

and combined to give a brown solid (6; 10.5 g). The crude product was added with 200 mL of CH₃CN and treated with SOCl₂ (15.0 mL). The resulting mixture was stirred at room temperature for 4 h and evaporated to dryness. The residue was added with 100 mL of H₂O basified with NH₄OH and extracted with 10% MeOH in CHCl₃ (4 × 75 mL). The combined extracts were dried and evaporated to give a dark oil (3.0 g). The oily residue was chromatographed on a silica gel column packed and eluted with Et₂O-CHCl₃-MeOH (80:20:3) to give 1.2 g of pure compound 1b. The free base thus obtained was dissolved in a minimal amount of CH₃OH and diluted with anhydrous Et₂O up to the point when the solution started to cloud. A few drops of CH₃OH was then added to clear the solution. An excess of ethereal HCl was added to the solution until no further precipitation occurred. Filtration of the mixture gave 1.1 g (10%) of light pink solid: mp 165–170 °C; UV max (EtOH) 305 nm (log ε 3.87), 279 (4.09), 270 (4.08); [α]_D²⁵₅₄₆ -266° (c 0.05, EtOH). Anal. (C₂₃H₂₆N₂O₄Cl₂·HCl·2H₂O) C, H.

Method B. A solution of 1d (1.7 g, 0.0034 mol) in 80 mL of CH₃OH and 48 mL of concentrated HCl was allowed to stand at room temperature for 16 h. The mixture was diluted with 150 mL of CHCl₃ and neutralized with aqueous NaHCO₃. The organic layer was separated and the aqueous phase extracted with another 50 mL of CHCl₃. The combined CHCl₃ solutions were dried and evaporated to dryness to give about 1.4 g of product. The product was dissolved in a mixture of 10 mL of CH₃OH and 30 mL of ether and acidified with ethereal HCl to give a gummy precipitate. Trituration with fresh ether gave a crystalline solid weighing 1.24 g (74%), mp 165–170 °C, and has the identical R_f as 1b obtained through method A.

N-(2-Chloroethyl)norapocodeine Hydrochloride (1e). A mixture of 9^b (13.24 g, 0.0425 mol) in 350 mL of CH₃CN was treated with SOCl₂ (20.0 g, 0.168 mol), and the reaction mixture was worked up in the same manner as previously described⁵ to give the free base of 1e (4.55 g, 32%) after column chromatography. The HCl salt was prepared in the usual manner, mp 212–215 °C. Anal. (C₁₉H₂₀NCIO₂·HCl) C, H, N.

N-[2-(2-Chloroethoxy)ethyl]norapocodeine Hydrochloride Hemihydrate (1f). A solution of 9 (0.90 g, 2.9 mmol) and SOCl₂ (2.0 g, 16.8 mmol) in 25 mL of CH₃CN was stirred at room temperature for 20 h. The reaction mixture was evaporated to a residue, which was then added to 20 mL of H₂O, basified with NaHCO₃, and extracted with Et₂O (3 × 40 mL). The combined extracts were dried (Na₂SO₄) and evaporated to an oily residue. The residue was chromatographed on a silica gel column packed and eluted with Et₂O-petroleum ether (1:3) to give sequentially (a) compound 1e (0.15 g, 16%) and (b) compound 1f (0.45 g, 40%): NMR (CDCl₃) δ 2.40–4.0 [m, 19, H at C-4, C-5, C-6a, C-7, OCH₃, NCH₂CH₂OCH₂CH₂Cl, OH], 6.63–7.27 (m, 4, aromatic), 8.03–8.27 (dd, 1, aromatic); MS *m/e* 373 (M⁺), 100 (base); UV max (EtOH) 310 nm (log ε 3.81), 276 (4.38); [α]_D²⁵₅₄₆ -40° (c 0.05, EtOH); for ¹³C NMR, see Table I. The HCl salt was prepared in the usual

manner, mp 202–205 °C. Anal. (C₂₁H₂₄ClNO₃·HCl·0.5H₂O) C, H, N.

N-[[[N'-(2-Chloroethyl)carbonyloxy]ethyl]norapocodeine (1g) and N-[[[N'-(2-Chloroethyl)carbonyloxy]ethyl]-10-methoxy-11-(chloroethyl)carbonyl]aporphine (1h). A solution of 9 (1.01 g, 3.2 mmol) in 50 mL of THF was added dropwise via syringe to chloroethyl isocyanate (3.75 g, 35.5 mmol). The solution was further diluted with 25 mL of THF and allowed to reflux for 24 h. The reaction mixture was cooled and filtered to obtain a white solid (0.13 g, 13%), which was identified as the unreacted N-(hydroxyethyl)norapocodeine. The filtrate was evaporated to a residue, dissolved with 25 mL of 10% HCl, and washed with Et₂O (2 × 25 mL). The acidic aqueous layer was neutralized with NH₄OH and extracted with CHCl₃ (3 × 50 mL). The combined extracts were dried and evaporated to give a dark oil, which was chromatographed on a silica gel column packed and eluted with Et₂O-CHCl₃-MeOH (85:13.5:1.5) to give three fractions (I–III). Fraction I (1g; 0.27 g, 23%): UV max (EtOH) 300 nm (log ε 3.70), 275 (4.71); MS *m/e* 416 (M⁺), 266 (base); [α]_D²⁵₅₄₆ -25° (c 0.06, EtOH). The HCl salt was prepared in the normal manner, mp 185–188 °C. Anal. (C₂₂H₂₅ClN₂O₄·HCl·1.5H₂O) C, H, N. Fractions II and III were also identified. Fraction II contained a mixture of 1g and 1h (0.35 g) and fraction III contained pure 1h (0.33 g, 22%); MS *m/e* 436 (M⁺), 266 (base); UV max (EtOH) 300 nm (log ε 3.46), 268 (4.15); [α]_D²⁵₅₄₆ -9.7°. The HCl salt was prepared in the normal manner, mp 178–182 °C (softened at 80 °C). Anal. (C₂₅H₂₉Cl₂N₃O₅·HCl·1.5H₂O) C, H, N.

1-(Aminoethyl)-3,5-dihydroxy-6-methoxyphenanthrene Hydrochloride (4a). A solution of 3 (0.150 g, 0.31 mmol) in 3 mL of concentrated HCl was heated at 110–120 °C under N₂ for 20 min. The reaction mixture was cooled and filtered to give a pink solid, which was washed with cold concentrated HCl and Et₂O and dried in a desiccator at 40–50 °C, giving 50 mg (50%) of 4a·HCl: mp 240 °C dec; NMR (CDCl₃-Me₂SO-*d*₆) δ 2.75–3.70 (br signal, 4, CH₂CH₂N), 3.93 (s, 3, OCH₃), 7.0–7.90 (m, 7, aromatic H and phenolic OH), 8.10–8.90 (br signal, 3, NH₃⁺), 9.20 (d, 1, aromatic H at C-4); UV max (EtOH) 321 nm (log ε 4.19), 298 (4.17), 257 (4.70), 240 (4.55).

Acknowledgment. The help and encouragement of Mrs. Nancita Lomax and Dr. V. Narayanan are greatly appreciated. We also thank Dr. Paul Vouros for mass spectral interpretations, Dr. Catherine Costello (MIT) for the acquisition and interpretation of the high-resolution mass spectrum for 1f, Larry Thomas (NEN) for the ¹³C NMR spectrum of 1f, Professor C. Hansch and Dr. A. J. Leo for log *P* determinations, and Mallinckrodt, Inc., for generous samples of thebaine. This investigation was supported by the National Cancer Institute (NC 1-CM-53741).

Retinoic Acid Analogues. Synthesis and Potential as Cancer Chemopreventive Agents

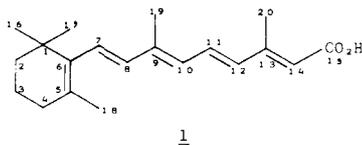
Marcia I. Dawson,* Peter D. Hobbs, Karl Kuhlmann, Victor A. Fung, C. Tucker Helmes, and Wan-Ru Chao

Bio-Organic Chemistry Laboratory, SRI International, Menlo Park, California 94025. Received September 24, 1979

Analogues of retinoic acid have been synthesized as potential chemopreventive agents against epithelial cancer. Ethyl (*E*)-9-(2-norbornenyl)-3,7-dimethylnona-2,4,6,8-tetraenoate (9), (*E*)-3,7-dimethyl-9-(2-ethyl-6,6-dimethyl-1-cyclohexen-1-yl)nona-2,4,6,8-tetraenoic acid (25), and 2-(2'-methoxyethoxy)ethyl retinoate (26) displayed good activity in the inhibition of tumor promoter-induced mouse epidermal ornithine decarboxylase assay. (*E*)-1-(3-Acetoxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)hexa-1,3,5-triene (34) had low activity. (*E*)-5-[2,6-Dimethyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)octa-1,3,5,7-tetraen-1-yl]tetrazole (40) was inactive.

The progressive loss of the regulation of cellular differentiation by epithelial cells can result in cancer. Retinoic acid (1) and some of its analogues (retinoids) prevent

the expression of these unfavorable cellular changes at a fundamental level. The mechanism by which chemoprevention of carcinogenesis occurs has not yet been estab-

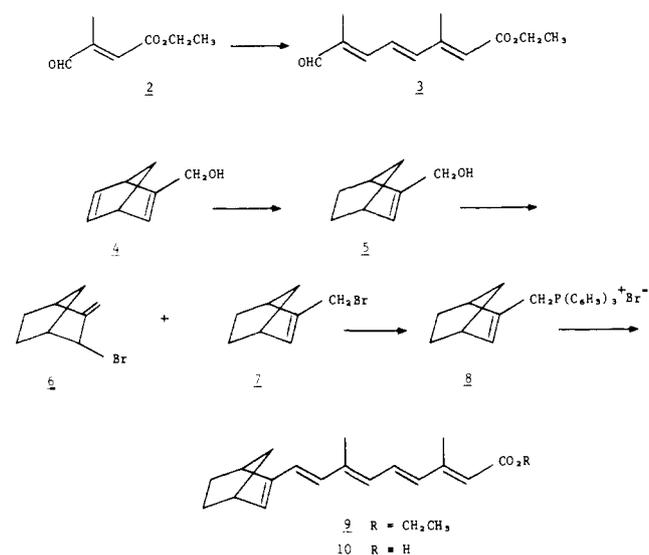


lished, even though the effectiveness of the retinoids in suppressing or reversing the transformation of premalignant cells to a malignant state is well documented.¹ These compounds are capable of effecting the regression of epithelial papillomas induced by carcinogens in experimental animals² and of potently inhibiting the tumor-promotion activity of phorbol esters.³ However, because retinoic acid damages lysosomal membranes, is systemically toxic, and has a poor tissue distribution pattern,^{1a} less toxic, more effective retinoids are needed. Much of the current successful synthetic effort has focused on derivation of the active retinoids by modification of the polar terminus—for example, by conversion of retinoic acid to its *N*-(2-hydroxyethyl)⁴ and *N*-(4-hydroxyphenyl)⁵ amides and by conversion of retinal to condensation products with 1,3-diketones.^{1a} Modifications of the β -cyclogeranylidene ring^{6,7} and tetraene chain^{1b,c} have also been performed.

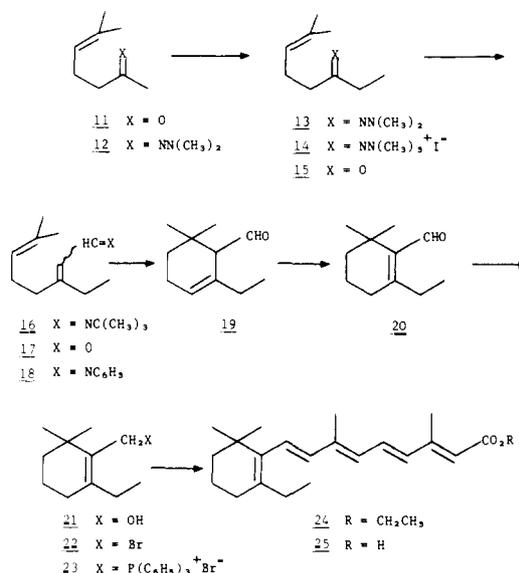
As part of a program to synthesize more effective retinoids for the chemoprevention of cancer and to learn more about retinoid structure-activity relationships, we prepared five retinoids that have modifications either in the ring or polar terminus.

In retinoic acid, steric interactions between the C-16 and C-17 methyl groups or the C-18 methyl group and the C-8 hydrogen prevent the ring and the tetraene chain from assuming a coplanar conformation.⁸ Retinoids **10** and **25** were designed to give information on how varying the steric dimensions at the ring position would affect activity. In

Scheme I



Scheme II



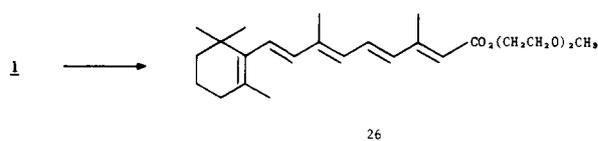
the norbornenyl analogue, **10**, steric interactions are minimized, whereas in the homologue **25**, which has a more bulky ethyl group at the 5 position of the ring, less interaction between the ring and chain was predicted to occur.

The norbornenyl retinoid was prepared from the trienal ester **3** and the phosphonium salt **8**. The reaction sequence is shown in Scheme I. The trienal ester was prepared from ethyl β -formylcrotonate by a series of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed vinyl ether-acetal condensations,⁹ followed by NaOAc/HOAc -catalyzed eliminations.¹⁰ Catalytic reduction¹¹ of norbornadienylcarbinol **4**¹² in the presence of NaNO_2 to decrease hydrogenolysis of the hydroxyl group afforded the known norbornenylcarbinol **5**,¹³ which, on treatment with $\text{PBr}_3/\text{pyridine}$ at -50°C , gave a 1:9 mixture of the

- (1) (a) M. B. Sporn, D. L. Newton, J. M. Smith, N. Acton, A. E. Jacobson, and A. Brossi, in "Carcinogens: Identification and Mechanism of Action", A. C. Griffin and C. R. Shaw, Eds., Raven Press, New York, 1979, pp 441-453; (b) M. B. Sporn, N. M. Dunlop, D. L. Newton, and J. M. Smith, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **35**, 1332 (1976); (c) M. B. Sporn, N. M. Dunlop, D. L. Newton, and W. R. Henderson, *Nature (London)*, **263**, 110 (1976); (d) M. B. Sporn and D. L. Newton, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **38**, 2528 (1979); (e) G. J. Todaro, J. E. DeLarco, and M. B. Sporn, *Nature (London)*, **276**, 272 (1978).
- (2) (a) M. B. Sporn, R. A. Squire, C. C. Brown, J. M. Smith, M. L. Wenk, and S. Springer, *Science*, **195**, 487 (1977); (b) P. J. Becci, H. J. Thompson, C. J. Grubbs, R. A. Squire, C. C. Brown, M. B. Sporn, and R. C. Moon, *Cancer Res.*, **38**, 4463 (1978); (c) W. Bollag, *Cancer Chemother. Rep.*, **55**, 53 (1971); (d) R. C. Moon, C. J. Grubbs, M. B. Sporn, and D. G. Goodman, *Nature (London)*, **267**, 620 (1977).
- (3) (a) A. K. Verma, B. G. Shapas, H. M. Rice, and R. K. Boutwell, *Cancer Res.*, **39**, 419 (1979); (b) A. K. Verma, H. M. Rice, B. G. Shapas, and R. K. Boutwell, *ibid.*, **38**, 793 (1978); (c) A. K. Verma and R. K. Boutwell, *ibid.*, **37**, 2196-2201 (1977).
- (4) (a) D. R. Bard and I. Lasnitzki, *Br. J. Cancer*, **35**, 115 (1977); (b) W. Bollag, R. Ruegg, and R. Ryser (Hoffmann-LaRoche), German Patent 2 102 586, Aug 12, 1971; *Chem. Abstr.*, **75**, P98697d (1971).
- (5) R. J. Gander and J. A. Gurney (Johnson and Johnson), Belgian Patent 847 942, May 3, 1977; *Chem. Abstr.*, **88**, P89892e (1978).
- (6) (a) W. Bollag, *Eur. J. Cancer*, **10**, 731 (1974); (b) G. H. Clamon, M. B. Sporn, J. M. Smith, and U. Saffiotti, *Nature (London)*, **250**, 64 (1974); (c) M. B. Sporn, G. H. Clamon, N. M. Dunlop, D. L. Newton, J. M. Smith, and U. Saffiotti, *ibid.*, **253**, 47 (1975).
- (7) B. A. Pawson, H.-C. Cheung, R.-J. Han, P. W. Trown, M. Buck, R. Hansen, W. Bollag, U. Ineichen, H. Pleil, R. Ruegg, N. M. Dunlop, D. L. Newton, and M. B. Sporn, *J. Med. Chem.*, **20**, 918 (1977).
- (8) W. H. Sebrell, Jr., and R. S. Harris, "The Vitamins", Vol. 1, Academic Press, New York, 1967.

- (9) (a) O. Isler and P. Schudel, *Adv. Org. Chem.*, **4**, 128 (1963); (b) H. Pommer, *Angew. Chem.*, **72**, 811 (1960).
- (10) G. I. Samokhvalov, L. A. Lukyanova, T. V. Men, L. T. Zhikhareva, V. I. Koltunova, and N. A. Preobrazhenskii, *J. Gen. Chem. USSR*, **29**, 2538 (1959).
- (11) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).
- (12) P. J. Graham, E. L. Buhle, and N. Pappas, *J. Org. Chem.*, **26**, 4658 (1961).
- (13) C. W. Jefford and W. Wojnarowski, *Helv. Chim. Acta*, **53**, 1194 (1970).

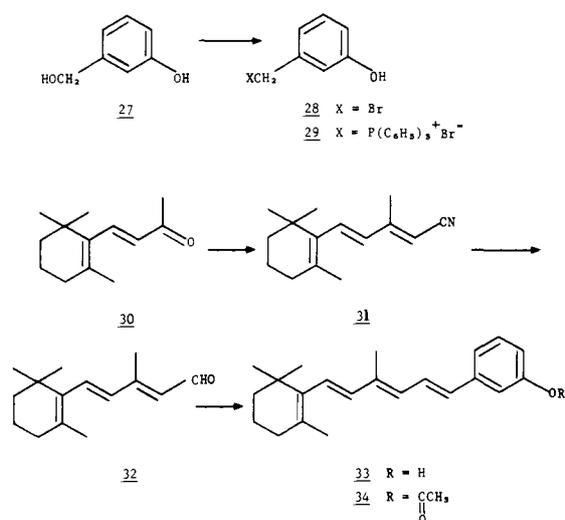
Scheme III



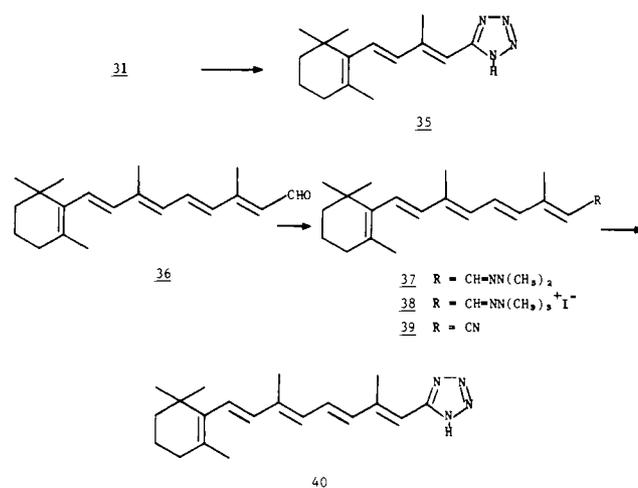
allylic bromides **6** and **7**.¹⁴ Higher reaction temperatures resulted in the formation of more of the rearranged bromide **6**. The bromides, on reaction with triphenylphosphine in benzene, afforded the phosphonium salt **8**, from which the unreacted bromide **6** was removed by washing with benzene. Attempted rearrangement of **6** with triphenylphosphine failed. Wittig reaction of **3** and **8** gave a 47% yield of a 3:2 *8E/8Z* mixture of esters, from which was isolated the crystalline (*all-E*)-ester **9**. Its UV absorption maximum occurred at 369 nm, whereas that for ethyl retinoate is reported to occur at 354 nm.⁸ The hypsochromic shift of the maximum indicates increased conjugative interaction and, therefore, decreased steric interaction between the ring double bond and tetraene chain. Hydrolysis of **9** afforded the acid **10**, which was a very labile compound and polymerized readily. Pharmacological studies were therefore performed on the ester.

The homo- β -cyclocitral precursor (**17**) of homologue **25** was prepared by alkylation, followed by citral imine-type cyclization¹⁵ (Scheme II). Methylation^{16,17} of the dimethylhydrazone (**12**) of 6-methylhept-5-en-2-one (**11**) to the dimethylhydrazone **13** was highly regioselective. The standard oxidative^{17,18} cleavage of **13** to the ethyl ketone **15**¹⁹ was successful but not amenable to large-scale synthesis; therefore, quaternization,¹⁶ followed by mild basic hydrolysis^{16,20} of the trimethylhydrazonium salt **14**, was employed. Reaction of the anion of trimethylsilylacetaldehyde *tert*-butylimine²¹ and **15** and hydrolysis with oxalic acid afforded the dienal **17**²² as a 1:1 *E/Z* mixture. The dienals were converted to the phenyl imines **18**. Preparation of **18** from **15** and the phenylimino ethyl phosphonate reagent $(\text{CH}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{HC}=\text{NC}_6\text{H}_5$ failed. Low-temperature cyclization¹⁵ of **18** with sulfuric acid afforded the α -cyclocitral homologue **19**. Extremely efficient stirring during the addition of **18** proved to be crucial; otherwise, polymeric and aromatic products predominated. Equilibration of the cyclized material with sodium methoxide gave a 4:1 β/α isomer ratio of cyclocitral

Scheme IV



Scheme V



homologues. A model study starting with citral phenylimine afforded, after equilibration, an 85:15 β/α ratio of cyclocitral. The mixture of aldehydes **19** and **20** was reduced with 9-BBN to afford the more readily separable mixture of alcohols, from which allylic alcohol **21** was isolated by chromatography. Conversion to the allylic bromide **22**, and then to the phosphonium salt **23**, and Wittig reaction with trienal **3** afforded the ethyl ester **24**, which on hydrolysis gave the retinoic acid C-5 homologue **25**. The UV maximum of this analogue was at 342 nm, which is not significantly different from that of retinoic acid (343 nm). The ethyl group at the C-5 position does not appear to significantly affect the dihedral angle between the ring and chain.

The 2-(2'-methoxyethoxy)ethyl ester (**26**) of retinoic acid was prepared to obtain an analogue whose polarity would be comparable to that of retinoic acid. Such an analogue, lacking a carboxyl group, might have reduced membrane labilization properties. The ester was prepared using the *N,N'*-carbonyldiimidazole coupling procedure of Staab and Mannschreck²³ (Scheme III). Comparison of chromatographic R_f values indicated that **26** was only slightly more polar than the acid.

The *m*-acetoxyphenyl tetraene **34** was envisioned as an analogue of **1** in which the 1', 2', and 3' carbons of the aromatic ring would replace the *trans*- $\Delta^{13(14)}$ -15-CO₂H

- (14) C. W. Jefford and W. Wojnarowski, *Helv. Chim. Acta*, **55**, 2244 (1972).
- (15) (a) L. Colombi, A. Bosshard, H. Schinz, and C. F. Seidel, *Helv. Chim. Acta*, **34**, 265 (1951); (b) H. B. Henbest, B. L. Shaw, and G. Woods, *J. Chem. Soc.*, 1154 (1952).
- (16) G. Stork and J. Benaim, *J. Am. Chem. Soc.*, **93**, 5938 (1971).
- (17) E. J. Corey and D. Enders, *Tetrahedron Lett.*, **3** (1976).
- (18) R. E. Erickson, P. J. Andrusis, Jr., J. C. Collins, M. L. Lungle, and G. D. Mercer, *J. Org. Chem.*, **34**, 2961 (1969).
- (19) (a) M. Z. Krimer, V. I. Spektor, G. E. Mantyan, and A. A. Shamshurin, *Zh. Org. Khim.*, **10**, 1614 (1974); (b) J. Václav, K. Hejno, K. Sláma, and F. Sorm, U.S. Patent 3 657 291, Apr 18, 1972; (c) K. Mori, B. Stalla-Bourdillon, M. Ohki, M. Matsui, and W. S. Bowers, *Tetrahedron*, **25**, 1667 (1969); (d) W. C. Meuly and P. Gradeff (Rhone-Pouleuc), Belgian Patent 640 555, May 28, 1964; *Chem. Abstr.*, **63**, P6864b (1965); (e) Hoffmann-LaRoche, Belgian Patent 634 738, Jan 10, 1964; *Chem. Abstr.*, **62**, P3941c (1965).
- (20) M. Avaro, J. Levisalles, and H. Rudler, *J. Chem. Soc., Chem. Commun.*, 445 (1969).
- (21) E. J. Corey, D. Enders, and M. G. Bock, *Tetrahedron Lett.*, **7** (1976).
- (22) (a) P. Chabardes and Y. Querou (Rhone-Pouleuc), French Patent 1 554 805, Jan 25, 1969; *Chem. Abstr.*, **72**, P43923g (1970); (b) P. Chabardes (Rhone-Pouleuc), German Patent 1 811 517, July 17, 1969; *Chem. Abstr.*, **71**, P80695j (1969).

- (23) H. A. Staab and A. Mannschreck, *Chem. Ber.*, **95**, 1284 (1962).

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

retinoid	nmol applied	% inhibn of ODC
retinoic acid	1.7	91
9	1.7	46
	17	63
	170	95
25	1.7	66
	17	86
	170	87
26	1.7	70
	17	92
	170	97
34	1.7	3
	17	46
	170	92
40	1.7	3
	17	13
	170	2

moiety of 1. It was prepared by the route outlined in Scheme IV. Knoevenagel condensation of β -ionone (**30**) with cyanoacetic acid,²⁴ followed by decarboxylation,²⁵ afforded a 3.2:1 mixture of (*E*)- and (*Z*)-ionylideneacetonitriles. Horner-Wadsworth-Emmons reaction of **30** with diethyl cyanomethyl phosphonate²⁶ afforded more of the *Z* isomer. Reduction of the mixture with DIBAL²⁷ and chromatography yielded the (*E*)-ionylideneacetaldehyde **32**. The aldehyde underwent Wittig reaction with the ylide derived from *m*-hydroxybenzyltriphenylphosphonium bromide to afford a 3:2 *E/Z* mixture of the *m*-hydroxyphenyl tetraenes. After acetylation, the mixture was separated to give the more polar (*E*)-*m*-acetoxyphenyl tetraene **34** and its less polar *Z* isomer.²⁸

We also undertook the synthesis of the tetrazole **40**, in which the tetrazole group replaces the carboxylic acid moiety of 1. The 1-H proton of tetrazole has a pK_a comparable to that of acetic acid,²⁹ and the tetrazole group has been used as a carboxyl group equivalent in various drugs such as prostaglandins.³⁰ Ionylideneacetonitrile (**31**) was used as a model to investigate the reaction of an azide with a conjugated nitrile (Scheme V). Sodium azide in DMF produced only polymeric material. Tetrazoles have also been prepared by the electrocyclic reaction of aluminum azide with nitriles.³¹ Aluminum azide, generated in situ from sodium azide and aluminum chloride, provided **35** after prolonged refluxing in THF. (*all-E*)-Retinonitrile (**39**) was prepared in high overall yield by conversion of retinal (**36**) to the quaternized retinal dimethylhydrazone **38** followed by base treatment. Treatment of **39** with aluminum azide afforded **40**.

The stereochemistry of these retinoids was established by comparison of their ¹H NMR³² and ¹³C NMR³³ spectra

- (24) N. V. Philips' Gloeilampenfabrieken, British Patent 813 517, May 21, 1959; *Chem. Abstr.*, **53**, P22068g (1959).
 (25) A. Smit, *Recl. Trav. Chim. Pays-Bas*, **80**, 891 (1961).
 (26) W. Stilz and H. Pommer (BASF A. G.), German Patent 1 108 208, Mar 4, 1959; *Chem. Abstr.*, **56**, P11422e (1962).
 (27) G. Cainelli, G. Cardillo, M. Contento, P. Grasselli, and A. U. Ronchi, *Gazz. Chim. Ital.*, **103**, 117 (1973).
 (28) (a) C. Von Planta, U. Schwieter, L. Chopard-dit-Jean, R. Rüegg, M. Kofler, and O. Isler, *Helv. Chim. Acta*, **45**, 548 (1962); (b) M. Vecchi, J. Vesely, and G. Oesterhelt, *J. Chromatogr.*, **83**, 447 (1973); (c) M. J. Pettei, F. G. Pilkiewicz, and K. Nakanishi, *Tetrahedron Lett.*, 2083 (1977).
 (29) H. A. Staab, *Angew. Chem., Int. Ed. Engl.*, **1**, 351 (1962).
 (30) H. J. E. Hess, T. K. Schaaf, and L. J. Czuba (Pfizer Inc.), French Patent 2 283 136, Mar 26, 1976; *Chem. Abstr.*, **86**, P106596q (1977).
 (31) C. Arnold, Jr., and D. N. Thatcher, *J. Org. Chem.*, **34**, 1141 (1969).

Table II. 17-nmol Dose Level Study

retinoid	% inhibn of ODC (mean \pm SE)	no. groups of 4 mice tested ^b
retinoic acid ^a	92 \pm 2	6
9	54 \pm 10	4
25	91 \pm 5	4
26	90 \pm 2	4
34	45 \pm 7	3

^a 1.7 nmol. ^b Seven groups of mice tested in control.

with those of known retinoids (see Experimental Section). The stereochemical assignments were supported by the larger ϵ values for the *all-E* isomers.^{8,28a}

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 established by Boutwell and co-workers.³ 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. Administration of an active retinoid 1 h before TPA treatment substantially depresses the induction of this enzyme.^{3a} Each retinoid was 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). For tumor promotion experiments, which are currently in progress, the ODC activity of those retinoids having activity in the preliminary screen was confirmed in multiple experiments at the 17 nmol dose level (Table II). In the screen, the tetrazole **40** was inactive. The ring-modified retinoids—the norbornene **9** and the homologue **25**—showed good activity. The homologue had an activity profile similar to that of retinoic acid. The polar ester **26** was also very active. The polarity of the ester group was not sufficient to inhibit penetration of this analogue into the epidermal cells. The *m*-acetoxyphenyl tetraene **34** had some activity in this screen. This result is of interest, since it indicates that the polar terminus may be modified substantially without complete loss of activity. Compounds of this type are being investigated and will be reported in the future.

Experimental Section

General Procedures. 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 30 \times 3.9 cm μ -Porasil or μ -Bondapak/C18 column.

- (32) (a) R. Rowan III, A. Warshel, B. D. Sykes, and M. Karplus, *Biochemistry*, **13**, 970 (1974); (b) R. Rowan III and B. D. Sykes, *J. Am. Chem. Soc.*, **97**, 1023 (1975); (c) V. Ramamurthy, G. Tustin, C. C. Yau, and R. S. H. Liu, *Tetrahedron*, **31**, 193 (1975); (d) V. Ramamurthy and R. S. H. Liu, *Tetrahedron*, **31**, 201 (1975); (e) M. Mousseron-Canet and J.-C. Mani, *Bull. Chim. Soc. Fr.*, 3285 (1966); (f) D. J. Patel, *Nature (London)*, **221**, 825 (1969); (g) G. Englert, S. Weber, and M. Klaus, *Helv. Chem. Acta*, **61**, 2697 (1978); (h) W. Vetter, G. Englert, N. Rigassi, and U. Schwieter, in "Carotenoids", O. Isler, H. Gutmann, and V. Solms, Eds., Birkhaeuser-Verlag, Basel, 1971, pp 214-225; (i) R. S. Becker, S. Berger, D. K. Dalling, D. M. Grant, and R. J. Pugmire, *J. Am. Chem. Soc.*, **96**, 7008 (1974).

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. ^1H NMR³² and ^{13}C NMR³³ signals were assigned by comparison with those reported for other retinoids. 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.

2-Norbornenylmethyltriphenylphosphonium Bromide (8). 2-(Hydroxymethyl)norborn-2-ene (5),¹² obtained by reduction of 2-(hydroxymethyl)-2,5-norbornadiene (4),¹² was converted to a mixture of bromides 6 and 7, which was then used without further purification in the synthesis of the phosphonium salt. To a cold (-50°C) solution of 19.3 g (0.15 mol) of 5 in 150 mL of anhydrous Et_2O and 3.1 mL (0.038 mol) of dry pyridine was added 15 g (0.056 mol) of PBr_3 over a period of 10 min. There was an immediate white precipitate. The mixture was stirred at -50°C for 1 h and gradually warmed to -20°C over 1 h. It was then poured into 500 mL of water overlaid with 300 mL of pentane. The aqueous layer was extracted with pentane (2×100 mL). The combined pentane extracts were washed with cold 1 N HCl until the aqueous layer was acidic, then with water, saturated NaHCO_3 , water, and saturated brine, and then dried (MgSO_4). Removal of solvent under reduced pressure left 20 g (70% crude yield) of a light yellow oil: TLC [30% Et_2O /petroleum ether] 1 spot, R_f 0.9 (5 has R_f 0.3 under identical conditions); IR (film) 1600 cm^{-1} (C=C) (no OH absorption); ^1H NMR (CDCl_3) δ 1.05–2.10 (m, 6, CH_2), 2.84 (m, 2, CH), 4.03 (s, 2, CH_2Br), 5.10 [m, 0.2, C=CH₂ exo compound], 5.95 (m, 0.9, C=CH). The spectral data agree with those reported by Jefford and Wojnarowski.¹⁴

Triphenylphosphine (25.3 g, 96 mmol) was added to a solution of the above bromide mixture in 20 mL of benzene. The reaction mixture was stirred at room temperature for 16 h. The white solid that precipitated during the course of the reaction was washed well with benzene and dried in vacuo for 5 h to give 34 g (50% yield) of 8: mp 218–220 $^{\circ}\text{C}$; IR (mull) 1620 (C=C), 1500, 1450, 750 cm^{-1} (Ar); ^1H NMR (CDCl_3) δ 0.8–1.30 (m, 4, C-5, C-6 CH_2), 1.50 (m, 2, C-7 CH_2), 2.35 and 2.75 (m, 2, CH), 4.80 (m, 2, CH_2P), 5.90 (m, 1, C=CH), 7.6–8.1 (m, 15, ArH). Anal. Calcd for $\text{C}_{26}\text{H}_{26}\text{BrP}$: C, 69.48; H, 5.83; Br, 17.78; P, 6.89. Found: C, 69.55; H, 5.87; Br, 18.04; P, 6.82.

Ethyl (E)-9-(2-Norbornenyl)-3,7-dimethylnona-2,4,6,8-tetraenoate (9). A 15-mL portion of a 1.50 M solution of *n*-BuLi (22.5 mmol) in hexane was added dropwise over 5 min to a mixture of 10.2 g (22.6 mmol) of phosphonium salt 8 in 50 mL of dry THF at room temperature. The red mixture was stirred for 30 min. Then a solution of 4.4 g (21 mmol) of trienal 3³⁴ in 20 mL of THF was added over a period of 15 min. The mixture was stirred at 50 – 60°C for 2 h, cooled to room temperature, poured into water, and extracted with Et_2O . The combined extracts were washed with water and saturated brine and dried (Na_2SO_4). The residue, after removal of solvent at reduced pressure, was eluted through about 40 g of Florisil with 10% Et_2O /petroleum ether to afford 3.2 g (47% crude yield) of a yellow semisolid, which was crystallized twice from hexane/ EtOAc to afford 0.84 g (12.4% yield) of a yellow solid: mp 110 – 111°C ; high-performance LC (μ -Porasil, 3% EtOAc /hexane) t_R 5.8 (>98% peak area) and 4.8 min (minor peak). (The major peak was presumed to be the all-trans product, since it has been observed^{28b} that *E* isomers have longer retention

times than do the *Z* isomers under these conditions.) High-performance LC analysis of the mother liquor showed essentially a 9:8 mixture of the *E/Z* isomers: high-performance LC (reverse phase, 260 nm, 20% water/ CH_3CN) t_R 15 (major peak), 2.8 min (trace peaks, $\sim 2\%$ peak area); TLC (10% Et_2O /petroleum ether) R_f 0.59; IR (KBr) 1700 (C=O), 1600 cm^{-1} (C=C); ^1H NMR (CDCl_3) δ 1.10–1.80 (t and m, 9, CH_2CH_3 and 3 CH_3), 2.00 (s, 3, C=CCH₃), 2.36 (d, $J = 0.5$ Hz, 3, $\text{CH}_3\text{C}=\text{CCO}_2$), 2.90 and 3.16 (m, 2, norbornenyl ring CH), 4.18 (q, $J = 7$ Hz, 2, CH_2CH_3), 5.80 (s, 1, C=CHCO), 6.00 (d, $J = 3$ Hz, 1, C-3 C=CH), 6.20 (d, $J = 16$ Hz, 1, C-9 HC=CH), 6.21 (d, $J = 15$ Hz, 1, C-13 HC=CH), 6.23 (d, $J = 11$ Hz, 1, C-11 C=CH), 6.47 (d, $J = 16$ Hz, 1, C-8 HC=CH), 7.00 (dd, $J = 11$ and 15 Hz, 1, C-12 HC=CH); ^{13}C NMR (CDCl_3) 12.9 (C-10 CH_3), 13.8 (C-14 CH_3), 14.4 (C-20), 24.9 and 27.4 (C-5 and C-6), 41.6 and 43.0 (C-1 and C-4), 47.5 (C-7), 59.5 (C-19), 118.9 (C-15), 124.9 (C-8), 130.7 and 130.8 (C-11 and C-12), 132.1 (C-3), 135.3 and 135.5 (C-9 and C-13), 139.3 (C-10), 148.2 (C-2), 152.5 (C-14), 167.0 ppm (C-16). The above assignments were made by comparison of the spectra with those reported for the 7-(*E*) and 7-(*Z*) polyenes of the retinoid series^{32,33} and the 2-norbornene system.³⁵ Carbon-1 to carbon-7 follow standard norbornenyl numbering; carbon-8 to carbon-16 designate the chain beginning from the ring. The finding that the C-8 proton is not shifted upfield to δ 6.0 supports an 8-(*E*) geometrical assignment.^{32c,d} The proton spectrum is also in agreement with that reported for (*all-E*)-1,1,5-tridemethylretinoic acid:^{32h} UV λ_{max} (MeOH) 214 nm (ϵ 1.4×10^3), 267 (ϵ 9.03×10^2), 369 (ϵ 7.28×10^4). MS Calcd for $\text{C}_{26}\text{H}_{26}\text{O}_2$: 298.1933. Found: 298.1917.

7-Methyloct-6-en-3-one N,N-Dimethylhydrazone (13). A 360-mL portion of 1.42 M *n*-BuLi in hexane (0.51 mol) was added at 0°C over a 20-min period to 51.5 g (0.51 mol) of redistilled (*i*-Pr)₂NH in 150 mL of Et_2O under argon. After 3 h at 0°C , the resulting LDA solution was diluted with 600 mL of THF and introduced dropwise to 78.0 g (0.464 mol) of 12 in 1 L of THF at 0°C over a 2.5-h period. The yellow-orange anion solution was stirred at 0°C for a further 40 min, cooled to -78°C , and treated with 85 g (0.6 mol) of MeI in 100 mL of THF over a 10-min period. The reaction was allowed to proceed for 1 h at -78°C and then was warmed to room temperature overnight. On warming, the color faded and a white precipitate gradually separated. The suspension was poured into 2.5 L of water and extracted with CH_2Cl_2 (3×750 mL). The extract was washed once with 750 mL of brine, dried (Na_2SO_4), and evaporated. The orange oil, which contained solid LiI, was used without purification. A sample from a similar reaction employing 5.88 g (35 mmol) of the hydrazone was distilled to give 6.03 g (95% yield) of 13, a pale yellow liquid: bp 40.5 – 43.5°C (0.4 mm); IR (film) 2750, 1620 (C=N), 1160, 1120, 1030, 975 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.09 (t, $J = 7.5$ Hz, 3, C-1 CH_3), 1.62 (s, 3, C-8 CH_3), 1.67 (s, 3, C-9 CH_3), 2.1–2.6 (m, 6, CH_2), 2.38 [s, 6, $\text{N}(\text{CH}_3)_2$], 5.10 (m, 1, C=CH).

7-Methyloct-6-en-one (15)¹⁹ Prepared by Oxidative Cleavage of 13. A phosphate buffer (pH 7, 0.8 M) was prepared by mixing 0.8 M solutions of NaH_2PO_4 and Na_2HPO_4 in the ratio 39:61 (v/v). To a stirred solution of 5.11 g (28 mmol) of 13 in 400 mL of MeOH was added 80 mL of this buffer solution, followed by a solution of 13.3 g (62 mmol) of NaIO_4 in 140 mL of water. The MeOH precipitated much inorganic salt. The oxidation produced an immediate pink color and a mild exotherm. A further white precipitate of NaIO_3 separated within minutes, and the color of the solution rapidly changed to yellow. The suspension was stirred overnight at room temperature, filtered, diluted with 1 L of water, and extracted with CH_2Cl_2 (2×500 mL). The organic layer was washed with 250 mL of brine, dried (Na_2SO_4), and evaporated. Distillation yielded 2.97 g (76%) of pale yellow liquid, bp 30 – 33°C (0.5 mm), containing <5% of 11 as a contaminant, which was detected by NMR and TLC (10% EtOAc /hexane): IR (film) 1715 (C=O), 1125 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.05 (t, $J = 7$ Hz, 3, C-1 CH_3), 1.63 (s, 3, C-8 CH_3), 1.67 (s, 3, C-9 CH_3), 2.1–2.5 (m, 6, CH_2), 5.05 (m, 1, C=CH).

7-Methyloct-6-en-3-one (15) Prepared by Quaternization of 13 and Mild Alkaline Hydrolysis. The crude 13 (0.43 mol)

(33) G. Englert, *Helv. Chim. Acta*, **58**, 2367 (1975).

(34) (a) O. Isler and P. Schudel, *Adv. Org. Chem.*, **4**, 115 (1963); (b) BASF A. G., British Patent 784 628, Oct 9, 1957; *Chem. Abstr.*, **52**, P7346d (1958).

(35) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970).

and 213 g (1.50 mol) of MeI were refluxed in 415 mL of 95% EtOH for 4.25 h, at which time TLC (10% EtOAc/hexane) demonstrated complete quaternization and partial hydrolysis to the ethyl ketone. On cooling, much quaternary salt crystallized out. The solution was decanted and evaporated, and the total residue and solid were dissolved in 2.15 L of 0.1 N NaHCO₃ and 850 mL of benzene. The two-phase system was divided in two and each was stirred vigorously overnight at room temperature. The benzene solution was separated and the lower layer was extracted with 800 mL of benzene. The total extract was washed with 200 mL of brine, dried (Na₂SO₄), and evaporated. The orange-brown liquid (69.0 g) was distilled through a 30-cm Vigreux column. A fraction [3.25 g, bp 84–95 °C (30 mm)] was discarded. The 51.2 g (85%) of **15** [bp 95–97 °C (30 mm)] contained a trace (<5%) of the methyl ketone **11** by ¹H NMR (2.08, s, CH₃C=O).

3-Ethyl-7-methylocta-2,6-dienal (17).²² A LDA solution was prepared at 0 °C from 31.8 g (315 mmol) of (*i*-Pr)₂NH in 100 mL of Et₂O treated with 231 mL of 1.30 M *n*-BuLi in hexane (300 mmol) and diluted with 500 mL of THF. A solution of 51.3 g (300 mmol) of Me₃SiCH₂CH=N-*t*-Bu²¹ in 40 mL of THF was added over a 15-min period. The orange solution was cooled to –78 °C and treated with 39.2 g (280 mmol) of **15** in 30 mL of THF over a 1.5-h period. The solution remained orange after warming to –15 °C over a 3.5-h period. The remaining anion was quenched with 300 mL of water; 50 g of oxalic acid dihydrate was added, and the yellow two-phase system was stirred for 13 h at room temperature. Another 50-g portion of oxalic acid was added and stirring was continued for 2 h. The liquid phases were decanted and separated, and the precipitate (lithium oxalate) and aqueous phase were filtered. The precipitate was washed with 500 mL of ether and the filtrate was used to extract the aqueous solution. The combined organic solutions were washed with 300-mL volumes of brine, saturated NaHCO₃, and again with brine, dried (K₂CO₃, 1 h), and concentrated to give 53.9 g of yellow liquid. The ¹H NMR spectrum demonstrated complete hydrolysis of the imine and that some (Me₃Si)₂O was also present. Distillation (in 3 aliquots) gave 41.8 g (90%) of very pale yellow aldehyde: bp 95–99 °C (3.5 mm); IR (film) 1675 (CHO), 1635, 1205, 1170, 1140, 885 cm⁻¹; ¹H NMR (CDCl₃) δ 1.10 and 1.17 (2 t, *J* = 7.5 Hz, 3, CH₃CH₂), 1.61 (s, 3, C-8 CH₃), 1.69 (s, 3, C-9 CH₃), 2.0–2.8 (m, 6, CH₂), 5.10 (m, 1, C=CH), 5.79 and 5.82 (2 d, *J* = 8 Hz, 1, C-2 C=CH), 9.89 and 9.95 (2 d, *J* = 8 Hz, 1, CHO). The NMR spectrum indicated that the aldehyde was a 1:1 mixture of C-2, C-3 double-bond isomers.

2-Ethyl-6,6-dimethylcyclohexenecarboxaldehydes 19 and 20. A solution of 18.1 g (110 mmol) of **17** in 50 mL of Et₂O was treated with 10.4 g (110 mmol) of aniline. A yellow color developed; the solution warmed and became cloudy after 10–15 min. Water had separated while the solution was standing for 3 h. The Et₂O solution was decanted. Then, over a period of 65 min, it was carefully added (by means of a dropping funnel with a Teflon extension that directed the solution away from the side of the flask) to 250 mL of vigorously stirred concentrated sulfuric acid containing 10 g of ice, which was cooled to –20 to –25 °C. The cooling was continued for 45 min more, and the product was poured carefully onto 1 kg of ice/water. Hexane (3 × 500 mL) extracted virtually all the product, for—according to TLC and ¹H NMR—subsequent Et₂O extraction yielded only the polar products of hydration. The hexane solution was washed with brine (2 × 500 mL, 200 mL), dried (Na₂SO₄, 1 h), and evaporated to give 11.4 g of yellow liquid consisting largely of the α-isomer **19**, trace amounts of the β-isomer **20**, and small amounts of aromatic and enone byproducts. Less efficient stirring during addition of the imine produced more of these byproducts as well as polymer: ¹H NMR (CDCl₃) δ 0.91 (s, 3, C-16 CH₃), 1.00 (s, 3, C-17 CH₃), 0.95 (t, *J* = 7 Hz, 3, CH₃CH₂), 1.70 (t, *J* = 7 Hz, 2, C-3 CH₂), 1.85–2.22 (m, 4, CH₂), 2.43 (d, *J* = 5 Hz, 1, C-6 CH), 5.68 (m, 1, C-4 HC=C), 6.8–7.25 (m, 0.5, ArH impurities), 7.55 (d, *J* = 8 Hz, 0.1, enone impurity), 9.42 (d, *J* = 5 Hz, 1, CHO).

The 11.3 g of product mixture was dissolved in 50 mL of MeOH, treated with 3.09 g (55 mmol) of NaOMe (mild exotherm), and allowed to stand for 24 h. The addition of 5 mL of acetic acid discharged the orange-brown color. The mixture was then concentrated, and the 20 mL of residue was diluted with 100 mL of water and extracted with Et₂O (2 × 100 mL). The organic layer was washed with brine (50 mL), NaHCO₃ (2 × 50 mL), and brine

(2 × 50 mL), dried (MgSO₄), and evaporated to leave 10.2 g of orange liquid. Distillation yielded (a) 1.71 g of a mixture of the α and β isomers [bp 79–83 °C (4.5 mm)] and (b) 4.17 g that contained less of the α isomer [bp 84–85 °C (4.5 mm)]: IR (film) 2750 (CHO), 1720 (C=O α isomer), 1675 C=O β isomer), 1615, 1390, 1370, 1320, 1150, 1135, 850 cm⁻¹; ¹H NMR (CDCl₃) δ 1.12 (t, *J* = 7.5 Hz, 3, CH₃CH₂), 1.23 (s, 6, C-16 and C-17 CH₃), 1.4–1.9 (m, 4, CH₂), 2.1–2.4 (m, 2, C-4 CH₂), 2.47 (q, *J* = 7.5 Hz, 2, CH₃CH₂), 5.7 (m, 0.14, HC=C α isomer), 9.45 (d, *J* = 5 Hz, 0.15, CHO α isomer), 10.08 (s, 0.85, CHO β isomer). The combined yield of aldehydes **19** and **20** was 33%. A large high-boiling fraction [bp 115 °C (3.5 mm)] was also obtained. Further sodium methoxide treatment (room temperature for 24 h) of a sample of the undistilled material showed no change in the α/β isomer ratio after workup. Hence, the product is a 15:85 equilibrium mixture. This material was used without further purification in the next reaction.

1-Ethyl-2-(hydroxymethyl)-3,3-dimethylcyclohex-1-ene (21). A 75-mL portion of 0.5 M 9-BBN solution in THF (37.5 mmol) was added all at once under argon to 5.0 g (30 mmol) of the aldehyde mixture (distillation fraction 2 of the preceding experiment) in 15 mL of THF, with cooling in ice-water. After 5 h at room temperature, the THF was evaporated and the residue was treated with 90 mL of Et₂O and 2.25 g (37.5 mmol) of ethanolamine. The solution warmed and the white aminoethyl borinate complex crystallized out almost immediately. The solution was cooled in the refrigerator overnight and filtered; the solvent was then evaporated. The pale yellow oil was chromatographed by preparative high-performance LC, in two runs using 15% Et₂O/hexane at 0.2 L/min, to yield 2.85 g (56%) of the allylic alcohol **21**, which, on crystallization from hexane, gave waxy needles, mp 41–41.5 °C, and 1.87 g (36%) of material contaminated with the less polar α isomer. A similar reduction and chromatography of the aldehyde fraction 1, which contained more of the β,γ-unsaturated aldehyde **19**, yielded a sample of the pure homoallylic alcohol as a colorless oil. β-Isomer **21**: IR (mull) 3250 (OH), 1390, 1010, 815, 740 cm⁻¹; ¹H NMR (CDCl₃) δ 1.00 (t, *J* = 7 Hz, 3, CH₃CH₂), 1.03 (s, 6, C-16 and C-17 CH₃), 1.25–2.35 (m, 9, 4 CH₂ and OH), 4.13 (s, 2, C-7 CH₂O). MS Calcd for C₁₁H₂₀O: 168.1514. Found: 168.1506. α Isomer: IR (film) 3330 (OH), 1390, 1370, 1075, 1030, 745 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (s, 3, C-16 CH₃), 1.02 (s, 3, C-17 CH₃), 1.0–2.35 [m, 11, (CH₂)₂, CH₂CH₃, and CHCOH], 3.67 (d, *J* = 4 Hz, 2, CH₂O), 5.57 (m, 1, HC=C).

(1-Ethyl-3,3-dimethylcyclohex-1-en-2-yl)methyltriphenylphosphonium Bromide (23). A solution of 276 mg (1.6 mmol) of alcohol **21** in 0.5 mL of hexane and 2 mL of Et₂O containing 1 drop of pyridine at –10 °C under argon was treated, with stirring, with 0.20 g of PBr₃ (0.75 mmol) in 0.35 mL of hexane (20% solution, v/v) over a 15-min period. An immediate white precipitate resulted. After standing at 0 to –5 °C for 1.75 h, the product was treated with 10 mL of brine and extracted with Et₂O (2 × 10 mL). The organic extract was washed successively with brine (10 mL), saturated NaHCO₃ (2 × 10 mL), and brine (3 × 10 mL) and was then dried (MgSO₄) and evaporated. The residual oily bromide **22** was dissolved in 1 mL of CH₂Cl₂ and 0.6 g (2.3 mmol) of triphenylphosphine was added. The reaction mixture was allowed to stand at room temperature for 68 h. Treatment with 25 mL of EtOAc immediately initiated crystallization of the salt. The suspension was cooled to 0 °C overnight and filtered. The product was washed twice with 10 mL of EtOAc and dried at 40 °C (4 mm). A yield of 678 mg (86%) of dense white crystals, mp 210–210.5 °C, was obtained. Crystallization from 11% CHCl₃/EtOAc and drying at 40 °C (under vacuum) afforded the analytical sample: mp 212–213 °C; IR (mull) 1590, 1445, 1120, 760, 740, 705 cm⁻¹; ¹H NMR (CDCl₃) δ 0.71 (t, *J* = 5.5 Hz, 3, CH₃CH₂), 0.82 (s, 6, C-16 and C-17 CH₃), 0.9–2.5 (m, 8, CH₂), 4.24 (d, *J* = 14 Hz, 2, C-7 CH₂), 7.4–7.8 [m, 15, P(C₆H₅)₃]. Anal. Calcd for C₂₉H₃₄BrP: C, 70.58; H, 6.94; Br, 16.19; P, 6.28. Found: C, 70.69; H, 6.97; Br, 16.19; P, 6.10.

Ethyl (E)-3,7-Dimethyl-9-(2-ethyl-6,6-dimethyl-1-cyclohexen-1-yl)nona-2,4,6,8-tetraenoate (24). A mixture of 5.90 g (12 mmol) of the salt **23** (mp 209–209.5 °C after crystallization from 11% CHCl₃/EtOAc) and 2.50 g (12 mmol) of twice-crystallized (cyclohexane) **3** in 2 mL of *t*-BuOH and 10 mL of THF was cooled to –10 °C. A solution of 1.35 g (12 mmol) of KO-*t*-Bu in 12 mL of *t*-BuOH was then added over a 5-min period. The

deep-red solution was warmed to room temperature over a 35-min period and then heated at 55 °C for 16 h. TLC (10% EtOAc/hexane) indicated a single yellow nonpolar product. Antioxidant (*tert*-butylhydroquinone, TBHQ, 100 mg) was added, and the reaction mixture was poured into 100 mL of brine and extracted with 10% Et₂O/hexane (2 × 50 mL). Much of the triphenylphosphine oxide remained as a semisolid tar that was partly soluble in the organic layer. The extract was washed twice with brine, dried (Na₂SO₄), and concentrated. A silica gel precolumn was eluted with 15% EtOAc/hexane, which yielded 2.79 g of viscous orange oil (68% crude yield). After the addition of 100 mg of TBHQ, the product was stored at -5 °C. Preparative high-performance LC (0.8% EtOAc/hexane) gave 1.97 g (48%) of viscous yellow ester **24** as a single isomer to analytical high-performance LC (3% EtOAc/hexane): IR (film) 1695 (C=O), 1600 (C=C), 1580, 1390, 1350, 1240, 1150, 1040, 975, 890, 840 cm⁻¹; ¹H NMR (CDCl₃) δ 1.00 (t, *J* = 8 Hz, 3, CH₃CH₂C), 1.07 (s, 6, C-16 and C-17 CH₃), 1.32 (t, *J* = 6 Hz, 3, CH₃CH₂O), 1.4-1.7 (m, 4, C-2 and C-3 CH₂), 2.02 (s, 3, C-19 CH₃), 1.9-2.15 (m, 4, C-4 and C-18 CH₂), 2.39 (d, *J* = 1 Hz, 3, C-20 CH₃), 4.19 (q, *J* = 7.5 Hz, 2, COOCH₂), 5.78 (s, 1, C-14 C=CH), 6.03-6.40 (m, 4, C-7, C-8, and C-12 HC=CH, C-10 C=CH), 6.94 and 7.06 (dd, *J* = 15 and 12 Hz, 1, C-11 HC=CH); ¹³C NMR (CDCl₃) 13.0 (C-19), 13.5 and 14.0 (C-20, CCH₂CH₃), 14.4 (OCH₂CH₃), 19.6 (C-3), 28.0 (CH₂CH₃), 29.1 (C-16 and C-17), 30.0 (C-4), 34.5 (C-1), 40.1 (C-2), 59.5 (OCH₂), 118.8 (C-14), 128.8, 129.6, and 130.8 (C-7, C-10 and C-11), 135.4 and 135.7 (C-5 and C-12), 136.6 and 137.7 (C-6 and C-8), 139.4 (C-9), 152.4 (C-13), 167.0 ppm (C-15); UV λ_{max} (EtOH) 351 nm (ε 3.37 × 10⁴), 242 (ε 8.6 × 10³). MS Calcd for C₂₃H₃₄O₂: 342.2559. Found: 342.2540.

(*E*)-3,7-Dimethyl-9-(2-ethyl-6,6-dimethyl-1-cyclohexen-1-yl)nona-2,4,6,8-tetraenoic Acid (**25**). To a cooled, degassed, stirred solution of 1.2 g (20 mmol) of KOH pellets in 7.5 mL of EtOH and 2.5 mL of water was added by syringe 2.10 g (6.1 mmol) of the pure ethyl ester **24** in 5 mL of EtOH. The solution was heated to 80 °C (external temperature) over a 30-min period. The orange solution was cooled and acidified with 8 mL of 50% HOAc. The acid separated as a yellow solid. The product was diluted with 30 mL of water and extracted with Et₂O (50 mL). The yellow solution was washed with brine (3 × 15 mL), dried (Na₂SO₄), and concentrated. The crude acid weighed 1.85 g (96%). Crystallization from 3 mL of EtOAc yielded 1.08 g (57%) of bright-yellow needles, mp 170-171 °C. The mother liquor was retained for recovery of more product: high-performance LC (reverse phase, 80% MeCN/H₂O, 1 mL/min, 280 nm) *t*_R 9.4 (97%), 3.3 (0.7%), 1.7 min (2%); IR (mull) 3200-2350 (COOH), 1690 (C=O), 1650 (C=C), 1570, 1265, 1200, 1175, 990, 980 cm⁻¹; ¹H NMR (CDCl₃) δ 0.98 (t, *J* = 8 Hz, 3, CH₂CH₃), 1.05 (s, 6, C-16 and C-17 CH₃), 1.35-1.75 (m, 4, C-2 and C-3 CH₂), 2.01 (s, 3, C-19 CH₃), 1.9-2.15 (m, 4, C-4 and C-18 CH₂), 2.38 (d, *J* = 1 Hz, 3, C-20 CH₃), 5.80 (s, 1, C-14 C=CH), 6.03-6.41 (m, 4, C-7, C-8, and C-12 HC=CH, C-10 C=CH), 7.00 and 7.11 (dd, *J* = 15 and 11 Hz, 1, C-11 HC=CH); ¹³C NMR (CDCl₃) 13.0 (C-19), 13.6 (C-20), 14.1 (C-H₂CH₃), 19.4 (C-3), 28.0 (CH₂CH₃), 29.0 (C-16 and C-17), 29.9 (C-4), 34.3 (C-1), 40.0 (C-2), 117.9 (C-14), 129.2 and 129.5 (C-7 and C-10), 131.8 (C-11), 135.0 and 135.8 (C-5 and C-12), 136.4 and 137.5 (C-6 and C-8), 140.2 (C-9), 155.2 (C-13), 172.8 ppm (C-15); UV λ_{max} (EtOH) 342 nm (ε 4.45 × 10⁴), 244 (ε 4.73 × 10³). MS Calcd for C₂₁H₃₀O₂: 314.2246. Found: 314.2234.

2-(2'-Methoxyethoxy)ethyl Retinoate (**26**). The procedure of Staab and Mannschreck²³ was adapted. To a degassed solution of 3.0 g (10.0 mmol) of retinoic acid and 33 mg of BHA in 40 mL of anhydrous benzene and 6 mL of dry DMF was added 1.76 g (23.6 mmol) of *N,N'*-carbonyldiimidazole. This solution was stirred for 1 h. Then a solution prepared from 0.113 g (4.96 mmol) of sodium in 2.8 mL (23.6 mmol) of 2-(2'-methoxyethoxy)ethanol was added. After 24 h, the reaction mixture was diluted with 20 mL of benzene and washed with two 20-mL portions of water, saturated NaHCO₃, water, and saturated brine. It was then dried (Na₂SO₄) and concentrated at reduced pressure to 3.6 g of a deep yellow oil: TLC (10% EtOAc/benzene) showed a major spot, *R*_f 0.32 (ester), and minor spots, *R*_f 0.21, 0.39 (acid), and 0.79; preparative high-performance LC with 10% EtOAc/benzene afforded 1.89 g (47% yield) of the ester as a viscous yellow oil; analytical high-performance LC (330 nm) in the same solvent system showed two peaks, *t*_R 9.4 (99.5% peak area) and 11.4 min

(0.5% peak area); IR (film) 1710 (C=O), 1605, 1595, 1245, 1150, 970 cm⁻¹; ¹H NMR (CDCl₃) δ 1.05 (s, 6, C-16 and C-17 CH₃), 1.35-1.7 (m, 4, C-2 and C-3 CH₂), 1.72 (s, 3, C-18 CH₃), 1.95-2.1 (m, 2, C-4 CH₂), 2.01 (s, 3, C-19 CH₃), 2.36 (s, 3, C-20 CH₃), 3.40 (s, 3, OCH₂), 3.5-3.85 (m, 6, OCH₂), 4.27 (m, 2, CO₂CH₂), 5.79 (br s, 1, C=CHCO), 6.0-6.4 (m, 4, C-7, C-8, C-10, and C-12 C=CH), 6.98 (dd, *J* = 11 and 12 Hz, 1, C-11 C=CH); ¹³C NMR (CDCl₃) 12.8 (C-19), 13.7 (C-20), 19.3 (C-3), 21.7 (C-18), 29.0 (C-16 and C-17), 33.1 (C-4), 34.2 (C-1), 39.6 (C-2), 58.8 (C-25), 62.7 (C-21), 69.3, 70.4, and 71.9 (C-22, C-23, and C-24), 118.4 (C-14), 128.5 (C-7), 129.7 (C-5 and C-10), 130.9 (C-11), 135.2 (C-12), 137.3 (C-8), 137.7 (C-6), 139.3 (C-9), 152.9 (C-13), 166.6 ppm (C-15); UV λ_{max} (EtOH) 353 nm (ε 2.62 × 10⁴). MS Calcd for C₂₅H₃₈O₄: 401.2930. Found: 401.2953.

m-Hydroxybenzyltriphenylphosphonium Bromide (**29**). A suspension of 23.6 g (87 mmol) of PBr₃ in 20 mL of CH₃CN at -5 to -10 °C under argon was treated with 3.7 g (47 mmol) of pyridine in 5 mL of CH₃CN over 5 min and then with a solution of 24.8 g (200 mmol) of *m*-hydroxybenzyl alcohol in 30 mL of CH₃CN containing 1.2 g (15 mmol) of pyridine over 1.25 h, while maintaining the cooling bath below -5 °C. The lower layer of PBr₃ dissolved. The reaction was stirred overnight at room temperature, the solvent was evaporated, and the product was extracted with CH₂Cl₂ (2 × 50 mL). The extract was eluted through a short silica gel column (300 g) in 5% and then 10% EtOAc/CH₂Cl₂.

The crude *m*-hydroxybenzyl bromide (**28**), a pale yellow, unstable oil, was dissolved in 400 mL of benzene, treated with 55 g (0.21 mol) of triphenylphosphine, and heated at 80 °C overnight. An oil quickly separated on heating and gradually crystallized. The cold suspension was filtered, washed with 1 L of benzene, and dried for 67 h at 140 °C (1 mm) to afford 73.2 g (82% overall yield) of white powder: mp 290.5-291.5 °C; IR (mull) 3100 (OH), 1620, 1595, 1490, 1445, 1305, 1125, 820, 760, 735, 710 cm⁻¹; ¹H NMR (CDCl₃) δ 2.55 (m, 1, OH), 5.00 (d, *J* = 15 Hz, 2, CH₂P), 6.2-7.1 (m, 4, C₆H₄), 7.4-7.8 [m, 15, P(C₆H₅)₃]. Anal. Calcd for C₂₅H₂₂BrOP: C, 66.82; H, 4.94; Br, 17.79; P, 6.89. Found: C, 67.02; H, 5.03; Br, 17.84; P, 7.02.

(*E*)-1-(3-Hydroxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)hexa-1,3,5-triene (**33**). NaH, 50% suspension in mineral oil (1.80 g, 37.5 mmol), was washed with hexane (3 × 5 mL) under argon. Then 20 mL of Me₂SO was introduced and the suspension was heated at 65 °C for 1 h. The cooled, pale-green solution was added to 9.5 g (21 mmol) of **29** in 10 mL of Me₂SO at room temperature and stirred for 15 min to yield a deep-red solution. Next, 2.74 g (12.5 mmol) of **32**, prepared by DIBAL reduction of **31**,^{24,25} in 5 mL of Me₂SO was introduced over 5 min while cooling in ice-water. Stirring was continued for 22 h at room temperature. After the addition of 100 mg of TBHQ, the reaction mixture was poured into 300 mL of water containing 3 mL of HOAc and extracted with ether (2 × 150 mL). The extract was washed with saturated brine (2 × 100 mL), dried (MgSO₄), and concentrated. Triphenylphosphine oxide was partly removed by elution through a short silica gel column (200 g) with 20% EtOAc/hexane. The first 600 mL yielded 5.05 g of an orange oil consisting of two major and one minor component. Preparative high-performance LC of 3.0 g of crude product using 3% EtOAc/hexane as eluant gave (a) the less polar component, 11-(*Z*) isomer, an orange-yellow viscous oil, 717 mg; (b) a mixture of a minor component and the more polar major 11-(*E*) isomer **33**, 903 mg; and (c) the more polar major isomer, 1.927 g. The total yield was 3.55 g (92%). Because **33**, a viscous orange oil, could not be crystallized, it was purified by chromatographing (high-performance LC) twice with 3% EtOAc/hexane to afford 0.66 g of material. 11-(*Z*)-Isomer: IR (film) 3350 (OH), 1600, 1495, 1170, 1060, 985, 815, 715 cm⁻¹; ¹H NMR (CDCl₃) δ 1.04 (s, 6, C-16 and C-17 CH₃), 1.69 (s, 3, C-18 CH₃), 2.00 (s, 3, C-19 CH₃), 1.4-2.3 (m, 6, C-2, C-3, and C-4 CH₂), 6.0-7.25 (m, 9, C-7, C-8, C-10, C-11, and C-12 C=CH and C-2', C-4', C-5', and C-6' C₆H₄); ¹³C NMR 12.4 (C-19), 19.3 (C-3), 21.7 (C-18), 29.0 (C-16 and C-17), 33.0 (C-4), 34.3 (C-1), 39.6 (C-2), 114.0, 115.9, 121.7, 125.9, 126.6, 127.5, 128.9, 129.4, 137.9 and 138.3 (C-6 and C-8), 139.4 (C-9), 155.6 ppm (C-1'); UV λ_{max} (EtOH) 330 nm (ε 2.19 × 10⁴). MS Calcd for C₂₂H₂₈O: 308.2140. Found: 308.2137. 11-(*E*)-Isomer: IR (film) 3320 (OH), 1595, 1495, 1270, 1165, 1035, 980, 885, 795, 705 cm⁻¹; ¹H NMR (CDCl₃) δ 1.06 (s, 6, C-16 and C-17 CH₃), 1.73 (s, 3, C-18 CH₃),

2.02 (s, 3, C-19 CH₃), 1.4–2.3 (m, 6, C-2, C-3, and C-4 CH₂), 2.29 (s, 1, OH), 6.47 (d, $J = 15$ Hz, 1), 5.9–7.3 (m, 8), (C-7, C-8, C-10, C-11, and C-12 C=CH and C-2', C-4', C-5', and C-6' C₆H₄); ¹³C NMR (CDCl₃) 12.6 (C-19), 19.1 (C-3), 21.6 (C-18), 28.8 (C-16 and C-17), 32.9 (C-4), 34.1 (C-1), 39.5 (C-2), 112.7, 114.4, 118.9, 125.7, 126.9, 129.2, 129.6, 129.9, 131.5, 136.5, 137.5, 137.7, 139.5 (C-9), 155.9 ppm (C-1'); UV λ_{\max} (EtOH) 340 nm ($\epsilon 2.82 \times 10^4$). MS Calcd for C₂₂H₂₈O: 308.2140. Found: 308.2122.

(*E*)-1-(3-Acetoxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)hexa-1,3,5-triene (34). A mixture of the phenols was prepared as described above, using the same quantities. The crude unchromatographed product was dissolved in 40 mL of dry Et₂O and treated with 4 mL of acetic anhydride in 5 mL of pyridine at 20 °C. After 5 h, TLC (10% Et₂O/hexane) indicated complete acetylation. The solution was diluted with 40 mL of Et₂O, washed with water (2 × 40 mL), and dried (MgSO₄). After evaporation, the residue was extracted with hexane (2 × 50 mL), filtered, and evaporated to give 6.2 g of a yellow oil. Preparative high-performance LC employing 6% Et₂O/hexane yielded (a) 0.75 g of the less polar 11-(*Z*) isomer as a yellow-orange oil, (b) 2.19 g of unseparated isomers, and (c) 1.26 g of the 11-(*E*) isomer as an orange oil. Total yield was 4.20 g (96%). A subsequent purification of fraction c employed 0.8% EtOAc/hexane. Two crystallizations from degassed EtOAc/hexane, with cooling to -20 °C for 24 h after crystallization was initiated at 0 °C, yielded yellow crystals, mp 72.5–73.5 °C, pure to Porasil and reverse-phase analytical high-performance LC. 11-(*Z*)-Isomer: IR (film) 1765 (C=O), 1605, 1585, 1495, 1220, 1160, 1030, 985, 910, 820, 715 cm⁻¹; ¹H NMR (CDCl₃) δ 1.06 (s, 6, C-16 and C-17 CH₃), 1.49 and 1.64 (2 m, 4, C-2 and C-3 CH₂), 1.74 (s, 3, C-18 CH₃), 2.02 (m, 2, C-4 CH₂), 2.02 (s, 3, C-19 CH₃), 2.31 (s, 3, OCOCH₃), 6.16 [d, $J = 16$ Hz, 1, C-8 (*E*)-HC=CH], 6.27 [d, $J = 16$ Hz, 1, C-7 (*E*)-HC=CH], 6.43 [d, $J = 11$ Hz, 1, C-12 (*Z*)-HC=CH], 6.58 [d, $J = 12$ Hz, 1, C-10 (*E*)-C=CH], 6.64 [dd, $J = 11$ and 12 Hz, 1, C-11 (*Z*)-HC=CH], 6.98 and 7.25 (2 d, $J = 8$ and 8 Hz, 2, 4',6'-H), 7.11 (br s, 1, 2'-H), 7.36 (dd, $J = 8$ and 8 Hz, 1, 5'-H); ¹³C NMR (CDCl₃) 12.4 (C-19), 19.2 (C-3), 21.0 (acetate CH₃), 21.6 (C-18), 28.9 (C-16 and C-17), 32.9 (C-4), 34.2 (C-1), 39.5 (C-2), 119.7 and 122.0 (C-11 and C-2'), 125.5 and 126.5 (C-4' and C-10), 127.1, 127.6, and 128.0 (C-6', C-7, and C-12), 129.0 and 129.4 (C-5 and C-5'), 137.6 (C-8 and C-9), 138.7 and 139.3 (C-1' and C-6), 150.5 (C-3'), and 169.1 ppm (CO₂); UV λ_{\max} (CCl₄) 333 nm ($\epsilon 2.70 \times 10^4$). MS Calcd for C₂₄H₃₀O₂: 350.2246. Found: 350.2229. 11-(*E*)-Isomer: IR (mull) 1755 (C=O), 1575, 1150, 1090, 920, 900, 805, 780, 740, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 1.04 (s, 6, C-16 and C-17 CH₃), 1.47 and 1.62 (2 m, 4, C-2 and C-3 CH₂), 1.73 (s, 3, C-18 CH₃), 2.02 (m, 2, C-4 CH₂), 2.02 (s, 3, C-19 CH₃), 2.31 (s, 3, OCOCH₃), 6.15 [d, $J = 16$ Hz, 1, C-8 (*E*)-HC=CH], 6.19 [d, $J = 12$ Hz, 1, C-10 (*E*)-C=CH], 6.23 [d, $J = 16$ Hz, 1, C-7 (*E*)-HC=CH], 6.52 [d, $J = 16$ Hz, 1, C-12 (*E*)-HC=CH], 6.92 and 7.26 (2 d, $J = 8$ and 8 Hz, 2, 4',6'-H), 7.15 (br s, 1, 2'-H), 7.15 [dd, $J = 12$ and 16 Hz, 1, C-11 (*E*)-HC=CH], 7.30 (dd, $J = 8$ and 8 Hz, 1, 5'-H); ¹³C NMR (CDCl₃) 12.7 (C-19), 19.2 (C-3), 21.0 (acetate CH₃), 21.7 (C-18), 28.9 (C-16 and C-17), 33.0 (C-4), 34.2 (C-1), 39.6 (C-2), 118.8 and 120.1 (C-11 and C-2'), 123.9, 126.5, and 127.4 (C-4', C-7, and C-6'), 129.4, 129.4, 129.7, and 130.7 (C-5, C-10, C-12, and C-5'), 137.2 and 137.4 (C-8 and C-9), 137.5 and 139.6 (C-1' and C-6), 151.0 (C-3'), and 169.3 ppm (CO₂); UV λ_{\max} (CCl₄) 348 nm ($\epsilon 3.39 \times 10^4$). MS Calcd for C₂₄H₃₀O₂: 350.2246. Found: 350.2247.

To verify the stereochemical assignments of the 11-(*E*) and 11-(*Z*) isomers, the 11-(*E*) isomer was prepared by a different route in which the stereochemistry at the 11 position was preselected by using (*E*)-3-hydroxycinnamaldehyde as the starting material. Formation of the 9,10 double bond would result in a mixture of isomers. A suspension of 3.8 g (7.3 mmol) of β -ionyltriphenylphosphonium bromide in 6 mL of THF and 2 mL of *t*-BuOH was cooled in ice-water under argon and treated with a solution of 0.78 g (7.0 mmol) of KO-*t*-Bu in 7 mL of *t*-BuOH (2-mL rinse). This deep-red ylide solution was added within 5 min to the yellow-orange suspension formed by treating a solution of 0.98 g (6.6 mmol) of (*E*)-3-hydroxycinnamaldehyde⁸⁶ in 3 mL of THF and 2 mL of *t*-BuOH at 0 °C with a solution of 0.75 g (6.6 mmol)

of KO-*t*-Bu in 8 mL of *t*-BuOH (2-mL rinse). The reaction mixture was allowed to warm to room temperature, stirred for 64 h, then treated with 2 mL of acetic anhydride, and stirred for 1.75 h. The color faded to a yellow-brown. TLC (10% EtOAc/hexane) indicated complete acetylation and one less polar spot. The reaction mixture was poured into 120 mL of water containing 2 mL of HOAc and extracted with 10% EtOAc/hexane (100 and 50 mL). The extract was washed with brine (3 × 50 mL), dried (Na₂SO₄), and concentrated at reduced pressure to give 1.13 g (49% yield) of a yellow gum after high-performance LC (1% EtOAc/hexane). High-performance LC (2% Et₂O/hexane with multiple recyclings) separated the 9-(*E*) and 9-(*Z*) isomers. These isomers were much more difficult to separate than the 11-(*E*) and 11-(*Z*) isomers. In addition, the desired 9-(*E*) isomer was the minor product. The more polar isomer (95 mg, 4% yield) was isolated as a yellow gum. This isomer was spectrally identical (IR, ¹H NMR, ¹³C NMR, UV) with the compound classified as the 11-(*E*) isomer in the preceding synthesis. The less polar 9-(*Z*) isomer (204 mg, 9% yield) was isolated as a pale yellow gum: IR (film) 1760 (C=O), 1600, 1585, 1485, 1205, 1145, 1015, 965, 915, 895, 795, 770, 690 cm⁻¹; ¹H NMR (CDCl₃) δ (s, 6, C-16 and C-17 CH₃), 1.50 and 1.66 (2 m, 4, C-2 and C-3 CH₂), 1.78 (s, 3, C-18 CH₃), 2.02 (s, 3, C-19 CH₃), 2.07 (t, $J = 6.5$ Hz, 2, C-4 CH₂), 2.32 (s, 3, OCOCH₃), 6.11 [d, $J = 11.5$ Hz, 1, C-10 (*Z*)-C=CH], 6.24 [d, $J = 16$ Hz, 1, C-7 (*E*)-HC=CH], 6.47 [d, $J = 15.5$ Hz, 1, C-12 (*E*)-HC=CH], 6.71 [d, $J = 16$ Hz, 1, C-8 (*E*)-HC=CH], 6.93 and 7.27 (2 d, $J = 8$ and 8 Hz, 2, 4',6'-H), 7.13 (br s, 1, 2'-H), 7.23 [dd, $J = 15.5$ and 11.5 Hz, 1, C-11 (*E*)-HC=CH], 7.31 (dd, $J = 8$ and 8 Hz, 1, 5'-H); ¹³C NMR (CDCl₃) 19.2 (C-19), 20.7 (C-3), 21.0 (acetate CH₃), 21.8 (C-18), 28.9 (C-16 and C-17), 32.9 (C-4), 34.2 (C-1), 39.4 (C-2), 118.9 and 120.1 (C-11 and C-2'), 123.8 and 125.3 (C-4' and C-6'), 128.3 (C-7), 129.1, 129.3, 129.4, and 129.8 (C-5, C-10, C-12, and C-5'), 130.1 (C-8), 135.8 (C-9), 138.1 and 139.6 (C-6 and C-1'), 151.0 (C-3'), and 169.2 ppm (CO₂); UV λ_{\max} (CCl₄) 335.5 (3.0 × 10⁴). MS Calcd for C₂₄H₃₀O₂: 350.2246. Found: 350.2281.

Since 100-MHz ¹H NMR did not adequately resolve the aromatic and vinylic proton signals to permit an unambiguous assignment, 360-MHz ¹H NMR was employed. The only coupling constants for signals below δ 6.9 in the proton spectrum of the 11-(*Z*) isomer were either 8 Hz or less than 2 Hz, which would correspond to an aromatic ortho coupling ($J = 8$ Hz) and a meta, para, or an allylic coupling ($J \leq 3$ Hz). Hence, the aromatic and olefinic regions were completely separated. The number of ortho couplings observed determined the assignments of the protons at positions 2' and 5'. The chemical shifts of the protons ortho and para to the acetoxy and to the vinyl groups are similar, and the protons at the 4' and 6' positions are expected to possess similar meta couplings. Therefore, these signals were not completely assigned, although allylic-type coupling between the 6' proton and the C-12 proton may explain the 1–2 Hz coupling observed in the doublet at δ 6.98. The two doublets at δ 6.16 and 6.27 ($J = 16$ Hz) are coupled and must be from the (*E*)-7,8 double bond. The broadened δ 6.27 doublet was assigned to the C-7 proton. The doublet of doublets was assigned to the C-11 proton. It was coupled to two doublets at δ 6.58 ($J = 12$ Hz) and 6.43 ($J = 11$ Hz) and was assigned *Z* stereochemistry. The signal at δ 6.58 was assigned to the C-10 proton, since it showed broadening caused by allylic coupling to the C-19 CH₃. The sharp doublet at δ 6.43 was assigned to the C-12 proton on a *Z* double bond. Further information on the configuration at the 9,10 position was made by comparison with the retinoids of known configuration.

The aromatic region of the 11-(*E*) isomer was very similar to that of the 11-(*Z*) and, so, was similarly assigned. The C-11 proton doublet of doublets at δ 7.15 showed couplings at 12 and 16 Hz [(*E*)-HC=CH] and was coupled to the C-12 proton doublet at δ 6.52 ($J = 16$ Hz). The C-7, C-8, and C-10 protons were superimposed and found to be two coupled doublets ($J = 16$ Hz) indicative of a 7,8-(*E*) double bond and a broadened doublet ($J = 12$ Hz) caused by coupling of the C-10 proton with the C-19 CH₃.

The aromatic signals of the 9-(*Z*) isomer were very similar to those of the 11-(*E*) isomer, which suggests that the 11,12 double bond in both compounds has the same configuration. The C-11 proton signal pattern centered at δ 7.23 was indicative of an 11,12-(*E*) double bond. The C-7, C-8 proton doublets ($J = 16$

Hz) indicated 7,8-(*E*) stereochemistry.

Comparison of the ^1H NMR spectra of these three isomers with those of retinoids with various terminal groups^{39e,f,h,i} indicated that the 9-(*Z*) isomer possesses the characteristic large downfield shift of the C-8 proton. In contrast, the 11-(*Z*) isomer had a large downfield shift for the C-10 proton and a large upfield shift for the C-11 proton. The peak heights of the C-19 CH_3 singlets were greater for the 11-(*E*) and 11-(*Z*) isomers than for the 9-(*Z*) isomer. This decrease would be expected from cis-allylic coupling with the C-10 proton. The C-4 methylene proton signals were superimposable in the 11-(*E*) and 11-(*Z*) isomers and not in the 9-(*Z*) isomer. In the latter isomer, the C-18 CH_3 signal was shifted slightly downfield, which is characteristic of the 9,10-(*Z*) configuration. The aromatic terminal group may also have contributed to these shifts.

To assist in the interpretation of the ^{13}C NMR spectra, (*E*- and (*Z*)-(3'-acetoxyphenyl)-1-propene were prepared. Since the shift differences of the aromatic signals in the models and the aryltetraenes were substantial, assignment of these signals was not conclusive. More accurate assignments could be made on comparison of the spectra of the three isomers.^{32a,i,33} The signals at 137.4 and 137.2 ppm assigned to C-8 and C-9 of the 11-(*E*) isomer were shifted to 130.1 and 135.8 ppm, respectively, in the 9-(*Z*) isomer. The C-7 signal in the 123.9 to 127.4 ppm range was shifted downfield to 128 ppm. These shifts would be expected on changing the stereochemistry at the 9,10 double bond. The C-10 signal of the 11-(*E*) isomer in the 129.4 to 130.7 ppm range was shifted to 126.5 ppm or less in the 11-(*Z*) isomer, as would be expected on changing the configuration at the 11,12 double bond from *E* to *Z*.

As observed for the (*all-E*)-retinoids, the 11-(*E*) isomer had the highest absorption maximum and the largest extinction coefficient.^{8,26a} The meta-substituted aryl group did not introduce any additional steric constraints to negate this interpretation.

(*E*)-5-[2-Methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-buta-1,3-dien-1-yl]tetrazole (35). A mixture of 9-(*Z*)- and 9-(*E*)-ionylideneacetonitriles (1:3 ratio) was prepared as described.^{24,25} The mixture was used without separation. To a stirred suspension of 75 g (1.15 mol) of NaN_3 in 750 mL of THF, under a rapid stream of argon, was added 53.5 g (0.4 mol) of powdered AlCl_3 in 3-g aliquots over a 1.5-h period (vigorous exotherm). The reagent was refluxed for 30 min and cooled. Then 39 g (0.16 mol) of crude nitrile mixture was added all at once in 75 mL of THF. Refluxing was resumed for 10 days. The cooled, pale-brown solution contained a precipitate of NaCl . The total reaction mixture was poured into 0.8 L of stirred 3 N HCl in ice/water. The flask residue was mixed with the acidic solution until all solid had dissolved. The solution was handled carefully under a hood because of the HN_3 liberated. An organic phase separated and was extracted with EtOAc (2 \times 1 L) to give an orange solution. The organic layer was washed with brine (3 \times 1 L), dried (Na_2SO_4 , overnight), and concentrated. The aqueous layer was discarded after neutralization with 2 N NaOH with ice cooling. The organic concentrate (53.5 g) was extracted with 1 L of hexane. A fawn solid remained. The hexane extract yielded 26.9 g of brown oil consisting of unreacted nitriles and some tetrazole 35 (TLC, 10% EtOAc /hexane). The solid crude tetrazole was recrystallized three times from 60 to 80 mL of EtOAc to give 12.1 g [39% yield based on 9-(*E*)-nitrile] of large white needles: mp 154–156.5 $^\circ\text{C}$; IR (mull) 3070, 3000–2300, 2700, 2600 (NH), 1625 (C=C, C=N), 1550 (C=N), 1295, 1280, 1225, 1125, 1100, 1070, 980, 935, 880, 850, 820, 725 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.07 (s, 6, C-16 and C-17 CH_3), 1.45–1.6 (m, 4, C-2 and C-3 CH_2), 1.73 (s, 3, C-18 CH_3), 1.9–2.1 (m, 2, C-4 CH_2), 2.48 (s, 3, C-19 CH_3), 6.24 (d, $J = 16$ Hz, 1, C-8 $\text{HC}=\text{CH}$), 6.49 (s, 1, C-10 $\text{C}=\text{CH}$), 6.57 (d, $J = 16$ Hz, 1, C-7 $\text{HC}=\text{CH}$); ^{13}C NMR ($\text{Me}_2\text{SO}-d_6/\text{CDCl}_3$) 14.7 (C-19), 19.1 (C-3), 21.6 (C-18), 28.9 (C-16 and C-17), 32.9 (C-4), 34.1 (C-1), 39.4 (C-2), 109.5 (C-10), 130.5 (C-5), 131.9 and 136.0 (C-7 and C-8), 146.0 (C-11), and 153.9 ppm (C-9); UV λ_{max} (EtOH) 292 nm (ϵ 1.87 \times 10⁴). MS Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_4$: 258.1844. Found: 258.1831.

(*E*)-Retinonitrile (39)³⁷ from (*E*)-Retinal (36). A solution

of 3.1 g (11 mmol) of (*E*)-retinal and 10 g (0.165 mol) of 1,1-dimethylhydrazine in 20 mL of benzene was allowed to stand for 15 h and then was evaporated at atmospheric pressure. The evaporation with 10 g of the reagent in 20 mL of benzene was repeated, and the residual gum was heated at 70 to 80 $^\circ\text{C}$ under reduced pressure for 1.5 h. The product was gradient eluted through a 3 \times 35 cm silica gel column using 300-mL volumes of 2, 4, 6, 8, 10, and 15% EtOAc /hexane. Elution with 6 to 8% EtOAc and concentration yielded 3.65 g (100%) of dimethylhydrazine 37 as orange-yellow needles, pure to TLC (10% EtOAc /hexane): IR (mull) 1560, 1525 (C=N, C=C), 1265, 1125, 1040, 1000, 970, 955, 890, 825, 810 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.04 (s, 6, C-16 and C-17 CH_3), 1.4–1.6 (m, 4, C-2 and C-3 CH_2), 1.71 (s, 3, C-18 CH_3), 1.9 (m, 2, C-4 CH_2), 1.97 (s, 6, C-19 and C-20 CH_3), 2.94 [s, 6, (CH_3)₂N], 5.9–6.7 (m, 5, C-7, C-8, and C-12 $\text{HC}=\text{CH}$, C-10 and C-14 $\text{C}=\text{CH}$), 7.1–7.35 (m, 1, C-11 $\text{C}=\text{CH}$); MS 326 (M^+), 311 ($\text{M}^+ - \text{CH}_3$).

A solution of 3.55 g (10.9 mmol) of 37 and 9 g of MeI in 28 mL of EtOH was heated at reflux for 2 h. The very dark solution was cooled and dark green crystals of the quaternary salt 38 separated. The supernatant solution was decanted and concentrated to afford more solid: IR (mull) 1585, 1545 (C=N, C=C), 1315, 1235, 1205, 1175, 960, 955, 885, 820 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.04 (s, 6, C-16 and C-17 CH_3), 1.4–1.6 (m, 4, C-2 and C-3 CH_2), 1.71 (s, 3, C-18 CH_3), 1.9–2.1 (m, 2, C-4 CH_2), 2.03 (s, 3, C-19 CH_3), 2.28 (s, 3, C-20 CH_3), 3.57 [s, 9, (CH_3)₃ N^+], 6.05–7.1 (m, 6, C-7, C-8, C-11, and C-12 $\text{HC}=\text{CH}$, C-10 and C-14 $\text{C}=\text{CH}$), 9.02 (d, $J = 10$ Hz, 1, C-15 $\text{HC}=\text{N}-\text{N}$).

The quaternary salt was treated with base in three batches. The crystalline salt (less 0.5 g) was treated with 75 mL of degassed 2 N KOH in 67% MeOH /water with stirring overnight. The resultant yellow milky suspension was diluted with 225 mL of water, acidified with HOAc , and extracted with an equal volume of Et_2O . No solid remained. The yellow organic extract was combined with the crude extracts from similar reactions on 0.5 g of crystalline salt and the solid, washed twice with water, dried (MgSO_4), and evaporated to give 2.86 g of brown oil. TLC (10% EtOAc /hexane) demonstrated that the oil contained one major product, nitrile 39, and a trace of 36. The crude nitrile was applied to a 3 \times 35 cm silica gel column and eluted with 300 mL of 1.5% EtOAc /hexane, followed by 200 mL each of 2, 2.5, and 3% EtOAc /hexane. Pure (*E*)-retinonitrile (2.6 g, 93% overall yield for three steps) eluted as an orange liquid: IR (film) 2200 (C=N), 1580 (1560 sh) (C=C), 1450, 1400, 1370, 1355, 1280, 1210, 1175, 1130, 970, 800 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.05 (s, 6, C-16 and C-17 CH_3), 1.2–1.6 (m, 4, C-2 and C-3 CH_2), 1.72 (s, 3, C-18 CH_3), 1.9–2.1 (m, 2, C-4 CH_2), 2.01 (s, 3, C-19 CH_3), 2.20 (s, 3, C-20 CH_3), 5.16 (s, 1, C-14 $\text{C}=\text{CH}$), 5.9–6.4 (m, 4, C-7 and C-8 $\text{HC}=\text{CH}$, C-10 and C-12 $\text{C}=\text{CH}$), 6.97 (dd, $J = 14.5$ and 11 Hz, 1, C-11 $\text{HC}=\text{CH}$); UV λ_{max} (EtOH) 355 nm (ϵ 3.40 \times 10⁴), 239 (5.2 \times 10³); MS 281 (M^+), 266 ($\text{M}^+ - \text{CH}_3$).

(*E*)-5-[2,6-Dimethyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)octa-1,3,5,7-tetraen-1-yl]tetrazole (40). To a suspension of 10.4 g (0.16 mol) of NaN_3 in 60 mL of anhydrous THF, cooled in ice/water, was added under argon 5.4 g (0.040 mol) of AlCl_3 in about 10 portions (exotherm). The mixture was heated at reflux for 30 min, then cooled, and 2.6 g (9.2 mmol) of 45 in 30 mL of THF was introduced by syringe. The yellow suspension was heated at reflux for 10 days. The solution, which remained yellow, was poured into 200 mL of 3 N HCl in ice/water, and the flask was rinsed with the acid under a hood. The product was extracted with EtOAc (2 \times 150 mL), washed with brine (3 \times 100 mL), dried (Na_2SO_4), and concentrated. The 3.4 g of yellow, partly solid product was chromatographed on a 3 \times 30 cm silica gel column with 300-mL volumes of 10, 20, 40, 60, and 80% EtOAc /hexane. Unreacted 39 (1.176 g) rapidly eluted as an orange oil, followed by 2.37 g of very polar crude tetrazole as a yellow solid. Crystallization from 7 mL of EtOAc and 6 mL of hexane yielded 1.241 g (41% yield) of pure 40, mp 176–176.5 $^\circ\text{C}$. If recovered nitrile is considered, the yield rises to 76%: high-performance LC (reverse phase, 280 nm, 20% water/ CH_3CN) showed two peaks, t_R 2.3 (3.5% peak area) and 3.5 min (96.5% peak area); IR (mull) 3120, 2740, 1630 (C=N, C=C), 1595, 1550, 1120, 1060, 970, 900, 835, 735 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.07 (s, 6, C-16 and C-17 CH_3), 1.4–1.8 (m, 4, C-2 and C-3 CH_2), 1.74 (s, 3, C-18 CH_3), 1.95–2.15 (m, 2, C-4 CH_2), 2.04 (s, 3, C-19 CH_3), 2.51 (s, 3, C-20 CH_3),

(37) P. H. VanLeeuwen, J. R. Roborgh, and P. G. S. Wesselman, *Int. Z. Vitaminforsch.*, **38**, 138 (1968); *Chem. Abstr.*, **69**, 74852a (1968).

6.05–6.45 (m, 5, C-7, C-8, and C-12 HC=CH, C-10 and C-14 C=CH), 7.01 (dd, $J = 15$ and 11 Hz, 1, C-11 HC=CH), 13.5 (very broad s, 1, NH); ^{13}C NMR (CDCl_3) 12.9 (C-19), 15.4 (C-20), 19.3 (C-3), 21.7 (C-18), 29.0 (C-16 and C-17), 33.2 (C-4), 34.3 (C-1), 39.8 (C-2), 109.0 (C-14), 128.7, 129.5, 130.0, and 130.5 (C-5, C-7, C-10, and C-11), 134.7 (C-12), 137.3, 137.8, and 139.5 (C-6, C-8, and C-9), 147.9 and 154.3 ppm (C-13 and C-15); UV λ_{max} (EtOH) 341 nm ($\epsilon = 5.48 \times 10^4$). MS Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_4$: 324.2314. Found: 324.2312.

The *all-E* configuration was assigned by ^1H and ^{13}C NMR comparison with the retinoic acid isomers. The proton chemical shifts of H-12 and H-8 ($\delta < 6.4$) are not in agreement with those of the 13-(*Z*) and 9-(*Z*) acids, respectively. The chemical shift (δ 2.51) of the singlet due to the methyl on C-13 is indicative of the 13-(*E*) configuration, and the 11-(*E*) geometry is apparent from the coupling constants (15 and 11 Hz) of H-11.^{32b} The ^{13}C NMR spectrum provides further support for a 9-(*E*) assignment, since C-8 falls in the range 137.3–139.5 ppm, and the C-9 methyl (C-19) shift (12.9 ppm) is in exact agreement with that of (*all-E*)-retinoic acid and not that of the 9-(*Z*) acid (20.5 ppm).

ODC Assay. The ODC assay is rapid, reliable, and inexpensive. Female Charles River CD-1 mice were obtained from Charles River Breeding Laboratories, Wilmington, Mass., and were used when 7 to 9 weeks old. The dorsal hair of the mice was shaved 1 to 2 days before testing, and only mice showing no hair regrowth were used. A single dose of TPA (10.5 μg , 17 nmol) in 0.2 mL of acetone was applied topically. The synthetic retinoid at one of three dose levels (1.7, 17, and 170 mmol), dissolved in 0.2 mL of acetone, was applied 1 h before the TPA treatment. The mice were killed by cervical dislocation 5 h after TPA treatment.

The epidermis was obtained essentially as described by Raineri et al.³⁸ To obtain sufficient material, we pooled the dorsal skins from the five mice in each treatment group. The depilatory agent Nudit (Helena Rubinstein, N.Y.) was applied to the shaved area of the skin; after 5 min, it was washed off thoroughly with cold tap water. Then the skin was excised and plunged immediately into ice-cold water; it then was placed in a 55 °C water bath for 30 s and reimmersed in ice-cold water for at least another 30 s. The skin was placed epidermis side up on a cold plate, and the epidermis was scraped off with a razor blade. The pooled epi-

dermal sheets were homogenized (Polytron PT-10 homogenizer) at 0 to 4 °C for 15–20 s in 50 mM sodium phosphate buffer containing 0.1 mM pyridoxal phosphate and 0.1 mM EDTA. The supernatant fraction remaining after centrifugation of the homogenate at 30000g for 30 min at 0 °C was used for the enzyme assay.

Enzyme activity was determined according to the procedure of O'Brien et al.,³⁹ i.e., by measuring the release of $^{14}\text{CO}_2$ from DL-[1- ^{14}C]ornithine (58 mCi/mmol) after incubation with the 30000g supernatant. The incubations were carried out in 25-mL Erlenmeyer flasks equipped with a rubber stopper–polyethylene center well assembly (Kontes Glass Co., Vineland, N.J.) containing 0.2 mL of ethanolamine/2-methoxyethanol (2:1, v/v). The incubation mixtures consisted of a final volume of 2.0 mL, containing 0.4 μmol of pyridoxal phosphate, 1.0 μmol of dithiothreitol, 0.2 μmol of L-ornithine, 100 μmol of sodium phosphate (pH 7.2), 0.5 mL of the 30000g supernatant, containing 0.5–1.0 mg of protein, and approximately 0.5 μCi of DL-[1- ^{14}C]ornithine (58 mCi/mmol). Incubations routinely were carried out at 37 °C for 30 to 60 min. The reaction was stopped by the addition of 1.0 mL of 2 M citric acid, and incubation was then continued for an additional 30 min to ensure complete absorption of $^{14}\text{CO}_2$. We measured radioactivity using a toluene-based scintillant (4 g of PPO and 50 mg of POPOP/L of toluene) in a Beckman LS-250 liquid scintillation counter. Enzyme activity was determined in triplicate and expressed as nmol of CO_2 in 30 min per mg of protein. Enzyme activity was linear for the protein concentration used. The protein concentrations of the epidermal extracts were determined by the Lowry procedure, using bovine serum albumin as the standard.

Acknowledgment. The support of the synthetic portion of this work by Contract N01-CP-7-5931 from the Lung Cancer Branch, National Cancer Institute, is gratefully acknowledged. We also thank Dr. Michael B. Sporn, NCI, for his advice and encouragement and BASF-AG, Germany, for a generous supply of ethyl β -formylcrotonate. We thank Lewis W. Cary for running the 100-MHz NMR spectra and Dr. David Thomas for conducting the mass spectral analysis.

(38) R. Raineri, R. C. Simsiman, and R. K. Boutwell, *Cancer Res.*, **33**, 134 (1973).

(39) T. G. O'Brien, R. C. Simsiman, and R. K. Boutwell, *Cancer Res.*, **35**, 1662 (1975).

Evaluation of Rotenone and Related Compounds as Antagonists of Slow-Reacting Substance of Anaphylaxis

Richard J. Ashack, Leslie P. McCarty, Rebecca S. Malek, Frank R. Goodman, and Norton P. Peet*

Pharmaceutical Research and Development, The Dow Chemical Company, Indianapolis, Indiana 46268.
Received September 17, 1979

Rotenone (1), dihydrorotenone (2), isorotenone (3), mutarotenone (4), and deguelin (12) were found to be potent antagonists of slow-reacting substance of anaphylaxis (SRS-A) *in vitro*. However, these compounds were also shown to inhibit histamine, serotonin, and acetylcholine at only ten times their IC_{50} concentrations for SRS-A antagonism. Rotenone (1) and several related compounds were also evaluated in an *in vivo* guinea pig anaphylaxis model. Several of these compounds and FPL 55712 (I) were effective in prolonging collapse times of animals which received an aerosol challenge of an antigen to which they had been sensitized.

Rotenone (1) is an abundant natural product, occurring in the roots of tropical plants belonging to the Leguminosae family. These natural sources have supplied the rotenone which has been and still is widely used as a fish and insect poison. Rotenone is a useful insecticide, effective against mosquitoes and mosquito larvae, and is nonpersistent in the environment.

Rotenone was first isolated in 1895.¹ Its structure, however, was not elucidated until 1933,² which is not

surprising in view of the structural complexity (pentacyclic; three asymmetric centers). Since then, partial and total syntheses of 1 have been reported.³

Pharmacology, which has been performed with rotenone, includes several studies dealing with its effects on various muscle preparations. Rotenone, at a concentration of 0.1 $\mu\text{g}/\text{mL}$, has been shown to inhibit the contractions of isolated guinea pig atria.⁴ Another related study showed

(1) E. Geoffrey, *Ann. Inst. Colon. Marseille*, **2**, 1 (1895).

(2) F. B. LaForge, H. L. Haller, and L. E. Smith, *Chem. Rev.*, **12**, 181 (1933).

(3) T. J. Haley, *J. Environ. Pathol. Toxicol.*, **1**, 315 (1978).