, 2, 2,6-ArH); ^{13}C NMR ($CDCl_3$) 12.9, 14.3, 19.2, 21.7, 28.9, 33.1, 34.2, 39.6, 60.8, 125.9, 128.0, 128.7, 129.7, 129.9, 130.3, 130.6, 137.4, 137.8, 138.1, 142.3, 166.4 ppm; UV (EtOH) λ_{max} 223 nm (ϵ 8.4 × 10^3), 246 (9.3 × 10^3), 361 (5.6 × 10^4); MS calcd for $C_{25}H_{32}O_2$ 364.2402, found 364.2406.

To 639 mg (1.75 mmol) of **26** in 1.5 mL of EtOH was added a solution of 279 mg (4.23 mmol) of 85% KOH in 0.7 mL of water and 1.8 mL of EtOH. This suspension was degassed (argon) and then heated for 30 min in an 80 °C oil bath. The resultant orange solution was cooled to room temperature, diluted with 1.5 mL of HOAc and 2.5 mL of H_2O, and then partitioned between 75 mL of Et_2O and 25 mL of water. The aqueous layer was extracted with 25 mL of Et_2O. The organic extracts were washed with H_2O and brine (2 × 20 mL), dried (Na_2SO_4), and concentrated to 0.60 g of a yellow solid, which on crystallization from MeOH afforded 0.37 g (63% yield) of **4** as deep yellow prisms: mp 217–219 °C; LC (Radialpak A, MeOH, 2.0 mL/min, 260 nm) t_R 2.6 (99.7%), 5.0 min (0.3%); IR ($CHCl_3$) 2300–3200 (COOH), 1690, 1595 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.04 (s, 6, 16,17$_R$-CH_3), 1.48 and 1.63 (2 m, 4, 2,3$_R$-CH_2), 1.73 (s, 3, 18$_R$-CH_3), 2.03 (m, 2, 4$_R$-CH_2), 2.06 (s, 3, 19$_R$-CH_3), 6.17 (d, J = 15 Hz, 1, 8$_R$-HC=C*H*), 6.24 (d, J = 11 Hz, 1, 10$_R$-C=CH), 6.28 (d, J = 15 Hz, 1, 7$_R$-*H*C=CH), 6.59 (d, J = 15 Hz, 1, 12$_R$-HC=C*H*), 7.31 (dd, J = 11 Hz, J = 15 Hz, 1, 11$_R$-*H*C=CH), 7.50 (d, J = 8 Hz, 2, 3,5-ArH), 8.04 (d, J = 8 Hz, 2, 2,6-ArH); ^{13}C NMR ($CDCl_3$) δ 12.9, 19.4, 21.6, 29.0, 33.2, 34.4, 40.0, 126.2, 127.7, 128.5, 128.7, 129.6, 129.8, 130.7, 137.4, 138.1, 138.7, 143.6, 170.3 ppm; UV (EtOH) λ_{max} 222 nm (ϵ 1.0 × 10^4), 239 (9.1 × 10^3), 349 (5.2 × 10^4); MS calcd for $C_{23}H_{28}O_2$ 336.2089, found 336.2087.

7,8-Dihydro-β-ionone (28). To a stirred ice-cooled solution of 17.3 g (90 mmol) of β-ionone (**27**) in 150 mL of THF was added, under argon over a period of 15 min, 200 mL (100 mmol) of a 0.5 M solution of 9-BBN in THF. The solution was stirred with cooling for an additional 15 min and then at room temperature for 3.5 h. The excess 9-BBN was destroyed by the addition of 5 mL of aqueous THF. The resultant yellow solution was stirred for 30 min more and then concentrated at reduced pressure. The residue was cooled in an ice/water bath and treated in succession with 500 mL of Et_2O and 6.3 g (0.103 mol) of $HOCH_2CH_2NH_2$. Shaking and periodic cooling for 5 min afforded a white suspension, which was allowed to stand for 16 h at −5 °C and then filtered (100 mL of Et_2O). The filtrate was concentrated at reduced pressure to give a yellow oil, which was chromatographed on silica gel (15% Et_2O/hexane, then 20% Et_2O/hexane) to give, in turn, (1) 8.8 g (50%) of **28** [IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 6, C(CH_3)$_2$), 1.50 (m, 4, 2,3$_R$-CH_2), 1.57 (s, 3, 18$_R$-CH_3), 1.90 (m, 2, 4$_R$-CH_2), 2.13 (s, 3, $COCH_3$), 2.40 (m, 4, 7,8$_R$-CH_2)] and (2) 6.7 g (38%) of β-ionol (**29**) [IR ($CHCl_3$) 3600, 3430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 6, C(CH_3)$_2$), 1.32 (d, J = 7 Hz, 3, $CHCH_3$), 1.50 (m, 4, 2,3$_R$-CH_2), 1.67 (s, 3, 18$_R$-CH_3), 1.73 (s, 1, OH, exchanged D_2O), 2.00 (m, 2, 4$_R$-CH_2), 4.37 (m, 1, *C*HOH), 5.48 (dd, J = 16 Hz, J = 7 Hz, 1, 8$_R$-HC=C*H*), 6.10 (d, J = 16 Hz, 1, 7$_R$-*H*C=CH)].

4-[(*E*)-2-Methyl-4-(2,6,6-trimethylcyclohexenyl)butenyl]benzoic Acid (5). A 1.7-g portion of 60% NaH–mineral oil dispersion (42.5 mmol of NaH) was washed under argon with hexane (3 × 15 mL). The residue was suspended in 300 mL of freshly distilled THF. To this suspension was added a mixture

(33) (a) N. V. Philips' Gloeilampenfabricken, British Patent 813 517, May 21, 1959; *Chem. Abstr.* **1959**, *53*, P22068g. (b) Smit, A. *Recl. Trav. Chim. Pays-Bas.* **1961**, *80*, 891–904.

of 0.3 g of 15-crown-5, 7.5 g (38.8 mmol) of **28**, and 11.65 g (38.8 mmol) of **25** in 20 mL of THF. The mixture was stirred at room temperature for 20 h, at which time TLC (10% Et_2O/hexane) still showed a significant amount of **28** present. Therefore, 0.30 g of 15-crown-5 in 8 mL of THF was added, and the reaction mixture was stirred for an additional 24 h. Although some **28** remained, the mixture was poured into 900 mL of H_2O. Extraction with Et_2O (4 × 200 mL), washing with brine (2 × 100 mL), drying (Na_2SO_4), and concentration gave 15.0 g of a yellow, oily solid, which was filtered through silica gel (5% Et_2O/hexane) to give 8.9 g (68%) of a clear, yellow oil. Analytical LC (Radialpak B, 1% Et_2O/hexane, 2.0 mL/min, 260 nm) showed two peaks, t_R 5.2 (18%) and 6.0 min (82%). One pass on preparative LC (1% Et_2O/hexane) gave 4.4 g (33%) of benzoate **30** as a pale-yellow oil: LC t_R 6.0 min (98%); IR ($CHCl_3$) 2950, 1710, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (s, 6, 16,17$_R$-CH_3), 1.2–1.6 (m, 10, 2,3$_R$-CH_2, CH_2CH_3, 18$_R$-CH_3), 1.9 (br s, 5, 4$_R$-CH_2, 19$_R$-CH_3), 2.2 (br s, 4, 7,8$_R$-CH_2), 4.40 (q, J = 7 Hz, 2, CH_2CH_3), 6.35 (s, 1, 10$_R$-C=CH), 7.25 (d, J = 8 Hz, 2, 3,5-ArH), 8.05 (d, J = 8 Hz, 2, 2,6-ArH).

A solution of 3.25 g (49 mmol) of 85% KOH in 9 mL of H_2O and 14.5 mL of EtOH was degassed (argon) and added to a suspension of 4.3 g (12.7 mmol) of **30** in 16 mL of EtOH. The mixture was again degassed and heated to 80 °C for 45 min. The cooled solution was acidified with 35 mL of 50% HOAc and extracted with Et_2O. The Et_2O layer was washed with brine (2 × 125 mL), dried (Na_2SO_4), and concentrated to give 3.4 g (85%) of a white solid. Recrystallization from EtOAc/hexane gave 2.87 g (72%) of white crystals: mp 162–163 °C; LC (Radialpak A, MeOH, 1.0 mL/min, 260 nm) t_R 3.8 (2%), 6.2 min (98%); IR ($CHCl_3$) 2950 (br), 1695, 1615 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.04 (s, 6, 16,17$_R$-CH_3), 1.46 and 1.58 (2 m, 4, 2,3$_R$-CH_2), 1.66 (s, 3, 18$_R$-CH_3), 1.94 (m, 2, 4$_R$-CH_2), 1.95 (d, J = 1 Hz, 3, 19$_R$-CH_3), 2.22 (m, 4, 7,8$_R$-CH_2), 6.34 (s, 1, 10$_R$-C=CH), 7.35 (d, J = 8 Hz, 2, 3,5-ArH), 8.08 (d, J = 8 Hz, 2, 2,6-ArH), 11.0 (s, 1, CO_2H); ^{13}C NMR ($CDCl_3$) 18.3, 19.6, 19.9, 27.8, 28.7, 32.8, 35.1, 39.9, 41.6, 123.7, 126.5, 127.5, 128.8, 130.1, 136.9, 143.0, 144.4, 172.3 ppm; UV (EtOH) λ_{max} 217 nm (ϵ 1.7 × 10^4), 272 (2.7 × 10^4); MS calcd for $C_{21}H_{28}O_2$ 312.2089, found 312.2090.

***trans*-1-Acetyl-2-(2,6,6-trimethylcyclohexenyl)cyclopropane (32).** To the Zn–Cu couple prepared from 2.0 g (0.031 mol) of Zn and 91 mg of $Cu(OAc)_2 \cdot H_2O$ in 5 mL of HOAc at 90 °C was added 15 mL of Et_2O, a crystal of I_2, and 1.5 mL (18.6 mmol) of CH_2I_2. The stirred mixture was heated at reflux for 35 min before 1.18 g (6.07 mmol) of β-ionol (**29**),[34] which had been prepared by reduction of β-ionone with $NaBH_4$, in 1 mL of Et_2O (3-mL Et_2O rinse) was added. The reaction mixture was heated at reflux for 2 h, cooled to room temperature, and worked up by partitioning between Et_2O and 5% NaOH. The Et_2O layer was washed with brine, dried (Na_2SO_4), and concentrated at room temperature to give an oil, which was chromatographed on Woelm alumina (activity III). Elution with hexane (200 mL) afforded unreacted CH_2I_2. Further elution with Et_2O gave 1.02 g (81%) of the cyclopropylcarbinol **31** as a colorless oil: IR (film) 3350, 1460, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.6 (m, 2, cyclopropyl CH_2), 0.8–2.1 (m, 9, $(CH_2)_3$, cyclopropyl CH, OH, exchanged D_2O), 1.10 and 1.11 (2 s, 6, $C(CH_3)_2$), 1.23 and 1.37 (2 d, J = 6 Hz, 3, $CHCH_3$), 1.70 and 1.74 (2 s, 3, C=CCH_3), 3.40 (m, 1, CHOH).

This mixture of diastereomers could be separated by LC chromatography (25% Et_2O/hexane) to give (a) the minor isomer as a very pale-yellow oil [^1H NMR ($CDCl_3$) δ 0.57 (m, 2, cyclopropyl CH_2), 0.8–2.0 (m, 8, $(CH_2)_3$, cyclopropyl CH), 1.10 (s, 6, $C(CH_3)_2$), 1.23 (d, J = 6.5 Hz, 3, $CHCH_3$), 1.74 (s, 3, C=CCH_3), 1.81 (s, 1, OH, exchanged D_2O), 3.38 (m, 1, CHOH)] and (b) the major isomer as a very pale-yellow oil [^1H NMR ($CDCl_3$) δ 0.61 (m, 2, cyclopropyl CH_2), 0.8–2.1 (m, 9, $(CH_2)_3$, cyclopropyl CH, OH, exchanged D_2O), 1.11 (s, 6, $C(CH_3)_2$), 1.37 (d, J = 6 Hz, 3, $CHCH_3$), 1.70 (s, 3, C=CCH_3), 3.43 (m, 1, CHOH)]. Oxidation of either of these diastereomers produced the same cyclopropyl ketone.

To Collins reagent prepared from 2.93 g (29.3 mmol) of CrO_3 and 4.8 mL (59.0 mmol) of pyridine in 25 mL of CH_2Cl_2 was added with stirring 1.02 g (4.9 mmol) of the cyclopropylcarbinol diastereomeric mixture in 3 mL of CH_2Cl_2. After 1 h, the dark brown reaction mixture was washed through Florisil with CH_2Cl_2. The filtrate was concentrated and purified by LC (2% EtOAc/hexane) to give 0.87 g (86% from the carbinol, 70% overall) of ketone **32** as a colorless oil: IR (film) 2870, 2840, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–2.2 (m, 10, $(CH_2)_3$, cyclopropyl CH_2 and CH), 1.03 and 1.13 (2 s, 6, $C(CH_3)_2$), 1.68 (s, 3, C=CCH_3), 2.23 (s, 3, $COCH_3$); MS calcd for $C_{14}H_{22}O$ 206.1671, found 206.1675.

Ethyl 4-[(*E*)-*trans*-3,4-Methano-2-methyl-4-(2,6,6-trimethylcyclohexenyl)butenyl]benzoate (6). To a slurry of NaH (4.4 mmol), obtained from 180 mg of 59% NaH dispersion in mineral oil that was washed with hexane (2 × 2 mL), in 4 mL of THF at room temperature was added a solution of 1.15 g (3.78 mmol) of **25** and 0.45 g (2.18 mmol) of **32** in 7 mL of THF containing 2 drops of 15-crown-5.[8] The reaction mixture was stirred at room temperature for 15 h to give a dark red solution and an insoluble gum. The mixture was then treated with 60 mL of water and extracted with Et_2O (2 × 5 mL). The yellow extract was washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated. The residue was extracted with hexane (2 × 50 mL), and the extract was concentrated to give 0.72 g of yellow oil. The product was partially purified by LC (2% Et_2O/hexane) by using the recycle technique to give two very pale-yellow fractions: (a) 0.125 g; LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 4.3 (52.3%), 4.8 (33.4%), 5.4 min (14.3%); and (b) 0.432 g; LC t_R 4.5 (sh, 14.7%), 4.8 (79.9%), 5.5 min (5.4%). The combined yield of olefins was 0.56 g (73%). The crude products were combined with the products of a similar reaction, which employed 0.31 g (1.5 mmol) of ketone **32**. The combined products were purified by LC (2.5% Et_2O/hexane) by using the recycle technique to give a total of 0.44 g (34%) of the benzoate **6** as a white solid: mp 60–60.5 °C; LC (Radialpak A, MeCN, 1.0 mL/min, 260 nm) t_R 4.3 (0.7%), 4.7 (0.5%), 12.1 min (98.8%); LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 7.0 (3.4%), 7.5 (95.6%), 8.2 min (1.0%); IR ($CHCl_3$) 1700, 1630, 1605 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.0 (m, 2, cyclopropyl CH_2), 1.08 and 1.15 (2 s, 6, 16,17$_R$-CH_3), 1.39 (t, J = 7 Hz, 3, CH_2CH_3), 1.4 and 1.6 (2 m, 6, 2,3$_R$-CH_2, cyclopropyl CH), 1.72 and 1.73 (2 s, 6, 18,19$_R$-CH_3), 1.95 (m, 2, 4$_R$-CH_2), 4.37 (q, J = 7 Hz, 2, CH_2CH_3), 6.41 (s, 1, 10$_R$-C=CH), 7.30 (d, J = 8 Hz, 2, 3,5-ArH), 7.98 (d, J = 8 Hz, 2, 2,6-ArH); ^{13}C NMR ($CDCl_3$) 14.3, 14.6, 14.9, 19.4, 20.3, 20.8, 29.1, 29.1, 29.3, 33.6, 35.7, 41.6, 60.6, 123.1, 128.0, 128.6, 129.3, 130.7, 136.2, 141.8, 143.4, 166.0 ppm; UV (EtOH) λ_{max} 294 nm (ϵ 2.3 × 10^4); MS calcd for $C_{24}H_{32}O_2$ 352.2402, found 352.2380.

A small sample (32 mg, 2.5%) of the minor, *Z* isomer of **6**, which had the shorter LC retention time, was recovered for comparison of its spectra with that of the major component: IR ($CHCl_3$) 1700, 1600, 1450 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 0.91 and 1.00 (2 s, 6, 16,17$_R$-CH_3), 1.03 (m, 2, cyclopropyl CH_2), 1.32 and 1.5 (2 m, 4, 2,3$_R$-CH_2), 1.39 (t, J = 7 Hz, 3, CH_2CH_3), 1.52 (d, J = 0.7 Hz, 3, 18$_R$-CH_3), 1.66 (d, J = 1 Hz, 3, 19$_R$-CH_3), 1.85 (m, 2, 4$_R$-CH_2), 2.0 (m, 2, cyclopropyl CH), 4.36 (q, J = 7 Hz, 2, CH_2CH_3), 6.42 (s, 1, 10$_R$-C=CH), 7.38 (d, J = 8 Hz, 2, 3,5-ArH), 7.97 (d, J = 8 Hz, 2, 2,6-ArH); UV (EtOH) λ_{max} 290 nm (ϵ 1.8 × 10^4); MS calcd for $C_{24}H_{32}O_2$ 352.2402, found 352.2380.

1,4-Methano-1,2,3,4-tetrahydronaphthalene (33). To 16.0 g (0.113 mol) of 1,4-methano-1,4-dihydronaphthalene[12] in 150 mL of absolute EtOH was added 1.0 g of 5% Pd/C. This mixture was hydrogenated at room temperature and atmospheric pressure. After 20 h, TLC indicated that no starting material remained. The reaction mixture was filtered, concentrated, and distilled to afford 10.0 g (62%) of **33** as a colorless oil: bp 67 °C (4.5 mm); IR (film) 3070, 3030, 2980, 2880, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.5 and 1.5–2.1 (m, 6, $CHCH_2CH$, $(CH_2)_2$), 3.35–3.5 (m, 2, CH), 7.0–7.3 (m, 4, ArH); MS calcd for $C_{11}H_{12}$ 144.0939, found 144.0930.

6-Acetyl-1,4-methano-1,2,3,4-tetrahydronaphthalene (34). A mixture of 6.9 g (47.9 mmol) of **33** and 4.14 g (52.7 mmol) of AcCl was added dropwise over a period of 20 min to a stirred suspension of 7.34 g (55 mmol) of $AlCl_3$ in 50 mL of $ClCH_2CH_2Cl$, which was cooled in a water bath at 20 °C. When the addition was complete, the mixture was stirred at room temperature for 1 h. The reaction was quenched with 100 mL of ice–water and extracted with Et_2O (2 × 150 mL). The Et_2O layer was dried (Na_2SO_4) and concentrated to give 10.6 g of a yellow oil. Distillation gave 8.1 g (91%) of **34** as a pale-yellow oil: bp 102 °C (0.2 mm); IR (film) 3000, 2900, 1690, 1630, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–1.3 and 1.4–2.1 (2 m, 6, $CHCH_2CH$, $(CH_2)_2$), 2.57

(34) Ruzicka, L.; Seidel, C. F.; Schinz, H.; Tavel, Ch. *Helv. Chim. Acta* **1948**, *31*, 257–281.

(s, 3, CH_3CO), 3.3–3.5 (m, 2, 1,4-H), 7.27 (d, J = 8 Hz, 1, 8-H), 7.77 (dd, J = 2 Hz, J = 8 Hz, 1, 7-H), 7.83 (d, J = 2 Hz, 1, 5-H); MS calcd for $C_{13}H_{14}O$ 186.1045, found 186.1036.

Ethyl 4-[(*E*)-2-(1,4-Methano-1,2,3,4-tetrahydro-6-naphthyl)propenyl]benzoate (35). A solution of 13.8 g (46 mmol) of **25** in 150 mL of THF was cooled to −20 °C, while 30 mL of a 1.52 M (45.6 mmol) solution of *n*-BuLi in hexane was added over a period of 15 min. The dark brown solution was warmed to 0 °C, and 8.6 g (46.2 mmol) of **34** in 10 mL of THF was added. The mixture was stirred at room temperature for 16 h, then poured into 500 mL of ice–water, and extracted with Et_2O (3 × 200 mL). The Et_2O layer was dried (Na_2SO_4) and concentrated to give 20 g of a yellow oil. This oil was partially purified on silica gel (7% Et_2O/hexane) to give 3.0 g of unreacted **34** and 7.0 g (70% based on **34** consumed) of a 2:1 mixture of benzoates **36** and **35**, respectively. Purification of the mixture by LC (1% Et_2O/hexane) gave 3.0 g of a mixture containing over 90% of the Z isomer **36** and 3.5 g of a 1:1 mixture of Z and E isomers. A solution of 3.0 g of the 9:1 Z/E mixture in 500 mL of CH_2Cl_2 was irradiated with a medium-pressure Hanovia Hg-arc lamp for 5 h to give a 1:1 mixture of the Z and E isomers. The combined mixtures were purified by multiple passes on LC (1% Et_2O/hexane) to give 2.0 g (13%) of the E isomer **35** and 2.1 g (14%) of the Z isomer **36**.

35: LC (Radialpak B, 2% Et_2O/hexane, 3.0 mL/min, 260 nm) t_R 5.0 (0.5%), 5.7 min (99.5%); LC (Radialpak A, 5% H_2O/MeCN, 2.0 mL/min, 260 nm) t_R 6.2 min (100%); IR (film) 1730, 1620, 1580 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.12 (d, J = 8 Hz, 2, endo-2,3-H), 1.56 (m, 1, anti-9-H), 1.77 (d, J = 8 Hz, 1, syn-9-H), 1.94 (d, J = 8 Hz, 2, exo-2,3-H), 1.41 (t, J = 7 Hz, 3, CH_2CH_3), 2.29 (s, 3, CH_3), 3.37 (s, 2, 1,4-H), 4.38 (q, J = 7 Hz, 2, CH_2CH_3), 6.81 (s, 1, C=CH), 7.16 and 7.24 (2 d, J = 8 Hz, 2, 7,8-H), 7.35 (s, 1, 5-H), 7.40 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 8.03 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); ^{13}C NMR ($CDCl_3$) 14.3, 17.8, 27.0, 43.4, 43.8, 49.2, 60.7, 118.2, 120.2, 123.3, 125.8, 128.0, 128.9, 129.3, 140.1, 141.0, 143.3, 147.8, 148.3, 166.4 ppm; UV (EtOH) λ_{max} 308 nm (ϵ 2.7 × 10^4), 233 (1.5 × 10^4); MS calcd for $C_{23}H_{24}O_2$ 332.1776, found 332.1757.

36: LC (Radialpak B, 2% Et_2O/hexane, 3.0 mL/min, 260 nm) t_R 5.0 (99%), 5.7 min (1%); LC (Radialpak A, 5% H_2O/MeCN, 2.0 mL/min, 260 nm) t_R 5.9 min (100%); IR (film) 1730, 1620, 1580 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.10–1.20 (2 m, 2, endo-2,3-H), 1.35 (t, J = 7 Hz, 3, CH_2CH_3), 1.50 (d, J = 8 Hz, 1, anti-9-H), 1.74 (d, J = 8 Hz, 1, syn-9-H), 1.88 (m, 2, exo-2,3-H), 2.21 (s, 3, CH_3), 3.25 and 3.34 (2 s, 2, 1,4-H), 4.34 (q, J = 7 Hz, 2, CH_2CH_3), 6.42 (s, 1, C=CH), 6.85 (d, J = 8 Hz, 1, 7-H), 6.94 (s, 1, 5-H), 6.95 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.06 (d, J = 8 Hz, 1, 8-H), 7.73 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); ^{13}C NMR ($CDCl_3$) 14.3, 27.1, 27.5, 43.5, 43.7, 49.1, 60.6, 120.1, 120.5, 124.9, 125.2, 127.6, 128.6, 128.9, 138.7, 142.5, 142.7, 147.4, 148.5, 166.5 ppm; UV (EtOH) λ_{max} 300 nm (ϵ 1.7 × 10^4), 239 (1.7 × 10^4); MS calcd for $C_{23}H_{24}O_2$ 332.1776, found 332.1741.

4-[(*E*)-2-(1,4-Methano-1,2,3,4-tetrahydro-6-naphthyl)propenyl]benzoic Acid (9). A solution of 1.5 g (22.8 mmol) of 85% KOH in 2 mL of H_2O and 3 mL of EtOH was added to a warm solution of 2.0 g (6.02 mmol) of **35** in 20 mL of EtOH. The mixture was degassed (argon) and then heated at 80 °C for 30 min, cooled, and acidified with 20 mL of 50% H_2O/HOAc. The acid was extracted with 100 mL of Et_2O. The extract was washed with brine (100 mL), dried ($MgSO_4$), and concentrated to give 1.8 g of the crude acid, which was recrystallized (EtOAc) to afford 1.2 g (66%) of **9** as white crystals: mp 209 °C; LC (Radialpak A, 40% H_2O/MeCN, 2.0 mL/min, 260 nm) t_R 1.25 min (100%); IR (mull) 1690, 1610 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.15 (d, J = 8 Hz, 2, endo-2,3-H), 1.55 (m, 1, anti-9-H), 1.76 (d, J = 8 Hz, 1, syn-9-H), 1.95 (d, J = 8 Hz, 2, exo-2,3-H), 2.31 (s, 3, CH_3), 3.38 (s, 2, 1,4-H), 6.82 (s, 1, C=CH), 7.16 and 7.25 (2 d, J = 8 Hz, 2, 7,8-H), 7.36 (s, 1, 5-H), 7.45 (d, J = 8 Hz, 2, ArH meta to CO_2H), 8.08 (d, J = 8 Hz, 2, ArH ortho to CO_2H), 8.4–9.0 (br s, 1, CO_2H); ^{13}C NMR ($CDCl_3$/Me_2SO-d_6) 17.7, 26.8, 43.2, 43.6, 49.0, 118.0, 120.0, 123.1, 125.7, 128.7, 129.4, 139.8, 140.8, 142.9, 147.6, 148.2, 168.4 ppm; UV (EtOH) λ_{max} 301 nm (ϵ 2.5 × 10^4), 227 (1.4 × 10^4); MS calcd for $C_{21}H_{20}O_2$ 304.1463, found 304.1451.

1,4-Methano-1,2,3,4-tetrahydro-6-naphthalenecarboxylic Acid (37). To a solution of 60 g (1.5 mol) of NaOH in 300 mL of H_2O cooled to −5 °C was added 25.6 mL (0.5 mol) of Br_2 over a period of 5 min. The resulting solution of NaOBr was kept below 0 °C, while a solution of 18.6 g (0.1 mol) of **34** in 10 mL of dioxane was added. The temperature of the reaction mixture was gradually raised to 60–65 °C with a hot-water bath and was maintained there for 0.5 h. The reaction mixture was then cooled to room temperature, before a solution of 50 g (0.48 mol) of $NaHSO_3$ in 200 mL of H_2O was added. The yellow reaction mixture turned colorless. The mixture was acidified with concentrated HCl (about 120 mL), and the white, precipitated acid was extracted into Et_2O (800 mL). The Et_2O extract was dried (Na_2SO_4) and concentrated. The crude product was crystallized (EtOAc) to give a total of 17.67 g (94%) of acid **37** as white needles: mp 153–154 °C; IR (mull) 2900–3200, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–2.2 (m, 6, $(CH_2)_2$, CH_2), 3.45 (s, 2, 2 CH), 7.2–7.4 and 7.9–8.15 (2 m, 3, ArH), 11.65 (br s, 1, CO_2H); MS calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0818.

1,4-Methano-1,2,3,4-tetrahydro-6-naphthalenecarboxaldehyde (38). Naphthalenecarboxylic acid **37** (9.4 g, 0.05 mol) was added slowly to a stirred suspension of 1.0 g (26.4 mmol) of $LiAlH_4$ in 100 mL of THF. Another 0.6-g (15.8 mmol) portion of $LiAlH_4$ was then added. This mixture was stirred at room temperature for 2 h, when TLC (25% EtOAc/hexane) indicated that no starting material remained. To the reaction mixture were slowly added 1.6 mL of H_2O, 4.8 mL of 15% aqueous NaOH, and 1.6 mL of H_2O. The mixture was filtered through Celite (100-mL Et_2O wash). The filtrate was concentrated, and the resulting colorless oil was purified by chromatography on silica gel (30% Et_2O/hexane) to give 8.8 g (100%) of 1,4-methano-1,2,3,4-tetrahydro-6-naphthalenecarbinol as a colorless oil: IR (film) 3200–3600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95–2.0 (m, 6, $(CH_2)_2$, CH_2), 2.93 (s, 1, OH), 3.15–3.40 (m, 2, 2 CH), 4.48 (s, 2, CH_2OH), 6.9–7.25 (m, 3, ArH); MS calcd for $C_{12}H_{14}O$ 174.1045, found 174.1058.

To Collins reagent,[7] prepared from 31 g (0.31 mol) of CrO_3 and 50 mL (0.62 mol) of pyridine, in 250 mL of CH_2Cl_2 was added with ice-bath cooling 8.6 g (49 mmol) of the alcohol in 5 mL of CH_2Cl_2. This mixture was stirred at 0 °C for 20 min, when TLC (25% Et_2O/hexane) indicated that reaction was complete. The reaction mixture was filtered through Florisil (500-mL CH_2Cl_2 wash). The filtrate was concentrated and passed through silica gel (25% Et_2O/hexane) to give 6.8 g (80%) of **38** as a pale-yellow oil: IR (film) 1700, 1620, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–2.1 (m, 6, $(CH_2)_2$, CH_2), 3.45 (br s, 2, 2 CH), 7.3–7.8 (m, 3, ArH), 10.0 (s, 1, CHO); MS calcd for $C_{12}H_{12}O$ 172.0888, found 172.0898.

Ethyl 4-[(*E*)-2-(1,4-Methano-1,2,3,4-tetrahydro-6-naphthyl)ethenyl]benzoate (10). To a suspension of 27.4 mmol of NaH, obtained by washing 1.00 g of 59% NaH–mineral oil dispersion with pentane, in 100 mL of THF was added a mixture of 4.7 g (27.3 mmol) of **38**, 8.19 g (27.3 mmol) of **25**, and 100 mg of 15-crown-5[8] in 25 mL of THF. Hydrogen gas slowly evolved. The reaction mixture was stirred at room temperature for 2 h, diluted with 300 mL of H_2O, and extracted with Et_2O (3 × 100 mL). The ethereal extracts were washed with brine (2 × 200 mL), dried (Na_2SO_4), and concentrated at reduced pressure to give a white solid, which was recrystallized (EtOAc) to give 7.7 g (87%) of **10** as white crystals: mp 113–114 °C; LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 12.8 min (100%); LC (Radialpak A, 10% H_2O/MeCN, 2.0 mL/min, 260 nm) t_R 7.55 min (100%); IR (mull) 1710, 1610 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 8 Hz, 2, endo-2,3-H), 1.40 (t, J = 7 Hz, 3, CH_2CH_3), 1.55 (d, J = 8 Hz, 1, anti-9-H), 1.77 (d, J = 8 Hz, 1, syn-9-H), 1.94 (d, J = 8 Hz, 2, exo-2,3-H), 3.38 (br s, 2, 1,4-H), 4.38 (q, J = 7 Hz, 2, CH_2CH_3), 7.07 (d, J = 16 Hz, 1, 2-HC=CH), 7.16 and 7.22 (2 d, J = 9 Hz, 2, 7,8-H), 7.20 (d, J = 16 Hz, 1, 1-HC=CH), 7.40 (s, 1, 5-H), 7.54 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 8.01 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); ^{13}C NMR ($CDCl_3$) 14.3, 27.0, 27.1, 43.5, 43.6, 49.0, 60.8, 118.2, 120.7, 125.1, 126.0, 128.8, 129.9, 131.9, 134.2, 142.1, 148.8, 148.9, 166.4 ppm; UV (EtOH) λ_{max} 208 nm (ϵ 2.3 × 10^4), 238 (1.3 × 10^4), 332 (4.0 × 10^4); MS calcd for $C_{22}H_{22}O_2$ 318.1620, found 318.1607.

6-Ethenyl-1,4-methano-1,2,3,4-tetrahydronaphthalene (39). To a suspension of 12.46 g (34.8 mmol) of methyltriphenylphosphonium bromide in 200 mL of THF, which was cooled to −20 °C, was added 22.6 mL (34.6 mmol) of a 1.53 M solution of *n*-BuLi in hexane over a period of 15 min. The mixture was then warmed to −5 °C, when a clear yellow solution was obtained. A solution of 6.0 g (34.9 mmol) of **38** in 5 mL of THF was added dropwise. When all the aldehyde had been added, the initially

formed white precipitate disappeared to give a clear solution. After stirring for 2 h at room temperature, a white precipitate came out. The mixture was heated to 60 °C for 1 h, cooled, filtered, and concentrated. The residual oil was purified on silica gel (5% Et_2O/hexane) to give 5.4 g (91%) of **39** as a very pale-yellow oil: IR (film) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.0 (m, 6, 2,3,9-H), 3.2–3.4 (m, 2, 1,4-H), 5.12 (dd, J = 1.5 Hz, J = 11 Hz, 1, cis-HC=CH_2), 5.65 (dd, J = 1.5 Hz, J = 16 Hz, 1, trans-HC=CH_2), 6.74 (dd, J = 11 Hz, J = 16 Hz, 1, CH=CH_2), 7.12 (s, 2, 5,7-H), 7.30 (s, 1, 8-H); MS calcd for $C_{13}H_{14}$ 170.1095, found 170.1109.

***cis*- and *trans*-1-(4-Carbethoxyphenyl)-2-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)cyclopropanes (11 and 12).** A solution of 14.24 g (80.0 mmol) of 4-carbethoxybenzaldehyde in 10 mL of EtOH was added to 3.2 g of 95% $(NH_2)_2$ in 30 mL of EtOH, which was cooled in an ice bath. The mixture was gradually warmed to room temperature. After 3 h, TLC (50% Et_2O/hexane) indicated that almost all the aldehyde had reacted. A small amount of insoluble yellow precipitate (the azine) was also formed. The reaction mixture was concentrated to remove EtOH. The crude hydrazone [^1H NMR ($CDCl_3$/Me_2SO-d_6) δ 1.32 (t, J = 7.5 Hz, 3, CH_2CH_3), 4.33 (q, J = 7.5 Hz, 2, CH_2CH_3), 6.3–7.0 (br m, 2, NH_2), 7.4–8.2 (m, 5, HC=N, ArH)] was dissolved in 10 mL of Et_2O, cooled to 0 °C, and rapidly added to a stirred mixture of 24.0 g (0.11 mol) of yellow HgO[35] and 52 mL of 0.11 N KOH in EtOH at 0 °C. The mixture, which turned a greyish color immediately, was stirred at 0 °C for 5 min and filtered three times through cotton wool onto KOH pellets. The liquid was decanted from the KOH pellets and concentrated on a rotary evaporator at 0 °C. The resulting orange solid (**40**) was mixed with 10 mL of Et_2O and 6.8 g (0.04 mol) of **39** and added dropwise into a 100-mL flask heated to about 150 °C. After 2 h, TLC (10% Et_2O/hexane) indicated **37**, one major product, and several more polar minor products. The crude reaction mixture was purified on silica gel (10% Et_2O/hexane) to give 3.0 g of **39** and 4.3 g (58% based on amount of **39** consumed) of the product, which by analytical LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 260 nm) was a mixture of two isomers: t_R 5.0 (22%) and 5.5 min (78%). Purification by preparative LC (0.75% and 1% Et_2O/hexane) gave 1.1 g (8%) of **11** and 2.3 g (17%) of **12** as colorless oils.

11: LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 5.2 (99.4%), 5.8 min (0.6%); LC (Radialpak A, MeOH, 2.0 mL/min, 260 nm) t_R 1.8 (0.8%), 2.9 min (99.2%); IR (film) 1730, 1620 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 0.90 and 1.03 (2 m, 2, cyclopropyl CH_2), 1.25–1.35 (3 m, 3, endo-2,3-H, anti-9-H), 1.34 (t, J = 7 Hz, 3, CH_2CH_3), 1.63 (m, 1, syn-9-H), 1.80 (m, 2, exo-2,3-H), 2.42 and 2.55 (2 m, 2, cyclopropyl CH), 3.15 and 3.23 (2 s, 2, 1,4-H), 4.30 (q, J = 7 Hz, 2, CH_2CH_3), 6.65–6.77 (2 m, 2, 5,7-H), 6.85–6.95 (2 m, 3, 8-H, ArH meta to CO_2Et), 7.72 and 7.73 (2 d, J = 8 Hz, 2, ArH ortho to CO_2Et); ^{13}C NMR ($CDCl_3$) 12.3, 14.3, 23.9, 24.6, 27.1, 43.6, 49.0, 60.5, 119.8, 121.4, 121.8, 126.2, 126.8, 128.2, 128.5, 128.6, 134.5, 144.8, 145.9, 147.9, 166.7 ppm; UV (EtOH) λ_{max} 207 nm (ϵ 2.7 × 10^4), 234 (1.3 × 10^4), 251 (1.2 × 10^4); MS calcd for $C_{23}H_{24}O_2$ 332.1776, found 332.1774.

12: LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 5.2 (0.4%), 5.8 min (99.6%); LC (Radialpak A, MeOH, 2.0 mL/min, 260 nm) t_R 1.8 (0.4%), 2.1 (0.1%), 3.2 min (99.5%); IR (film) 1730, 1620 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 0.90 and 1.15 (2 m, 2, cyclopropyl CH_2), 1.22–1.32 and 1.35–1.55 (2 m, 3, endo-2,3-H, anti-9-H), 1.37 (t, J = 7 Hz, 3, CH_2CH_3), 1.73 (m, 1, syn-9-H), 1.88 (m, 2, exo-2,3-H), 2.18 (m, 2, cyclopropyl CH), 3.31 (s, 2, 1,4-H), 4.35 (q, J = 7 Hz, 2, CH_2CH_3), 6.84 (dd, J = 0.5 Hz, J = 8 Hz, 1, 7-H), 6.90 (d, J = 0.5 Hz, 1, 5-H), 7.06 (d, J = 8 Hz, 1, 8-H), 7.15 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.95 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); ^{13}C NMR ($CDCl_3$) 14.3, 18.7, 27.0, 27.1, 27.9, 29.1, 43.4, 43.8, 49.2, 60.6, 118.0, 120.3, 122.9, 125.4, 127.8, 129.6, 138.9, 146.1, 148.4, 166.4 ppm; UV (EtOH) λ_{max} 207 nm (ϵ 2.8 × 10^4), 263 (1.8 × 10^4); MS calcd for $C_{23}H_{24}O_2$ 332.1776, found 332.1774.

4,4-Dimethyl-3,4-dihydro-2*H*-1-benzopyran (46a). Method A. A reported procedure[19] was modified. To an ice-cooled solution of 12.2 g (0.142 mol) of 3-methyl-3-buten-1-ol and 11.9 g (0.150 mol) of pyridine in 100 mL of THF was added over a period of 10 min a solution of 38.5 g (0.143 mol) of $(C_6H_5O)_2POCl$ in 100 mL of THF. The mixture was heated at reflux for 3 h and cooled. The white suspension was filtered, and the filtrate was concentrated and diluted with 400 mL of 50% Et_2O/hexane. The solution was washed with water (2 × 200 mL), dried ($MgSO_4$), and concentrated to give 45.1 g (100%) of crude diphenyl 3-methyl-3-buten-1-yl phosphate as a pale-yellow oil: IR ($CHCl_3$) 1650, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3, CH_3C=C), 2.42 (t, J = 7 Hz, 2, C=CCH_2), 4.37 (q, J = 7 Hz, 2, CH_2O), 4.78 (m, 2, C=CH_2), 7.30 (m, 10, ArH).

To 35.5 g (0.136 mol) of $SnCl_4$, cooled in ice, was added 63.0 g (0.669 mol) of C_6H_5OH with stirring. After 5 min, a yellow liquid was obtained. To this complex was added over a 10-min period 44.0 g (0.138 mol) of the crude phosphate, followed by a 5-mL CS_2 rinse. The resultant orange syrup was stirred at room temperature for 17 h, poured onto a mixture of 700 g of ice and 1 L of 1.5 N NaOH, and extracted with Et_2O (2 × 600 mL). The extract was washed with 2 N NaOH (200 mL) and dilute brine (2 × 200 mL), dried ($MgSO_4$), and concentrated to give 25.3 g of colorless, viscous liquid, which was chromatographed on silica gel (2% Et_2O/hexane) to give 12.2 g (54% from 3-methyl-3-buten-1-ol) of **46a** as a colorless liquid: IR ($CHCl_3$) 1610, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 6, $C(CH_3)_2$), 1.80 (t, J = 5.5 Hz, 2, $CH_2C(CH_3)_2$), 4.17 (t, J = 5.5 Hz, 2, CH_2O), 7.0 (m, 4, ArH); ^{13}C NMR ($CDCl_3$) 30.5, 31.1, 37.8, 62.9, 117.0, 120.5, 126.9, 127.0, 131.6, 153.7 ppm.

Method B. To a degassed (three times, argon) suspension of NaH, obtained from 2.15 g (54 mmol NaH) of 60% NaH/mineral oil which had been washed with hexane (3 × 10 mL), in 20 mL of THF was added over a 5-min period with stirring and cooling in ice a solution of 5.0 g (53 mmol) of C_6H_5OH in 55 mL of THF. The suspension was stirred for 10 min more, treated with a solution of 7.0 g (59 mmol) of Me_2C=CHCOCl in 27 mL of THF over a 5-min period, and then allowed to warm to room temperature over a 3-h period. The suspension was poured into 150 mL of water containing 1 mL of HOAc. The mixture was stirred for 15 min and extracted with 150 mL of Et_2O. The extract was washed with dilute brine (2 × 100 mL) and water (100 mL), dried (Na_2SO_4), and concentrated to give a pale-yellow liquid, which was chromatographed on silica gel (10% Et_2O/hexane) to give 9.2 g (98%) of phenyl 3,3-dimethylacrylate (**42a**)[17] as a pale-yellow liquid: IR ($CHCl_3$) 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 and 2.22 (2 s, 6, $C(CH_3)_2$), 5.92 (m, 1, C=CH), 7.25 (m, 5, ArH).

Ester **42a** (9.0 g, 51.1 mmol) in 50 mL of CH_2Cl_2 was added to a stirred, ice-cooled suspension of 12.0 g (90 mmol) of $AlCl_3$ in 200 mL of CH_2Cl_2. This suspension was stirred at room temperature for 63 h to give a dark-brown solution, which was poured onto 500 mL of ice/brine and then extracted with CH_2Cl_2 (150 mL). The brown extract, which contained some suspended solid and an aqueous emulsion, was filtered to separate out the dark-red organic phase. The organic solution was washed with dilute brine (3 × 250 mL), dried (Na_2SO_4), and concentrated to give a dark-red oil, which was chromatographed on silica gel (10% Et_2O/hexane) to give 6.90 g (77%) of the lactone **43a**[17] as a colorless, viscous oil: IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 6, $C(CH_3)_2$), 2.60 (s, 2, CH_2CO), 7.20 (m, 4, ArH).

An ice-cooled suspension of 5.0 g (132 mmol) of $LiAlH_4$ in 75 mL of THF was degassed (argon) and then treated with a solution of 6.0 g (34.0 mmol) of **43a** in 35 mL of THF. The suspension was heated at reflux for 2 h and then cooled in ice. Excess $LiAlH_4$ was destroyed by the dropwise addition of 20% EtOAc/THF. The thick suspension was poured into 200 mL of 2 N H_2SO_4/ice. This mixture was saturated with NaCl and extracted with Et_2O (3 × 200 mL). The extract was washed with dilute brine (3 × 100 mL), dried (Na_2SO_4), and concentrated to give 6.2 g of a white solid, the crude diol **44a**:[18] IR ($CHCl_3$) 3580, 3300 cm^{-1}; ^1H NMR ($CDCl_3$/Me_2SO-d_6) δ 1.38 (s, 6, $C(CH_3)_2$), 2.13 (t, J = 7.5 Hz, 2, $CH_2C(CH_3)_2$), 3.35 (t, J = 7.5 Hz, 2, CH_2O), 3.4 (br s, 1, OH, exchanged D_2O), 6.9 (m, 4, ArH), 8.75 (br s, 1, ArOH, exchanged D_2O).

A solution of 5.1 g (28.3 mmol) of **44a** in 60 mL of pyridine was treated with 4.3 g (37.5 mmol) of $MeSO_2Cl$ with stirring and cooling in an ice bath and then stirred at ice-bath temperature for 1 h. The mixture was poured into 200 mL of brine and

(35) Day, A. C.; Raymond, P.; McSoutham, R.; Whiting, M. C. *J. Chem. Soc. C* **1966**, 467–469.

extracted with Et_2O (3 × 100 mL). The extract was washed with dilute brine (100 mL), 1 N HCl (2 × 200 mL), and dilute brine (2 × 100 mL), dried ($MgSO_4$, 1 H), and concentrated to give an oil. This crude mesylate was dissolved in 60 mL of dioxane and stirred with 75 mL of 1 N NaOH at room temperature for 2.25 h. The two-phase mixture was diluted with brine (100 mL) and extracted with Et_2O (3 × 100 mL). The extract was washed with 75 mL of dilute brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed on silica gel (3% Et_2O/hexane) to give 4.31 g (95% from **43a**) of **46a**,[17,19] which was spectrally identical (IR, ^1H NMR) with the sample prepared by method A.

6-Acetyl-4,4-dimethyl-3,4-dihydro-2*H*-1-benzopyran (47a). A solution of 6.7 g (85.4 mmol) of AcCl and 12.0 g (74.0 mmol) of **46a** in 150 mL of CS_2[23] was added dropwise over a period of 30 min to 30.0 g (115.2 mmol) of $SnCl_4$ with stirring and cooling in an ice bath. The mixture was stirred at room temperature for 3 h to give a blue-purple suspension and then poured onto 1 kg of ice/brine. The resultant purple suspension was shaken with 1.8 L of saturated $NaHCO_3$ and 800 mL of CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (400 mL). The combined extracts were washed with $NaHCO_3$ (400 mL), brine (2 × 300 mL), and water (300 mL) and dried (Na_2SO_4). The yellow solution was concentrated to give 17.5 g of a viscous orange-brown oil, which was chromatographed on silica gel (10% EtOAc/hexane) to give 14.1 g of a viscous yellow liquid. Bulb-to-bulb distillation of this liquid at 105–110 °C (0.05 mm) yielded 13.5 g (89%) of **47a** as a colorless viscous liquid: IR ($CHCl_3$) 1670, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 6, $C(CH_3)_2$), 1.83 (t, J = 5.5 Hz, 2, $CH_2C(CH_3)_2$), 2.53 (s, 3, CH_3CO), 4.24 (t, J = 5.5 Hz, 2, CH_2O), 6.82 (d, J = 8.5 Hz, 1, H-8), 7.72 (dd, J = 8.5 Hz, J = 2 Hz, 1, H-7), 7.98 (d, J = 2 Hz, 1, H-5); UV (MeCN) λ_{max} 222 nm (ϵ 1.3 × 10^4), 272 (1.5 × 10^4); MS calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1146.

4,4-Dimethyl-6-[(*E*)-1-(4-carbethoxyphenyl)-1-propen-2-yl]-3,4-dihydro-2*H*-1-benzopyran (48a). A degassed (argon), stirred suspension of NaH, obtained from 0.52 g (13 mmol of NaH) of 60% NaH/mineral oil dispersion that was washed with hexane (3 × 3 mL), in 15 mL of THF was treated at room temperature over a 5-min period with a solution of 2.04 g (10 mmol) of **47a**, 3.6 g (12 mmol) of **25**, and 0.45 g (2.0 mmol) of 15-crown-5 in 35 mL of THF. The suspension was stirred at room temperature for 16 h to give a red gum and a red solution. The reaction mixture was treated with 200 mL of brine containing 1 mL of HOAc and extracted with Et_2O (2 × 150 mL). The extract was washed with water (150 mL), dried (Na_2SO_4), and concentrated. The yellow oil was eluted through silica gel (7% Et_2O/hexane) to give 3.0 g of an almost colorless gum: LC (Radialpak B, 5% Et_2O/hexane, 1.0 mL/min, 280 nm) t_R 7.3 (84.5%), 8.6 min (15.5%). Two crystallizations of this product from hexane (4 mL, then 3 mL) gave 1.98 g (57%) of **48a** as white needles: mp 70–71.5 °C; LC (Radialpak A, MeCN, 1.0 mL/min, 280 nm) t_R 6.2 (98.3%), 7.0 min (1.7%); LC (Radialpak B, 5% Et_2O/hexane, 1.0 mL/min, 280 nm) t_R 7.4 (99.7%), 8.6 min (0.3%); IR ($CHCl_3$) 1700, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6, $C(CH_3)_2$), 1.40 (t, J = 7.5 Hz, 3, CH_2CH_3), 1.85 (t, J = 5.5 Hz, 2, $CH_2C(CH_3)_2$), 2.28 (s, 3, CH_3C=CH), 4.23 (t, J = 5.5 Hz, 2, CH_2O), 4.40 (q, J = 7.5 Hz, 2, CH_2CH_3), 6.78 (s, 1, C=CH), 6.82 (d, J = 8.5 Hz, 1, 8-ArH), 7.2–7.5 (m, 2, 5,7-ArH), 7.45 (d, J = 8.5 Hz, 2, ArH meta to CO_2Et), 8.08 (d, J = 8.5 Hz, 2, ArH ortho to CO_2Et); ^{13}C NMR ($CDCl_3$) 14.7, 18.0, 31.0, 31.3, 37.9, 61.1, 63.3, 117.1, 124.7, 125.1, 125.4, 128.3, 129.2, 129.7, 131.6, 136.0, 139.7, 143.6, 153.7, 166.8 ppm; UV (EtOH) λ_{max} 236 nm (ϵ 1.4 × 10^4), 316 (2.4 × 10^4); MS calcd for $C_{23}H_{26}O_3$ 350.1882, found 350.1893.

A sample of the gum obtained by concentration of the crystallization mother liquors was purified by using the LC recycle technique (Et_2O/hexane) to give an impure sample of the *Z* isomer of **48a** as a very pale-yellow gum: LC (Radialpak B, 5% Et_2O/hexane, 1.0 mL/min, 280 nm) t_R 7.2 (7.4%), 8.4 min (92.6%); IR ($CHCl_3$) 1705, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 6, $C(CH_3)_2$), 1.32 (t, J = 7.5 Hz, 3, CH_2CH_3), 1.77 (t, J = 5.5 Hz, 2, $CH_2C(CH_3)_2$), 2.20 (d, J = 1.5 Hz, 3, CH_3C=CH), 4.15 (t, J = 5.5 Hz, 2, CH_2O), 4.32 (q, J = 7.5 Hz, 2, CH_2CH_3), 6.45 (s, 1, C=CH), 6.65–7.2 (m, 5, 5,7,8-ArH, ArH meta to CO_2Et), 7.85 (d, J = 8.5 Hz, 2, ArH ortho to CO_2Et); UV (EtOH) λ_{max} 244 nm (ϵ 1.7 × 10^4), 306 (1.2 × 10^4); MS calcd for $C_{23}H_{26}O_3$ 350.1882, found 350.1887.

4,4-Dimethyl-6-[(*E*)-1-(4-carboxyphenyl)-1-propen-2-yl]-3,4-dihydro-2*H*-1-benzopyran (13). To a degassed (argon) solution of 0.8 g (12.1 mmol) of 85% KOH in 6 mL of EtOH and 1.5 mL of H_2O was added 1.56 g (4.45 mmol) of **48a**. This suspension was degassed (argon) and stirred in a 100–110 °C oil bath for 35 min. The resultant clear solution was cooled and treated with 10-mL portions of 50% HOAc and brine and extracted with Et_2O (2 × 30 mL). The extract was washed with dilute brine (2 × 20 mL), dried ($MgSO_4$), and concentrated to a white solid, which was recrystallized from 30 mL of MeOH to give 1.13 g (79%) of **13** as fine, white needles: mp 180–181 °C; LC (Radialpak A, 40% H_2O/MeCN, 1.5 mL/min, 280 nm) t_R 2.8 min (100%); IR ($CHCl_3$) 2400–3500, 1690, 1605 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 1.39 (s, 6, $C(CH_3)_2$), 1.87 (m, 2, CH_2C), 2.29 (d, J = 1.1 Hz, 3, CH_3C=CH), 4.22 (m, 2, CH_2O), 6.77 (s, 1, C=CH), 6.81 (d, J = 8.5 Hz, 1, 8-ArH), 7.27 (dd, J = 8.5 Hz, J = 2.3 Hz, 1, 7-ArH), 7.43 (d, J = 2.3 Hz, 1, 5-ArH), 7.46 (d, J = 8.4 Hz, 2, ArH meta to CO_2H), 8.11 (d, J = 8.4 Hz, 2, ArH ortho to CO_2H); ^{13}C NMR (Me_2SO-d_6/$CDCl_3$) 16.4, 29.3, 29.7, 36.2, 61.6, 115.4, 123.1, 123.4, 123.6, 127.2, 127.6, 128.2, 130.0, 134.1, 137.7, 141.6, 152.0, 166.6 ppm; UV (95% EtOH) λ_{max} 231 nm (ϵ 1.3 × 10^4), 307 (2.5 × 10^4). Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.04; H, 6.96.

***S*-Phenyl 3,3-Dimethylthioacrylate (42b).** To a degassed (argon) suspension of NaH, which was obtained from 3.2 g (80 mmol) of 60% NaH/mineral oil dispersion, which had been washed with hexane (3 × 15 mL) under argon, in 30 mL of THF was added over a period of 5 min with stirring and cooling in ice a solution of 8.8 g (80 mmol) of C_6H_5SH in 80 mL of THF. The suspension was stirred for 15 min and then treated over a period of 10 min with a solution of 10.1 g (85 mmol) of Me_2C=CHCOCl in 40 mL of THF and then allowed to warm to room temperature over a 2-h period. The suspension was poured into 200 mL of water containing 2 mL of HOAc, stirred for 15 min, and extracted with 200 mL of Et_2O. The extract was washed with dilute brine (3 × 100 mL), dried (Na_2SO_4), and concentrated to give a yellow oil. Distillation yielded 15.0 g (98%) of **42b** as a colorless liquid: bp 105–106 °C (0.7 mm); IR ($CHCl_3$) 1680, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 and 2.14 (2 s, 6, $C(CH_3)_2$), 6.07 (m, 1, C=CH), 7.43 (m, 5, ArH); MS calcd for $C_{11}H_{12}OS$ 192.061, found 192.059.

4,4-Dimethyl-2-oxo-3,4-dihydro-2*H*-1-benzothiopyran (43b). A stirred, ice-cooled suspension of 14.0 g (105 mmol) of $AlCl_3$ in 100 mL of CH_2Cl_2 was treated with a solution of 13.44 g (70 mmol) of **42b** in 70 mL of CH_2Cl_2. The reaction mixture was allowed to stand at 0 °C for 15 h and then was poured onto 200 g of ice/brine. The aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined CH_2Cl_2 solutions were washed with dilute brine (2 × 150 mL) and water (150 mL), dried (Na_2SO_4), and concentrated. The pale-yellow liquid (13.5 g) was chromatographed on silica gel (10% Et_2O/hexane) to give 12.24 g (91%) of **43b** as a solid: mp 34–35 °C; IR ($CHCl_3$) 1680, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 6, $C(CH_3)_2$), 2.65 (s, 2, CH_2CO), 7.15–7.63 (m, 4, ArH); MS calcd for $C_{11}H_{12}OS$ 192.061, found 192.059.

4,4-Dimethyl-3,4-dihydro-2*H*-1-benzothiopyran (46b). Method A. To an ice-cooled suspension of 12.0 g (316 mmol) of $LiAlH_4$ in 180 mL of THF was added 13.2 g (68.6 mmol) of **43b** in 75 mL of THF dropwise at room temperature. The reaction mixture was then refluxed for 4 h and cooled in ice/water. The excess $LiAlH_4$ was destroyed by the dropwise addition of 20% EtOAc/THF. The mixture was poured into 750 mL of 2 N H_2SO_4 and extracted with Et_2O (2 × 300 mL). The extract was washed with dilute brine (3 × 150 mL), dried ($MgSO_4$), and concentrated. The colorless oil (15.0 g) was chromatographed on silica gel (2% Et_2O/hexane, then 40% Et_2O/hexane) to give (a) 5.51 g (45%) of **46b**[21] as a colorless liquid [IR ($CHCl_3$) 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 6, $C(CH_3)_2$), 1.90 (m, 2, CCH_2), 2.98 (m, 2, CH_2S), 6.87 (m, 3, ArH), 7.27 (m, 1, ArH); ^{13}C NMR ($CDCl_3$) 22.8, 29.9, 32.6, 37.4, 123.7, 125.6, 126.1, 126.1, 131.5, 141.5 ppm; MS calcd for $C_{11}H_{14}S$ 178.081, found 178.080] and (b) 7.28 g (54%) of **44b** as a colorless gum [IR ($CHCl_3$) 3600, 3430, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 6, $C(CH_3)_2$), 2.12 (br s, 1, OH, exchanged D_2O), 2.23 (t, J = 8 Hz, 2, CCH_2), 3.38 (t, J = 8 Hz, 2, CH_2O), 3.60 (br s, 1, H, exchanged D_2O), 6.90–7.38 (m, 4, ArH); MS calcd for $C_{11}H_{16}OS$ 196.092, found 196.089].

Method B. A stirred suspension of NaH, which was obtained by washing (3 × 15 mL of hexane) 3.0 g (75 mmol) of 60% NaH/mineral oil dispersion, in 20 mL of THF was cooled in

ice/water and treated with 7.15 g (65 mmol) of C_6H_5SH in 65 mL of THF over a 10-min period. The suspension was stirred for 40 min before a solution of 9.3 g (62.4 mmol) of $Me_2C{=}CHCH_2Br$ in 25 mL of THF was added over a 10-min period, while the reaction mixture was maintained at ice-bath temperature. The mixture was stirred for a further 45 min and then allowed to warm to room temperature over a 1.25-h period. The white suspension was poured into 300 mL of water. The organic phase was washed with 1 N NaOH (150 mL) and twice with dilute brine (150 mL) and dried (Na_2SO_4, overnight). The colorless solution was concentrated, and the resulting oil was chromatographed on silica gel (2 L of hexane, followed by 1% Et_2O/hexane) to give 10.3 g of a colorless oil. This oil was distilled to give 9.76 g (88%) of **45**[20] as a colorless, foul-smelling liquid: bp 83–85 °C (0.8 mm); IR ($CHCl_3$) 1665, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 and 1.70 (2 s, 6, $C(CH_3)_2$), 3.52 (d, J = 8 Hz, 2, CH_2S), 5.30 (t, J = 8 Hz, 1, C=CH), 7.28 (m, 5, ArH); MS calcd for $C_{11}H_{14}S$ 178.081, found 178.080.

To 22.9 g (88 mmol) of $SnCl_4$ in 200 mL of CH_2Cl_2, cooled in ice, was added 7.83 g (44 mmol) of **45** in 40 mL of CH_2Cl_2. The solution was stirred at 0–5 °C for 20 min and then at room temperature for 20 h. The red solution was poured onto 500 g of ice/brine, and the organic extract was washed successively with 250-mL volumes of brine, aqueous $NaHCO_3$, and water (three times). The CH_2Cl_2 solution, which contained suspended inorganic material, was dried (Na_2SO_4), filtered, and concentrated. The 7.4 g of yellow liquid was chromatographed twice on silica gel (0.75% Et_2O/hexane) to give 4.11 g (52%) of **46b** as a colorless liquid. The product was spectrally (IR, ^1H NMR) identical with the sample prepared by $LiAlH_4$ reduction of **43b**.

6-Acetyl-4,4-dimethyl-3,4-dihydro-2*H*-1-benzothiopyran (47b). A solution of 1.3 g (16.6 mmol) of AcCl and 2.85 g (16.0 mmol) of **46b** in 50 mL of CS_2[24] was added dropwise over a 15-min period to 3.2 g (24.0 mmol) of $AlCl_3$ with stirring and cooling in ice. The addition funnel was rinsed with 10 mL of CS_2. The reaction mixture was stirred at room temperature for 2.25 h, before the resultant orange suspension was treated with 50 mL of ice/brine. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with dilute brine (3 × 50 mL), dried (Na_2SO_4), and concentrated. The pale-yellow, viscous oil was chromatographed on silica gel (10% Et_2O/hexane) to give 2.92 g (83%) of **47b** as a pale-yellow, viscous liquid: IR ($CHCl_3$) 1670, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 6, $C(CH_3)_2$), 1.93 (m, 2, CCH_2), 2.53 (s, 3, CH_3CO), 3.05 (m, 2, CH_2S), 7.12 (d, J = 8.5 Hz, 1, 8-ArH), 7.57 (dd, J = 8.5 Hz, J = 2 Hz, 1, 7-ArH), 8.00 (d, J = 2 Hz, 1, 5-ArH); UV (MeCN) λ_{max} 237 nm (ϵ 6.3 × 10^3), 242 (6.2 × 10^3), 310 (1.8 × 10^4); MS calcd for $C_{13}H_{16}OS$ 220.092, found 220.090.

4,4-Dimethyl-6-[(*E*)-1-(4-carbethoxyphenyl)-1-propen-2-yl]-3,4-dihydro-2*H*-1-benzothiopyran (48b). To a suspension of NaH, which was obtained from 0.52 g (13 mmol) of 60% NaH/mineral oil dispersion washed three times with 2 mL of hexane, in 20 mL of THF was added over a period of 50 min a solution of 2.2 g (10.0 mmol) of **47b**, 3.6 g (12.0 mmol) of **25**, and 0.45 g (2.0 mmol) of 15-crown-5 in 30 mL of THF. The orange suspension was stirred at room temperature for 17 h to give a red solution and a red-orange gum. This mixture was treated with 200 g of ice/brine containing 1 mL of HOAc and extracted with Et_2O (2 × 50 mL). The extract was washed with 50 mL of dilute brine, dried (Na_2SO_4), and concentrated. The yellow solid was chromatographed on silica gel (7% Et_2O/hexane) to give 3.2 g (87%) of the crude product, which was further purified by preparative LC (7% Et_2O/hexane) to give 3.14 g (86%) of **48b**. ^1H NMR and analytical LC (Radialpak B, 5% Et_2O/hexane, 1.0 mL/min, 280 nm), t_R 3.6 (99.1%), 4.1 min (0.9%), indicated essentially a single isomer. Two crystallizations from 20 to 30 mL of 10% EtOAc/hexane gave 1.70 g (46%) of the pure *E* ester **48b**, mp 94–94.5 °C. A further 0.56 g (15%) of **48b** was obtained by two more crystallizations of the material recovered from the crystallization mother liquor. The combined yield of white crystals was 2.26 g (62%): LC (Radialpak A, MeCN, 1.0 mL/min, 280 nm) t_R 7.8 min (100%); LC (Radialpak B, 5% Et_2O/hexane, 1.0 mL/min, 280 nm) t_R 7.3 min (100%); IR ($CHCl_3$) 1705, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6, $C(CH_3)_2$), 1.41 (t, J = 7 Hz, 3, CH_2CH_3), 1.99 (m, 2, CCH_2), 2.27 (d, J = 1 Hz, 3, $CH_3C{=}C$), 3.05 (m, 2, CH_2S), 4.39 (q, J = 7 Hz, CH_2CH_3), 6.79 (br s, 1, C=CH), 7.09 (d, J = 8 Hz, 1, 8-ArH), 7.21 (dd, J = 8 Hz, J = 2 Hz, 1, 7-ArH), 7.41 (d, J = 8 Hz, 2, ArH meta to CO_2Et), 7.51 (d, J = 2 Hz, 1, 5-ArH), 8.04 (d, J = 8 Hz, 2, ArH ortho to CO_2Et); ^{13}C NMR ($CDCl_3$) 14.3, 17.6, 23.1, 30.2, 33.1, 37.7, 60.7, 123.5, 123.8, 125.5, 126.2, 128.0, 128.7, 129.2, 131.2, 139.1, 139.1, 141.5, 142.8, 166.1 ppm; UV (EtOH) λ_{max} 244 nm (ϵ 1.2 × 10^4), 326 (2.6 × 10^4); MS calcd for $C_{23}H_{26}O_2S$ 366.165, found 366.163.

4,4-Dimethyl-6-[(*E*)-1-(4-carboxyphenyl)-1-propen-2-yl]-3,4-dihydro-2*H*-1-benzothiopyran (14). To a degassed (three times, argon) suspension of 1.50 g (4.1 mmol) of **48b** in 7.5 mL of EtOH was added a degassed (two times, argon) solution of 0.75 g (11.4 mmol) of 85% KOH in 2.25 mL of water, followed by a 0.5-mL H_2O rinse. The mixture was again degassed (twice) and then heated at reflux in a 100–110 °C oil bath for 40 min. The ester dissolved within 15 min to give a pale-yellow solution. The reaction mixture was cooled to room temperature, quenched with a solution of 2 mL of HOAc in 10 mL of H_2O, and then diluted with 10 mL of brine. The white solid carboxylic acid was extracted with EtOAc (100, then 50 mL). The very pale-yellow extract was washed with dilute brine (2 × 25 mL) and water (25 mL), dried (Na_2SO_4), and concentrated. The almost white powder was recrystallized twice (60 mL of EtOAc) to give 1.05 g (75%) of white crystals: mp 217–217.5 °C; LC (Radialpak A, 40% H_2O/MeCN, 1.0 mL/min, 280 nm) t_R 1.6 (0.3%), 2.1 (1.5%), 4.3 min (98.2%); IR (mull) 2200–3200, 1680, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6, $C(CH_3)_2$), 1.99 (m, 2, CCH_2), 2.29 (s, 3, $CH_3C{=}C$), 3.05 (m, 2, CH_2S), 6.80 (s, 1, C=CH), 7.10 (d, J = 8.6 Hz, 1, 8-ArH), 7.22 (dd, J = 8.3 Hz, J = 1.7 Hz, 1, 7-ArH), 7.46 (d, J = 8.3 Hz, 2, ArH meta to CO_2H), 7.52 (d, J = 1.8 Hz, 1, 5-ArH), 8.11 (d, J = 8.3 Hz, 2, ArH ortho to CO_2H); ^{13}C NMR ($CDCl_3$/Me_2SO-d_6) 16.5, 21.8, 29.0, 31.9, 36.4, 122.3, 122.7, 124.3, 125.0, 127.4, 127.6, 128.2, 130.0, 137.7, 138.8, 140.4, 141.3, 166.4 ppm; UV (EtOH) λ_{max} 233 nm (ϵ 1.1 × 10^4), 319 (2.5 × 10^4); MS calcd for $C_{21}H_{22}O_2S$ 338.134, found 338.132. Anal. Calcd for $C_{21}H_{22}O_2S$: C, 74.52; H, 6.55; S, 9.47. Found: C, 74.53; H, 6.68; S, 9.61.

2-(4-Bromo-2-methylphenyl)-1,3-dioxolane (50). To a stirred suspension of 9.38 g (43.6 mmol) of **49** in 17 mL of THF, which was cooled in an ice bath, was added over a period of 10 min 56 mL (56 mmol) of 1 M BH_3·THF in THF. The reaction mixture was allowed to reach room temperature over a period of 1 h and then was cooled in an ice bath and quenched by the dropwise addition of 10 mL of 50% aqueous THF. This mixture was dried (Na_2CO_3, 1 h) and concentrated. The residue was extracted with Et_2O (100 mL). The extract was washed with water (2 × 100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL). The aqueous washes were back-extracted with Et_2O (100 mL), and this extract was washed with $NaHCO_3$ and brine (50 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give 8.75 g (100%) of 4-bromo-2-methylbenzyl alcohol:[36] IR ($CHCl_3$) 3600, 3430, 1600, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3, $ArCH_3$), 2.78 (s, 1, OH, exchanged D_2O), 4.53 (s, 2, CH_2O), 7.28 (m, 3, ArH).

A solution of 5.5 g (27.4 mmol) of the alcohol in 150 mL of CH_2Cl_2 was added dropwise over a period of 15 min to a slurry of 12.5 g (58.0 mmol) of PCC in 400 mL of CH_2Cl_2. The reaction mixture was stirred for 2.5 h, diluted with 800 mL of Et_2O, and filtered through Florisil (1.5-L Et_2O rinse). The filtrate was concentrated to give 5.52 g of crude 4-bromo-2-methylbenzaldehyde[36] as a yellow-green oil. A mixture of the crude aldehyde, 25 mL (0.45 mol) of $(CH_2OH)_2$, and 0.25 g of *p*-TsOH·H_2O in 250 mL of C_6H_6 was heated at reflux under a Dean–Stark trap for 17 h and cooled. The mixture was washed with saturated $NaHCO_3$ (300 mL) and water (2 × 200 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed on silica gel (10% Et_2O/hexane) to give 6.03 g (91%) of **50** as a colorless oil: IR ($CHCl_3$) 1600, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3, CH_3), 4.07 (m, 4, CH_2O), 5.88 (s, 1, OCHO), 7.37 (m, 3, ArH); MS calcd for $C_{10}H_{11}O_2{}^{79}Br$ 241.9943, found 241.9921.

2-[4-(1-Hydroxy-2,2,6-trimethylcyclohexyl)-2-methylphenyl]-1,3-dioxolane (52). To a solution of 8.71 g (35.8 mmol) of **50** in 70 mL of THF at −78 °C was added under argon 22.1 mL (34.0 mmol) of 1.54 M *n*-BuLi in hexane. The solution became

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red and then green, and a white solid separated. After 10 min, a solution of 7.5 g (53.5 mmol) of **51** in 35 mL of THF was added dropwise over a period of 5 min. The resultant clear yellow solution was stirred for 15 min at −78 °C and then warmed to room temperature over a period of 1.5 h. The reaction mixture was then cooled in an ice bath and quenched with 30 mL of water. The suspension was diluted with brine (50 mL) and extracted with Et_2O (2 × 50 mL). The yellow extract was washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated to give 14.0 g of oil, from which white crystals separated on standing. The mixture was chromatographed on silica gel (8–10% EtOAc/hexane) to give successively (a) 2.92 g (39% recovery) of **51**, (b) 0.54 g (6% recovery) of **50**, and (c) 9.1 g of crude **52**. The third fraction was crystallized (50% Et_2O/hexane) to give 6.58 g (64%) of **52** as white crystals, mp 99–100 °C. A sample was recrystallized (50% Et_2O/hexane) for characterization: mp 101–102 °C; IR ($CHCl_3$) 3600, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.59 (d, J = 7 Hz, 3, $CHCH_3$), 0.73 and 0.87 (2 s, 6, $C(CH_3)_2$), 1.0–1.8 (m, 8, $(CH_2)_3CH$, OH, exchanged D_2O), 2.43 (s, 3, $ArCH_3$), 4.10 (m, 4, CH_2O), 5.95 (s, 1, OCHO), 7.0 (m, 1, ArH), 7.5 (m, 2, ArH); MS calcd for $C_{19}H_{28}O_3$ 304.2038, found 304.2066.

The mother liquor from crystallization of the crude product was concentrated to give 2.5 g of an oil. Silica gel chromatography (8% EtOAc/hexane) of a sample gave 4-(1-hydroxy-2,2,6-trimethylcyclohexyl)-2-methylbenzaldehyde as a colorless gum: IR ($CHCl_3$) 3600, 1690, 1605, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.62 (d, J = 7 Hz, 3, $CHCH_3$), 0.75 and 0.92 (2 s, 6, $C(CH_3)_2$), 1.1–2.0 (m, 8, $(CH_2)_3CH$, OH, exchanged D_2O), 2.70 (s, 3, $ArCH_3$), 7.2 (m, 1, ArH), 7.75 (m, 2, ArH), 10.35 (d, J = 2 Hz, 1, CHO). The remainder of this oil was dissolved in 60 mL of benzene, treated with 5 mL (90 mmol) of $(CH_2OH)_2$ and 50 mg of p-TsOH·H_2O, and heated at reflux for 17.5 h. The cooled mixture was washed with saturated $NaHCO_3$ (60 mL) and H_2O (2 × 25 mL), dried (Na_2SO_4), and concentrated. The product was chromatographed on silica gel (8-10% EtOAc/hexane) to give an additional 1.39 g (13%) of **52**. The total yield was 7.97 g (77%).

2-Methyl-4-(2,6,6-trimethylcyclohexenyl)benzaldehyde (53). A solution of 3.04 g (10.0 mmol) of **52** in 50 mL of pyridine was cooled in ice and treated with 10 mL (107 mmol) of $POCl_3$. The solution was heated in a 110 °C oil bath for 17.5 h. The pale-yellow solution rapidly became brown on heating. The cooled, very dark solution was poured into 500 mL of 2 N HCl, which was cooled in ice. The mixture was stirred at room temperature for 2.75 h. The product was extracted with CH_2Cl_2 (300, 150 mL). The purple extract was washed with dilute brine (4 × 300 mL), dried (Na_2SO_4), and concentrated. The resultant dark oil was chromatographed on silica gel (7% Et_2O/hexane) to give 1.36 g (56%) of **53** as a yellow oil: IR ($CHCl_3$) 1685, 1600, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (s, 6, $C(CH_3)_2$), 1.28 (s, 3, $C{=}CCH_3$), 1.4–2.2 (m, 6, CH_2), 2.69 (s, 3, $ArCH_3$), 7.02 (m, 2, ArH), 7.77 (d, J = 8 Hz, 1, 6-ArH), 10.30 (s, 1, CHO); UV (MeCN) λ_{max} 258 nm (ϵ 1.5 × 10^4); MS calcd for $C_{17}H_{22}O$ 242.1671, found 242.1676.

Ethyl (*E*)-3-Methyl-5-[2-methyl-4-(2,6,6-trimethylcyclohexenyl)phenyl]-2,4-pentadienoate (55). A solution of 4.2 g (15.9 mmol) of **54**[37] in 12 mL of THF at −78 °C was treated with 8.7 mL (13.4 mmol) of 1.54 M n-BuLi in hexane and then stirred for 10 min to give a yellow solution. Next, a solution of 2.95 g (12.2 mmol) of **53** in 12 mL of THF was added over a period of 5 min. The reaction mixture was warmed to room temperature after a further 20 min at −78 °C and stirred at room temperature for 4 h. The yellow solution was treated with brine (150 mL) and extracted with hexane (100, 30 mL). The extract was washed with dilute brine (75 mL), dried (Na_2SO_4), and concentrated to give 5.6 g of yellow oil, which was eluted through silica gel (10% Et_2O/hexane) to give 4.3 g of the crude ester isomer mixture.

The isomers were separated by preparative LC (2% Et_2O/hexane) to give 0.164 g (4%) of 13_RZ isomer **56** as a pale-yellow oil: LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 280 nm) t_R 2.5 (98.8%), 3.5 min (1.2%, 13_RE isomer); IR ($CHCl_3$) 1690, 1620 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 0.93 (s, 6, $16,17_R$-CH_3), 1.29 (s, 3, 18_R-CH_3), 1.31 (t, J = 7 Hz, 3, CH_2CH_3), 1.56 and 1.71 (2 m, 4, $2,3_R$-CH_2), 2.04 (m, 2, 4_R-CH_2), 2.15 (d, J = 0.8 Hz, 3, 20_R-CH_3), 2.39 (s, 3, $ArCH_3$), 4.20 (q, J = 7 Hz, 2, CH_2CH_3), 5.73 (s, 1, 14_R-C=CH), 6.82 (m, 2, ArH), 7.18 (d, J = 16.2 Hz, 1, 11_R-HC=CH), 7.60 (d, J = 7.9 Hz, 1, 6-ArH), 8.30 (d, J = 16.2 Hz, 1, 12_R-HC=CH); ^{13}C NMR ($CDCl_3$) 14.3, 19.5, 19.6, 20.7, 21.2, 28.9, 32.2, 34.4, 39.8, 59.5, 117.5, 125.5, 126.7, 128.3, 128.8, 132.2, 132.9, 135.4, 140.9, 142.6, 150.7, 166.2 ppm; UV (EtOH) λ_{max} 235 nm (ϵ 1.9 × 10^4), 326 (3.2 × 10^4); MS calcd for $C_{24}H_{32}O_2$ 352.2402, found 352.2397.

In addition, 3.60 g (84%) of the 13_RE isomer **55** was obtained. This material was further purified by LC in the same solvent to give 3.07 g (71%) of **55** as a white solid: mp 76.5–78.5 °C; LC (Radialpak A, MeCN, 2.0 mL/min, 280 nm) t_R 3.8 (<0.2%), 5.8 (<0.2%), 6.6 min (>99.5%); LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 280 nm) t_R 3.3 min (100%); IR ($CHCl_3$) 1700, 1605 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 0.93 (s, 6, $16,17_R$-CH_3), 1.29 (s, 3, 18_R-CH_3), 1.31 (t, J = 7 Hz, 3, CH_2CH_3), 1.56 and 1.71 (2 m, 4, $2,3_R$-CH_2), 2.04 (m, 2, 4_R-CH_2), 2.39 (s, 3, $ArCH_3$), 2.43 (d, J = 0.8 Hz, 3, 20_R-CH_3), 4.20 (q, J = 7 Hz, 2, CH_2CH_3), 5.90 (s, 1, 14_R-C=CH), 6.73 (d, J = 16 Hz, 1, 12_R-HC=CH), 6.84 (m, 2, ArH), 7.19 (d, J = 16 Hz, 1, 11_R-HC=CH), 7.46 (d, J = 7.7 Hz, 1, 6-ArH); ^{13}C NMR ($CDCl_3$) 13.9, 14.3, 19.5, 19.6, 21.2, 28.9, 32.2, 32.4, 39.8, 59.5, 119.3, 124.8, 128.3, 129.0, 131.7, 132.4, 132.4, 132.5, 135.2, 140.9, 142.6, 152.2, 167.0 ppm; UV (EtOH) λ_{max} 237 nm (ϵ 1.5 × 10^4), 322 (3.9 × 10^4); MS calcd for $C_{24}H_{32}O_2$ 352.2402, found 352.2411.

(*E*)-3-Methyl-5-[2-methyl-4-(2,6,6-trimethylcyclohexenyl)phenyl]-2,4-pentadienoic Acid (15). To a degassed (argon) solution of 1.5 g (23 mmol) of 85% KOH in 9 mL of EtOH and 4 mL of H_2O was added 2.91 g (8.25 mmol) of **55** (3-mL EtOH rinse). The suspension was again degassed before heating in an oil bath. The bath temperature was raised to 100 °C over a period of 15 min and maintained there for 35 min. The light-yellow solution was cooled and quenched with 15 mL of 50% HOAc. The suspension was diluted with 20 mL of brine and extracted with Et_2O (75, 35 mL). The extract was washed with brine (2 × 25 mL), dried (Na_2SO_4), and concentrated. The solid, white residue was dissolved in Et_2O and filtered. The filtrate was concentrated to give 2.73 g of crude acid **15**. This product was crystallized (MeOH) under argon to give 2.34 g (87%) of white crystals: mp 165–166.5 °C; LC (Radialpak A, 30% H_2O/MeCN, 1.0 mL/min, 280 nm) t_R 1.5 (trace), 1.8 (trace), 2.2 (>99.5%), 3.8 min (trace); IR ($CHCl_3$) 2300–3300, 1675, 1600 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 0.93 (s, 6, $16,17_R$-CH_3), 1.30 (s, 3, 18_R-CH_3), 1.56 and 1.72 (2 m, 4, $2,3_R$-CH_2), 2.05 (m, 2, 4_R-CH_2), 2.40 (s, 3, $ArCH_3$), 2.45 (d, J = 0.8 Hz, 3, 20_R-CH_3), 5.94 (s, 1, 14_R-C=CH), 6.77 (d, J = 16 Hz, 1, 12_R-HC=CH), 6.85 (m, 2, ArH), 7.26 (d, J = 16 Hz, 1, 11_R-HC=CH), 7.48 (d, J = 7.8 Hz, 1, 6-ArH); ^{13}C NMR ($CDCl_3$) 14.2, 19.5, 19.8, 21.3, 29.0, 32.1, 34.4, 39.7, 118.5, 124.8, 128.4, 128.9, 132.1, 132.4, 132.5, 132.8, 135.5, 140.6, 142.7, 155.1, 172.4 ppm; UV (EtOH) λ_{max} 236 nm (ϵ 9.9 × 10^3), 313 (3.0 × 10^4); MS calcd for $C_{22}H_{28}O_2$ 324.2089, found 324.2089.

[4-(4-Bromophenyl)phenyl]methanol (57). A mixture of 4.00 g (16.2 mmol) of 4-(4-bromophenyl)toluene and 3.03 g (17.0 mmol) of NBS in 60 mL of CCl_4 containing 10 mg of AIBN was heated at reflux for 15 min. The reaction mixture was cooled, diluted with Et_2O (175 mL), and washed with H_2O (50 mL), saturated $NaHCO_3$ (50 mL), and brine (15 mL). The organic solution was dried ($MgSO_4$) and concentrated to give 5.25 g (100%) of crude dibromide.

To the dibromide was added 100 mL of EtOH and 15.9 g (162 mmol) of KOAc. The resulting mixture was heated at reflux for 1 h and cooled to room temperature. A solution of 4.5 g of 85% KOH in 30 mL of EtOH was added. After being stirred overnight, the reaction mixture was concentrated until its volume was reduced by 60 mL. The residue was partitioned between H_2O (100 mL) and Et_2O (100 mL). The Et_2O phase was washed with 3 N HCl (2 × 75 mL), saturated $NaHCO_3$ (75 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated. Chromatography on silica gel (3% Et_2O/CH_2Cl_2) afforded 2.92 g (69%) of **57** as a colorless solid: ^1H NMR ($CDCl_3$) δ 1.75 (br s, 1, OH), 4.72 (s, 2, $ArCH_2$), 7.48 (apparent q_{AB}, $\Delta\nu$ = 13.5 Hz, J = 9 Hz, 8, ArH). Crystallization (Et_2O) afforded the analytical sample as white crystals: mp 130.5–131.5 °C; IR ($CHCl_3$) 3300, 1475 cm^{-1}; MS calcd for $C_{13}H_{11}{}^{79}BrO$ 261.9994, found 262.0003. Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21. Found: C, 60.03; H, 4.29.

(37) (a) Stilz, W.; Pommer, H. (BASF). German Patent 1 109 671, Jan 11, 1962. (b) Pommer, H. *Angew. Chem.* **1960**, *72*, 811–819.

Methyl 4-[4-(1-Hydroxy-2,2,6-trimethylcyclohexyl)-phenyl]benzoate (59). To a solution of 263 mg (1.00 mmol) of **57** in 2 mL of THF, which was cooled to −78 °C (dry ice–acetone bath), was added 1.25 mL (2.00 mmol) of 1.6 M *n*-BuLi in hexane. Stirring at −78 °C was continued for 40 min before 210 mg (1.5 mmol) of **51** in 5 mL of THF was slowly added. After 10 min, the cooling bath was removed, and the reaction mixture was warmed to room temperature over a period of 15 min. After 15 min more, it was poured into Et_2O (150 mL), washed with saturated $NaHCO_3$ (2 × 25 mL), dried ($MgSO_4$), and concentrated. MPLC (silica gel, 3% Et_2O/CH_2Cl_2) gave 156 mg (48%) of **58** as a colorless foam: ^1H NMR ($CDCl_3$) δ 0.65 (d, J = 7 Hz, 3, $CHCH_3$), 0.78 (s, 3, CH_3), 0.90 (s, 3, CH_3), 1.0–2.5 (m, 9, CH, CH_2, OH), 4.67 (s, 2, $ArCH_2$), 7.2–7.8 (m, 8, ArH).

To a slurry of 432 mg (2.0 mmol) of PCC in 15 mL of CH_2Cl_2 was added a solution of 155 mg (0.48 mmol) of **58** in 10 mL of CH_2Cl_2. The reaction mixture was stirred for 1 h at room temperature, diluted with Et_2O (30 mL), and filtered through Florisil with Et_2O (150 mL). Concentration of the filtrate afforded 154 mg (100%) of crude aldehyde: ^1H NMR ($CDCl_3$) δ 10.0 (s, 1, CHO). A solution of the aldehyde in 5 mL of MeOH was added to a slurry of 0.5 g of activated MnO_2 (Beacon Chemical Co.) in 10 mL of MeOH containing 50 mg of NaCN.[38] A few drops of HOAc was added, and the resulting mixture was stirred overnight at room temperature before dilution with Et_2O (20 mL) and filtration through Celite. The filtrate was concentrated at reduced pressure, and the residue was partitioned between Et_2O (150 mL) and saturated $NaHCO_3$ (50 mL). The Et_2O extract was dried ($MgSO_4$), concentrated, and filtered through silica gel (CH_2Cl_2). Concentration and crystallization (Et_2O/petroleum ether) afforded 154 mg (91%, 44% from **57**) of **59** as colorless crystals: mp 152–153 °C; IR ($CHCl_3$) 3600, 1725, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.65 (d, J = 7 Hz, 3, $CHCH_3$), 0.78 (s, 3, CH_3), 0.90 (s, 3, CH_3), 1.1–2.8 (m, 7, CH, CH_2), 1.73 (s, 1, OH), 3.92 (s, 3, CO_2CH_3), 7.17 (br d, J = 9 Hz, 2, ArH meta to $ArCO_2Me$), 7.50 (br d, J = 9 Hz, 2, ArH ortho to $ArCO_2Me$), 7.62 (d, J = 8 Hz, 2, ArH meta to CO_2Me), 8.07 (d, J = 8 Hz, 2, ArH ortho to CO_2Me). Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.69; H, 7.71.

4-[4-(2,6,6-Trimethylcyclohexenyl)phenyl]benzoic Acid (16). A solution of 776 mg (2.20 mmol) of **59** in 15 mL of pyridine was cooled to 0 °C (ice bath) while 2.0 mL (21 mmol) of $POCl_3$ was added. The bath was removed, and the reaction mixture was heated in a 100–110 °C oil bath for 63 h. The mixture was cooled (ice bath), poured onto 3 N HCl/ice (50 mL/100 g) and extracted with Et_2O (150 mL). The extract was washed with 1 N HCl (25 mL), H_2O (25 mL), and saturated $NaHCO_3$ (50 mL). The aqueous phase was back-extracted with Et_2O (3 × 50 mL), and the combined extracts were dried ($MgSO_4$) and concentrated to an off-white solid that after chromatography on silica gel (5% Et_2O/petroleum ether) afforded 682 mg (93%) of ester **60** as colorless crystals: mp 90.5–91.5 °C (hexane); LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 240 nm) t_R 7.4 (96%), 7.9 min (4%); IR ($CHCl_3$) 1710, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 6, $16,17_R$-CH_3), 1.30 (s, 3, 18_R-CH_3), 1.4–1.9 (2 m, 4, $2,3_R$-CH_2), 2.07 (m, 2, 4_R-CH_2), 3.90 (s, 3, CO_2CH_3), 7.07 (d, J = 8 Hz, 2, ArH meta to C=C), 7.57 (d, J = 8 Hz, 2, ArH ortho to C=C), 7.67 (d, J = 8 Hz, 2, ArH meta to CO_2Me), 8.08 (d, J = 8 Hz, 2, ArH ortho to CO_2Me). Anal. Calcd for $C_{23}H_{26}O_2$: C, 82.60; H, 7.84. Found: C, 82.84; H, 7.59.

A solution of 682 mg (2.04 mmol) of **60** and 1.1 g (17 mmol) of 85% KOH in 15 mL of MeOH was heated at reflux for 6 h under N_2. The reaction mixture was cooled in an ice bath, treated with 8 mL of 50% HOAc, and partitioned between Et_2O (100 mL) and H_2O (100 mL). The Et_2O extract was washed with brine (3 × 15 mL), and the aqueous phase was back-extracted with Et_2O (3 × 50 mL). The Et_2O extracts were dried (Na_2SO_4) and concentrated to afford 649 mg (99%) of **16** as a white solid. Crystallization (Et_2O/petroleum ether) afforded 550 mg (84%) of **16** as white crystals: mp 214–219 °C dec; LC (Radialpak A, 20% H_2O/MeCN, 1.0 mL/min, 260 nm) t_R 3.9 (1.7%), 5.1 min (98.3%); IR ($CHCl_3$) 3000, 1690, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 6, $16,17_R$-CH_3), 1.32 (s, 3, 18_R-CH_3), 1.4–1.9 (2 m, 4, $2,3_R$-CH_2), 2.08 (m, 2, 4_R-CH_2), 7.10 (d, J = 8 Hz, 2, ArH meta to C=C), 7.58 (d, J = 8 Hz, 2, ArH ortho to C=C), 7.73 (d, J = 8 Hz, 2, ArH meta to CO_2H), 8.21 (d, J = 8 Hz, 2, ArH ortho to CO_2H); ^{13}C NMR ($CDCl_3$/Me_2SO-d_6) 17.9, 20.0, 27.5, 30.6, 32.9, 38.0, 124.8, 125.1, 127.5, 128.2, 128.8, 129.3, 135.5, 138.8, 140.3, 143.4, 166.4 ppm; UV (EtOH) 278 nm (ε 2.2 × 10^4); MS calcd for $C_{22}H_{24}O_2$ 320.1776, found 320.1786. Anal. Calcd for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.40; H, 7.53.

TOC and ODC Assays. The experimental protocols used for these assays were essentially those described by the groups of Sporn[2b] and Verma and Boutwell,[39] respectively, and were conducted as described.[40]

Antipapilloma Assay. The tumor induction protocol of Verma and Boutwell[3a,b] was used. Female Charles River CD-1 mice, 8 weeks of age, were divided randomly into groups of 25–30. They were housed in a constant-temperature room with regulated lighting and maintained on laboratory chow and tap water ad libitum. The backs of all mice were shaved 2 days prior to initiation. On the day of initiation, 200 nmol of DMBA in 0.2 mL of acetone was applied to the back of each mouse. Two weeks after initiation, all animals were treated with 8.5 nmol of TPA in 0.2 mL of acetone twice weekly for the duration of the 20-week treatment period. One hour before promotion with TPA, the positive control group was treated with 0.2 mL of acetone and the other groups with a specified dose of retinoid in 0.2 mL of acetone. The number of papillomas appearing on each mouse was recorded weekly until the end of the experiment. The animals were also weighed at the beginning and end of the experiment.

Toxicity Assay.[41] Adult female Swiss mice weighing 20–25 g at the beginning of the experiment were maintained on a diet of standard laboratory chow and tap water ad libitum with housing and lighting as described above. The food and water were readily accessible to all animals at all times during the course of the experiment. Each dose group consisted of 10 mice. The homogenized retinoid suspension in an aqueous solution of 8% Cremophor EL (Sigma) and 10% propylene glycol (Sigma) was administered by ip injection over a period of 14 days in 10 separate injections given on weekdays and starting on Monday. The injection volume was 0.2 mL. The control group was injected with vehicle alone. All surviving animals were weighed individually on days 1, 5, 10, and 15; the date of death of the others was recorded.

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Registry No. 1, 302-79-4; **2**, 75664-66-3; **3**, 91587-00-7; **4**, 91587-01-8; **5**, 91587-02-9; (*E*)-**6**, 91587-03-0; (*Z*)-**6**, 91684-41-2; **7**, 71441-28-6; **8**, 74596-82-0; **9**, 91587-04-1; **10**, 91587-05-2; **11**, 91587-06-3; **13**, 88579-29-7; **14**, 91587-07-4; **15**, 91587-08-5; **16**, 91587-09-6; **17**, 91587-10-9; **18**, 86471-13-8; **19**, 86471-16-1; **20**, 79026-14-5; **21**, 91587-11-0; (*E*)-**22**, 91587-12-1; (*Z*)-**22**, 91587-13-2; **23**, 56013-01-5; **24**, 3917-41-7; **25**, 71441-08-2; **26**, 91587-14-3; **27**, 79-77-6; **28**, 17283-81-7; **29**, 472-80-0; (*E*)-**30**, 91587-15-4; (*Z*)-**30**, 91587-16-5; **31** (isomer 1), 91587-17-6; **31** (isomer 2), 91684-42-3;

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32, 91587-18-7; 33, 4486-29-7; 34, 4228-39-1; (E)-35, 91587-20-1; 36, 91587-21-2; 37, 91587-22-3; 38, 91780-92-6; 39, 91587-23-4; 40, 91587-24-5; 41 (X = O), 108-95-2; 41 (X = S), 108-98-5; 42 (X = O), 54897-52-8; 42 (X = S), 70030-51-2; 43 (X = O), 29598-22-9; 43 (X = S), 91587-25-6; 44 (X = O), 40614-20-8; 44 (X = S), 91587-26-7; 45, 10276-04-7; 46 (X = O), 40614-27-5; 46 (X = S), 66165-06-8; 47 (X = O), 88579-19-5; 47 (X = S), 88579-23-1; 48 (X = O), 88579-28-6; 48 (X = S), 88579-35-5; 49, 68837-59-2; 50, 91587-27-8; 51, 2408-37-9; 52, 91587-28-9; 53, 91587-29-0; 54, 41891-54-7; 55, 91587-30-3; 56, 91587-31-4; 57, 84337-86-0; 58, 91587-32-5; 59, 91587-33-6; 60, 91587-34-7; $(C_6H_5O)_2POCl$, 2524-64-3; $Me_2C{=}CHCH_2Br$, 870-63-3; ethyl 3-(bromomethyl)-benzoate, 62290-17-9; 1,4-methano-1,4-dihydronaphthalene, 4453-90-1; 3-methyl-3-buten-1-ol, 763-32-6; diphenyl 3-methyl-3-buten-1-yl phosphate, 42007-25-0; 4-bromo-2-methylbenzaldehyde, 24078-12-4; 4-(1-hydroxy-2,2,6-trimethylcyclohexyl)-2-methylbenzaldehyde, 91587-35-8; 4-(4-bromophenyl)toluene, 50670-49-0; vitamin A, 11103-57-4; acetone, 67-64-1.

Notes

A Theoretical Investigation of Histamine Tautomerism

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Geometry optimizations of the structures of histamine (neutral and monocation) in the N(3)-H and N(1)-H tautomeric forms were performed at the ab initio Hartree–Fock level with the STO-3G basis set. Values of the structural parameters and their changes upon protonation and/or tautomerization are in good agreement with data from X-ray crystal-structure analysis of histamine and several analogues. Earlier predictions of the tautomeric preference from calculations using frozen geometries based on crystal-structure data are confirmed by calculations of energies of histamine in the fully optimized geometries with both the STO-3G and LP-3G basis sets and by comparisons of the minima in the molecular electrostatic potentials of the two tautomers. These results support a previously proposed model for the activation of the histamine H_2 receptor.

There are two possible tautomers of the imidazole ring of histamine in both the neutral (free base) and the cationic (protonated at the side-chain nitrogen) forms. In the N(3)-H tautomer the N(3) nitrogen of the imidazole ring of histamine bears a hydrogen while the N(1) nitrogen does not; this is reversed in the N(1)-H tautomer. In the crystal of the cation[1] only the N(3)-H tautomer is found, whereas the N(1)-H tautomer is found when the neutral species is crystallized.[2] In aqueous solutions the N(3)-H form is predominant at both acidic and basic pH, but the relative ratio of the N(3)-H to N(1)-H forms is much greater when histamine monocation is the main species in solution.[3] Ab initio quantum chemical calculations of the various forms of the histamine molecule kept in frozen geometries show the same preference of the N(3)-H form over the N(1)-H form as a function of the protonation state of the side chain.[5,7] The evidence from structure–activity relationships showing that imidazole ring tautomerism is required for activity at the H_2 receptor[4] led to a proposed mechanistic model describing the possible involvement of the change in the proton affinity of the imidazole nitrogen as a function of side-chain protonation in the activation of the receptor.[5] In this model, histamine, which is predominantly in the cationic form at physiological pH, is assumed to approach the receptor as the N(3)-H tautomer. The cationic side chain interacts with a negative region of the receptor. As the side chain is anchored, the neutralization causes a shift in the tautomeric preference to N(1)-H. N(1) could then attract a proton from a proton-donor site on the receptor while N(3) could act as a proton donor for a proton-acceptor site. Thus the change in the tautomeric preference induced by the neutralization of the side chain leads to a proton-relay process at the receptor[5].

This hypothesis was explored with ab initio quantum chemical calculations of the neutral and cationic forms of histamine in the N(1)-H and N(3)-H tautomeric forms.[5] The calculations were done with the Whitman–Hornback basis set, with histamine in the geometries taken from crystallographic data for the cation and the free base. Thus, geometries of the four possible species shown in Scheme I were modeled[5,6] by the crystal structures of 1 and 4 only. The results provided the basis for the proposed mechanism which depends on the change in tautomeric preference from nearly full N(3)-H preference to a higher probability for the N(1)-H tautomer when the cation is neutralized.

The theoretical conclusions on the difference in tautomeric preference between the free base and the monocation of histamine were found to be unchanged for several choices of the geometry of the imidazole ring. Attempts to improve on these approximations[7] in order to construct better frozen geometries for the species for which the crystal structures are not available, i.e., 2 and 3, also did not change the conclusions about the tautomeric preferences; nevertheless, the question of the best geometry to be chosen for these calculations remained open.[7] We report here on the effect that full geometry optimization has on the conclusions regarding the tautomeric preference in the four structures in Scheme I.

Methods

In order to obtain reliable structures for all four species

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