in atrial rate, the preparation was washed, allowing to reequilibrate, and a second isoproterenol dose–response curve was obtained. Preliminary experiments revealed that the initial isoproterenol dose–response curve was displaced to the left relative to subsequent curves. The second curve was used as a control. After the preparation was washed and was allowed to reequilibrate, 1 μg of (±)-propranolol and 10 μg of **5a–j** or **6a–e** were individually added to the bath and, after 0.25 h, another isoproterenol dose–response curve was obtained. The extent to which this curve was displaced to the right of the control curve was taken as a measure of β_1-receptor antagonist activity. In all cases, curves obtained after addition of test compounds were parallel to and achieved the same maximum value as control curves.

Isolated Tracheal Strips. The isolated guinea pig tracheal strip was used for evaluation of β_2-receptor blocking activity.[9,10] Carbachol (10^{-5} mol) was added to the tissue bath to produce maximal contraction of tracheal smooth muscle 0.25 h prior to addition of the first aliquot of isoproterenol. The effect of carbachol was shown to persist for more than 1 h. Cumulative dose–response curves for isoproterenol, in the presence and absence of 1 μg of (±)-propranolol or 10 μg of compounds **5a–j** or **6a–e** were determined in a manner analagous to that described for isolated atria. In this case, the degree to which the antagonist blocked isoproterenol-induced relaxation of the tracheal smooth muscle was taken as a measure of β_2-receptor antagonist activity. In all cases, curves obtained after addition of test compounds were parallel to and achieved the same maximum value as control curves.

Results were plotted using linear regression (log dose vs. probit of percent of response) and the EC_{50} was determined from these plots.

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Retinoic Acid Analogues with Ring Modifications. Synthesis and Pharmacological Activity

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Analogues of retinoic acid that have their major modifications in the 5,6 double bond and 4-methylene group regions of the β-cyclogeranylidene ring have been synthesized as potential agents for the treatment and prevention of epithelial cancer. These modifications were intended to reduce retinoid toxicity by lowering the effective treatment dose because the major metabolic deactivation pathway would be inhibited. Ethyl (*E*)-3,7-dimethyl-9-(*exo*-2-bicyclo[2.2.1]-heptyl)-2,4,6,8-nonatetraenoate (**7**), ethyl (*E*)-3,7-dimethyl-9-(2,2,6-trimethylbicyclo[4.1.0]hept-1-yl)-2,4,6,8-nonatetraenoate (**18**), (*E*)-1-(4-carbethoxyphenyl)-2-methyl-4-(2,2,6-trimethylbicyclo[4.1.0]hept-1-yl)-1,3-butadiene (**28**), (*E*)-retinoic acid-*4,4,18,18,18-d*$_5$ (**39**), and ethyl (*E*)-3,7-dimethyl-9-(3,3-ethano-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (**47**) displayed moderate to excellent activity in an assay for the inhibition of tumor promoter-induced mouse epidermal ornithine decarboxylase.

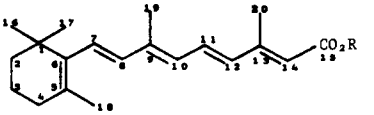
The reversal or prevention of the transformation of epithelial cells to a neoplastic state by both natural and synthetic retinoids is well established by both in vitro and in vivo experiments.[1] Unfortunately, the dose level of retinoids necessary for therapeutic effectiveness can also produce toxic side effects.[2] However, dose levels could be reduced if the metabolic deactivation of these compounds were reduced or eliminated. A major pathway for metabolic deactivation is allylic oxidation at the 4_R position[3] of the β-cyclogeranylidene ring of the retinoid skeleton.[4] Interference with this hydrogen-abstraction process may therefore produce less toxic and more effective retinoids. We have undertaken the design and synthesis of retinoid analogues that have their major modifications in the region of the $5,6_R$ double bond to reduce the allylic nature of the 4_R protons (**7**, **18**, and **28**) or that have substituents replacing the 4_R protons (**39** and **47**).

The $5,6_R$ bond of norbornyl analogue **7** is saturated. This compound was proposed as an analogue of the labile, but active, 2-norbornenylretinoid **9**[5] and 5,6-dihydro-

(1) (a) Sporn, M. B.; Dunlop, N. M.; Newton, D. L.; Smith, J. M. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1976**, *35*, 1332. (b) Sporn, M. B.; Dunlop, N. M.; Newton, D. L.; Henderson, W. R. *Nature (London)* **1976**, *263*, 110. (c) Sporn, M. B.; Squire, R. A.; Brown, C. C.; Smith, J. M.; Wenk, M. L.; Springer, S. *Science* **1977**, *195*, 487. (d) Moon, R. C.; Grubbs, C. J.; Sporn, M. B.; Goodman, D. G. *Nature (London)* **1977**, *267*, 620. (e) Todaro, G. J.; De Larco, J. E.; Sporn, M. B. *Ibid.* **1978**, *276*, 272. (f) Becci, P. J.; Thompson, H. J.; Grubbs, C. J.; Squire, R. A.; Brown, C. C.; Sporn, M. B.; Moon, R. C. *Cancer Res.* **1978**, *38*, 4463. (g) Sporn, M. B.; Newton, D. L.; Smith, J. M.; Acton, N.; Jacobson, A. E.; Brossi, A. In "Carcinogens: Identification and Mechanism of Action"; Annual Symposium on Fundamental Cancer Research, 31st, M. D. Anderson Hospital and Tumor Research Institute, Houston, 1978, Griffin, A. C.; Shaw, C. R., Eds.; Raven Press: New York, 1979; pp 441–453. (h) Bollag, W. *Cancer Chemother. Pharmacol.* **1979**, *3*, 207. (i) Sporn, M. B.; Newton, D. L.; Roberts, A. B.; De Larco, J. E.; Todaro, G. J. In "Molecular Actions and Targets for Cancer Chemotherapeutic Agents"; Sartorelli, A. C.; Bertino, J. R.; Lazo, J. S., Eds.; Academic Press: New York, 1980.

(2) (a) Bard, D. R.; Lasnitzki, I. *Br. J. Cancer* **1977**, *35*, 115. (b) Hixson, E. J.; Denine, E. P. *Toxicol. Appl. Pharmacol.*, **1978**, *44*, 29. (c) Hixson, E. J.; Burdeshaw, J. A.; Denine, E. P.; Harrison, S. D., Jr. *Ibid.* **1979**, *47*, 359.

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



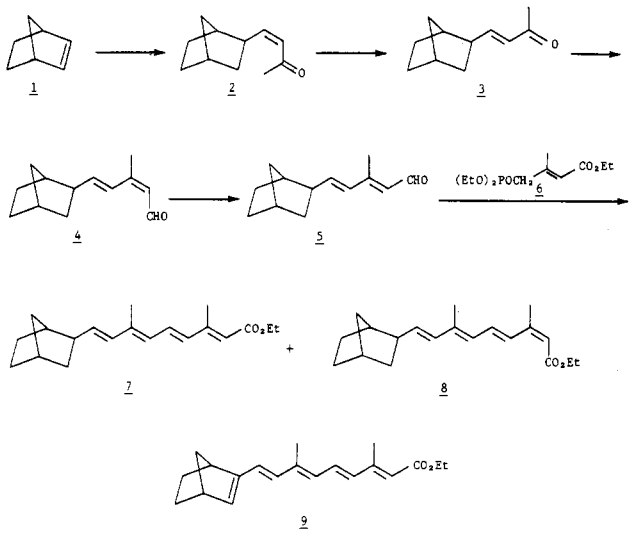
Similar proton and carbon atoms in the analogues have been denoted by the subscript R. Aryl carbon atoms have been denoted in the spectral tabulations as 1′ and 6′. The position bearing the polyene substituent is numbered 1′ and the remaining positions are numbered in the direction of lowest numerical assignment to the other substituents. The norbornyl ring has also been numbered 1′ to 7′ following standard numbering.

(4) (a) Roberts, A. B.; Nichols, N. D.; Newton, D. L.; Sporn, M. B. *J. Biol. Chem.* **1979**, *254*, 6296. (b) Roberts, A. B.; Lamb, L. C.; Sporn, M. B. *Arch. Biochem. Biophys.* **1980**, *199*, 374.

(5) Dawson, M. I.; Hobbs, P. D.; Kuhlmann, K.; Fung, V. A.; Helmes, C. T.; Chao, W.-R. *J. Med. Chem.* **1980**, *23*, 1013.

0022-2623/81/1824-1214$01.25/0

Scheme I



retinoic acid.[6] Both of these compounds showed good activity in two in vitro biological assays—the reversal by retinoids of keratinization in hamster tracheal organ cultures[1,7] and the inhibition by retinoids of the induction of ornithine decarboxylase (ODC) in mouse epidermis by tumor-promoting phorbol esters.[8] Activity in these tests correlates well with the ability to inhibit tumor promotion.

The synthesis of **7** is given in Scheme I. *exo*-(*E*)-Enone **3** was prepared by the radical-initiated reaction[9] of tris-(2-norbornyl)borane with butynone, followed by in situ hydrolysis of the intermediate borinate and an iodine-catalyzed isomerization of the resulting mixture of *exo*-(*Z*)- and *exo*-(*E*)-enones. No endo isomers were formed by this route. Condensation of enone **3** with the anion of trimethylsilylacetaldehyde *tert*-butylimine[10] and acidic hydrolysis gave a mixture of (2*Z*)- and (2*E*)-3-methyl-5-(*exo*-2-bicyclo[2.2.1]heptyl)-2,4-pentadienals (**4** and **5**), with the 2*Z* isomer predominating (2*Z*/2*E*, 60:40). Treatment of the *Z* isomer **4** with less than 1 mol % of I_2 gave an equilibrium mixture of aldehydes within 15 min, with the 2*E* isomer predominating (2*E*/2*Z*, 70:30). I_2 was removed rapidly by elution through a silica gel column because prolonged contact led to polymerization. NMR, high-performance liquid chromatography (LC), and GC–MS did not indicate any epimeric *endo*-2-norbornyl isomer in the product obtained either from the alkylation reaction or from the 2*Z* to 2*E* equilibration. Condensation of dienal **5** with the lithio anion of diethyl (*E*)-3-carbethoxy-2-methyl-2-propenylphosphonate (**6**)[11] yielded a mixture of the (*E*)-tetraenoate **7** and its 13_RZ isomer **8** but none of the 11_RZ isomer. Heathcock also found that the 13*Z* isomer was the second major product in the synthesis of a 7,8-epoxyretinoid.[12] Each isomer was isolated by repetitive LC purification (1% EtOAc/hexane). Since some epimerization of the *exo*-2-norbornyl function could result on hydrolysis, the ethyl ester was submitted for testing.

In retinoids **18** and **28**, the $5,6_R$ double bond has been replaced by a cyclopropyl ring. These compounds were designed as carbocyclic analogues of the biologically active $5,6_R$-epoxides **21** and **31**.[13] 5,6-Epoxy-5,6-dihydroretinoic acid (**21**), which is a metabolite of retinoic acid, is reported to have biological activity comparable to that of retinoic acid in the ODC assay and in a skin tumor-promotion experiment.[6] Epoxide **31**, the air-oxidation product of the *p*-carbethoxyphenyl triene **30**, was found to have activity comparable to that of **30** in the ODC assay.[12] It has not as yet been submitted to the other screen.

Since Simmons–Smith cyclopropanation of methyl retinoate resulted in the formation of a geometric isomer of the starting material and a product derived from reaction at a side-chain double bond rather than at the 5,6 double bond, a stepwise sequence was used for the preparation of **18** (Scheme II). Cyclopropanation of the β-cyclogeranylidene ring was best performed by activation of the double bond with the allylic hydroxyl group of β-cyclogeraniol (**10**). Oxidation of the product afforded the hindered aldehyde **12**.

To avoid handling the sensitive vinylcyclopropane intermediates through several steps, a convergent synthesis of **18** was first attempted starting with **12**. Horner–Emmons reaction of the aldehyde with the anion of phosphonate **13**[11] at room temperature produced a negligible amount of product after several days. In Me_2SO at 65 °C with sodium hydride as the base, the reaction was faster and yielded a mixture, none of which was the desired product. The major isomer appeared to be the (*E*)-*exo*-methylenecycloheptyltetraenoate **14**: ^1H NMR ($CDCl_3$) δ 0.87 and 0.90 (2 s, 6, C_R-16 and C_R-17 CH_3), 1.31 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 1.8–2.4 [ms, 9, $(CH_2)_3$, C=CCHCH$_2$C=C], 1.96 (s, 3, C_R-19 CH_3), 2.37 (d, J = 0.5 Hz, 3, C_R-20 CH_3), 4.20 (q, J = 7 Hz, 2, $CO_2CH_2CH_3$), 4.70 (br s, 2, C=CH_2), 5.6–6.4 (ms, 5, C_R-7, C_R-8 and C_R-12 HC=CH, C_R-10 and C_R-14 C=CH), 6.98 (dd, J = 15 and 12 Hz, 1, C_R-11 HC=CH); IR (film) 1728, 1650, 1620, 1610, 1040, 893 cm^{-1}. The second most significant product was an isomer of **14**. In contrast to the reported thermal rearrangement of 4-(2,2,6-trimethylbicyclo[4.1.0]hept-1-yl)-butenone to the corresponding 4-(2,2-dimethyl-6-methylenecyclohept-1-yl)butenone,[14] rearrangement of **12** did not appear to be thermally induced. No rearrangement occurred on heating at 65 °C in the absence of base. Abstraction of a proton from the methyl group of **12** by the base could lead to rearrangement to the less-hindered cycloheptylcarboxaldehyde, which could then react with the weakly nucleophilic anion of **13**. In contrast, the anion of **6** was more reactive and rearrangement did not occur. At room temperature, it reacted slowly with the aldehyde

(6) (a) 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. (b) Verma, A. K.; Slaga, T. J.; Wertz, P. W.; Mueller, G. C.; Boutwell, R. K. *Cancer Res.* **1980**, *40*, 2367.

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(10) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7.

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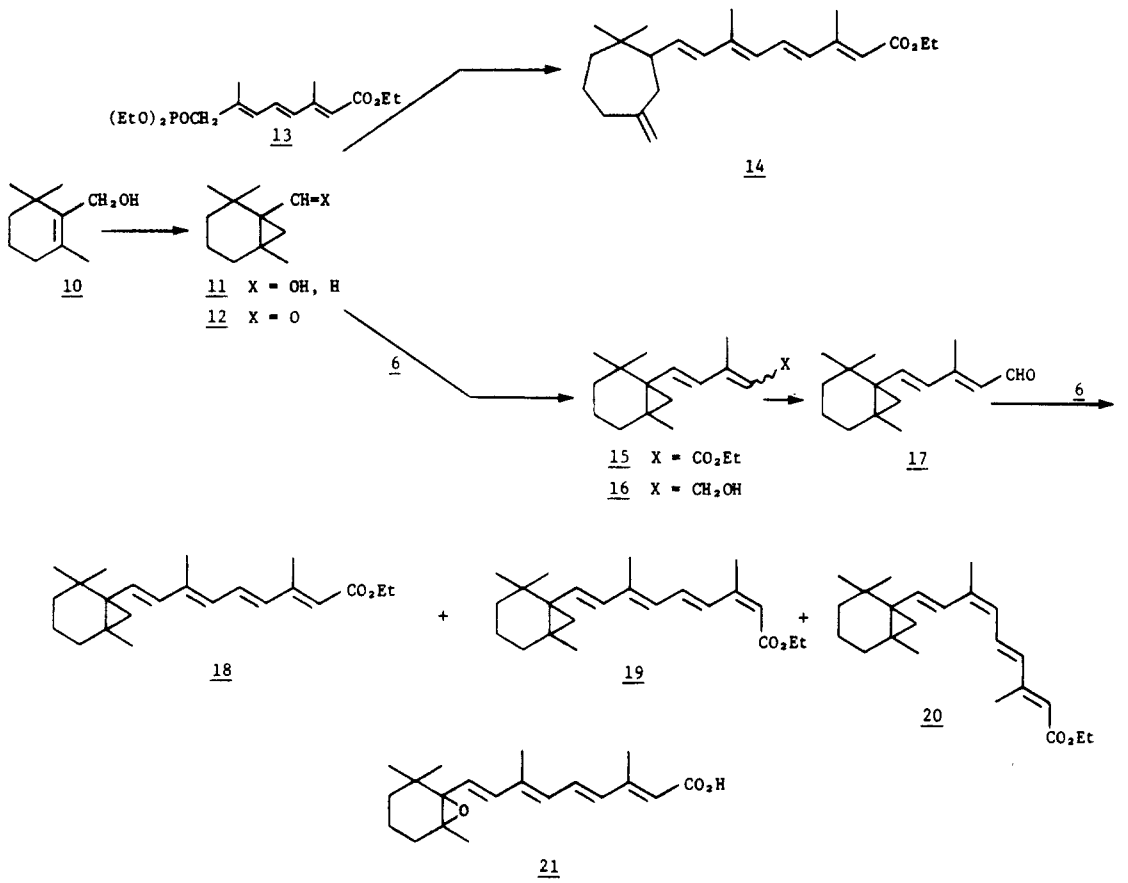
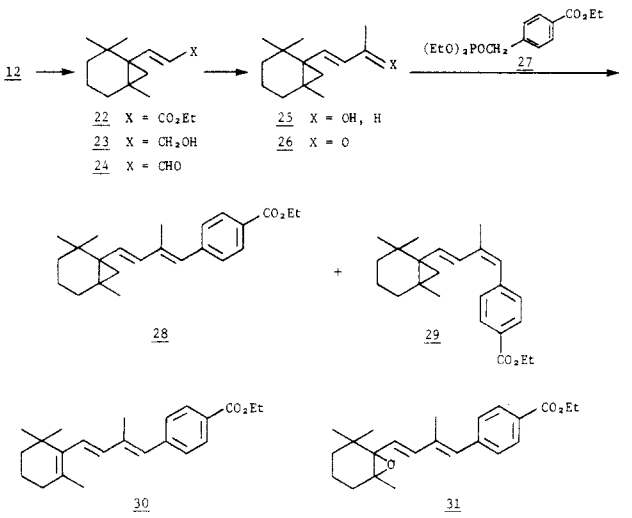
(14) Ishii, K.; Wolf, H. R.; Jeger, O. *Helv. Chim. Acta* **1980**, *63*, 1520.

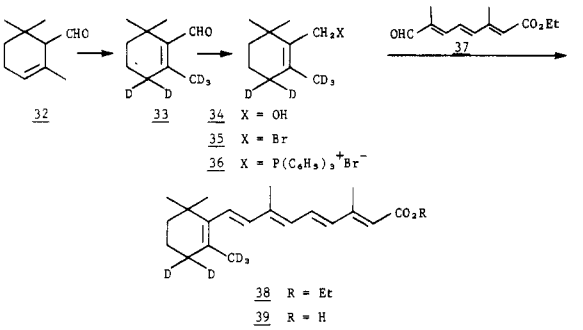
Scheme II



Scheme III



Scheme IV



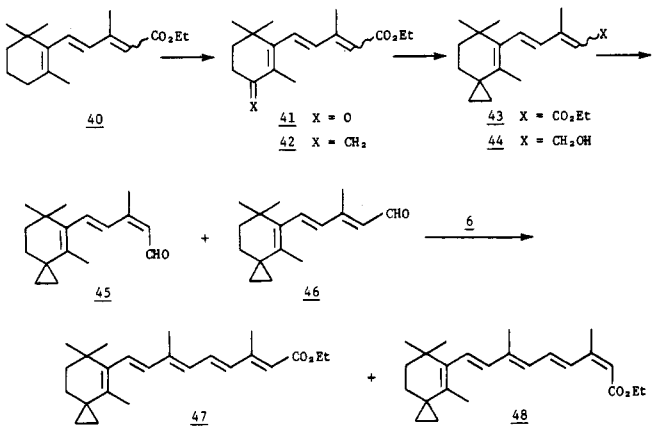
12 to afford an isomeric mixture of esters (*t*-BuOK/*t*-BuOH/THF; NaH/Me_2SO). Reaction at a higher temperature in Me_2SO at 65 °C was more rapid, giving a 1:4 mixture of esters, as indicated by ^1H NMR. The anion of **6** evidently is more nucleophilic because the charge is not delocalized over the polyene chain. Since the two isomeric esters (**15**) were difficult to separate, they were reduced with DIBAL to the corresponding alcohols (**16**), which were converted to the aldehydes by MnO_2 oxidation. Dienal **17** was obtained on LC purification. Reaction with the anion of **6** afforded three major isomers—**18** (64%), **19** (21%), and **20** (13%)—and a minor isomer as shown by analytical LC.

The carbocyclic analogue **28** was also prepared in a stepwise fashion from cyclopropanecarboxaldehyde **12** to avoid rearrangement problems (Scheme III). **12** was converted to the methanodihydro-β-ionone **26** by standard methods. Condensation of **26** with the anion of diethyl *p*-carbethoxybenzylphosphonate (**27**)[15] afforded an isomeric mixture of products, of which **28** (76%) and **29** (20%) predominated (LC analysis). To minimize rearrangements, both methanoretinoids **18** and **28** and their isomers **19** and **29** were submitted for testing as the esters.

The pentadeuterioretinoid **39** was designed to decrease metabolism at the 4_R position by the kinetic isotope effect through substitution of deuterium for hydrogen. The stability of β-cyclocitral to nonaqueous base (NaOMe/MeOH) permitted the introduction of deuterium on the C_R-18 allylic methyl and C_R-4 methylene positions by base-catalyzed exchange. Purified α-cyclocitral (**32**) was equilibrated to the β isomer with NaOMe in methyl alcohol-*d* (99.5+ atom % d), and the base was quenched with acetic acid-d_4 (99.5 atom % d) (Scheme IV). This equilibration was repeated twice to give deuterated β-cy-

(15) Kreutzkamp, N.; Cordes, G. *Arch. Pharm. (Weinheim, Ger.)* **1961**, *294*, 49.

Scheme V



clocitral. To facilitate separation, the aldehydes were reduced with 9-borabicyclo[3.3.1]nonane (9-BBN), and the deuterated β-cyclogeraniol (**34**) was purified by silica gel chromatography. The phosphonium salt **36**[16] was prepared and converted to the ylide, which was allowed to react with trienal ester **37**.[16] The deuterated ethyl (*E*)-retinoate (**38**) was purified by LC (1% EtOAc/hexane). In the MS analysis for the extent of deuterium substitution, corrections to the peak intensities for the ^{13}C contribution were applied. The product analyzed as 0.6% (d_3), 7.1% (d_4), 90.5% (d_5), 1.1% (d_6), and 0.5% (d_7). The corresponding acid (**39**) was obtained by alkaline hydrolysis, followed by crystallization from MeOH. The retinoic acid was found to be 0.8% (d_3), 7.0% (d_4), 90.5% (d_5), and 1.7% (d_6) by MS analysis. The absence of ^1H or ^{13}C NMR signals for the C_R-4 CH_2 or C_R-18 CH_3 functions confirmed the sites of deuteration. The UV spectrum was the same as that of retinoic acid.

Retinoid **47** has an ethano group at the 4_R position in place of the hydrogens. A model study indicates that the introduction of this spiro system does not significantly deform the cyclohexene ring of the retinoid. The starting material for the synthesis of **47** was the ethyl ionylideneacetates **40**, which were prepared in 41% yield by reaction of sodium triethyl phosphonoacetate with β-ionone (Scheme V). ^1H NMR analysis of the starting material indicated that the *E*/*Z* isomer ratio at the trisubstituted double bond was 60:40. Purification at this stage was not performed because the step involving NBS oxidation in *t*-BuOH/H_2O was reported to isomerize the $9_R E$ double bond.[17] Oxidation afforded a 33% yield of the ethyl 4_R-oxoionylideneacetates (**41**) and a 34% yield of the ethyl 4_R-hydroxyionylideneacetates. On MnO_2 oxidation, the alcohol was converted to the ketone in 30% yield. Wittig reaction on ketone **41** using methylenetriphenylphosphorane afforded a 52% yield of the unstable *exo*-methylenetriene esters **42**, which, in turn, afforded the $4,4_R$-ethanotriene esters **43** on Simmons–Smith cyclopropanation (67%). Reduction with $LiAlH_4$ (80%) and oxidation with MnO_2 afforded the cyclopropyltrienals **45** and **46**. Separation of the aldehydes by preparative LC afforded a 40% yield of the (2*E*,4*E*)-trienal **46** and a 16% yield of the less polar (2*Z*,4*E*)-trienal **45**. Reaction of the (2*E*,4*E*)-trienal **46** with the anion of **6** afforded a mixture containing two major isomers, **47** (83%) and **48** (7%), by LC analysis. These two isomers were isolated in 29 and 14% yields, respectively, by repetitive LC. To minimize the possibility of rearrangements, only the esters were submitted to biological testing.

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

retinoid	amount applied, nmol	% inhibn of ODC (mean ± SE)	no. of groups of mice tested (no. of mice/group)
control			3 (3)
retinoic acid	1.7	92 ± 2	6 (4)
(13*Z*)-retinoic acid	17	96 ± 1	3 (3)
7	17	64 ± 1	3 (3)
9[a]	17	54 ± 10	4 (4)
18	17	70 ± 1	3 (3)
19	17	45 ± 2	3 (3)
28	17	80 ± 4	3 (3)
29	17	0 ± 2	3 (3)
30[b]	17	80 ± 2	3 (3)
31[b]	17	80 ± 2	3 (3)
39	1.7	90 ± 2	3 (3)
	17	90 ± 0	3 (3)
47	17	72 ± 2	3 (3)
48	17	67 ± 2	3 (3)

[a] Reference 5. [b] Reference 13.

The stereochemistry of these retinoids and their isomers was established by comparison of their 100- and 360-MHz NMR spectra with those of retinoids that we have previously synthesized and those published by other investigators. Spectral and stereochemical assignments are discussed under Experimental Section.

Pharmacological Activity. The correlation between the inhibition by retinoids of tumor promoter-induced mouse ODC activity and their inhibition of skin tumor promotion has been well established by Boutwell and coworkers.[8] 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. The protocol for this procedure has been described previously.[5] We applied each retinoid at either a 1.7- or 17-nmol dose level to the backs of three groups of three mice. The results are given in Table I.

In this assay, the norbornyl retinoid **7** showed moderate activity, comparable to that exhibited by the norbornenyl retinoid **9**. However, **7** was much less active than **9** in the reversal of keratinization assay, having at 10^{-9} M 9% of the activity of retinoic acid compared to 60% for **9**.[18] In contrast, the activities of **39**, **47**, and other retinoids that we have tested usually correlate well. Both the $4,4_R$-ethanoretinoid **47** and its $13_R Z$ isomer showed moderate and similar activity in the ODC test. The pentadeuterioretinoic acid **39** had the same activity as retinoic acid. The methano compounds **18** and **19** were both active. However, in this case the 13*Z* isomer (**19**) had about 60% of the activity of the *all-E* isomer. The methano analogue **28** had the same activity as did the *p*-carbethoxyphenyl triene **30** and its $5,6_R$-epoxide **31**. As expected, the $9_R Z$ isomer (**29**) of **28** was inactive. The number of compounds synthesized is still too small for any extensive structure–activity analysis; however, the biological results show that modifications of the retinoid skeleton can be made in the regions of the 5,6 double bond and 4-methylene group without substantial loss of activity in the inhibition of the induction of ODC by tumor promoters. The effectiveness

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(18) Sporn, M. B.; Newton, D. L. National Cancer Institute, Bethesda, MD, unpublished results.

of some of these retinoids is being compared to that of retinoic acid in a long-term antitumor-promotion experiment in mice.

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, on a 360-MHz Bruker spectrometer, using $(CH_3)_4Si$ 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. LC analyses were done on a Waters Associates ALC 210 equipped with either a Radialpak A or B cartridge, of a 30 cm × 3.9 mm μBondapak/C18 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. ^1H NMR[19] and ^{13}C NMR[20] signals were assigned by comparison with those reported for other retinoids. The stereochemical assignments were supported by the larger ϵ values for the *all-E* isomers.[21]

(*E*)-1-(*exo*-2-Bicyclo[2.2.1]heptyl)-1-buten-3-one (3).[22] A solution of 47.7 g (0.51 mol) of norbornene in 30 mL of dry THF was added over 20 min to an ice-cooled solution of 162 mL (0.162 mol) of 1 M B_2H_6 in THF under argon. The solution was heated to 50 °C and the temperature was maintained for 3 h. After the solution was cooled to room temperature, 5.4 g (0.3 mol) of water was introduced, followed by a solution of 10.0 g (0.147 mol) of butynone in 20 mL of THF. A slow stream of air was passed over the surface of the stirred yellow solution for 18 h, and the solvent was evaporated to leave 73 g of a yellow viscous oil, which had a powerful odor of 2-norbornanol. TLC (9:1 hexane/EtOAc, developed H_2SO_4) showed six spots, two of which were apparent under UV light. The total crude mixture was dissolved in 100 mL of Et_2O, applied to a 9 × 60 cm silica gel column, and eluted successively with 4.5 L each of 1, 1.5, 2, and 2.5% EtOAc/hexane followed by 3 L each of 3, 3.5, and 4% EtOAc/hexane (500-mL fractions). The first 1.5 L of eluate was discarded. Fractions 24 to 28 yielded 8.5 g of the crude (*Z*)-enone **2** and an impurity. The pure (*E*)-enone **3** (5.5 g, 23%) was eluted from fractions 41 to 52 as a pale yellow liquid. A solution of 7.1 g of the crude (*Z*)-enone in 30 mL of THF was treated with 0.5 g of I_2 and stirred overnight at room temperature. The solvent was removed at reduced pressure, the black residue was treated with 100 mL of Et_2O, and the solution was decanted. The organic solution was washed with saturated $NaHSO_3$ (2 × 50 mL) and then with brine (3 × 80 mL), dried (Na_2SO_4, 4 h), and concentrated. The dark oil (6.0 g) was chromatographed on a 4 × 35 cm silica gel column with 400-mL volumes of 1.5, 2, 3, 4, and 5% EtOAc/hexane (100- to 200-mL fractions). The impurity in the starting material eluted in fractions 1 to 5 (about 2 g) followed by 2.87 g (12%) of the (*E*)-enone **3** in fractions 6 to 9. No (*Z*)-enone was obtained. The total yield of **3** was 8.4 g (37%): IR (film) 1670 (C=O), 1625, 1455, 1430, 1255, 1215, 1185, 980, 920, 890, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–1.8 (m, 8, CH_2), 2.1–2.45 (m, 3, CH), 2.23 (s, 3, CH_3C=O), 5.95 (d, J = 16 Hz, 1, HC=C*H*CO), 6.68 (dd, J = 16 and 7 Hz, 1, *H*C=CHCO); MS *m/e* 164 (M^+), 149 (M − CH_3), 135 (M − CHO), 121 (M − CH_3CO).

The crude (*Z*)-enone—obtained from 47.7 g (0.51 mol) of norbornene, 162 mL of 1 M B_2H_6 (0.16 mol) in THF, and 10.0 g (0.15 mol) of butynone as described above—was dissolved in 750 mL of Et_2O, treated with 0.5 g of I_2, and stirred at room temperature for 3.5 h. The solvent was evaporated away, and the residue was extracted with 1 L of 10% Et_2O/hexane, which then was concentrated. Chromatography on a 9 × 60 cm silica gel column with 8-L portions of 3, 4, and 5% EtOAc/hexane (500-mL fractions) gave in fractions 30 to 40, 10.4 (43%) of **2**, which was spectrally identical with the previously characterized sample.

(*E*)-3-Methyl-5-(*exo*-2-bicyclo[2.2.1]heptyl)-2,4-pentadienal (5). A solution of 6.9 g (69 mmol) of $(i\text{-}Pr)_2NH$ in 30 mL of Et_2O was cooled in ice under argon while 52 mL of 1.30 M *n*-BuLi (67.5 mmol) in hexane and 90 mL of THF were added. To the base was added 11.7 g (68 mmol) of trimethylsilylacetaldehyde *tert*-butylimine[10] in 20 mL of THF over a 45-min period. The anion solution was cooled in dry ice–acetone, and then a solution of 7.12 g (43.4 mmol) of *exo*-(*E*)-enone **3** in 20 mL of THF was introduced over a 20-min period. The temperature then was raised to −22 °C over a 2-h period, and the reaction was quenched with 35 g (0.32 mol) of $(CO_2H)_2{\cdot}H_2O$ followed by 120 mL of water. The two-phase system was stirred vigorously under argon for 16 h at room temperature to give a yellow-orange organic layer and a light yellow aqueous layer. Another 200-mL portion of water was added, and the product was extracted twice into ether (200 mL, 100 mL), washed with 100-mL volumes of water, saturated $NaHCO_3$, and brine (twice), dried (Na_2SO_4), and concentrated at reduced pressure under nitrogen. A 5 × 50 cm silica gel column, which was eluted successively with 4.5 L of 1.5%, 3.5 L of 2%, and finally with 2.5% EtOAc/hexane until product elution was complete (500-mL fractions), first yielded 4.00 g (30%) of the (2*Z*,4*E*)-dienal **4**, followed by 2.72 g (21%) of the (2*E*,4*E*)-dienal **5**, as yellow oils with a camphor-like odor. A solution of 3.8 g (20.0 mmol) of **4** in 190 mL of $C_6H_5CH_3$ and 380 mL of Et_2O was treated with 35 mg (0.007 equiv) of I_2 and stirred under argon for 15 min. The solution, which darkened rapidly, was concentrated to 125 mL and immediately applied to a 3 × 30 cm silica gel column, which was eluted with 4% EtOAc/hexane (150-mL fractions). The mixture of aldehydes eluted rapidly. The eluate was concentrated and applied to a 5 × 50 cm silica gel column, which was eluted with 4 L of 2% and 2 L of 2.5% EtOAc/hexane (150- to 250-mL fractions). The recovered **4** (1.01 g, 27%) eluted first, followed by 2.45 g (65%) of **5**. The total yield of (*E*)-dienal **5** was 40%.

(2*Z*,4*E*)-Dienal 4: IR (film) 2750 (CHO), 1670 (C=O), 1635, 1590, 1410, 1320, 1210, 1120, 1025, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.7 (m, 8, CH_2), 2.04 (d, J = 1 Hz, 3, CH_3), 2.0–2.4 (m, 3, CH), 5.82 (d, J = 8 Hz, 1, C=C*H*CHO), 6.09 (dd, J = 15.5 and 8 Hz, 1, HCC*H*=CH), 7.02 (d, J = 15.5 Hz, 1, HC=C*H*C=C), 10.01 (d, J = 8 Hz, 1, C=CHC*H*O); ^{13}C NMR ($CDCl_3$) 190.1 (C=O), 155.3 (C_R-9), 145.7 (C_R-7), 127.5 (C_R-8), 123.2 (C_R-10), 45.9 (C-2′), 42.6 (C-1′), 37.9 (C-7′), 36.7 (C-4′), 36.0 (C-3′), 29.8 (C-5′), 28.9 (C-6′), 21.4 ppm (CH_3); UV (EtOH) λ_{max} 285 nm (ϵ 1.97 × 10^4); MS calcd for $C_{13}H_{18}O$, 190.1358; found, 190.1360.

(2*E*,4*E*)-Dienal 5: IR (film) 2780 (CHO), 2720, 1665 (C=O), 1630, 1340, 1320, 1215, 1130 (1110 sh), 970, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.7 (m, 8, CH_2), 2.05–2.4 (m, 3, CH), 2.13 (s, 3, CH_3), 5.91 (d, J = 8 Hz, 1, C=C*H*CHO), 6.0–6.4 (m, 2, HC=CH), 10.13 (d, J = 8 Hz, 1, C=CHC*H*O); UV (EtOH) λ_{max} 286 nm (ϵ 2.32 × 10^4); MS calcd for $C_{13}H_{18}O$, 190.1358; found, 190.1342.

Ethyl (*E*)-3,7-Dimethyl-9-(*exo*-2-bicyclo[2.2.1]heptyl)-2,4,6,8-nonatetraenoate (7). A solution of 6.60 g (25.0 mmol) of **6**[11] in 25 mL of dry THF was degassed under argon (3 times) and cooled to −30 °C; then 18.9 mL of 1.30 M *n*-BuLi (24.5 mmol) in hexane was added. The orange solution was treated after 5 min at −30 °C with 4.95 g (26 mmol) of the (2*E*,4*E*)-dienal **5** in 7 mL of THF (3-mL rinse) over a 15-min period. The solution,

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which became yellow and then orange during the addition, was allowed to reach room temperature over a 16-h period and then treated with 250 mL of brine containing 3 mL of HOAc and 100 mg of TBHQ (*tert*-butylhydroquinone). The product was extracted into 150 mL of 10% EtOAc/hexane, washed twice with 100 mL of brine, dried (Na_2SO_4), and concentrated to give 8.7 g of an orange oil. The most polar of the two major and one minor components (silica gel TLC, 10% EtOAc/hexane) was isolated by LC (1% EtOAc/hexane). The crude material was chromatographed in two portions to give 2.11 g of a mixture and 3.76 g of the crude more polar isomer. The second fraction was rechromatographed in two portions to yield 1.27 g of a mixture of two components and 1.56 g of the most polar isomer. A final purification of the (*E*)-ester was performed similarly in two portions to afford 1.19 g (15%) of ester **7** as a yellow crystalline solid, mp 46–47 °C. A sample of the major of the two less polar isomers was purified in the same manner. Three successive LC purifications of the mixture recovered from the first chromatography of the reaction product yielded 0.23 g (3%) of the 13_RZ isomer **8** as a bright yellow oil. ***E*-Isomer 7**: LC (Radialpak A, reverse phase, 80% MeOH/water, 2.4 mL/min, 290 nm) t_R 7.4 (1.5%), 12.4 (0.7%), 19.9 (95%), 22.1 min (shoulder, 2.7%); LC (Radialpak B, 1% Et_2O/hexane, 2.0 mL/min, 280 nm) t_R 8.2 (99.8%), 10.4 min (<0.2%); IR (mull) 1710 (C=O), 1615, 1590, 1370, 1355, 1240, 1150, 1050, 965, 840 cm^{-1}; UV (EtOH) λ_{max} 344 nm (ϵ 4.92 × 10^4), 241 (4.0 × 10^3); MS calcd for $C_{20}H_{28}O_2$, 300.2089; found, 300.2074.

13_RZ-Isomer 8: IR (film) 1710 (C=O), 1610, 1590, 1565, 1275, 1240, 1195, 1155, 1100, 1055, 975, 870, 855 cm^{-1}; UV (EtOH) λ_{max} 344 nm (ϵ 4.28 × 10^4), 241 (1.0 × 10^4); MS calcd for $C_{20}H_{28}O_2$, 300.2089; found, 300.2118.

The ^1H NMR spectra of the isomeric esters were compared with the published spectra of retinoic acid and retinoate ester isomers.[19a,b] The chemical shifts of H_{11R} (δ 6.95), H_{12R} (δ 6.23), H_{14R} (δ 5.75), and the C_R-20 methyl group (δ 2.34) of **7** are in close agreement with those observed for methyl (*E*)-retinoate (δ 6.99, 6.27, 5.79, and 2.36, respectively).[20] H_{7R} (δ 5.69) showed the expected coupling (J = 7 Hz) with the adjacent methine proton of the norbornyl function. The ^{13}C NMR signals for C_R-7 to C_R-14, C_R-19, and C_R-20 were closely similar to those published[20] for methyl (*E*)-retinoate. Comparison of the signals for C-1′ to C-7′ of the norbornyl spectrum with published tabulations[23] of exo and endo 2-substituted norbornanes confirmed the exo configuration of the polyene substituent. The C-6′ ^{13}C NMR signal was observed at 29.1 ppm. A C-2′ endo substituent would have shifted this signal upfield to 20.4–25.3 ppm. The ^1H NMR spectrum of the 13_RZ isomer (**8**) displayed the characteristic upfield shift of H_{14R}, the downfield shift of H_{12R}, and the 16-Hz coupling of H_{11R} with H_{12R} found in the (13*Z*)-retinoids.[19a] The downfield shift of H_{11R} (δ 7.77) and the upfield shift of the C_R-20 methyl group (δ 2.03) also established the 13*Z* configuration. Again, a close correlation of the ^{13}C NMR signals for C_R-7 to C_R-16, C_R-19, and C_R-20 with those of methyl (13*Z*)-retinoate[20] was observed. The C-6′ signal at 28.9 ppm again indicated the exo configuration at C-2′.

(2,2,6-Trimethylbicyclo[4.1.0]hept-1-yl)methanol (11). A solution of 0.4 g of $Cu(OAc)_2·H_2O$ in 20 mL of hot HOAc was treated with 8.8 g (0.13 g-atom) of Zn dust with shaking for 3 min, and the acid was decanted. The Zn–Cu couple was washed by decantation with 30 mL of 1:1 HOAc/Et_2O, followed by Et_2O (6 × 30 mL). Next, 20 mL of Et_2O was added together with a crystal of I_2.[24] A mixture of 18.8 g (70 mmol) of CH_2I_2 and 3.08 g (20 mmol) of **10**[25] was added dropwise over a 20-min period, with warming to maintain a gentle reflux. Heating at reflux was continued for an additional 2 h. The cooled solution was decanted, the residue was washed with Et_2O, and the total Et_2O volume was brought to 200 mL. The solution was cooled in ice/H_2O, and pyridine (8 to 9 mL) was added dropwise until no further ZnI_2–pyridine complex separated. The reaction was cooled to −5 °C overnight, filtered twice, and evaporated. Further complex separated on evaporation. TLC (9:1 hexane/EtOAc) demonstrated a single product. The crude oil was eluted through a 3 × 25 cm silica gel column by 9:1 hexane/Et_2O, followed by 1:1 hexane/Et_2O. The spectrally pure, colorless oil weighed 3.4 g (quant): IR (film) 3400 (OH), 1460, 1385, 1365, 1155, 1035, 1010, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.22 (d, J = 4.5 Hz, 1, cyclopropyl H), 0.49 (d, J = 4.5 Hz, 1, cyclopropyl H), 0.99 (s, 3, CH_3), 1.21 (s, 3, CH_3), 1.26 (s, 3, CH_3), 1.0–1.8 [m, 7, $(CH_2)_3$, OH], 3.51 and 3.92 (d, J = 12 Hz, 1, and dd, J = 12 and 3.5 Hz, 1, CH_2O); ^{13}C NMR ($CDCl_3$) 65.8, 38.0, 35.5, 31.9, 31.3, 29.2, 27.4, 23.9, 22.5, 21.7, 18.0 ppm; MS calcd for $C_{11}H_{20}O$, 168.1514; found, 168.1521.

(2,2,6-Trimethylbicyclo[4.1.0]hept-1-yl)carboxaldehyde (12). To a solution of 50 mL of pyridine (0.62 mol) in 120 mL of CH_2Cl_2 at 0 °C was added 32 g (0.32 mol) of CrO_3 in several portions. A solution of 6.72 g (40 mmol) of **11** in 5 mL of CH_2Cl_2 was added dropwise to the orange-brown mixture. The reaction mixture was allowed to warm to room temperature for 1 h and then was filtered through 50 g of Florisil (300 mL of CH_2Cl_2 wash). The filtrate was concentrated to give 6 g of a pale yellow oil, which was filtered through a column containing 200 g of silica gel with CH_2Cl_2. The 4.93 g (74%) of product was obtained as a colorless oil: IR (film) 2750 (CHO), 1700 (C=O), 1460, 1385, 1370, 1290, 1210, 1155, 1090, 1075, 995, 930, 910, 855 cm^{-1}; ^1H NMR (CCl_4) δ 0.84 (d, J = 5 Hz, 1, cyclopropyl H), 1.09–1.9 (m, 6, CH_2, and 1, cyclopropyl H), 1.03 (s, 3, CH_3), 1.13 (s, 3, CH_3), 1.44 (s, 3, CH_3), 9.64 (s, 1, CHO); ^{13}C NMR ($CDCl_3$) 202.9, 45.4, 36.5, 30.3, 29.9, 29.8, 29.6, 26.5, 22.4, 21.9, 17.0 ppm; MS calcd for $C_{11}H_{18}O$, 166.1358; found, 166.1364.

(4*E*)-3-Methyl-5-(2,2,6-trimethylbicyclo[4.1.0]hept-1-yl)-2,4-pentadien-1-ol (16). A solution of 26 g (98 mmol) of diethyl (*E*)-3-(carbethoxy)-2-methyl-2-propenylphosphonate (**6**) in 15 mL of THF was cooled to −78 °C, and 62.5 mL of a 1.46 M solution of *n*-BuLi in hexane (91 mmol) was added over a 20-min period, followed by 4.7 g (28.3 mmol) of **12** in 5 mL of THF. The reaction mixture was stirred at room temperature for 48 h, diluted with 100 mL of H_2O, and extracted with hexane (3 × 50 mL). The combined hexane extract was washed with brine (2 × 100 mL), dried (Na_2SO_4), and evaporated to give 10.3 g of a light yellow oil, which was chromatographed on 350 g of silica gel with 5% Et_2O/hexane. A total of 6.0 g (77% yield) of a 1:4 mixture by ^1H NMR of the 2*Z* and 2*E* isomers of **15** was obtained as a colorless oil: IR (film) 2900, 1720, 1640, 1620, 1450, 1370, 1240, 1160, 1060, 980, 880 cm^{-1}; ^1H NMR ($CDCl_3$) 0.47, 0.53 (2 d, J = 5 Hz, 2, cyclopropyl CH_2), 0.87, 0.95, 1.08 (3 s, 9, C_R-16, C_R-17, and C_R-18 CH_3), 1.0–1.75 [m, 6, $(CH_2)_3$], 1.27 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 2.00 and 2.30 (2 s, 3, 2*Z* and 2*E* C=CCH_3, respectively), 4.16 (q, J = 7 Hz, 2, $CO_2CH_2CH_3$), 5.5–5.75 (m, 1, C=$CHCO_2$) 6.32 and 6.37 (2 d, J = 16 Hz, 1, 2*E* and 2*Z* C-5 *H*C=CH, respectively), 6.1 and 7.52 (2 d, J = 16 Hz, 1, 2*E* and 2*Z* C-4 HC=C*H*, respectively). The assignments agree closely with those reported for methyl (2*E*,4*E*)- and (2*Z*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienoate.[19b]

A 5.8-g (21 mmol) portion of diene ester **15** was dissolved in 100 mL of Et_2O, cooled to 0 °C, and treated with 45 mL (45 mmol) of a 1 M solution of DIBAL in hexane over a 15-min period. The mixture was warmed up to room temperature over 30 min, at which time TLC (1:1 hexane/Et_2O) indicated that reaction was complete. MeOH (5 mL) was added dropwise to the reaction mixture, with cooling, to decompose excess reagent, and the resultant white precipitate was filtered (500-mL ether wash). The ethereal solution was concentrated to give 4.88 g of a colorless, viscous oil, which was purified on 150 g of silica gel with 25% Et_2O/hexane to give 4.2 g of a mixture of the 2*E* and 2*Z* isomers of **16**, followed by 0.5 g of the pure 2*E*,4*E* isomer (96% total yield): IR (film) 3250 (OH), 2900, 1470, 1390, 1370, 1090, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.33–0.55 (m, 2, cyclopropyl CH_2), 0.83, 0.94, 1.00 (3 s, 9, C_R-16, C_R-17, and C_R-18 CH_3), 1.05–1.75 [m, 6, $(CH_2)_3$], 1.77 (s, 3, C=CCH_3), 4.21 (d, J = 7 Hz, 2, CH_2OH), 5.53 (t, J = 7 Hz, 1, C=CH), 5.93 (s, 2, C_R-7 and C_R-8 HC=CH); MS calcd for $C_{16}H_{26}O$, 234.1984; found, 234.1975. ^1H NMR studies on the isomer mixture showed that the signal for the C_R-9 methyl protons appeared at lower field (δ 1.87) for the 2*Z* isomer of **16** than for the 2*E* isomer (δ 1.77). Also, in the 2*E* isomer, H_{7R} and H_{8R} appear

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as a singlet at δ 5.93, whereas they appear as two doublets (J = 16 Hz) at δ 6.37 (H_{8R}) and 5.95 (H_{7R}) in the 2Z isomer. These ^{1}H NMR signals were assigned by comparison with those of (2E,4E)- and (2Z,4E)-3-methyl-5-(3,3-ethano-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadien-1-ols (**44**) and (2E,4E)- and (2Z,4E)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienols.[19b,c]

(*E*)-3-Methyl-5-(2,2,6-trimethylbicyclo[4.1.0]hept-1-yl)-2,4-pentadienal (17). A mixture of 3.5 g (15 mmol) of the alcohol mixture **16** [7:1 (2E)/(2Z) by ^{1}H NMR] and 60 g (0.69 mol) of activated MnO_2 (Alfa) in 50 mL of hexane and 150 mL of CH_2Cl_2 was stirred at room temperature for 60 h and then filtered through Celite (300 mL of CH_2Cl_2 wash). The filtrate and washings were concentrated to give a colorless oil, which was chromatographed on 120 g of silica gel with 25% Et_2O/hexane to give 2.75 g (79% yield) of a mixture of aldehydes. The aldehydes were separated by two passes on preparative LC (4% Et_2O/hexane) to afford 1.6 g (46% yield) of the pure 2E-isomer **17** as a colorless oil and 0.47 g (14% yield) of its 2Z isomer, also a colorless oil. **2*E*,4*E*-Isomer 17**: IR (film) 2950, 2750 (CHO), 1720 (C=O), 1680, 1640, 1450, 1210, 1110, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.57, 0.72 (2 d, J = 6 Hz, 2, cyclopropyl CH_2), 0.92, 1.00, 1.15 (3 s, 9, C_R-16, C_R-17, and C_R-18 CH_3), 1.1–1.9 [m, 6, $(CH_2)_3$], 2.35 (d, J = 1 Hz, 3, C=CCH_3), 5.98 (d, J = 8 Hz, 1, C=CH), 6.19 (d, J = 16 Hz, 1, C_R-7 *H*C=CH), 6.70 (d, J = 16 Hz, 1, C_R-8 HC=C*H*), 10.18 (d, J = 8 Hz, 1, CHO); MS calcd for $C_{16}H_{24}O$, 232.1827; found, 232.1844. **2*Z*,4*E*-Isomer**: IR (film) 2950, 2750 (CHO), 1720 (C=O), 1680, 1640, 1430, 1350, 1250, 1100, 1060, 960, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.5–0.8 (m, 2, cyclopropyl CH_2), 0.92, 1.02, 1.13 (3 s, 9, C_R-16, C_R-17, and C_R-18 CH_3), 1.1–2.0 [m, 6, $(CH_2)_3$], 2.10 (s, 3, C=CCH_3), 5.88 (d, J = 8 Hz, 1, C=CH), 6.50 (d, J = 16 Hz, 1, C_R-8 HC=C*H*), 7.10 (d, J = 16 Hz, 1, C_R-7 *H*C=CH), 10.23 (d, J = 8 Hz, 1, CHO). The configuration of the isomers was assigned on the basis of their ^{1}H NMR signals, which agree closely with those of (2Z,4E)- and (2E,4E)-3-methyl-5-(3,3-ethano-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienals (**45** and **46**).

Ethyl (*E*)-3,7-Dimethyl-9-(2,2,6-trimethylbicyclo[4.1.0]-hept-1-yl)-2,4,6,8-nonatetraenoate [Ethyl (*E*)-5,6-Methano-5,6-dihydroretinoate, 18]. A solution of 2.11 g (8 mmol) of the phosphonate **6** in 4 mL of THF at −78 °C was treated with 5 mL of a 1.46 M solution of n-BuLi in hexane (7.3 mmol). The solution was stirred for 10 min; then 1.5 g (6.46 mmol) of **17** in 5 mL of THF was added. The mixture was warmed up to room temperature over a period of 1 h. After another 2 h, TLC (1:1 hexane/Et_2O) indicated that the reaction was complete. The reaction mixture was diluted with 50 mL of brine and extracted with hexane (3 × 50 mL). The combined hexane extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4), and concentrated to give 3.0 g of a yellow viscous oil, which was passed over a precolumn of 120 g of silica gel with 25% Et_2O/hexane to give 1.6 g of a very pale yellow oil. LC analysis (0.5% Et_2O/hexane, 260 nm, Radialpak B) revealed four peaks: t_R 13.4 (21%), 15.8 (shoulder, 2%), 16.7 (13%), and 19.5 min (64%). The three major isomers were separated by multiple passes on preparative LC (0.5% Et_2O/hexane, 1% EtOAc/hexane). A total of 0.8 g (36% yield) of the desired *all-E*-isomer **18** was obtained as a very pale yellow oil, which gradually crystallized on standing: mp 57–58 °C; LC (Radialpak B, 0.5% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 16.7 (0.1%) and 19.5 min (99.9%); LC (Radialpak A, 5% H_2O/MeOH, 2.0 mL/min, 260 nm) t_R 12.9 min (100%); IR (film) 2900, 1720 (C=O), 1600, 1450, 1350, 1250, 1150, 1050, 980, 880, 830 cm^{-1}; UV (EtOH) λ_{max} 344 nm (ε 4.8 × 10^4), 234 (4.0 × 10^3); MS calcd for $C_{23}H_{34}O_2$, 342.2559; found, 342.2540. About 0.17 g (8% yield) of the 13$_R$$Z$-isomer **19** was obtained as a pale yellow oil: LC (Radialpak B, 0.5% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 13.4 (99%) and 15.8 min (1%); LC (Radialpak A, 5% H_2O/MeOH, 2 mL/min, 260 nm) t_R 10.6 min (>99%); IR (film) 2900, 1720 (C=O), 1600, 1450, 1380, 1240, 1160, 1060, 980 cm^{-1}; UV (EtOH) λ_{max} 346 nm (ε 3.5 × 10^4), 238 (7.1 × 10^3); MS calcd for $C_{23}H_{34}O_2$, 342.2559; found, 342.2540. Also, 0.08 g (4% yield) of the 9$_R$$Z$-isomer **20** was obtained: LC (Radialpak B, 0.5% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 16.7 min (>99%); LC (Radialpak A, 5% H_2O/MeOH, 2 mL/min, 260 nm) t_R 11.9 min (100%); MS calcd for $C_{23}H_{34}O_2$, 342.2559; found, 342.2557.

The stereochemistry of these isomers was determined by their 360-MHz ^{1}H NMR spectra. Thus, the C_R-20 methyl protons in the 13$_R$$Z$-isomer **19** are shifted upfield by about 0.3 ppm to δ 2.05 relative to those for **18** (δ 2.34) and **20** (δ 2.36). In the 9$_R$$Z$-isomer **20**, the signals of H_{7R} and H_{8R} are differentiated, appearing at δ 6.11 and 6.58, respectively, rather than as a single peak at δ 6.08, as they do for both **18** and **20**. Changes in chemical shifts of similar magnitude have been reported for similar isomers.[19]

Ethyl (*E*)-3-(2,2,6-Trimethylbicyclo[4.1.0]hept-1-yl)-2-propenoate (22). To a solution of 20 g (89 mmol) of triethyl phosphonoacetate in 30 mL of THF at −60 °C was added 61 mL of 1.44 M n-BuLi (88 mmol) in hexane. A solution of 7.4 g (44.5 mmol) of **12** in 10 mL of THF was then added. The mixture was warmed to room temperature and stirred for 16 h. ^{1}H NMR analysis of a worked-up aliquot indicated that about 45% of the aldehyde remained unreacted. A second batch of the anion of triethyl phosphonoacetate was prepared from 20 g (89 mmol) of triethyl phosphonoacetate in 20 mL of THF at −60 °C and 60 mL of 1.44 M n-BuLi (86.4 mmol) in hexane and added to the reaction mixture. After stirring at room temperature for 6 h and storage at 0 °C for 60 h, the reaction mixture was diluted with 50 mL of H_2O and extracted with 1:1 hexane/Et_2O (3 × 100 mL). The organic layer was washed with brine (2 × 100 mL), dried (Na_2SO_4), and concentrated to give a light yellow oil. ^{1}H NMR indicated that it still contained about 15% of unreacted aldehyde. The crude product was passed over 200 g of silica gel (5% Et_2O/hexane) to give 9.0 g of a colorless oil. To this oil dissolved in 25 mL of THF at 0 °C was added 16 mL of 0.5 M 9-BBN (8 mmol) in THF. The mixture was allowed to warm to room temperature over 30 min. After another 30 min, the mixture was concentrated to about 15 mL and diluted with 200 mL of Et_2O before 0.45 mL (7.5 mmol) of ethanolamine was added. The mixture was kept at 0 °C for 1 h, filtered, concentrated, and chromatographed over 150 g of silica gel with 5% Et_2O/hexane. A total of 8.1 g (77%) of **22** was obtained as a colorless oil: IR (film) 2950, 1730 (C=O), 1650, 1460, 1375, 1320, 1280, 1180, 1050, 1000, 960, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.48 and 0.62 (2 d, J = 5 Hz, 2, cyclopropyl CH_2), 0.87, 0.97, and 1.12 (3 s, 9, C_R-16, C_R-17, and C_R-18 CH_3), 1.05–1.85 [m, 6, $(CH_2)_3$], 1.27 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 4.15 (q, J = 7 Hz, 2, $CO_2CH_2CH_3$), 5.68 (d, J = 15.5 Hz, 1, C_R-7 *H*C=CH), 7.22 (d, J = 15.5 Hz, 1, C_R-8 HC=C*H*); MS calcd for $C_{15}H_{24}O_2$, 236.1776; found, 236.1759.

(*E*)-3-(2,2,6-Trimethylbicyclo[4.1.0]hept-1-yl)-2-propenal (24). A solution of 8.0 g (33.9 mmol) of **22** in 50 mL of Et_2O was cooled in an ice bath while 100 mL of 1 M DIBAL (0.1 mol) in hexane was added over a 10-min period. The mixture was allowed to warm to room temperature over a 30-min period and stirred for 1 h. MeOH (5 mL) was added and the mixture was left to stand for 1 h. The precipitated aluminum salts were filtered (800-mL ether wash). The filtrate was concentrated to give 7.2 g of a colorless oil, which was chromatographed on 120 g of silica gel with 1 L of 15% Et_2O/hexane and 1 L of 40% Et_2O/hexane to give 6.3 g (93% yield) of the alcohol **23**: IR (film) 3350 (OH), 2950, 1670, 1460, 1385, 1365, 1210, 1110, 1080, 1020, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.43 (m, 2, cyclopropyl CH_2), 0.87, 0.98, and 1.05 (3 s, 9, C_R-16, C_R-17, and C_R-18 CH_3), 1.0–1.8 [m, 6, $(CH_2)_3$], 2.33 (br s, 1, OH), 4.12 (br s, 2, CH_2OH), 5.50 (m, 1, C_R-8 HC=C*H*), 5.93 (d, J = 16 Hz, 1, C_R-7 *H*C=CH); MS calcd for $C_{13}H_{22}O$, 194.1671; found, 194.1161.

To a solution of 6.0 g (31 mmol) of **23** in 50 mL of hexane and 150 mL of CH_2Cl_2 was added 80 g (0.92 mol) of activated MnO_2. The mixture was stirred at room temperature for 16 h and filtered. The filtrate was concentrated to give 5.1 g of a colorless oil, which was chromatographed on 120 g of silica gel with 1 L of 5% EtOAc/hexane and 600 mL of 30% EtOAc/hexane to give 4.7 g of aldehyde **24**, as a colorless oil, and 0.38 g of the unreacted alcohol **23**, which was treated with 5 g (57 mmol) of MnO_2, in 20 mL of CH_2Cl_2 for 18 h to give another 0.3 g of **24**. The total yield of **24** was 84%: IR (film) 2950, 2750 (CHO), 1710 (C=O), 1640, 1470, 1400, 1380, 1140, 990 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.63 and 0.83 (2 d, J = 5 Hz, 2, cyclopropyl CH_2) 0.93, 1.03, and 1.23 (3 s, 9, C_R-16, C_R-17, and C_R-18 CH_3), 1.1–1.95 [m, 6, $(CH_2)_3$], 6.09 (dd, J = 8 and 16 Hz, 1, C_R-8 HC=C*H*), 7.23 (d, J = 16 Hz, 1, C_R-7 *H*C=CH), 9.63 (d, J = 8 Hz, 1, CHO). The coupling constant (16 Hz) of the 7_R and 8_R vinylic protons indicates that these two protons are trans to each other;[19c] thus, the E configuration at this double bond was preserved.

1-(2,2,6-Trimethylbicyclo[4.1.0]hept-1-yl)-1-buten-3-one (26). To 5.5 mL (16.1 mmol) of 2.9 M MeMgBr in Et_2O and 25 mL of anhydrous THF was added 2.8 g (14.6 mmol) of **24** in 5 mL of THF over a 15-min period. The reaction mixture was maintained at 20 °C for 30 min when TLC (1:1 Et_2O/hexane) indicated that reaction was complete. Saturated NH_4Cl solution (2.5 mL) was added, and the reaction mixture was filtered (100-mL Et_2O wash). The filtrate was concentrated to give 3.4 g of a pale yellow oil, which was purified on a 150-g column of silica gel (20% EtOAc/hexane) to give 2.85 g (94%) of the pure secondary alcohol **25**: IR (film) 3350 (OH), 2950, 1680, 1470, 1400, 1380, 1300, 1170, 1080, 990, 960, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.42 and 0.53 (2 d, J = 4 Hz, 2, cyclopropyl CH_2), 0.90, 0.98, and 1.07 (3 s, 9, C_R-16, C_R-17, and C_R-18 CH_3), 1.0–1.8 [m, 6, $(CH_2)_3$], 1.29 (d, J = 6 Hz, 3, C_R-19 CH_3), 1.83 (s, 1, OH), 4.43 (q, J = 6 Hz, 1, C*H*OH), 5.53 (dd, J = 6 and 16 Hz, 1, C_R-8 HC=C*H*), 6.00 (d, J = 16 Hz, 1, C_R-7 *H*C=CH).

A mixture of 2.8 g (13.4 mmol) of **25** and 30 g (0.34 mol) of activated MnO_2 in 50 mL of CH_2Cl_2 and 20 mL of hexane was stirred at room temperature for 16 h. After filtration (200-mL ether rinse) and concentration, chromatography over 100 g of silica gel with 10% and 20% EtOAc/hexane gave 2.0 g (72%) of **26**, as a colorless oil, and 0.6 g of recovered **25**: IR (film) 2950, 1670 (C=O), 1620, 1450, 1360, 1250, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55 and 0.72 (2 d, J = 5 Hz, 2, cyclopropyl CH_2), 0.90, 1.00, and 1.16 (3 s, 9, C_R-16, C_R-17, and C_R-18 CH_3), 1.10–1.90 [m, 6, $(CH_2)_3$], 2.27 (s, 3, $COCH_3$), 6.03 (d, J = 16 Hz, 1, C_R-8 HC=C*H*), 7.17 (d, J = 16 Hz, 1, C_R-7 HC=C*H*); MS calcd for $C_{14}H_{22}O$, 206.1671; found, 206.1675.

(*E*)-1-(4-Carbethoxyphenyl)-2-methyl-4-(2,2,6-trimethylbicyclo[4.1.0]hept-1-yl)-1,3-butadiene (28). To a solution of 3.6 g (12 mmol) of diethyl *p*-carbethoxybenzylphosphonate (**27**)[15] in 10 mL of THF at −60 °C was added 8.2 mL of 1.4 M *n*-BuLi (11.5 mmol) in hexane. The cooling bath was removed and 1.2 g (5.8 mmol) of **26** in 6 mL of THF was added. The mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with 50 mL of H_2O and extracted with 10% EtOAc/hexane (2 × 50 mL). The organic layer was washed with brine (2 × 100 mL), dried (Na_2SO_4), and concentrated to give 3.5 g of a yellow oil. Chromatography on 100 g of silica gel (5% EtOAc/hexane) gave 1.5 g of a product mixture, which showed six peaks on LC analysis (Radialpak B, 1% Et_2O/hexane, 2 mL/min, 260 nm): t_R 7.6 (1%), 8.2 (1.5%), 10.2 (75.5%), 11.6 (20%), 14.2 (1%), and 17.3 min (1%). Multiple passes on preparative LC (0.4% Et_2O/hexane) using the recycle technique afforded 0.8 g (39% yield) of **29** and 0.33 g (16% yield) of the desired isomer **28** as light yellow viscous oils. **$7_RE,9_RE$-Isomer 28**: LC (Radialpak B, 1% Et_2O/hexane, 2 mL/min, 260 nm) t_R 11.6 min (>99%); LC (Radialpak A, 5% H_2O/MeOH, 2 mL/min, 260 nm), t_R 9.8 min (100%); IR (film) 2950, 1730 (C=O), 1610, 1280, 1110, 880, 770 cm^{-1}; UV (EtOH) λ_{max} 390 nm (ϵ 2.54 × 10^4), 232 (1.12 × 10^4); MS calcd for $C_{24}H_{32}O_2$, 352.2402; found, 352.2397. **$7_RE,9_RZ$-Isomer 29**: LC (Radialpak B, 1% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 10.2 min (99.9%); LC (Radialpak A, 5% H_2O/MeOH, 2 mL/min, 260 nm) t_R 9.8 min (100%); IR (film) 2950, 1730 (C=O), 1600, 1470, 1380, 1280, 1190, 1110, 1030, 890, 770, 710 cm^{-1}; UV (EtOH) λ_{max} 306 nm (ϵ 2.0 × 10^4), 231 (1.7 × 10^4); MS calcd for $C_{24}H_{32}O_2$, 352.2402; found, 352.2380.

The structural assignments for **28** and **29** are based on comparison of ^1H NMR spectra of similar compounds synthesized by us and others.[19b] For example, in the spectra of the 9_RE isomers, the signals for H_{7R} and H_{8R} are less than 0.1 ppm apart or appear as a single peak. In contrast, in the spectra of the 9_RZ isomers, the H_{8R} signal is shifted downfield by 0.3–0.5 ppm relative to that of H_{7R}. In (*E*)-1-(2-hydroxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene,[5] the H_{7R} and H_{8R} signals appear at δ 6.16 and 6.19 ppm, respectively, whereas in the corresponding 9_RZ isomer, they appear at δ 6.21 and 6.72. Similar shifts were found for **28** and its 9_RZ isomer. The spectral assignments were also in agreement with those of **30** and its 9_RZ isomer.[13]

6,6-Dimethyl-1-(hydroxymethyl)-2-(methyl-d_3)-1-cyclohexene-3,3-d_2 (34). A solution of 1 M NaOMe was prepared from 0.81 g (0.035 g-atom) of Na in 35 mL of MeOH-*d* (Aldrich, 99.5 atom % d). Purified α-cyclocitral (5.32 g, 35 mmol) in 3 mL of MeOH-*d* was introduced under argon. The orange solution was allowed to stand for 70 h, acidified with 3.5 g (55 mmol) of HOAc-d_4 (Aldrich, 99.5 atom % d), and diluted with 200 mL of water. The deuterated crude β-cyclocitral (**33**) was extracted into 100 mL of hexane, washed with brine (2 × 30 mL), and dried (Na_2SO_4); then the solvent was evaporated. The product was immediately dissolved in 3 mL of MeOH-*d* and added to 35 mL of a fresh solution of NaOMe in MeOH-*d* prepared as before. The second equilibration was allowed to proceed for 91 h and then quenched with 3 g (47 mmol) of HOAc-d_4. The aldehyde was isolated. A third equilibration was performed similarly. The base was neutralized after 69 h, and 4.7 g of **33** was obtained as an orange oil.

The total crude reaction product (4.7 g, 30 mmol) in 15 mL of THF was treated at room temperature under argon with 72 mL of 0.5 M 9-BBN (36 mmol) in THF. The reaction mixture was allowed to stand at room temperature for 24 h. The solvent was evaporated, the viscous residue was dissolved in 400 mL of ether, and 2.2 g (36 mmol) of 2-aminoethanol was added with stirring. After 80 min at room temperature and 1.5 h at −5 °C, the precipitate was filtered and washed with 100 mL of ether, and the filtrate was evaporated. The residue was chromatographed on a 4.5 × 40 cm silica gel column. Elution with 1.5-L volumes of 5, 6, 7, and 8% EtOAc/hexane (100- to 200-mL fractions) afforded a liquid mixture of deuterated α- and β-cyclogeraniols, followed by 3.90 g (70%) of crystalline β-cyclogeraniol-d_5 (**34**): IR (film) 3350 (OH), 2260, 2210, 2180, 2130, 2080 (CD), 1655, 1420, 1335, 1305, 1250, 1170, 1120, 1015, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 [s, 6, $(CH_3)_2C$], 1.25–2.0 [m, 4, C_R-2 and C_R-3 CH_2, 1, OH], 4.15 (s, 2, CH_2O); MS, m/e 157 (d_3), 0.4%; 158 (d_4), 6.4%; 159 (d_5), 87.4%; 160 (d_6), 5.8%; calcd for $C_{10}H_{13}D_5O$, 159.1671; found, 159.1670.

[6,6-Dimethyl-2-(methyl-d_3)-1-cyclohexen-3,3-d_2-1-yl]methyltriphenylphosphonium Bromide (36). The deuterated β-cyclogeraniol **34** (3.18 g, 20 mmol) dissolved in 6 mL of hexane and 25 mL of Et_2O containing 0.5 mL of pyridine was treated with a solution of 1.0 mL (10 mmol) of PBr_3 in 5 mL of hexane over a 65-min period at −10 to −15 °C. The mixture was cooled for 1 h and then allowed to warm to room temperature over 1.5 h. The product was extracted into 50 mL of hexane from 125 mL of ice–brine and washed with 50-mL volumes of brine, saturated $NaHCO_3$, and brine (twice). The solution was dried (Na_2SO_4) and concentrated at reduced pressure. The crude bromide was dissolved in 10 mL of CH_2Cl_2 containing 7.1 g (26 mmol) of $(C_6H_5)_3P$ and allowed to stand at room temperature for 40 h. The residue remaining after concentration was triturated with 80 mL of EtOAc to separate out an oil, which rapidly crystallized. After 7 h at room temperature and 70 h at −5 °C, the solid was filtered, dried at 120 °C (0.2 mm) for 4.5 h, washed successively with 100-mL portions of EtOAc and hexane, and again dried at 120–130 °C (0.2–0.4 mm) for 6 h. The white salt **36** weighed 8.10 g (84%): mp 206–207.5 °C; IR (mull) 2150, 2070 (CD), 1590, 1430, 1400, 1340, 1315, 1250, 1155, 1105, 1080, 1000, 890, 855, 815, 735, 720, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 [s, 6, $(CH_3)_2C$], 1.3–1.7 (m, 4, C_R-2 and C_R-3 CH_2, 0.35, remaining allylic CH_2 and CH_3), 4.37 (d, J = 14 Hz, 2, CH_2P), 7.6–8.0 [m, 15, $(C_6H_5)_3P$].

Ethyl (*E*)-Retinoate-4,4,18,18,18-d_5 (38). To a suspension of 7.9 g (16.3 mmol) of the deuterated β-cyclogeranylphosphonium salt **36** in 15 mL of THF at −30 °C under argon was added 13.5 mL of 1.19 M *n*-BuLi (16 mmol) in hexane. The deep red suspension was allowed to warm to 0 °C over a 1-h period before a solution of 3.75 g (18 mmol) of freshly recrystallized (cyclohexane) (*E*)-7-carbethoxy-2,6-dimethyl-2,4,6-heptatrienal (**37**) in 6 mL of THF was introduced. The reaction mixture was stirred at room temperature for 17 h and then heated at 60 °C for 1 h. The dark suspension was cooled next, poured into 120 mL of water containing 1 mL of HOAc and 0.1 g of TBHQ, and extracted with 100 mL of 10% EtOAc/hexane. The extract was washed twice with brine, dried (Na_2SO_4), and concentrated under nitrogen. The residue was chromatographed on a 4 × 40 cm silica gel column (1.5% EtOAc/hexane). The 4.17 g of crude ester, a yellow gum, contained a minor, less-polar impurity as shown by silica gel TLC (10% EtOAc/hexane) and, therefore, was repurified by LC on two Waters Prep Pak-500/silica gel cartridges in series (1% EtOAc/hexane). The resulting yellow oil (**38**) weighed 3.53 g (66%): IR (film) 2230, 2180, 2150, 2110, 2080 (CD), 1705 (C=O), 1610, 1585, 1390, 1240 (CO), 1150, 1100, 1050, 970, 880, 830 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 1.05 [s, 6, $(CH_3)_2C$], 1.30 (t, J = 7 Hz, 3, CH_3CH_2O), 1.4–1.75 [m, 4, C_R-2 and C_R-3 CH_2], 2.02 (s, 3, C_R-19 CH_3), 2.36 (d, J = 1 Hz, 3, C-20 CH_3), 4.19 (q, J = 7 Hz, 2, CH_3CH_2O), 5.78 (s, 1, C_R-14 HC=C), 6.0–6.42 (ms, 4, C_R-7 and C_R-8 HC=CH, C_R-10 and C_R-12 HC=C), 7.02 (dd, J = 15 and 12 Hz, 1, C_R-11 HC=CH); ^{13}C NMR 167.2 (C_R-15), 152.7 (C_R-13), 139.5 (C_R-9), 137.9 (C_R-6), 137.3 (C_R-8), 135.3 (C_R-12), 130.9 (C_R-11), 129.6 (C_R-5, C_R-10), 128.7 (C_R-7), 118.7 (C_R-14), 59.6 (ethyl CH_2), 39.7 (C_R-2), 34.3 (C_R-1), 29.0 (C_R-16, C_R-17), 19.1 (C_R-3), 14.4 (ethyl CH_3), 13.9 (C_R-20), 12.9 ppm (C_R-19); UV (EtOH) λ_{max} 355 nm (ε 4.52 × 10^4); MS, m/e 331 (d_3), 0.6%; 332 (d_4), 7.1%; 333 (d_5), 90.5%; 334 (d_6), 1.1%; 335 (d_7), 0.5%; calcd for $C_{22}H_{27}D_5O_2$, 333.2716; found, 333.2696.

(*E*)-Retinoic Acid-*4,4,18,18,18-d*$_5$ (39). A solution of 1.48 g (4.4 mmol) of the deuterated ethyl retinoate **38** in 4 mL of EtOH was added under argon to a degassed (4 times) solution of 0.7 g (12 mmol) of KOH in 2.5 mL of H_2O and 4 mL of EtOH. The suspension was heated to 80 °C for a 20-min period, and the temperature was maintained there for 12 min. The oil dissolved at 80 °C. The cooled yellow solution was acidified with 10 mL of 50% HOAc and diluted with 50 mL of H_2O. The precipitated acid was extracted into Et_2O (2 × 30 mL). The ethereal solution was washed with brine (2 × 15 mL) and dried (Na_2SO_4). The crude acid remaining after concentration was extracted under nitrogen with 20 mL of hot MeOH. The first crop of bright yellow crystals, mp 175.5–177.5 °C, was obtained on cooling and weighed 0.75 g (56%): LC (μBondapak/C18, 80% CH_3CN/H_2O, 2.0 mL/min, 280 nm) t_R 1.3 (0.4%), 4.4 min (99.6%); IR (mull) 3300–2300 (OH), 1685 (C=O), 1600, 1570, 1415, 1345, 1265, 1250, 1185, 1165, 970, 950, 925 cm^{-1}; UV (EtOH) λ_{max} 344 nm (ε 4.45 × 10^4); MS, m/e 303 (d_3), 0.8%; 304 (d_4), 7.0%; 305 (d_5), 90.5%; 306 (d_6), 1.7%; calcd for $C_{20}H_{23}D_5O_2$, 305.2403; found, 305.2386.

The *E* configuration of **39** was established by comparison of the 100-MHz ^{1}H NMR spectrum with that of an authentic sample of (*E*)-retinoic acid and with the published spectra[19a] of other isomers. The ^{13}C NMR spectrum was compared with the published spectra[20] of retinoic acid isomers and was also in agreement with the recorded spectrum of the *E* isomer, except for the absence of the signals for C_R-4 at 33.3 ppm and C_R-18 at 21.6 ppm.

Ethyl (4*E*)-3-Methyl-5-(3-oxo-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienoate (41). A reported procedure[17] was modified. To a solution of 39.8 g (0.15 mol) of ethyl ionylideneacetate in 500 mL of *t*-BuOH and 50 mL of H_2O was added 28.1 g (0.15 mol) of NBS. The orange solution was stirred at room temperature for 7 h, then diluted with 500 mL of Et_2O, washed with ice–water (2 × 100 mL), saturated $NaHCO_3$ (2 × 50 mL), and brine (2 × 50 mL), and dried (Na_2SO_4). Concentration afforded an orange oil, which was purified by preparative LC (10% EtOAc/hexane) to give 28.0 g of a fraction containing starting material, 7.6 g of ketone **41**, as a viscous yellow oil [IR (film) 1710, 1680, 1240, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 and 1.23 [2 s, 6, $C(CH_3)_2$], 1.27 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 1.82 and 1.88 (2 s, 3, C=CCH_3), 2.17 and 2.42 (2 d, J = 1 Hz, 3, CH_3C=CH), 4.25 (q, J = 7 Hz, 2, CO_2CH_2), 5.80–6.0 (m, 1, C=$CHCO_2$), 6.23 and 6.60 (2 d, J = 16 Hz, 1, 2*E* and 2*Z* C-5 *H*C=CH), 6.67 and 7.85 (2 d, J = 16 Hz, 1, 2*E* and 2*Z* C-4 HC=C*H*)], and 8.1 g of the corresponding alcohol, also as a viscous yellow oil [IR (film) 3400 (OH), 1720 (C=O), 1470, 1040 cm^{-1}].

The recovered starting material fraction was recycled with 21 g (0.12 mol) of NBS, 400 mL of *t*-BuOH, and 40 mL of H_2O to afford, after LC purification, 12.6 g of a nonpolar fraction, 6.1 g of ketone, and 6.2 g of alcohol. Recycling of the nonpolar fraction did not produce any of the desired two products. The yield of the ketone was 33% and that of the alcohol was 34%.

The 14.3 g (0.051 mol) of alcohol was oxidized with 100 g (1.15 mol) of MnO_2 in 300 mL of CH_2Cl_2 for 43 h. Dilution with 100 mL of CH_2Cl_2, filtration (EtOAc rinse), concentration, and purification by LC (10% EtOAc/hexane) afforded 4.3 g (30% yield) of **41**. The total yield of ketone was therefore 43%. Spectral data indicated that it was a 6:4 mixture of 2*E* and 2*Z* isomers.

Ethyl (4*E*)-3-Methyl-5-(3,3-methylene-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienoate (42). To a mechanically stirred mixture of 17.6 g (70 mmol) of methyltriphenylphosphonium bromide in 100 mL of THF (distilled from $LiAlH_4$) and 20 mL of *t*-BuOH was added dropwise a solution of 7.3 g (65 mmol) of *t*-BuOK in 60 mL of THF and 60 mL of *t*-BuOH over a period of 15 min. The bright yellow suspension was stirred for 30 min and then cooled in an ice bath while 17.6 g (64 mmol) of **41** in 75 mL of THF was added. The deep brown mixture was stirred overnight at room temperature, diluted with 500 mL of Et_2O containing 1 mL of HOAc, washed with water (2 × 100 mL) and brine, dried (Na_2SO_4), and concentrated (<35 °C) at reduced pressure. Triphenylphosphine oxide was removed from the 24.9 g of residue by trituration with 10% EtOAc/hexane. The resultant deep orange oil (TLC: 5% EtOAc/hexane, R_f 0.71, **42**; 0.41, **41**) was purified in two batches by LC (10% EtOAc/hexane) to give 3.57 g (20% recovery) of unreacted starting material and 9.03 g (52% yield, 64% yield based on recovered ketone) of *exo*-methylene triene ester **42** as an unstable, readily polymerizable yellow oil, the ^{1}H NMR spectrum of which indicated an approximate 6:4 ratio of 2*Z* and 2*E* isomers: IR (film) 3100, 1710 (C=O), 1620, 1460, 1240, 1160, 1060, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 and 1.08 [2 s, 6, 2*E* and 2*Z* $C(CH_3)_2$], 1.28 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 1.85 and 1.93 (2 s, 3, 2*E* and 2*Z* C=CCH_3), 2.07 and 2.35 (2 s, 3, 2*Z* and 2*E* CH_3C=CCO_2), 4.20 (q, J = 7 Hz, 2, $CO_2CH_2CH_3$), 4.92 (d, J = 8 Hz, 2, C=CH_2), 5.70 and 5.77 (2 m, 1, 2*Z* and 2*E* C=$CHCO_2$), 6.07 and 6.35 (2 br d, J = 15 Hz, 1, 2*E* and 2*Z* C-5 *H*C=CH), 6.63 and 7.39 (2 br d, J = 15 Hz, 1, 2*E* and 2*Z* C-4 HC=C*H*); MS calcd for $C_{18}H_{26}O_2$, 274.1933; found, 274.1930. ^{1}H NMR spectral assignments were made by comparison with those reported[19a,b] for methyl (2*E*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienoate [δ 2.33 (C-3 CH_3), 5.74 (H_2), 5.90–6.19 (H_4)] and its 2*Z*,4*E* isomer [δ 2.45 (C-3 CH_3), 5.58 (H_2), 7.53–7.81 (H_4)] and with the ^{1}H NMR signals for the separated cyclopropyltrienals **45** and **46**.

(4*E*)-3-Methyl-5-(3,3-ethano-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadien-1-ol (44). A Zn–Cu couple was prepared from 10.98 g (0.08 mol) of $Cu(OAc)_2 \cdot H_2O$ and 76.0 g (1.16 mol) of Zn dust in 640 mL of HOAc at 100 °C, washed with 500 mL of HOAc and 800 mL of anhydrous Et_2O, and vacuum-dried. To the couple in 500 mL of Et_2O (distilled from $LiAlH_4$), heated to a gentle reflux in a 40 °C oil bath, was added an I_2 crystal and then 32 mL (0.40 mol) of CH_2I_2 in 50 mL of Et_2O over a 45-min period so that a gentle reflux rate was maintained. After the reaction began, slow mechanical stirring was started. Heating and stirring was continued for 45 min; then the mixture was diluted with 100 mL of Et_2O, and 7.4 g (27 mmol) of **42** in 50 mL of Et_2O was added dropwise. Heating at a gentle reflux was continued for 24 h, at which time ^{1}H NMR monitoring of a worked-up aliquot indicated that less than 5% of the starting material remained. Excess reagent was decomposed by the slow addition of ice–water to the ice-cooled reaction mixture. Workup was accomplished by dilution with 300 mL of Et_2O, 400 mL of cold 5% NaOH, and 200 mL of 10% NaOH. The aqueous layer was extracted with Et_2O (3 × 300 mL). The organic extract was washed with two 200-mL portions of 10% NaOH, water, and brine, dried (Na_2SO_4), and concentrated (<40 °C) at reduced pressure to afford 7.4 g of a yellow oil, which was chromatographed on 200 g of neutral Woelm alumina, activity III. Hexane eluted, in fractions 2 to 4 (450 mL), 5.2 g (67% yield) of the cyclopropyltriene ester **43** as a yellow oil: IR (film) 3180, 1720, 1610, 1240, 1150, 780 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.28–0.50 (m, 2, cyclopropyl H), 0.67–0.87 (m, 2, cyclopropyl H next to C=C), 1.07 and 1.10 [2 s, 6, 2*Z* and 2*E* $C(CH_3)_2$], 1.27 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 1.38 and 1.55 (2 s, 3, 2*Z* and 2*E* C=CCH_3), 2.03 and 2.33 (2 s, 3, 2*E* and 2*Z* CH_3C=CCO_2), 4.12 (q, J = 7 Hz, 2, CO_2CH_2), 5.57 and 5.65 (2 m, 1, 2*Z* and 2*E* C=$CHCO_2$), 6.0 and 6.42 (2 br d, J = 15 Hz, 1, 2*E* and 2*Z* C-5 *H*C=CH), 6.72 and 7.60 (2 br d, J = 15 Hz, 1, 2*E* and 2*Z* C-4 HC=C*H*). Et_2O (300 mL) eluted 2.1 g of more polar material, the IR and ^{1}H NMR spectra of which indicated an ester group, but only two vinylic protons, and no 3,3-ethano group.

Since the 2*E* and 2*Z* isomers of both the exocyclic olefin ester and the cyclopropyl ester were very difficult to separate by preparative LC, it was decided to separate the isomers at a subsequent step. To a stirred suspension of 0.83 g (21.9 mmol) of $LiAlH_4$ in 30 mL of Et_2O (distilled from $LiAlH_4$) cooled in an ice bath was added 5.2 g (18.0 mmol) of **43** in 10 mL of Et_2O. Because TLC (5% EtOAc/hexane) indicated starting material, after 1 h, 0.10 g (2.6 mmol) more of $LiAlH_4$ was added, and, after 2 h, 0.20 g (5.2 mmol) of $LiAlH_4$ was added. After 3.5 h, TLC indicated alcohol (R_f 0.14) and only a trace of ester (R_f 0.74). After

ice–water was added to the ice-cooled reaction mixture to decompose the excess $LiAlH_4$, the mixture was diluted with 200 mL of Et_2O, 30 mL of 10% NaOH, and 30 mL of water. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with two 30-mL portions of 10% NaOH, H_2O and brine, dried (Na_2SO_4), and concentrated to yield 4.5 g of a yellow oil, which was purified in two portions by preparative LC (30% Et_2O/hexane) to afford 0.27 g (5% recovery) of ester and 3.58 g (80% yield) of cyclopropyltrienol as a yellow oil. A sample of the more polar (2*E*,4*E*)-alcohol was isolated by more extensive preparative LC and characterized: TLC (30% Et_2O/hexane) R_f 0.16; IR (film) 3320 (OH), 1080, 1010 (cyclopropane), 970 cm^{-1}; ^1H NMR (CCl_4) δ 0.2–0.45 (m, 2, cyclopropyl H), 0.65–0.9 (m, 2, cyclopropyl H next to C=C), 1.03 [s, 6, $C(CH_3)_2$], 1.52 (s, 3, $C{=}CCH_3$), 1.82 (s, 3, $HC{=}CCH_3$), 1.93 (s, 1, OH), 4.17 (d, J = 6 Hz, 2, CH_2O), 5.52 (t, J = 6 Hz, 1, C=CH), 5.98 (s, 2, HC=CH); MS calcd for $C_{17}H_{26}O$, 246.1984; found, 246.1979. In contrast, the ^1H NMR spectrum of the (2*Z*,4*E*)-alcohol had a multiplet at δ 6.17 (2, HC=CH) and a broad singlet at δ 1.87 (3, $HC{=}CCH_3$). The ^1H NMR signals of the 2*E*,4*E* isomer were assigned by comparison with those of (2*E*,4*E*)- and (2*Z*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienols.[19b,c] In the case of this 2*E* isomer, the signals for H_4 and H_5 appear as a singlet at δ 6.08, while the 2*Z* isomer signals for these protons are multiplets at δ 6.00–6.27 and 6.33–6.60. The C-3 methyl signal appears at lower field (δ 1.87) for the 2*E* isomer than for the 2*Z* isomer (δ 1.91).

(*E*)-3-Methyl-5-(3,3-ethano-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal (46). A mixture of 3.3 g (13.7 mmol) of alcohol mixture 44 and 10.1 g (116 mmol) of MnO_2 (Alfa) in 50 mL of CH_2Cl_2 and 50 mL of pentane was mechanically stirred for 14 h. TLC (5% EtOAc/hexane) indicated that alcohol (R_f 0.15) and aldehyde [R_f 0.4 (2*E*), 0.5 (2*Z*)] were both present; therefore, 3.0 g (35 mmol) of MnO_2 was added, followed by another 3.0 g (35 mmol) of MnO_2 6 h later. After 38 h, TLC indicated that only a trace of alcohol remained. The mixture was diluted with 100 mL of CH_2Cl_2 and filtered (3 × 100 mL of CH_2Cl_2 rinse). Concentration afforded 3.05 g of a mobile yellow oil, which was purified by preparative LC (2% Et_2O/hexane), using multiple passes, to afford 0.52 g (16% yield) of the less polar (2*Z*,4*E*)-aldehyde 45 and 1.35 g (40% yield) of the (2*E*,4*E*)-aldehyde 46. **(2*Z*,4*E*)-Aldehyde 45**: TLC (30% Et_2O/hexane) R_f 0.46; IR (film) 3080, 2770, 2730, 1660, 1615, 1590, 1450, 1385, 1205, 1130, 1120, 1020, 970 cm^{-1}; ^1H NMR (CCl_4) δ 0.3–0.45 (m, 2, cyclopropyl H), 0.75–0.95 (m, 2, cyclopropyl H), 1.13 [s, 6, $C(CH_3)_2$], 1.40 (s, 3, $C{=}CCH_3$), 1.53 [m, 4, $(CH_2)_2$], 2.08 (s, 3, $HC{=}CCH_3$), 5.76 (d, J = 7 Hz, 1, $C{=}CHCHO$), 6.48 (d, J = 16 Hz, 1, C-5 $HC{=}CH$), 7.10 (d, J = 16 Hz, 1, C-4 $HC{=}CH$), 8.02 (d, J = 7 Hz, 1, CHO); UV (cyclohexane) λ_{max} 320 nm (ϵ 1.04 × 10^4), 258 (1.30 × 10^4); UV (EtOH) λ_{max} 330 nm (ϵ 0.89 × 10^4), 266 (1.13 × 10^4); MS calcd for $C_{17}H_{24}O_2$, 244.1827; found, 244.1835. **(2*E*,4*E*)-Aldehyde 46**: TLC (30% Et_2O/hexane) R_f 0.36; IR (film) 3080, 2750, 1660, 1620, 1600 (sh), 1450, 1380, 1220, 1110, 960 cm^{-1}; ^1H NMR (CCl_4) δ 0.3–0.55 (m, 2, cyclopropyl H), 0.7–0.95 (m, 2, cyclopropyl H), 1.07 [s, 6, $C(CH_3)_2$], 1.37 (s, 3, $C{=}CCH_3$), 1.53 [m, 4, $(CH_2)_2$], 2.28 (s, 3, $HC{=}CCH_3$), 5.82 (d, J = 7 Hz, 1, $C{=}CHCHO$), 6.08 (d, J = 16 Hz, 1, C-5 $HC{=}CH$), 6.67 (d, J = 16 Hz, 1, C-4 $HC{=}CH$), 8.05 (d, J = 7 Hz, 1, CHO); UV (EtOH) λ_{max} 340 nm (ϵ 1.13 × 10^4), 272 (1.40 × 10^4); MS calcd for $C_{17}H_{24}O$, 244.1827; found, 244.1823. The stereochemistry of these aldehydes was assigned on the basis of their ^1H NMR spectral signals, which were in close agreement with those reported for the ionylideneacetaldehyde isomers.[19b,c]

Ethyl (*E*)-3,7-Dimethyl-9-(3,3-ethano-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (Ethyl 4,4-Ethanoretinoate, 47). To a solution of 1.38 g (5.92 mmol) of 6[26] in 14 mL of THF (distilled from $LiAlH_4$) cooled in a −25 °C dry ice–isopropyl alcohol bath, 3.7 mL of 1.6 M *n*-BuLi (5.92 mmol) in hexane was added dropwise over a 2-min period. The yellow solution was stirred for 15 min before 1.35 g (5.52 mmol) of 46 in 4 mL of THF (2 mL of THF rinse) was added. The cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 2.5 h, at which time TLC (5% EtOAc/hexane) indicated product, R_f 0.95, and no aldehyde, R_f 0.4. After cooling in ice, the mixture was diluted with 300 mL of 5% EtOAc/hexane containing 2 drops of HOAc and washed with ice–water (2 × 100 mL). The aqueous wash was extracted with 5% EtOAc/hexane (2 × 200 mL). The combined EtOAc/hexane extracts were washed with two 200-mL portions of water and brine, dried (Na_2SO_4/$MgSO_4$), and concentrated at reduced pressure to an orange oil, which had the following peaks: t_R 4.4 (1%), 4.8 (3%), 5.2 (7%), 5.6 (1%), 6.2 (1%), 7.2 (83%), and 7.8 min (shoulder, about 3%) on LC analysis (2% Et_2O/hexane, 260 nm). Laborious multiple LC separations with 0.5% EtOAc/hexane, 1% Et_2O/hexane, and 2% Et_2O/hexane afforded purified samples of the two major isomers—the desired *all-E* product 47 and its 13_RZ isomer 48. A total of 0.57 g (29% yield) of 47, as yellow prisms from EtOAc, mp 75–77 °C, was obtained: LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 5.2 (0.5%) and 7.2 min (99%); LC (μBondapak/C18, 10% water/MeOH, 2.0 mL/min, 260 nm) t_R 6.5 min (100%); IR ($CHCl_3$) 1690, 1610, 1590, 1160, 975 cm^{-1}; UV (EtOH) λ_{max} 357 nm (ϵ 5.0 × 10^4), 240 (shoulder); MS calcd for $C_{24}H_{34}O_2$, 354.2559; found, 354.2564. Also, 0.24 g (13% yield) of the (13_RZ)-retinoid isomer 48 was obtained as a yellow oil in two fractions: (1) 134 mg, LC (Radialpak B, 2% Et_2O/hexane, 2.0 mL/min, 260 nm) t_R 5.2 min (>99%); (2) 111 mg, LC t_R 5.2 (94%) and 7.2 min (5%). The first fraction was characterized: LC (μBondapak/C18, 10% H_2O/MeOH, 2.0 mL/min, 260 nm) t_R 6.0 min (>99%); IR (CCl_4) 2860, 1710, 1605, 1590, 1230, 1150, 1050, 980 cm^{-1}; UV (EtOH) λ_{max} 359 nm (ϵ 4.0 × 10^4), 250 (1.1 × 10^4); MS calcd for $C_{24}H_{34}O_2$, 354.2559; found, 354.2564.

^1H NMR spectral peak and coupling constant assignments for isomers 47 and 48 were made by comparison with those reported for methyl (*E*)-retinoate,[19d] (*E*)-retinoic acid,[19d] (13*E*)- and (13*Z*)-retinal,[19c] and cyclopropanes.[26] Of particular interest is the δ 0.14 upfield shift of the C-20 CH_3 group and the δ 1.14 downfield shift of H_{12} in (13*Z*)-retinal compared to those of its 13*E* isomer,[19c] which agree with shift differences found in compounds 48 and 47. ^{13}C NMR chemical shifts and shift differences of 47 and 48 are in agreement with those reported for the methyl esters of (13*E*)- and (13*Z*)-retinoic acid,[20] particularly for C-10 (*E*, 129.5; *Z*, 130.4), C-12 (*E*, 135.2; *Z*, 129.5), C-13 (*E*, 152.8; *Z*, 151.1), C-14 (*E*, 118.2; *Z*, 116.2), and C-20 (*E*, 13.9; *Z*, 20.8).

ODC Assay. The ODC assay was performed as previously described[5] using procedures reported by Raineri et al.[27] and O'Brien et al.[28]

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Supplementary Material Available: Full ^1H and ^{13}C NMR data (Tables II and III, respectively) for compounds 7, 8, 18–20, 28, 29, 39, 47, and 48 (4 pages). Ordering information is given on any current masthead page.

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