pounds was discussed above, but these workers's results appear to suggest that the hydrophobicity depends on the selection of compounds. This is a reemphasis of the necessity to examine compounds with more diverse structural variations.

The results of the present and the previous[5] quantitative studies strongly suggest a close relationship between sweet receptors for various kinds of compounds, as well as a close relationship between sweet and bitter receptors. The receptor model drawn in this study is different from that proposed recently by Temussi et al.,[30] which was based on qualitative interpretations of the many kinds of strongly sweet compounds, endorsing Shallenberger's A-H/B theory.[1] These acidic and basic sites are conventionally assigned in the aspartyl dipeptide analogues to the aspartic amino and carboxylic acid moieties, respectively.[3,27,30] The present results are not at all helpful in determining the basic interaction site, but they suggest an acidic site at either the amide hydrogen or carbon atom. The aspartic amino moiety is far apart from the electronic effect, being shielded by a methine group.

Acknowledgment. The author expresses his sincere thanks to Professor Toshio Fujito for his stimulating discussions and advice and to Professor Koichi Koshimizu for his support of this work. The regression analyses were carried out on a FACOM 230/75 computer of the Data Processing Center of this university.

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Aromatic Retinoic Acid Analogues. Synthesis and Pharmacological Activity

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Aromatic analogues of (*all-E*)- and 13(*Z*)-retinoic acids have been synthesized as potential chemopreventive agents for the treatment of epithelial cancer. In the *E* series, (1*E*,3*E*)-1-(4-carboxyphenyl)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadiene (**7a**), its ethyl ester **5a**, and the epoxy ethyl ester 14 displayed excellent activity in the assay for the inhibition of tumor promotor-induced mouse epidermal ornithine decarboxylase, while (1*E*,3*E*)-1-(4-carboethoxy-3-methylphenyl)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadiene (**5b**) was inactive. The 13(*Z*) analogues, (*E*)-1-(2-carboxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene (**19**) and (*E*)-1-(2-hydroxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene (**27**), had minimal activity.

Evidence that synthetic retinoids are capable of suppressing or reversing the transformation of premalignant epithelial cells to the malignant state[1] has prompted the search for new structurally modified retinoids that may possses enhanced prophylactic and therapeutic activity and reduced systemic toxicity (hypervitaminosis A).[2] The recent report[3] on the synthesis and favorable biological activity of a series of aromatic analogues of retinoic acid has prompted us to present our own results on a similar series of aromatic analogues.[4]

Our compounds were designed to probe what structural constraints on retinoid conformation are necessary for biological activity. The *p*-carboxyphenyl trienes **7a** and **7b** could be considered as analogues of (*all-E*)-retinoic acid. Carbons 1 to 4 of the aromatic ring would correspond to carbons 11 to 14 of the retinoid chain, in which the (*E*)-11,12 and (*E*)-13,14 double bonds are held in an *s*-cis or cisoid conformation.[5] The *o*-methyl substituent on the aromatic ring of **7b** would correspond to the C-20 methyl group of retinoic acid.

The *o*-carboxyphenyl tetraene **19** and the *o*-hydroxyphenyl tetraene **27** could be envisioned as analogues of 13(*Z*)-retinoic acid, which has been shown by Sporn et al.[6] to prevent nitrosamine-induced bladder lesions in the rat and by Hixson et al.[7] to be less toxic than the (*all-E*)-acid in the mouse. Carbons 1 and 2 of the aromatic ring of **19** and **27** would correspond to carbons 13 and 14 of the retinoid chain. In contrast to 13(*Z*)-retinoic acid, isomeri-

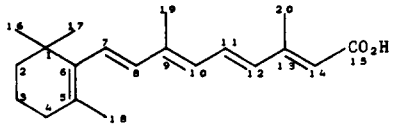
(1) (a) Sporn, M. B.; Newton, D. L.; Smith, J. M.; Acton, N.; Jacobson, A. E.; Brossi, A. In "Carcinogens: Identification and Mechanism of Action"; Griffin, A. C.; Shaw, C. R., Eds., Raven Press: New York, 1979; pp 441-453. (b) Sporn, M. B.; Dunlop, N. M.; Newton, D. L.; Smith, J. M. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1976**, *35*, 1332. (c) Sporn, M. B.; Dunlop, N. M.; Newton, D. L.; Henderson, W. R. *Nature (London)* **1976**, *263*, 110. (d) Sporn, M. B.; Newton, D. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 2528. (e) Todaro, G. J.; DeLarco, J. E.; Sporn, M. B. *Nature (London)*, **1978**, *276*, 272.

(2) (a) Acton, N.; Brossi, A.; Newton, D. L.; Sporn, M. B. *J. Med. Chem.* **1980**, *23*, 805. (b) Dawson, M. I.; Hobbs, P. D.; Kuhlmann, K.; Fung, V. A.; Helmes, C. T.; Chao, W.-R. *Ibid.* **1980**, *23*, 1013. (c) Dawson, M. I.; Hobbs, P. D. *Carbohydr. Res.* **1980**, *85*, 121. (d) Davalian, D.; Heathcock, C. H. *J. Org. Chem.* **1979**, *26*, 4988. (e) Davalian, D.; Heathcock, C. H. *Ibid.* **1979**, *26*, 4458. (f) Pawson, B. A.; Chan, K.-K.; DeNoble, J.; Han, R. L.; Piermattie, V.; Specian, A. C.; Srisethnil, S. *J. Med. Chem.* **1979**, *22*, 1059. (g) Pawson, B. A.; Cheung, H.-C.; Han, R.-J.; Trown, P. W.; Buck, M.; Hansen, R.; Bollag, W.; Ineichen, U.; Pleil, H.; Rüegg, R.; Dunlop, N. M.; Newton, D. L.; Sporn, M. B. *Ibid.* **1977**, *20*, 918. (h) Welch, S. C.; Gruber, S. *Ibid.* **1979**, *22*, 1532.

(3) Loeliger, P.; Bollag, W.; Mayer, H. *Eur. J. Med. Chem.* **1980**, *15*, 9.

(4) A preliminary account of this work was presented at the Second Chemical Congress of the North American Continent, Las Vegas, Nev., Aug, 1980.

(5) For structural comparisons standard retinoid numbering has been used:



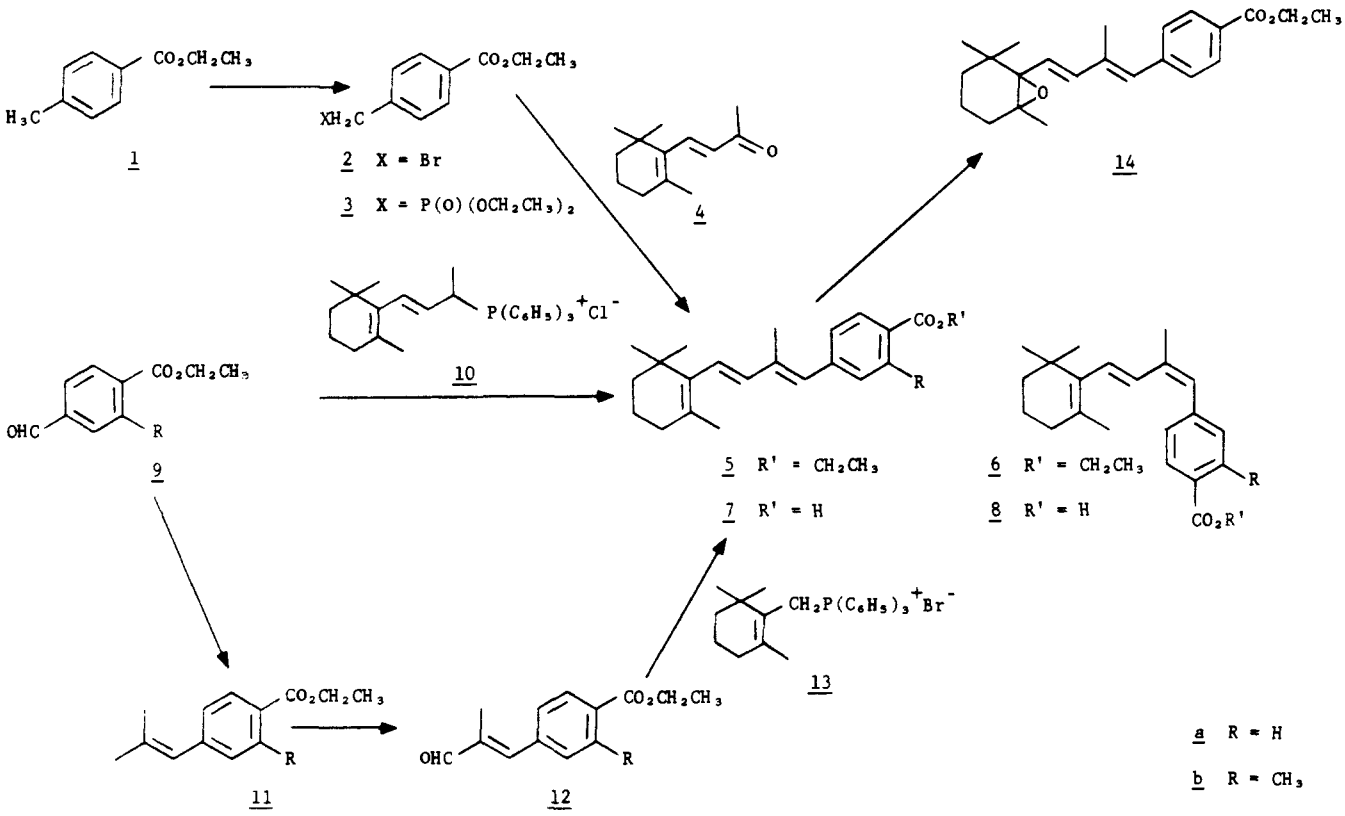
Similar proton and carbon atoms in the aromatic analogues have been denoted by the subscript R. The aryl carbon atoms of those retinoids have been denoted as 1′ to 6′. The position bearing the polyene substituent is numbered C-1′ and the remaining positions are numbered in the direction of lowest numerical assignment to the other substituents.

(6) Sporn, M. B.; Squire, R. A.; Brown, C. C.; Smith, J. M.; Wenk, M. L. *Science* **1977**, *195*, 487.

(7) Hixson, E. J.; Denine, E. P. *Toxicol. Appl. Pharmacol.* **1978**, *44*, 29.

0022-2623/81/1824-0583$01.25/0

Scheme I



zation from the Z to the E double-bond configuration is not possible. The selection of a phenolic hydroxyl group as a replacement of the polar carboxylic acid group was based on the finding that both the corresponding m-[2b] and p-hydroxyphenyltetraenes possess biological activity in the hamster tracheal organ culture test.[8]

The synthesis of **7a** was accomplished by both nonstereoselective and stereoselective routes as shown in Scheme I. The former route involving condensation of p-carboethoxybenzaldehyde with β-ionyltriphenylphosphorane afforded **7a** and its $9_R(Z)$ bond isomer **8a**.[5] ^{1}H NMR (360 MHz) was used to assign the correct double-bond geometries to these isomers.

The 16-Hz coupling constants of the 7_R- and 8_R-proton doublets at δ 6.31 and 6.22, respectively, were indicative of the 7(E) configuration of acid **7a**. The 7_R-proton was assigned to the doublet at 6.31, which was broadened by coupling to the C_R-18 methyl protons.[9] The chemical shifts of the singlet due to the 10_R-proton at 6.49 and the C_R-19 methyl singlet at 2.09 were not significantly different from those of the 9(Z) isomer, but the C_R-8 proton was shifted upfield to δ 6.22 relative to that of **8a**. The downfield shift of the C_R-8 proton of **8a** is a demonstration of the $9_R(Z)$ geometry and results from steric interaction of the C_R-8 proton and the C-2′ and C-6′ aromatic protons.[5,10] The ^{13}C NMR spectra of these isomers show very similar differences to those of (E)-retinoic acid and 9-(Z)-retinoic acid,[11] namely, the $9_R(Z)$ isomer **8a** has the C_R-8 signal shifted upfield by 6 ppm, C_R-9 upfield by 1 ppm, and C_R-19 downfield by 7 ppm relative to the signals of the 9(E) isomer **7a**. The UV spectra are not informative as they are similar. Aryl triene **7a** could also be prepared in lower yield by Horner-Emmons reaction of **3** with β-ionone (**4**).

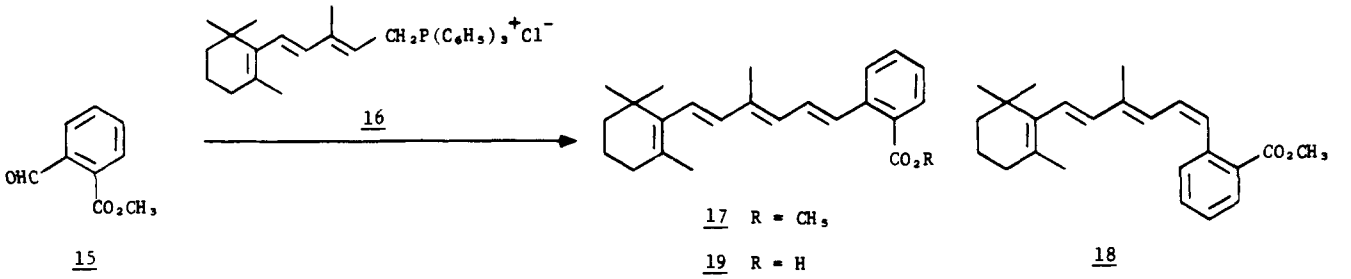
The structure of **7a** was verified by the second synthesis, which is based on the highly stereoselective SeO_2 oxidation of the least hindered methyl group of a 1,1-dimethyl substituted olefin.[12] Benzaldehyde **9a** was converted to the dimethylolefin **11a**, which on SeO_2 oxidation afforded the (E)-propenal **12a** [^{1}H NMR δ 7.27 (s)]. Wittig reaction using β-cyclogeranyltriphenylphosphonium bromide (**13**) gave ester **5a**, which on hydrolysis afforded **7a**.

The o-methyl analogue **7b** was also prepared using the stereospecific route. The chemical shifts of the olefinic protons in the 360-MHz ^{1}H NMR and 100-MHz ^{13}C NMR spectra of **7b** are very similar to those of **7a** and not **8a**, thereby supporting the E-double bond stereochemical assignment.

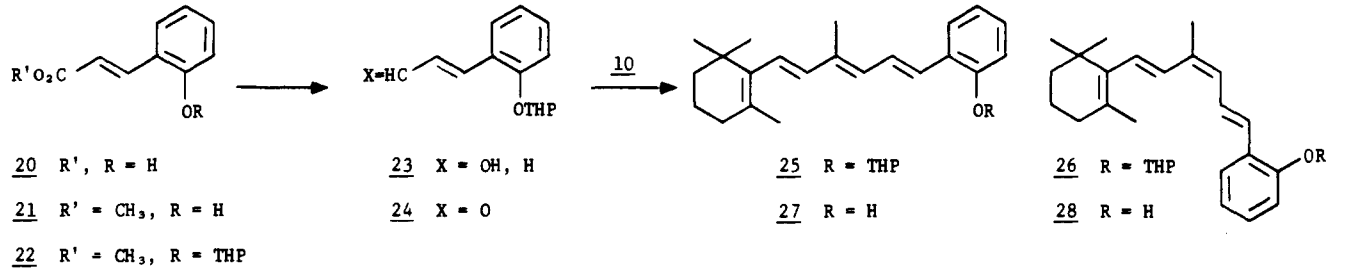
5,6-Dihydro-5,6-epoxyretinoic acid has been reported as a physiological metabolite of retinoic acid.[13] Although it has weak activity in the tracheal organ culture test,[14] it possesses activity comparable to that of retinoic acid in two other screens, the inhibition of ornithine decarboxylase induction by tumor-promoters and the inhibition of chemically induced papillomas.[15] The epoxide of the ethyl ester of **7a** was therefore prepared. Air-oxidation or peracid epoxidation of the ethyl ester **5a** yielded the $5,6_R$-epoxide **14**. The E configuraton of the $7,8_R$ double bond was apparent from the 16-Hz coupling constants of the 7_R-

(8) Sporn, M. B., private communication.
(9) Patel, D. J. *Nature (London)* **1969**, *221*, 825.
(10) Englert, G.; Weber, S.; Klaus, M. *Helv. Chim. Acta* **1978**, *61*, 2697.
(11) Englert, G. *Helv. Chim. Acta* **1975**, *58*, 2367.
(12) Miller, C. H.; Katzenellenbogen, J. A.; Bowlus, S. B. *Tetrahedron Lett.* **1973**, 285.
(13) McCormick, A. M.; Napoli, J. L.; Yoshizawa, S.; DeLuca, H. F. *Biochem. J.* **1980**, *186*, 475.
(14) Newton, D. L.; Henderson, W. R.; Sporn, M. B. "Structure–Activity Relationships of Retinoids. Tracheal Organ Culture Assay of Activity of Retinoids"; Laboratory of Chemoprevention, Division of Cancer Cause and Prevention, National Cancer Institute: Bethesda, MD, 1978.
(15) Verma, A. K.; Slaga, T. J.; Wertz, P. W.; Mueller, G. C.; Boutwell, R. K. *Cancer Res.* **1980**, *40*, 2367.

Scheme II



Scheme III



and 8_R-proton doublets in the 100-MHz ^1H NMR spectrum. The 10_R-proton signal (δ 6.53) was shifted slightly downfield relative to that of **5a** (δ 6.47). The same small shift difference has been reported for ethyl (*E*)-5,6-dihydro-5,6-epoxyretinoate and ethyl (*E*)-retinoate.[16] The chemical shift of the 7_R-proton (δ 6.00) of **14** is also very similar to that reported for the epoxide (δ 5.97). The ^{13}C NMR spectrum was in excellent agreement with that reported for the epoxyretinoate,[11] in particular the observed chemical shifts at 65.3 (C_R-5), 71.0 (C_R-6), and 25.9 ppm (C_R-16 and C_R-17).[11] The change in the UV absorption of **5a** is consistent with that reported for the 5,6-epoxidation of ethyl (*E*)-retinoate[17] and is quite different from that observed for the $5,8_R$-dihydrofuran rearrangement product.

Synthesis of the 13(*Z*) analogues was undertaken next. Reaction of 2-carbomethoxybenzaldehyde (**15**) with the phosphorane derived from salt **16** afforded mostly a 1:2 mixture of $11_R(E,Z)$ double-bond isomers **17** and **18** (Scheme II).

The assignment of the $11_R(Z)$ configuration to **18** was based on the UV spectra of **17** (345 nm, ϵ 3.61×10^4) and **18** (334 nm, ϵ 2.67×10^4), since the (*all-E*)-retinoid isomers are reported to have larger ϵ values.[18] Although both the 10_R- and 12_R-protons of 11,13(*Z*)-retinal are upfield (δ 6.20 and 6.11),[9,16] the spectrum of **18** has only one upfield proton (δ 6.28), which we have assigned to the 12_R-proton. The multiplet at δ 6.95 has been assigned to the 10_R-proton. A similar downfield shift occurs in the $11,12_R(Z)$ isomer of a *m*-acetoxyphenyl tetraene that we have synthesized.[2b]

Irradiation in the presence of iodine isomerized the mixture in favor of **17**, which on hydrolysis afforded the acid **19**. The fully resolved olefinic and aromatic proton region of the 360-MHz ^1H NMR spectrum demonstrated the *all-E* configuration of **19**. Coupling constants of 16 Hz were observed for the $7,8_R$ and $11,12_R$ double bond protons.

Table I. Effect of Retinoids on TPA-Induced Mouse Epidermal ODC Activity

retinoid	nmol applied	% inhibn of ODC
retinoic acid	1.7	91
7a	1.7	62
	17	77
	170	87
8a	1.7	33
	17	43
	170	64

The chemical shift of the 8_R-proton (δ 6.19) also demonstrated the $9,10_R(E)$ double-bond configuration,[16] which was confirmed by the ^{13}C NMR shifts for C_R-8 and C_R-19.[11]

The *o*-hydroxyphenyl tetraene **27** was prepared by the route outlined in Scheme III. It was necessary to protect the phenolic hydroxyl of the (*E*)-cinnamate **21** prior to reduction of the ester with either REDAL or DIBAL. Evidently, complexation of the reducing agent with the hydroxyl group favored 1,4-reduction. MnO_2 oxidation, followed by a Wittig reaction using **10**, gave an approximately 2:3 mixture of the $9_R(E)$ and $9_R(Z)$ isomers **25** and **26**. Because of the susceptibility of the target phenols **27** and **28** to air-oxidation, the ethers were separated in greater than 99% isomeric purity and then hydrolyzed separately under conditions that did not cause isomerization of the double bonds. The assignment of the $9_R(E)$ and $9R(Z)$ configuration **27** and **28**, respectively, was based on comparison of their 360-MHz ^1H NMR spectra with that reported for other retinoids.[19] The 8_R-proton is usually shifted 0.5-ppm upfield in the 9(*E*) isomer. This shift was observed for both isomers **27** and **28** and their tetrahydropyranyl ethers **25** and **26**. The coupling constants for the vinylic protons on the $7,8_R$ and $11,12_R$ double bonds of these four compounds are 16 Hz, which indicated that the *E* configuration about these double bonds was preserved.

Pharmacological Activity. The correlation between the inhibition by retinoids of tumor promoter-induced mouse epidermal ornithine decarboxylase (ODC) activity and their inhibition of skin tumor promotion has been

(16) Vetter, W.; Englert, G.; Rigassi, N.; Schwieter, U. In "Carotenoids"; Isler, O.; Gutmann, H.; Solms, V.; Eds., Birkhaeuser-Verlag: Basel, 1971; pp 214–225.
(17) John, K. V.; Lakshmanan, M. R.; Cama, H. R. *Biochem. J.* **1967**, *103*, 539.
(18) (a) Sebrell, W. H.; Harris, R. S. "The Vitamins"; Academic Press: New York, 1967; Vol. 1. (b) VonPlanta, C.; Schwieter, U.; Chopard-dit-Jean, L.; Rüegg, R.; Kofler, M.; Isler, O. *Helv. Chim. Acta* **1962**, *45*, 548.
(19) Mousseron-Canet, M.; Mani, J.-C. *Bull. Soc. Chim. Fr.* **1966**, 3291.

Table II. Effect of Retinoids at 17-nmol Dose Level on TPA-Induced Mouse ODC Activity

retinoid	% inhibn of ODC (mean ± SE)	no. of groups of 3 mice tested
control		3
retinoic acid[a]	92 ± 2	6
5a	80 ± 2	3
5b	0 ± 4	3
7a	77 ± 6	3
14	71 ± 6	3
13(*Z*)-retinoic acid	96 ± 1	3
19	7 ± 3	3
27	25 ± 5	3
28	0 ± 2	3

[a] 1.7 nmol.

established by Boutwell and co-workers.[20] The retinoids described in this study were screened for their ability to inhibit ODC induced by the topical application of 12-*O*-tetradecanoylphorbol 13-acetate (TPA) to mouse skin. Maximal ODC activity, about 200-fold above the basal level, occurs 4 to 5 h after TPA treatment. Topical administration of an active retinoid 1 h before TPA treatment substantially depresses the induction of this enzyme.[20a] In a preliminary experiment, the $9_R(E)$ and $9_R(Z)$ isomers **7a** and **8a** were tested on three groups of five mice at three different dose levels. The dorsal skin from each group was pooled, and the ODC activity was determined in triplicate (Table I). Isomer **7a** had good activity, while that of the isomer **8a** was lower. Since $9_R(Z)$-retinoids usually are inactive in such a screen, the activity may have been due to a small amount of **7a** impurity which was not detectable by high-performance LC or by isomerization during the assay. The ethyl (*E*)- and (*Z*)-*p*-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]-benzoates are reported to equilibrate in dilute solution on irradation.[3] For comparison purposes, multiple tests on **5a**, **7a**, **5b**, **14**, **19**, **27**, and **28** were performed at the 17-nmol dose level (Table II). The ethyl ester **5a** and epoxide **14** had activity comparable to that of the parent acid **7a**. Interestingly, the *o*-methyl analogue **5b** was essentially inactive. In contrast, the methyl analogue in the tetrahydrotetramethylnapthyl series is reported to have reduced antipapilloma activity.[3] The reduction reported is not as large as the activity differences here. Although Sporn and Newton[8] found that **5a** and **7a** have activity comparable to retinoic acid in the hamster tracheal organ culture screen, **5a** was far more toxic than retinoic acid in an in vivo hypervitaminosis A test. The aromatic analogues of 13(*Z*)-retinoic acid all demonstrated poor activity in the ODC test. Either steric hindrance by the aromatic ring or the inability to isomerize to the $13_R(E)$ isomer may have caused this reduction.

Experimental Section

Melting points are uncorrected. IR spectra were recorded with a Perkin-Elmer 710B infrared spectrophotometer. NMR spectra were obtained with a Varian A-60A, a Varian XL-100-F, or 360-MHz Bruker spectrometer, using tetramethylsilane as an internal standard (δ 0) and solvent as specified. High-resolution mass spectral analyses were conducted on a CEC-21-110B high-resolution mass spectrometer equipped with facilities for combination GC-MS. High-performance LC analyses were done on a Waters Associates ALC 210 equipped with either a Radialpak B cartridge or a 30 × 3.9 cm μPorasil, μBondapak/C_{18} or Spherisorb ODS column. Detection was by a Schoeffel Instrument Model 770 variable-wavelength UV monitor. Analyses were performed at ambient temperature at a flow rate of 2 mL/min. 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. Detection was by UV absorption or refractive index. UV spectra were taken on a Perkin-Elmer 575 spectrometer.

Where required, reactions and purifications were conducted with deoxygenated solvents and under inert gas (argon) and either subdued light or photographic red light. Retinoid intermediates were stored at −40 °C. Solvents were dried or distilled before use. TLC analyses were performed on Analtech silica gel analytical plates. Merck silica gel 60 was used for chromatography. Spectral signal designations were based on the retinoid numbering system. ^{1}H NMR[9,10,19] and ^{13}C NMR[11] signals were assigned by comparison with those reported for other retinoids. The ^{1}H and ^{13}C NMR signals for **7a**, **7b**, **8a**, **14**, **19**, **27**, and **28** are found in Tables III and IV, respectively. The stereochemical assignments were supported by the larger ϵ values for the *all-E* isomers.[18] The Experimental Section contains procedures for some known compounds for which preparative methods or spectral data are not readily accessible in the literature or where the reported method has been improved.

(1*E*,3*E*)- and (1*Z*,3*E*)-1-(4-Carboethoxyphenyl)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadienes (5a and 6a) from Diethyl 4-Carboethoxybenzylphosphonate (3). A 50% dispersion of NaH in mineral oil (7.2 g, 0.15 mol) was washed with hexane (3 × 30 mL) by syringe under argon. To the solid was added 60 mL of dry DMF, followed by a mixture of 48.0 g (0.16 mol) of phosphonate **3**[21] and 28.8 g (0.15 mol) of β-ionone (**4**) in 75 mL of DMF over 1 h with stirring in a water bath at room temperature. The deep red color did not fade. After an additional 1 h, the temperature was raised to 50–55 °C for 1.2 h, and then stirring was continued at room temperature for an additional 16 h. The red solution was next heated at 60 °C for 45 min, when TLC (19:1 hexane/EtOAc) revealed that little β-ionone remained. The reaction was treated with 0.5 g of *tert*-butylhydroquinone, poured into 60 mL of brine containing 12 mL of HOAc, and extracted with hexane (2 × 500 mL). The organic extract was washed with 400 mL of brine, dried (Na_2SO_4), and concentrated. The orange oil was dissolved in 30 mL of EtOAc and washed through a 7 × 13 cm silica gel pad on a Büchner funnel with 3% EtOAc/hexane. The yellow filtrate was evaporated to give 37.6 g of orange oil. The product was purified on a 9 × 60 cm silica gel column with 1 and 2% EtOAc/hexane to give 28 g (55%) of a yellow viscous oil, which, by the NMR spectrum, was a mixture of 39% 1(*E*) isomer, 61% 1(*Z*) isomer, and an impurity. β-Ionone was eluted subsequently. Further purification of the mixture by LC using 1% EtOAc/hexane and by refluxing with EtOH containing Norit decolorizing charcoal did not remove the deep yellow impurity. IR (film) 1715 (C=O), 1605, 1410, 1275 (1250 sh) (CO), 1175, 1105, 1025, 970, 885, 765, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03, 1.06 [2 s, 6, $(CH_3)_2$C of major and minor isomers], 1.2–2.2 (m, 6, C_R-2, C_R-3, C_R-4 CH_2), 1.38 (t, J = 7 Hz, 3, CH_3CH_2O), 1.72 (s, 3, C_R-18 CH_3), 2.08 (s, 3, C_R-19 CH_3), 4.36 (q, J = 7 Hz, 2, CH_3CH_2O), 6.23 [br m, 2.2, C_R-10 HC=C 1(*E*) and 1(*Z*) isomers, C_R-7, C_R-8 HC=CH 1(*Z*) isomer **6a**), 7.18–7.42 (m, 2, ArH), 7.98 (d, J = 8 Hz, 2, ArH).

Methyl Esters of (1*E*,3*E*)- and (1*Z*,3*E*)-1-(4-Carboxyphenyl)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadienes (7a and 8a). A mixture of 0.71 g (4 mmol) of **9a** and 2.62 g (5 mmol) of the phosphonium bromide **10**[22] was stirred at −20 °C under argon in 5 mL of THF and 2 mL of *t*-BuOH (distilled from CaH_2) while a solution of 0.56 g (5 mmol) of *t*-BuOK in 4 mL of *t*-BuOH was added dropwise over a 5-min period. The red ylide generated with each drop of base faded at once to afford a yellow solution. The reaction mixture was allowed to warm to room temperature over a 1.5-h period. A brown suspension resulted. The reaction was kept at room temperature overnight

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(21) Kreutzkamp, N.; Cordes, G. *Arch. Pharm.* **1961**, *294*, 49.

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Table III. ^{1}H NMR Spectral Characteristics of Aromatic Retinoids

proton	7a	7b	8a	14[a]	19	27	28
H_{2R}	1.49[b] (m)	1.48[b] (m)	1.46[b] (m)	1.45 (m)	1.47[b] (m)	1.47[b] (m)	1.48[b] (m)
H_{3R}	1.64[b] (m)	1.83[b] (m)	1.60[b] (m)	1.45 (m)	1.61[b] (m)	1.62[b] (m)	1.64[b] (m)
H_{4R}	2.04 (m)	2.03 (m)	2.01 (m)	1.82 (m)	2.01 (m)	2.06 (m)	2.02 (m)
H_{7R}	6.31 (d, J = 16 Hz)	6.29	6.39 (d, J = 16 Hz)	6.00 (d, J = 16 Hz)	6.24 (d, J = 16 Hz)	6.16[b] (d, J = 16 Hz)	6.21 (d, J = 16 Hz)
H_{8R}	6.22 (d, J = 16 Hz)	6.21 (d, J = 16 Hz)	6.47 (d, J = 16 Hz)	6.41 (d, J = 16 Hz)	6.19 (d, J = 16 Hz)	6.19[b] (d, J = 16 Hz)	6.72 (d, J = 16 Hz)
H_{10R}	6.49 (s)	6.43 (s)	6.45 (s)	6.53 (s)	6.34 (d, J = 12 Hz)	6.24 (d, J = 11 Hz)	6.14 (d, J = 16 Hz)
H_{11R}					7.13 (dd, J = 11, 16 Hz)	7.20 (dd, J = 11, 16 Hz)	7.27 (dd, J = 11, 16 Hz)
H_{12R}					7.56 (d, J = 16 Hz)	6.79 (d, J = 16 Hz)	6.72 (d, J = 16 Hz)
CH_3-16_R,17_R	1.06 (s)	1.05 (s)	1.02 (s)	0.97, 1.12[b] (s)	1.04 (s)	1.04 (s)	1.05 (s)
CH_3-18_R	1.75 (s)	1.75 (s)	1.72 (s)	1.19[b] (s)	1.73 (s)	1.72 (s)	1.76 (s)
CH_3-19_R	2.09 (s)	2.09 (s)	2.10 (s)	2.03 (d, J = 1 Hz)	2.02 (s)	2.01 (s)	1.99 (s)
$ArCH_3$		2.67 (s)					
ArH-2′	7.41 (d, J = 8 Hz)	7.19 (d, J = 8 Hz)	7.34 (d, J = 8 Hz)	7.34 (d, J = 8 Hz)			
ArH-3′	8.08 (d, J = 8 Hz)		8.06 (d, J = 8 Hz)	8.00 (d, J = 8 Hz)	8.05 (d, J = 8 Hz)	6.26 (d, J = 8 Hz)	6.75 (d, J = 8 Hz)
ArH-4′					7.27 (dd, J = 8, 8 Hz)	7.09 (dd, J = 8, 8 Hz)	7.07 (dd, J = 8, 8 Hz)
ArH-5′	8.08 (d, J = 8 Hz)	8.05 (d, J = 8 Hz)	8.06 (d, J = 8 Hz)	8.00 (d, J = 8 Hz)	7.49 (dd, J = 8, 8 Hz)	6.90 (dd, J = 8, 8 Hz)	6.89 (dd, J = 8, 8 Hz)
ArH-6′	7.41 (d, J = 8 Hz)	7.23 (d, J = 8 Hz)	7.34 (d, J = 8 Hz)	7.34 (d, J = 8 Hz)	7.69 (d, J = 8 Hz)	7.45 (d, J = 8 Hz)	7.42 (d, J = 8 Hz)
ethyl CH_3				1.39 (t, J = 6.5 Hz)			
ethyl CH_2				4.37 (q, J = 6.5 Hz)			

[a] 100-MHz spectrum; all others 360 MHz. All spectra were run in $CDCl_3$. [b] Assignment of adjacent signals may be reversed.

Table IV. ^{13}C NMR Chemical Shifts of Aromatic Retinoids

7a	7b	8a	14[a]	19	27	28
14.1 (19_R)	13.8 (19_R)	19.2 (3_R)	14.1 (19_R)	12.7 (19_R)	12.8 (19_R)	19.3 (3_R)
19.3 (3_R)	19.0 (3_R)	21.3 (19_R)	14.3 (ethyl CH_3)	19.0 (3_R)	19.3 (3_R)	20.7 (19_R)
21.7 (18_R)	21.6 (18_R)[b]	21.8 (18_R)	17.1 (3_R)	21.6 (18_R)	21.7 (18_R)	21.8 (18_R)
29.0 (16_R, 17_R)	21.7 ($ArCH_3$)[b]	29.0 (16_R, 17_R)	21.1 (18_R)	28.9 (16_R, 17_R)	29.0 (16_R, 17_R)	29.0 (16_R, 17_R)
33.1 (4_R)	28.8 (16_R, 17_R)	33.0 (4_R)	25.9 (16_R, 17_R)	32.7 (4_R)	33.1 (4_R)	33.0 (4_R)
34.3 (1_R)	32.6 (4_R)	34.3 (1_R)	30.0 (4_R)	33.9 (1_R)	34.3 (1_R)	34.2 (1_R)
39.7 (2_R)	33.9 (1_R)	39.6 (2_R)	33.7 (1_R)	39.3 (2_R)	39.7 (2_R)	36.9 (2_R)
126.8 (2′, 6′)	39.3 (2_R)	126.9 (2′, 6′)	35.7 (2_R)	126.2 (6′)	115.9 (3′)	115.9 (3′)
128.5 (10_R)[b]	126.1 (6′)	127.1 (10_R)[b]	60.6 (ethyl CH_2)	126.7	121.0 (5′)	121.9 (5′)
128.8 (7_R)[b]	127.2 (2′)	129.3 (5_R)[b]	65.3 (5_R)	127.6	125.3 (1′)	125.2 (1′)
129.2 (5_R)	127.9 (4′)	129.7 (4′)	71.0 (6_R)	128.8	126.0	126.1
129.7 (4′)	128.7	130.0 (3′, 5′)	125.3 (2′, 6′)	129.4	127.0	127.0
130.1 (3′, 5′)	128.9	130.9 (7_R)[b]	128.0 (4′)	130.0	127.1	128.2
137.7 (6_R)[b]	130.4	131.1 (8_R)[b]	128.7 (10_R)	130.6	128.2	128.7
137.9 (8_R)[b]	132.0 (5′)	137.6 (6_R)	129.0 (3′, 5′)	131.4	129.3 (5_R)[b]	129.0 (5_R)[b]
138.6 (9_R)	137.2 (6_R, 3′)[b]	137.9 (9_R)	129.9 (7_R)	136.7 (5′)	130.5 (4′)[b]	129.5 (4′)[b]
144.0 (1′)	137.6 (8_R)[b]	143.6 (1′)	136.4 (8_R)	137.1 (6_R)[b]	136.5 (9_R)[b]	129.9 (8_R)
172.0 (C=O)	139.2 (1′)	171.7 (C=O)	137.1 (9_R)	137.2 (8_R, 9_R)[b]	137.6 (8_R)[b]	135.1 (9_R)
	140.8 (9_R)		142.2 (1′)	137.9 (1′)	137.9 (6_R)	138.1 (6_R)
	168.2 (C=O)		166.0 (C=O)	168.5 (C=O)	152.8 (2′)	152.7 (2′)

[a] Spectrum run in Me_2SO-d_6. All other spectra run in $CDCl_3$. [b] Assignment of adjacent signals may be reversed.

perature overnight and then heated at 55 °C for 1.25 h. The cooled suspension was poured onto 50 mL of ice/water and extracted with hexane (3 × 50 mL). The hexane solution was washed with 50 mL of brine, dried (Na_2SO_4), and concentrated. The pale yellow oil contained some $(C_6H_5)_3PO$. TLC (9:1 hexane/EtOAc) demonstrated one major product. Preparative high-performance LC (1% EtOAc/hexane) afforded 1.30 g (96% yield) of the triene aryl esters **5a** and **6a** as a very pale yellow oil. Chromatography of the mixture of 1(*E*) and 1(*Z*) isomers by LC using 0.6% EtOAc/hexane, 9:2 hexane/benzene, or 9:2 hexane/benzene containing 0.3% EtOAc resulted in no useful separation. The R_f difference on silica gel TLC (19:1 hexane/EtOAc) was about 0.01: LC (μPorasil, 3:97 EtOAc/hexane, 1 mL/min, 280 nm) t_R 5.0 min, shoulder at 4.9 min.

The mixture of ethyl esters were hydrolyzed to the acids. A solution of 1.2 g of KOH in 7.5 mL of EtOH and 2.5 mL of water was degassed under argon and then 2.68 g (7.9 mmol) of the ester mixture in 5 mL of EtOH was introduced. The mixture was heated to 80 °C (oil bath) over a 30-min period and then cooled before 10 mL of 1:1 HOAc/water was added. The acids separated out as a white solid. The reaction was diluted with 50 mL of water, extracted with an equal volume of ether, washed with brine (3 × 10 mL), and dried (Na_2SO_4). Evaporation yielded 2.31 g (94%) of white solid. The mixture was crystallized once from ether and then twice from 1 mL of EtOAc and 3 mL of ether. The product was still a mixture, mp 135–140 °C. Samples of the esters enriched in each isomer were similarly hydrolyzed and recrystallized. The acid derived from the major, less polar ester **6a** was obtained almost pure, mp 160–161.5 °C. The acid from the polar ester could not be purified by crystallization. The 1(*E*) and 1(*Z*) isomers were characterized as a mixture: LC (μBondapak/C_{18}, reverse phase, 80:20 CH_3CN/water, 1 mL/min, 280 nm) t_R 4.5 (>99%), 1.6 min (<1%).

A solution of 1.765 g (5.2 mmol) of the mixture of (1*E*)- and (1*Z*)-acids **7a** and **8a**, which were obtained from the attempted purification by crystallization, in 15 mL of ether was treated at 5-min intervals with 1-mL aliquots of an ethereal solution of CH_2N_2 prepared from nitrosomethylurea and 40% aqueous KOH with cooling in ice/water until TLC (9:1 hexane/EtOAc) indicated complete esterification. A minor impurity was also present. The crude methyl esters were eluted through a short silica gel column with 100 mL of 3% EtOAc/hexane. Evaporation yielded 1.55 g of product as a very pale yellow viscous liquid.

The esters were separated in about 125-mg aliquots on a Chromatotron rotating disk chromatograph, using a 2-mm silica rotor and elution with 1.5% EtOAc/hexane at 5 mL/min and collecting 5-mL fractions. After each run, the rotor was washed with acetone or EtOAc and oven dried at 90–95 °C for at least 1.5 h. The products overlapped, and mixed fractions were recovered and rechromatographed. The total yield of the less polar major isomer, the methyl ester of **8a**, was 783 mg. This product crystallized at -15 °C and was recrystallized from 1 mL of ether: mp 79–79.5 °C; IR (mull) 2720, 1725 (C=O), 1610 (C=C), 1435, 1415, 1275, 1185, 1110, 1105, 1025, 990, 975, 885, 765, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 6, C_R-16, C_R-17 CH_3), 1.35–1.75 (m, 4, C_R-2, C_R-3 CH_2), 1.70 (s, 3, C_R-18 CH_3), 1.9–2.1 (m, 2, C_R-4 CH_2), 2.08 (d, J = 1.5 Hz, 3, C_R-19 CH_3), 3.92 (s, 3, CO_2CH_3), 6.43 (m, 3, C_R-7, C_R-8 HC=CH, C_R-10 C=CH), 7.30 (d, J = 8 Hz, 2, ArH), 7.99 (d, J = 8 Hz, 2, ArH); ^{13}C NMR ($CDCl_3$) 166.9 (C=O), 142.8 (C-1′), 137.9 (C_R-9), 137.1 (C_R-6), 131.0 (C_R-8), 130.8, 129.6, 129.3, 129.2, 127.9, 127.3, 51.8 (CH_3O), 39.7 (C_R-2), 34.3 (C_R-1), 33.0 (C_R-4) 29.0 (C_R-16, C_R-17), 21.8 and 21.2 (C_R-18, C_R-19), 19.3 ppm (C_R-3); UV (MeOH) λ_{max} 315.5 nm (ε 2.18 × 10^4), 231 (1.28 × 10^4). MS calcd for $C_{22}H_{28}O_2$, 324.2089; found, 324.2073. The more polar isomer, the methyl ester of **7a**, a viscous oil, weighed 398 mg and was repurified on the Chromatotron in three aliquots using the same conditions: IR (film) 2735, 1720 (C=O), 1605 (C=C), 1450, 1435, 1365, 1275 (CO), 1180, 1110, 1020, 970, 885, 765, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 6, C_R-16, C_R-17 CH_3), 1.35-1.8 (m, 4, C_R-2, C_R-3 CH_2), 1.75 (s, 3, C_R-18 CH_3), 1.9–2.1 (m, 2, C_R-4 CH_2), 2.09 (d, J = 1 Hz, 3, C_R-19 CH_3), 3.94 (s, 3, CO_2CH_3), 6.26 (m, 2, C_R-7, C_R-8 HC=CH), 6.48 (m, 1, C_R-10 C=CH), 7.38 (d, J = 8 Hz, 2, ArH), 8.02 (d, J = 8 Hz, 2, ArH); ^{13}C NMR ($CDCl_3$) δ 166.7 (C=O), 142.9 (C-1′), 138.2 (C_R-9), 138.0 and 137.7 (C_R-6, C_R-8), 129.4, 129.4, 129.0, 192.0, 128.2, 127.8, 51.8 (CH_3O), 39.7 (C_R-2), 34.3 (C_R-1), 33.0 (C_R-4), 29.0 (C_R-16, C_R-17), 21.7 (C_R-18), 19.4 (C_R-3), 14.0 ppm (C_R-19); UV (MeOH) λ_{max} 316 nm (ε 2.22 × 10^4), 232 (1.24 × 10^4). MS calcd for $C_{22}H_{28}O_2$, 324.2089; found, 324.2073.

(1*E*,3*E*)-1-(4-Carboxyphenyl)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadiene (7a). KOH (0.2 g, 85%, 3 mmol) was added to 3 mL of EtOH and 1 mL of water, and the mixture was degassed under argon (3 times). A solution of 0.25 g (0.77 mmol) of the methyl ester of **7a** in 0.5 mL of EtOH (1-mL EtOH rinse) was introduced, followed by 0.5 mL of water. The suspension was heated to 90 °C over a 40-min period, cooled, acidified with 1.5 mL of 1:1 HOAc/water, diluted with 12 mL of water, and extracted into 12 mL of ether. The extract was washed with brine (3 × 5 mL), dried (Na_2SO_4), and concentrated. The crude solid weighed 0.219 g (92%). Crystallization from EtOAc gave 0.162 g (59%) of small very pale yellow crystals: mp 153–156 °C; high-performance LC (Spherisorb ODS, reverse phase, 80% CH_3CN/water, 2.0 mL/min, 280 nm) t_R 4.4 (99%), 9.5 min (1%); IR (mull) 3200–2400 (OH), 1680 (C=O), 1600, 1565, 1425, 1320, 1290, 1185, 970, 945, 880, 770 cm^{-1}; UV (EtOH) λ_{max} 311.5 nm (ε 2.08 × 10^4), 229 (1.16 × 10^4). MS calcd for $C_{21}H_{26}O_2$, 310.1933; found, 310.1921.

(1*Z*,3*E*)-1-(4-Carboxyphenyl)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadiene (8a). KOH pellets (0.5 g, 85%, 7.5 mmol) were added to 6 mL of EtOH and 1.5 mL of water, and the mixture was degassed under argon (3 times). A solution of 0.60 g (1.85 mmol) of the methyl ester of **8a** in 1 mL of EtOH (2-mL EtOH rinse) was added, followed by 0.5 mL of water. The suspension was heated to 80 °C over a 45-min period, cooled, acidified with 3 mL of 1:1 HOAc/water, and diluted with 25 mL of water. The acid was extracted into 25 mL of ether; the extract was washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated. The crude pale yellow acid (0.552 g, 97%) was crystallized from 1.5 mL of EtOAc to give 0.443 g (78%) of large, faintly yellow crystals: mp 159.5–161 °C; high-performance LC (Spherisorb ODS, 80% CH_3CN/water, 2.0 mL/min, 280 nm) t_R 3.0 (0.8%), 4.5 (97.5%), 8.4 min (1.7%); IR (mull) 3200–2400 (OH), 1680 (C=O), 1605, 1565, 1425, 1315, 1300, 1290, 1180, 1135, 990, 950, 880, 820, 800, 770 cm^{-1}; UV (EtOH) λ_{max} 312 nm (ε 2.09 × 10^4), 229.5 (1.25 × 10^4). MS calcd for $C_{21}H_{26}O_2$, 310.1933; found, 310.1915.

1-(4-Carboethoxyphenyl)-2-methyl-1-propene (11a). A suspension of 32.4 g (75 mmol) of isopropyltriphenylphosphonium iodide in 75 mL of THF was stirred at -78 °C while 47 mL of 1.6 M *n*-BuLi (74 mmol) in hexane was added. A slight red color developed, but little of the salt dissolved. The reaction was warmed to room temperature to give a deep red ylide solution. Only a little solid remained after 20 min at room temperature. To the ylide solution, cooled in ice, was introduced 11.6 g (65 mmol) of 4-carboethoxybenzaldehyde[23] in 15 mL of THF. The reaction was allowed to reach room temperature overnight. The resultant brown suspension was heated to 60 °C over 30 min and then heated at 60 °C for 1 h. After cooling, the reaction was diluted with 500 mL of water and 10 mL of HOAc. The product was extracted into hexane (2 × 400 mL), washed with brine (200 mL), dried (Na_2SO_4), and concentrated. Unreacted phosphonium salt, which was insoluble in EtOAc, remained suspended in the aqueous phase. Some $(C_6H_5)_3PO$ separated out when the extract was concentrated. The product was purified with a 6 × 45 cm silica gel column using 1 and 2% EtOAc/hexane as the eluant. The 7.8 g (59%) of olefin was eluted in 750 mL of 2% EtOAc/hexane, as a colorless liquid. A minor product with bright green fluorescence followed. IR (film) 1715 (C=O), 1655, 1610, 1565, 1415, 1275 (1310 sh) (CO), 1180, 1105, 1025, 880, 765, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, J = 7 Hz, 3, CH_3CH_2O), 1,89 and 1.92 [2 s, 6, $(CH_3)_2C$=C], 4.35 (q, J = 7 Hz, 2, CH_3CH_2O), 6.26 (br s, 1, HC=C), 7.23 (d, J = 8 Hz, 2, ArH), 7.97 (d, J = 8 Hz, 2, ArH). MS calcd for $C_{13}H_{16}O_2$, 204.1150; found, 204.1146.

(*E*)-3-(4-Carboethoxyphenyl)-2-methylpropenal (12a). A mixture of 7.5 g (37 mmol) of arylmethylpropene **11a** and 9.8 g (81 mmol) of SeO_2[12] in 115 mL of 95% EtOH was heated at reflux

(23) (a) Mori, K.; Miyake, T.; Yoshimura, I.; Matsui, M. *Agr. Biol. Chem.* **1969**, *33*, 1745. (b) Synder, H. R.; Merica, E. P.; Force, C. G.; White, E. G. *J. Am. Chem. Soc.* **1958**, *80*, 4622. (c) Hass, H. B.; Bender, M. L. *J. Am. Chem. Soc.* **1949**, *71*, 1767.

under argon for 19 h, at which time TLC (9:1 hexane/EtOAc) demonstrated some starting material and two major products. Se was removed by filtration from the cooled suspension (100-mL EtOH rinse). The filtrate, after concentration, gave 17.1 g of residue containing some unreacted oxidant. The crude orange oil was extracted with hexane (3 × 20 mL), and the extract was applied to an 8 × 40 cm silica gel column. SeO_2 crystallized out when the crude material was treated with hexane. The column was gradient-eluted with 1.4-L volumes of 1, 2, 3, 5, 8, 12, 15, 20, 25, and 50% EtOAc/hexane (450-mL fractions). Fractions 7–9 yielded 0.26 g (3%) of unreacted olefin. Aldehyde **12a** (4.18 g, 52%) was eluted in fractions 16–19 and crystallized on standing, mp 41–42 °C (EtOAc/hexane): IR (film) 2720 (CHO), 1695 (C=O), 1625 (C=C), 1605, 1565, 1445, 1400, 1280 (CO), 1185, 1110, 1015, 900, 865, 820, 770, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (t, J = 7 Hz, 3, CH_3CH_2O), 2.08 (s, 3, CH_3C=C), 4.38 (q, J = 7 Hz, 2, CH_3CH_2O), 7.27 (br s, 1, HC=C), 7.54 (d, J = 8 Hz, 2, ArH), 8.08 (d, J = 8 Hz, 2, ArH), 9.60 (s, 1, CHO). MS calcd for $C_{13}H_{14}O_3$, 218.0943; found, 218.0936. The corresponding allylic alcohol (1.13 g, 14%) was obtained as a yellow viscous oil from fractions 30–31: IR (film) 3430 (OH), 1710 (C=O), 1610, 1570, 1410, 1275 (C=O), 1180, 1105, 1075, 1020, 880, 765, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7 Hz, 3, CH_3CH_2O), 1.90 (s, 3, CH_3C=C), 4.21 (s, 2, CH_2O), 3.85-4.3 (br s, 1, OH), 4.35 (q, J = 7 Hz, 2, CH_3CH_2O), 6.58 (br s, 1, HC=C), 7.27 (d, J = 8 Hz, 2, ArH), 7.97 (d, J = 8 Hz, 2, ArH). MS calcd for $C_{13}H_{16}O_3$, 220.1099; found, 220.1101. More polar products began to elute after fraction 31.

(1*E*,3*E*)-1-(4-Carboethoxyphenyl)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadiene (5a). A solution of 1.9 g (17 mmol) of *t*-BuOK in 15 mL of *t*-BuOH was added to a suspension of 8.15 g (17 mmol) of the β-cyclogeranyltriphenylphosphonium bromide[24] in 15 mL of THF and 5 mL of *t*-BuOH at 0 °C. The deep red solution was stirred for 15 min, and then 3.27 g (15 mmol) of the (*E*)-aldehyde **12a** in 5 mL of THF was introduced all at once. An additional 2 mL of THF was used to rinse the syringe. The color immediately faded to yellow. The reaction was stirred at 0 °C for 2 h and then at room temperature for 18 h. The product was isolated by extraction into hexane (2 × 300 mL) from 600 mL of water containing 3 mL of HOAc and 100 mg of TBHQ. The hexane solution was washed with brine (3 × 150 mL), dried (Na_2SO_4), and concentrated. Some $(C_6H_5)_3PO$ crystallized out. TLC (9:1 hexane/EtOAc) showed spots corresponding to one product and unreacted aldehyde. Chromatography on a 4.5 × 40 cm silica gel column, eluted with 2% EtOAc/hexane, yielded 4.45 g of ester **5a** togeter with a minor, less polar, compound. Purification by high-performance LC using 1% EtOAc/hexane yielded 2.80 g (55%) of pure ester as a viscous pale yellow oil and 0.84 g (17%) of less-pure material. IR (film) 1715 (C=O), 1600, 1565, 1410, 1270 (CO), 1180, 1105, 1070, 1025, 970, 885, 765, 735, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 [s, 6, $(CH_3)_2C$], 1.38 (t, J = 7 Hz, 3, CH_3CH_2O), 1.5–2.15 (m, 6, C_R-2, C_R-3, C_R-4 CH_2), 1.74 (s, 3, C_R-18 CH_3), 2.07 (d, J = 1 Hz, 3, C_R-19 CH_3), 4.37 (q, J = 7 Hz, 2, CH_3CH_2O), 6.24 (m, 2, C_R-7, C_R-8 HC=CH), 6.47 (m, 1, C_R-10 HC=C), 7.34 (d, J = 7.5 Hz, 2, ArH), 8.01 (d, J = 7.5 Hz, 2, ArH); ^{13}C NMR ($CDCl_3$) 166.3 (C=O), 142.7 (C-1′), 138.1 (C_R-9), 137.8 and 137.5 (C_R-6, C_R-8), 129.3, 129.2, 128.9, 128.8, 128.1, 128.0, 60.7 (ethyl CH_2), 39.5 (C_R-2), 34.2 (C_R-1), 32.9 (C_R-4), 28.9 (C_R-16, C_R-17), 21.6 (C_R-18), 19.2 (C_R-3), 14.3 (ethyl CH_3), 13.9 ppm (C_R-19); UV (EtOH) λ_{max} 319 nm (ϵ 3.07 × 10^4), 238 (1.13 × 10^4); GC–MS (3% UV-25, 220 °C) t_R 1.9 (2%), 3.2 (1%), 4.8 min (97%), three isomers with mass spectra identical: mass spectrum, m/e 338 (M^+), 323 (M − CH_3). MS calcd for $C_{23}H_{30}O_2$, 338.2246; found, 338.2227.

(1*E*,3*E*)-1-(4-Carboethoxyphenyl)-2-methyl-4-(1,2-epoxy-2,6,6-trimethylcyclohex-1-yl)-1,3-butadiene (14). A suspension of 3.5 g (13.2 mmol) of $Na_2HPO_4 \cdot 7H_2O$ in 10 mL of CH_2Cl_2 containing 1.50 g (4.4 mmol) of 4-carboethoxyphenyl triene **5a** was stirred under nitrogen in the dark while a solution of 0.90 g (4.4 mmol) of 85% MCPBA in 12 mL of CH_2Cl_2 was added at 0 °C over 40 min. The white suspension was stirred at 0 °C for 35 min more. TLC (10% EtOAc/hexane) demonstrated one major product, a minor, more polar product, and some remaining starting material. The reaction was diluted with 25 mL of CH_2Cl_2, washed with $NaHCO_3$ solution (2 × 25 mL) and brine (twice), dried (Na_2SO_4), and concentrated to give 1.64 g of a colorless, viscous oil.

The epoxide (1.17 g, 74%) was isolated as a colorless, viscous oil by chromatography on a 2 × 30 cm silica gel column, which was eluted with 1.5% EtOAc/hexane (75-mL fractions): LC (Radialpak B, 3% Et_2O/hexane, 1.0 mL/min, 280 nm) t_R 25.6 (99.2%), 30.0 min (0.8%); LC (μBondapak/C_{18}, reverse phase, 80% CH_3CN/water, 2.0 mL/min , 280 nm) t_R 6.7 min (100%); IR (film) 1715 (C=O), 1605, 1565, 1410, 1270, 1180, 1105, 1020, 975, 890, 770, 750, 710 cm^{-1}; UV (EtOH) λ_{max} 303 nm (ϵ 2.98 × 10^4), 230 (1.21 × 10^4). MS calcd for $C_{23}H_{30}O_3$, 354.2195; found, 354.2187.

Atmospheric Oxidation of (1*E*,3*E*)-1-(4-Carboethoxyphenyl)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadiene (5a). Samples (200 and 290 mg) of the pure **5a** were exposed to air in the dark (for 7 and 45 days, as the pure ester and the second as a solution in toluene/Et_2O, respectively). Silica gel TLC (10% EtOAc/hexane) showed the formation of a major product more polar than the ester, which corresponded to epoxide 14, as well as very polar compounds. The epoxide was isolated by silica gel column chromatography (1 × 25 cm column) with 200-mL volumes of 2 and then 3% EtOAc/hexane. The product was identical with the product of peracid oxidation of **5a** by IR, ^1H NMR, ^{13}C NMR, and MS.

4-Carboethoxy-3-methylbenzaldehyde (9b).[23] To 24.6 g (0.15 mol) of methyl 2,4-dimethylbenzoate in 100 mL of CCl_4 at reflux was added by means of a Gooch tube over a 50-min period a mixture of 28.6 g (0.16 mol) of NBS and 0.25 g of dibenzoyl peroxide. An additional 50 mL of CCl_4 was used to wash the addition flask and tube. Succinimide began to separate out and an orange color, due to bromine, appeared after the addition of the reagent was complete. Heating at reflux was discontinued after an additional 3.5 h, and the product was cooled and filtered. The solid was washed with 100 mL of CCl_4 and the filtrate concentrated. The crude material was distilled through a jacketed 15-cm Vigreux column at 0.15-0.65 mmHg. The yellow-orange liquid darkened rapidly to black on heating. Unreacted ester distilled at 70–75 °C (3.49 g, 14%). The ester was followed by 0.74 g of material, bp 75–129 °C, and 18.67 g of additional material, bp 129–131 °C. The third fraction solidified in the condenser and was melted out throughout the distillation. ^1H NMR indicated that the last two fractions were mixtures of 4-carbomethoxy-3-methylbenzyl bromide and 5-methylphthalide. The second and third fractions were combined and extracted into hot hexane (5 × 20 mL). The filtrate was concentrated to yield 12.1 g of crude benzyl halide as white needles. The insoluble phthalide, mp 117–118.5 °C (EtOAc/hexane), weighed 7.07 g (32%): IR (mull) 1740 (C=O), 1610, 1595, 1355, 1320, 1275, 1250, 1210 (1190 sh), 1120 (1110 sh), 1040, 995, 840, 770, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3, CH_3Ar), 5.27 (s, 2, CH_2O), 7.27 (s, 1, ArH), 7.33 (d, J = 8 Hz, 1, ArH), 7.79 (d, J = 8 Hz, 1, ArH). The crude bromide was purified by elution through a 6 × 40 cm silica gel column with 2–3% EtOAc/hexane. The purified product (10.93 g, 30%), white needles, mp 56–56.5 °C (hexane), was used to prepare the aldehyde **9b**: IR (film) 1720 (C=O), 1610, 1570, 1435, 1290, 1260 (1250 sh) (CO), 1190, 1155, 1085, 970, 895, 850, 815, 785, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (s, 3, CH_3Ar), 3.89 (s, 3, CH_3O), 4.43 (s, 2, CH_2Br), 7.25 (m, 2, ArH), 7.87 (d, J = 8 Hz, 1, ArH). MS calcd for $C_{10}H_{11}O_2{}^{79}Br$, 241.9943; found, 241.9944.

To a solution of NaOEt prepared from 1.05 g (0.044 g-atom) of Na and 40 mL of absolute EtOH was added a solution of 4.0 g (46 mmol) of 2-nitropropane in 5 mL of EtOH. A voluminous white solid separated out. A pure chromatographed 10.7-g (44-mmol) sample of 4-carbomethoxy-3-methylbenzyl bromide was added all at once, followed by a 15-mL EtOH rinse. The reaction was stirred and heated at reflux for 2.5 h with protection from moisture. A heavy white precipitate of NaBr formed. The yellow solution was cooled overnight and then filtered (20-mL EtOH rinse). On concentration of the filtrate, some acetone oxime sublimed onto the rotary evaporator apparatus. The residue was dissolved in 100 mL of Et_2O, washed with water (3 × 50 mL), dried (Na_2SO_4, 3 h), and concentrated to give 8.2 g of yellow liquid. ^1H NMR demonstrated a mixture of the desired ethyl ester **9b** and the corresponding methyl ester. Transesterification was completed

(24) Pommer, H.; Sarnecki, W. (BASF, A.G.) German Patent 1 068 707, 1960.

by adding the ester mixture to a solution of 0.5 g of NaOEt in 80 mL of EtOH and stirring at −5 °C for 63 h. The orange solution was quenched with 1 mL of HOAc and concentrated to a volume of 25 mL, which was diluted with 200 mL of water and extracted with 200 mL of 3:1 hexane/ether. The extract was washed with 100 mL of brine, dried (Na_2SO_4), and concentrated. The residue was purified by high-performance LC with 1% EtOAc/hexane. An unidentified product (1.04 g) was eluted first, followed by the pure ethyl ester (1.77 g, 21%) and the ethyl ester containing 3% of the methyl ester (2.21 g, 26%). **9b** oxidized rapidly in air. It solidified at 0 °C and remelted at room temperature: IR (film) 2720 (CHO), 1715 (C=O), 1610, 1575, 1450, 1285, 1260, 1080, 1020, 920, 845, 780, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (t, J = 7 Hz, 3, CH_3CH_2O), 2.69 (s, 3, CH_3Ar), 4.38 (q, J = 7 Hz, 2, CH_3CH_2O), 7.73 (m, 2, ArH), 8.00 (d, J = 8 Hz, 1, ArH), 10.02 (s, 1, CHO). MS calcd for $C_{11}H_{12}O_3$, 192.0786; found, 192.0789.

1-(4-**Carboethoxy-3-methylphenyl**)-**2-methyl**-1-**propene** (**11b**). A suspension of 19.0 g (44 mmol) of isopropyltriphenylphosphonium iodide in 45 mL of THF was treated under argon at −20 °C with 35.3 mL of 1.19 M n-BuLi (42 mmol) in hexane. Then the temperature was raised to 5 °C over a 65-min period. The ylide solution was next cooled in ice and then treated with a solution of 7.7 g (40 mmol) of the benzaldehyde **9b**[23] in 10 mL of THF. The reaction mixture was stirred at room temperature for 19 h. The solution, which remained a violet-blue color, was heated at 60 °C for 2.5 h, cooled, poured into 300 mL of water containing 3 mL of HOAc, and extracted with 300 mL of 10% EtOAc/hexane. The organic phase was washed twice with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a 5 × 50 cm silica gel column (1% EtOAc/hexane, 200-mL fractions). The product, a colorless liquid containing a trace of a more polar impurity by TLC with a strong green fluorescence, weighed 5.12 g (59%): IR (film) 1715 (C=O), 1660 (C=C), 1605, 1565, 1260 (1285, 1245 sh), 1175, 1155, 1085, 1020, 900, 860, 785, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3, CH_2CH_3), 1.87 [d, J = 1 Hz, 6, $C(CH_3)_2$], 2.60 (s, 3, CH_3Ar), 4.34 (q, J = 7 Hz, 2, CH_2CH_3), 6.23 (br s, 1, C=CH), 7.08 (s, 1, H-2′ ArH), 7.08 (d, J = 8 Hz, 1, H-6′ ArH), 7.90 (d, J = 8 Hz, 1, H-5′ ArH); UV (EtOH) λ_{max} 274 nm (ϵ 1.83 × 10^4). MS calcd for $C_{14}H_{18}O_2$, 218.1307; found, 218.1313.

(*E*)-3-(4-**Carboethoxy-3-methylphenyl**)-**2-methylpropenal** (**12b**). A solution of 6.77 g (21.9 mmol) of arylmethylpropene **11b** and 3.66 g (33 mmol) of SeO_2 in 45 mL of 95% EtOH was degassed (3 times) and then heated at reflux under argon for 22 h. After the solution cooled, the precipitated Se was removed by filtration (40-mL EtOH rinse). The filtrate was concentrated to give 7.2 g of a yellow-orange liquid. Chromatography on a 4 × 40 cm silica gel column with 700-mL volumes of 2, 3, 4, 8, 12, 14, 16, and 25% EtOAc/hexane (150-mL fractions) yielded successively 33 mg (1%) of unreacted olefin, 0.62 g of a mixture of three compounds including aldehyde **12b**, 3.11 g (61%) of **12b**, 0.71 g (14%) of the corresponding allylic alcohol, and more polar products. Aldehyde **12b**: IR (film) 2720 (CHO), 1715 (C=O), 1685 (CHO), 1630, 1610, 1565, 1300, 1260, 1190, 1160, 1085, 1025 (1010 sh), 910, 840, 785, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 6.5 Hz, 3, CH_2CH_3), 2.03 (d, J = 2 Hz, 3, CH_3C=C), 2.65 (s, 3, CH_3Ar), 4.36 (q, J = 6.5 Hz, 2, CH_2CH_3), 7.20 (br s, 1, H-2′ ArH), 7.38 (br d, J = 8.5 Hz, 1, H-6′ ArH), 7.93 (d, J = 8.5 Hz, 1, H-5′ ArH), 9.58 (s, 1, CHO); UV (EtOH) λ_{max} 289 nm (ϵ 2.84 × 10^4). MS calcd for $C_{14}H_{10}O_3$, 232.1099; found, 232,1105. Allylic alcohol: IR (film) 3420 (OH), 1715 (C=O), 1605, 1560, 1260 (1290 sh), 1155, 1080, 1020, 900, 865, 785, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, J = 7 Hz, 3, CH_2CH_3), 1.86 (s, 3, CH_3C=C), 2.57 (s, 3, CH_3Ar), 4.31 (q, J = 7 Hz, 2, CH_2CH_3), 6.46 (br s, 1, H-2′ ArH), 7.10 (br d, J = 7 Hz, 1, H-6′ ArH), 7.83 (d, J = 8.5 Hz, 1, H-5′ ArH); UV (EtOH) λ_{max} 273 nm (ϵ 1.81 × 10^4). MS calcd for $C_{14}H_{18}O_3$, 234.1256; found, 234.1259.

(1*E*,3*E*)- **and** (1*Z*,3*E*)-1-(4-**Carboethoxy-3-methylphenyl**)-**2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadienes** (**5b and 6b**). A solution of 11.9 g (26 mmol) of β-ionyltriphenylphosphonium bromide[22] and 3.7 g (19.2 mmol) of benzaldehyde **9b** in 20 mL of THF and 10 mL of t-BuOH was stirred at −10 °C under argon while a solution of 2.9 g (26 mmol) of t-BuOK in 30 mL of t-BuOH was added. A transient red color was observed. The Wittig reaction mixture was allowed to reach room temperature overnight; the resultant brown suspension was heated at 65 °C for 1 h and cooled. A 0.1-g portion of TBHQ was added, and the reaction mixture was poured into 300 mL of water and extracted with 3:1 hexane/EtOAc (150 and 50 mL). The extract was washed with water (2 × 150 mL) and dried (Na_2SO_4). On concentration, some $(C_6H_5)_3PO$ separated out. The crude material was extracted with 150 mL of hexane. Concentration gave a yellow oil, which was purified in two aliquots by high-performance LC using 1% EtOAc/hexane. A pale yellow oil, 5.88 g (78%), was obtained, and ^1H NMR demonstrated a 2:3 ratio of 1*E*/1*Z* isomers **5b** and **6b**. Attempted Chromatotron separation of these isomers, using 1–2% EtOAc/hexane, was unsuccessful. The product mixture oxidized rapidly in air: IR (film) 2720, 1710 (C=O), 1610, 1390, 1260 (1290 sh) (CO), 1150 (1170 sh), 1085, 1020, 980, 905, 850, 785, 755, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04, 1.07 (2 s, 6, C_R-16, C_R-17 CH_3, two isomers), 1.3–1.8 (m, 4, C_R-2, C_R-3 CH_2), 1.38 (t, J = 7 Hz, 3, CH_3CH_2), 1.73 (s, 3, C_R-18 CH_3), 1.85–2.1 (m, 2, C_R-4 CH_2), 2.08 (s, 3, C_R-18 CH_3), 2.61 (s, 3, CH_3Ar), 4.33 (q, J = 7 Hz, 2, CH_3CH_2), 6.22 [m, 0.85, C_R-7, C_R-8 HC=CH 1(*E*) isomer], 6.41 [m, 2.15, C-10 HC=C, C_R-7, C_R-8 HC=CH 1(*Z*) isomer], 7.12 (m, 2, ArH), 7.87 (d, J = 8 Hz, 1, ArH); UV (EtOH) λ_{max} 313 nm (ϵ 2.36 × 10^4), 233 (1.43 × 10^4).

(1*E*,3*E*)-1-(4-**Carboethoxy-3-methylphenyl**)-**2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadiene** (**5b**). A suspension of 4.75 g (9.5 mmol) of β-cyclogeranyltriphenylphosphonium bromide (**13**) in 12 mL of THF at −30 to −35 °C was treated with 7.1 mL of 1.27 M n-BuLi (9 mmol) in hexane. The red ylide was generated immediately. The reagent was warmed to 0 °C over a 50-min period, and a solution of 2.46 g (10.6 mmol) of aldehyde **12b** in 3 mL of THF (2-mL rinse) was added. The reaction mixture was allowed to warm to room temperature over a 2-h period. The color faded immediately after addition of the aldehyde. Next the reaction mixture was heated to 60 °C for 1.5 h, cooled, and poured into 150 mL of brine containing 4 mL of HOAc and 0.1 g of TBHQ. The ester was extracted into 10% EtOAc/hexane (2 × 100 mL), washed with brine (2 × 100 mL), dried (Na_2SO_4), and concentrated. Chromatography on a 3 × 35 cm silica gel column with 1.5% EtOAc/hexane (100-mL fractions) afforded the crude ester, which was rechromatographed in two portions by high-performance LC (1% EtOAc/hexane) to yield 2.47 g (78%) of pure ester **5b** as a pale yellow liquid and 0.24 g of impure ester containing a less polar compound on silica gel TLC (10% EtOAc/hexane). Ester **5b**: LC (Radialpak B, 3% Et_2O/hexane, 2.0 mL/min, 290 nm) t_R 6.2 (0.8%), 6.8 (1.2%), 7.4 min (98.0%); IR (film) 1715 (C=O), 1600, 1555, 1260, 1175, 1155, 1080, 1025, 970, 900, 850, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 6, C_R-16, C_R-17 CH_3), 1.39 (t, J = 7 Hz, 3, CH_2CH_3), 1.45–1.7 (m, 4, C_R-2, C_R-3 CH_2), 1.74 (s, 3, C_R-18 CH_3), 1.95–2.1 (m, 2, C_R-4 CH_2), 2.06 (d, J = 1 Hz, 3, C_R-19 CH_3), 2.60 (s, 3, CH_3Ar), 4.35 (q, J = 7 Hz, 2, CH_2CH_3), 6.22 and 6.42 (2 m, 3, C_R-7, C_R-8 HC=CH, C-10 C=CH), 7.15 (s, 1, H-2′ ArH), 7.19 (d, J = 8 Hz, 1, H-6′ ArH), 7.90 (d, J = 8 Hz, 1, H-5′ ArH); ^{13}C NMR ($CDCl_3$) 167.0 (C=O), 141.6 (C-1′), 139.7 (C_R-9), 137.7 and 137.4 (C_R-6, C_R-8), 132.1, 130.3, 129.1, 128.7 (C_R-7), 127.7, 127.1, 126.1, 60.4 (ethyl CH_2), 39.5 (C_R-2), 34.3 (C_R-1), 32.9 (C_R-4), 28.9 (C_R-16, C_R-17), 21.9 and 21.7 (C_R-18, CH_3Ar), 19.3 (C_R-3), 14.3 (ethyl CH_3), 13.9 ppm (C_R-19); UV (EtOH) λ_{max} 314 nm (ϵ 2.76 × 10^4), 235 (1.0 × 10^4). MS calcd for $C_{24}H_{32}O_2$, 352.2402; found, 352.2397.

(1*E*,3*E*)-1-(4-**Carboxy-3-methylphenyl**)-**2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadiene** (**7b**). A solution of 1.1 g (19 mmol) of KOH in 3.5 mL of water and 5.5 mL of EtOH was degassed (4 times) under nitrogen before a solution of 2.27 g (6.4 mmol) of **5b** in 2 mL of EtOH (1-mL rinse) was introduced at room temperature. The suspension was heated to 80 °C over a 20-min period, and the temperature maintained there for 15 min. The clear yellow solution was cooled and acidified with 15 mL of 50% HOAc to separate the solid acid. Water (50 mL) was added, and the acid was extracted into 50 mL of ether. The extract was washed with brine (2 × 40 mL), dried (Na_2SO_4), and concentrated. The product was recrystallized under nitrogen from 25 mL of MeOH to give as a first crop 1.62 g (87%) of very pale yellow crystals: mp 146.5–147.5 °C; LC (μBondapak/C_{18}, reverse phase, 80% CH_3CN/water, 2.0 mL/min, 280 nm), t_R 4.3 min (100%); IR (mull) 3250–2300 (OH), 1675 (COOH), 1600, 1555, 1495, 1415, 1275 (1290, 1305 sh), 1230, 1200, 1175, 1160, 1090, 970, 900, 855, 785 cm^{-1}; UV (EtOH) λ_{max} 309 nm (ϵ 2.89 × 10^4). MS

calcd for $C_{22}H_{28}O_2$, 374.2089; found, 324.2083.

(*E*)-1-(2-Carbomethoxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene (17). A slurry of 20 g (40 mmol) of β-ionylideneethyltriphenylphosphonium chloride (16)[22] and 5.9 g (36 mmol) of 2-carbomethoxybenzaldehyde (15)[25] in 13 mL of *t*-BuOH and 37 mL of THF was treated at 0 °C under argon with a solution of 4.26 g (38 mmol) of *t*-BuOK in 37 mL of *t*-BuOH. The deep red ylide solution immediately turned orange. The product was isolated after 22 h at room temperature by extraction into 200 mL of 10% EtOAc/hexane from 250 mL of water containing 3 mL of HOAc and 0.1 g of TBHQ. The extract was washed with brine (2 × 150 mL), dried (Na_2SO_4), and concentrated. The orange viscous oil was rapidly eluted through a 5 × 45 cm silica gel column with 4% EtOAc/hexane (350- to 500-mL fractions). A mixture of isomeric esters (3.93 g, 31%) was obtained as a yellow gum: LC (Radialpak B, 3% Et_2O/hexane, 1.0 mL/min, 290 nm) t_R 8.2 (30%), 9.1 (3%), 10.1 min (67%). To a solution of 1.73 g (4.9 mmol) of this ester mixture dissolved in 100 mL of ether and 75 mL of toluene under argon was added with stirring 20 mg of iodine. The dark soluton, on exposure to fluorescent room light for 1.75 h, darkened further. The solution was concentrated to about 15 mL and immediately eluted through a 3 × 35 cm silica gel column with 1.5% EtOAc/hexane. Concentration yielded 1.61 g of crude (*E*)-ester 17, which was used without further purificaton for the hydrolysis: LC (Radialpak B, 3% Et_2O/hexane, 1.0 mL/min, 290 nm) t_R 7.4 (10.7%), 8.0 (83.2%), 8.8 (3.2%), 9.8 min (2.9%).

A sample of the 1(*Z*) isomer 18 was obtained from the Wittig reaction product mixture before iodine-catalyzed isomerization. This 0.5-g sample had been stored under argon at room temperature and had isomerized considerably to the 1(*E*) isomer. Two successive LC purification steps employing 1% EtOAc/hexane yielded the 1(*Z*)-methyl ester 18 in 96% isomeric purity (LC, Radialpak B, 3% Et_2O/hexane, 1.0 mL/min, 280 nm): IR (film) 1720 (C=O), 1620, 1590, 1565, 1440, 1250, (1275, 1295 sh), 1195, 1130, 1080, 970, 775, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 6, C_R-16, C_R-17 CH_3), 1.4–1.65 (m, 4, C_R-2, C_R-3 CH_2), 1.72 (s, 3, C_R-18 CH_3), 2.02 (d, J = 1 Hz, 3, C_R-19 CH_3), 1.95–2.1 (m, 2, C_R-4 CH_2), 3.90 (s, 3, CH_3O), 6.10 and 6.26 (2 d, J = 16 Hz, 2, C_R-7, C_R-8 HC=CH), 6.28 (d, J = 12 Hz, 1, C_R-12 HC=C*H*), 6.95–7.55 (m, 4, C_R-10 C=CH, C_R-11 *H*C=CH, H-4′, H-5′ ArH), 7.67 (dd, J = 8 and 1.5 Hz, 1, H-6′ ArH), 7.85 (dd, J = 8 and 1.5 Hz, 1, H-3′ ArH); UV (EtOH) λ_{max} 347 nm (ε 3.73 × 10^4), 258 (8.6 × 10^3). MS calcd for $C_{24}H_{30}O_2$, 350.2246; found, 350.2264.

(*E*)-1-(2-Carboxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene (19). The crude (*E*)-ester 17 (1.86 g, 5.3 mmol)—which was obtained from the I_2 isomerization of the 11(*E*,*Z*)-ester mixture—in 1.5 mL of EtOH was added under argon to a degassed (4 times) solution of 0.6 g (10 mmol) of KOH in 2 mL of water and 2.5 mL of EtOH (7-mL EtOH rinse). The orange-brown suspension was heated to 80 °C over a 20-min period, and the temperature was maintained there for 10 min. After cooling, the clear solution was acidified with 12 mL of 50% aqueous HOAc, allowed to stand under argon for 15 h, and diluted with 50 mL of water. The precipitated acid was extracted into Et_2O (2 × 25 mL), washed twice with brine, dried (Na_2SO_4), and concentrated. The yellow solid was recrystallized under nitrogen from 20 mL of MeOH. The first crop was recrystallized a second time from 5 mL of MeOH: 1.19 g (67%) of pure acid 19 was obtained as bright yellow crystals; mp 146–149 °C; LC (μBondapak/C_{18}, reverse phase, 80% CH_3CN/water, 2.0 mL/min, 280 nm) t_R 2.0 min (100%); IR (mull) 3200–2300 (OH), 1670 (C=O), 1610, 1595, 1580, 1420, 1295, 1275, 1250, 1210, 1140, 1080, 960 (970 sh), 895, 790, 750, 730, 710, 665 cm^{-1}; UV (EtOH) λ_{max} 344 nm (ε 4.09 × 10^4), 253 (8 × 10^3). MS calcd for $C_{23}H_{28}O_2$, 336.2089; found, 336.2087.

A sample of the methyl ester 17 was prepared from recrystallized acid 19 and diazomethane. The ester was homogeneous to analytical high-performance LC (Radialpak B, 3% Et_2O/hexane, 1.0 mL/min, 290 nm) and corresponded to the isomer of shorter (8.2 min) retention time in the mixture prior to the isomerization step.

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Methyl 2-Hydroxy-*trans*-cinnamate (21). A solution of 8.2 g (0.05 mol) of 2-hydroxy-*trans*-cinnamic acid (20) and 0.6 g (3.2 mmol) of *p*-TsOH·H_2O in 40 mL of MeOH and 30 mL of $C_6H_5CH_3$ was heated under gentle reflux. The water/MeOH/$C_6H_5CH_3$ azeotrope (25 mL) was removed from a Dean–Stark trap every 1.5 h as more MeOH (20 mL) and $C_6H_5CH_3$ (5 mL) were added. After 5 h, the reaction mixture was concentrated to about 40 mL and added to 100 mL of ether. The ethereal solution was washed with saturated $NaHCO_3$ (3 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), and evaporated to give 8.2 g (92%) of a white powder. Recrystallization from $CHCl_3$ gave 6.5 g of white crystals: mp 137–137.5 °C (lit.[26] 136–137 °C); IR (mull) 3350 (OH), 1700 (C=O), 1640 (C=C) 1330, 1210, 1180, 760 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58 (s, 3, CH_3), 6.53 (d, J = 16 Hz, 1, $CHCO_2CH_3$), 6.7–7.6 (m, 4, ArH), 7.87 (d, J = 16 Hz, 1, ArHC=C), 10.09 (s, 1, OH).

2-(Tetrahydropyranyloxy)-*trans*-cinnamaldehyde (24). To a mixture of 20 mL (0.22 mol) of DHP and 0.01 g (0.05 mmol) of *p*-TsOH·H_2O cooled to 0 °C was added in one portion 6.0 g (34 mmol) of methyl 2-hydroxy-*trans*-cinnamate (21).[26] The violet reaction mixture was vigorously stirred at 0 °C for 15 min, at which time all of the crystals of the starting material had dissolved. The product was extracted with 100 mL of ether and washed with 100 mL of 5% Na_2CO_3. The organic layer was washed with 5% Na_2CO_3 (5 × 100 mL) and brine (2 × 100 mL), dried (Na_2SO_4), and evaporated to give 11 g (100% crude yield) of methyl 2-tetrahydropyranyloxy-*trans*-cinnamate (22) as a pale yellow oil containing some polymeric byproducts as shown by TLC (1:1 hexane/ether): IR (film) 2950, 1730 (C=O), 1650 (C=C), 1500, 1460, 1330, 1280, 1250, 1210, 1175, 1120, 1070, 1050, 970, 930, 880, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–2.2 and 3.4–4.2 [2 m, 8, $(CH_2)_4$], 3.83 (s, 3, CH_3), 5.57 (br s, 1, OCHO), 6.60 (d, J = 16 Hz, 1, $CHCO_2CH_3$), 6.8–7.7 (m, 4, ArH), 8.13 (d, J = 16 Hz, 1, ArHC=C).

To an ice-cooled solution of 10.0 g (0.038 mol) of **22** in 50 mL of ether was added 90 mL (0.09 mol) of a 1 M solution of DIBAL in hexane over a 15-min period. The reaction mixture was maintained at 0 °C for another 30 min. MeOH (50 mL) was added slowly to decompose any excess reagent. The precipitated aluminum salts were filtered after 1 h (200-mL ether wash). The filtrate was washed twice with 100-mL portions of brine, dried (Na_2SO_4), and evaporated to give 9.0 g (100% crude yield) of 2-(tetrahydropyranyloxy)-*trans*-cinnamyl alcohol (23) as a light yellow oil still contaminated with some polymeric materials from dihydropyran: IR (film) 3270 (OH) 2950, 1600, 1490, 1250, 1120, 980, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–2.0 and 3.3–3.9 [2 m, 8, $(CH_2)_4$], 4.37 (br s, 2, CH_2OH), 5.48 (br s, 1, OCHO), 6.2–6.6 (m, 1, C=C*H*CH_2), 6.7–7.5 (m, 5, ArH and ArHC=C).

An 8.0-g (34 mmol) portion of crude cinnamyl alcohol **23** was dissolved in 100 mL of ether, and 30 g (0.34 mol) of activated MnO_2 was added. The mixture was stirred overnight. An additional 20 g (0.23 mol) of MnO_2 was added, and the reaction mixture was stirred for another 4 h, at which time TLC (1:1 hexane/Et_2O) indicated that reaction was complete. The mixture was filtered (Celite) and the filtrate concentrated to give 7.0 g of a pale yellow oil. Purification by high-performance LC (20% Et_2O/hexane) afforded 4.9 g (61%) of the aldehyde containing about 8% by weight of polymeric material from DHP as shown by ^1H NMR. An analytically pure sample was obtained as a yellow solid, mp 46–47 °C, on repurification by chromatography (15% Et_2O/hexane): IR (film) 2950, 2750 (HCO), 1690 (C=O), 1630 (C=C), 1615, 1490, 1250, 1120, 1040, 970, 925, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–2.1 and 3.5–4.0 [2 m, 8, $(CH_2)_4$], 5.63 (br s, 1, OCHO), 6.90 (dd, J = 8 and 16 Hz, 1, *C*HCHO), 7.1–7.8 (m, 4, ArH), 7.98 (d, J = 16 Hz, 1, ArHC=C), 9.77 (d, J = 8 Hz, 1, CHO). MS calcd for $C_{14}H_{16}O_3$, 232.1099; found, 232.1105.

(*E*)-1-[2-(Tetrahydropyranyloxy)phenyl]-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene (25). NaH (375 mg, 59.3% dispersion in mineral oil, 9.2 mmol) was washed twice with 10-mL portions of pentane, and 20 mL of dry Me_2SO was added. The mixture was heated to 70 °C for 30 min to obtain a clear grayish solution and then cooled to room temperature. A solution of 4.77 g (9.2 mmol) of phosphonium bromide 10 in 20 mL of warm Me_2SO was added over a 10-min period. To the

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resulting deep red solution was added 2.09 g (9 mmol) of the aldehyde **24** in 20 mL of Me_2SO. The mixture was stirred at room temperature for 16 h and heated to 55–60 °C for 1 h. The reaction mixture was diluted with 30 mL of H_2O and extracted with pentane (5 × 50 mL). The pentane extract was washed wth 1:1 H_2O/Me_2SO (2 × 100 mL) and brine (3 × 100 mL), dried (Na_2SO_4), and concentrated. The crude product was filtered through 10 g of silica gel with 200 mL of 3:1 pentane/EtOAc and concentrated to give 3.3 g of a pale yellow oil (93% crude yield).

LC (Radialpak B, 1% Et_2O/hexane, 2.0 mL/min, 285 nm) revealed two major products, t_R 10.2 (60%, isomer **26**) and 10.9 min (40%, isomer **25**). The crude product (3.3 g) was subjected to preparative LC (0.3% Et_2O/hexane) using the recycle technique. At each cycle, fractions containing **26** of greater than 90% isomeric purity were collected and the rest recycled. With three successive recycles, it was possible to obtain 0.9 g of **26** (90% isomeric purity), 0.87 g of **25** (85% isomeric purity), and 0.59 g of an approximately 1:1 mixture of both isomers. A second injection with 1.4 g of another batch of similarly prepared crude product gave 0.66 g of **25** (>90% isomeric purity) and 0.6 g of **26** (>90% isomeric purity). A 1.53-g portion of the mixture containing 90% isomer **25** was subjected to LC with three recycles, to give 0.8 g of **25** (98% isomeric purity) as a pale yellow oil. This oil was repurified by LC (0.4% Et_2O/hexane, three recycles) to give 0.56 g of **25** (99.9% isomeric purity by analytical LC). A final purification of this product on LC (2% EtOAc/hexane) gave 0.52 g of isomerically pure **25**, followed by about 3% of some oxidation products by LC: analytical LC (Radialpak B, 1% Et_2O/hexane, 2.0 mL/min, 285 nm) t_R 10.9 min; IR (film) 2950, 1600, 1490, 1450, 1360, 1235, 1205, 1120, 1038, 960, 920, 870, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 6, C_R-16, C_R-17 CH_3), 1.4–1.8 and 1.85–2.2 [2 m, 12, C_R-2, C_R-3, C_R-4 CH_2, and $(CH_2)_3CHO$], 1.74 (s, 3, C-18 CH_3), 2.04 (s, 3, C_R-19 CH_3), 3.4–4.1 (m, 2, CH_2O), 5.45 (br s, 1, OCHO), 6.21 (s, 2, C_R-7, C_R-8 HC=CH), 6.27 (d, J = 11 Hz, 1, C_R-10 C=CH), 6.8–7.6 (m, 6, C_R-11, C_R-12, HC=CH, and ArH). MS calcd for $C_{27}H_{36}O_2$, 392.2715; found, 392.2720.

A 0.52-g sample of isomer **26** (99.9% isomerically pure) was obtained as a pale yellow oil from repeated runs on LC (0.3% Et_2O/hexane): analytical LC (Radialpak B, 1% Et_2O/hexane, 2.0 mL/min, 285 nm) t_R 10.2 min; IR (film) 2940, 1610, 1495, 1465, 1380, 1365, 1240, 1205, 1180, 1120, 1040, 965, 920, 875, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 6, C_R-16, C_R-17 CH_3), 1.4–1.7 and 1.8–2.1 [2 m, 12, C_R-2, C_R-3, C_R-4 CH_2 and $(CH_2)_3CHO$], 1.77 (s, 3, C_R-18 CH_3), 2.02 (s, 3, C_R-19 CH_3), 3.4–4.1 (m, 2, CH_2O), 5.48 (br s, 1, OCHO), 6.18 (d, J = 11 Hz, 1, C_R-10 C=CH), 6.21 (d, J = 16 Hz, 1, C_R-7 *HC*=CH), 6.68–7.53 (m, 7, C_R-8, C_R-11, C_R-12 HC=CH and ArH).

(*E*)-1-(2-Hydroxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene (27). To 0.42 g (1.07 mmol) of **25** dissolved in 5 mL of EtOAc was added 20 mL of a 0.03 M solution of *p*-TsOH·H_2O in MeOH. The solution was stirred under argon for 1 h when TLC (1:1 hexane/ether) indicated that reaction was complete. The product was diluted with 10 mL of EtOAc and washed with 50 mL of H_2O, 40 mL of saturated $NaHCO_3$, and 40 mL of brine (twice), filtered through 10 g of Na_2SO_4, and concentrated to give 0.32 g of an oil (97%) which gradually crystallized to give a yellow solid: mp 121–123 °C dec; the product showed only one peak on both normal phase (Radialpak B, 4% Et_2O/hexane, 2 mL/min, 285 nm, t_R 13.4 min) and reverse phase (μBondapak/C_{18}, 10% H_2O/MeOH, 2 mL/min, 285 nm, t_R 6.9 min) LC; IR (mull) 3550 (OH), 1610, 1330, 1260, 1150, 1085, 980, 750 cm^{-1}; UV (EtOH) λ_{max} 349 nm (ϵ 4.05 × 10^4), 240 (8.3 × 10^3). MS calcd for $C_{22}H_{28}O$, 308.2140; found, 308.2168.

(1*E*,3*Z*,5*E*)-1-(2-Hydroxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene (28). The 3(*Z*) isomer **28** was obtained as a light yellow solid from 0.42 g of the pure tetrahydropyranyl derivative **26** in 94% yield by the procedure used to convert **25** to **27**: compound **28** showed one peak on both normal phase (Radialpak B, 4% Et_2O/hexane, 2 mL/min, 285 nm, t_R 13.4 min) and reverse phase (μBondapak/C_{18}, 15% H_2O/MeOH, 2 mL/min, t_R 8.0 min) LC; IR (mull) 3250 (OH), 1600, 1350, 1230, 1205, 1190, 1160, 1090, 970, 750 cm^{-1}; UV (EtOH) λ_{max} 344 nm (ϵ 3.00 × 10^4), 250 (1.10 × 10^4). MS calcd for $C_{22}H_{28}O$, 308.2140; found, 308.2152.

ODC Assay. The ODC assay was performed as previously described[2b] using procedures reported by Raineri et al.[27] and O'Brien et al.[28]

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Synthesis and Anxiolytic Activity of 6-(Substituted-phenyl)-1,2,4-triazolo[4,3-*b*]pyridazines

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The synthesis of a series of 6-(substituted-phenyl)-1,2,4-triazolo[4,3-*b*]pyridazines (VIII) is reported. Some of these derivatives show activity in tests predictive of anxiolytic activity [(a) protection against pentylenetetrazole-induced convulsions; (b) thirsty rat conflict procedure]. They also represent a new class of compound which inhibits [^3H]diazepam binding. Structure–activity correlations, as well as the ability of structures VIII to inhibit [^3H]diazepam binding (in vitro), are discussed.

Intensive research in the benzodiazepine field has continued since the discovery and marketing of chlordiazepoxide and diazepam,[1] and this research has led to the discovery of many new derivatives with potent anxiolytic activity. However, very few new structures which are unrelated to benzodiazepines but which display potent anxiolytic activity have been reported. Many derivatives of 5-phenyl-1,4-benzodiazepine with a ring fused at the 1,2 positions have been investigated.[2,3] 1,2,4-Triazolo[4,3-*a*][1,4]benzodiazepines,[2-4] 1,2,4-triazolo[5,1-*a*][2,4]benzo-

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