($CDCl_3$, internal Me_4Si) δ 161.3 (s), 133.5, 133.3, 132.7, 132.2, 131.8, 131.4, 128.7, 127.7, 127.5, 118.5 (s), 117.6 (s), 60.2 (t), 14.0 (q), 10.8 (q). Anal. Calcd for $C_{20}H_{18}NO_2Cl$: C, 70.68; H, 5.34; N, 4.12. Found: C, 70.82; H, 5.19; N, 4.28.

Ethyl 5-(*p*-Chlorophenyl)-4-methyl-3-phenyl-2-pyrrolecarboxylate (8e). A mixture of 3-(*p*-chlorophenyl)-3-imino-2-methyl-*N*,1-diphenylprop-1-enamine (**1e**; 3.46 g, 10 mmol) and ethyl chloroacetate (1.22 g, 10 mmol) in pyridine was heated at 100 °C for 6 h and then slowly poured into ice-cooled 6 N H_2SO_4 (150 mL). The resulting mixture was extracted with ether, and the organic layer was dried over sodium sulfate, filtered, and evaporated. The residue was purified by recrystallization from hot hexane to afford **8e**: 2.50 g (74%); ^{13}C NMR ($CDCl_3$, internal Me_4Si) δ 161.7 (s), 134.7, 133.3, 132.6, 131.8, 129.8, 129.4, 128.7, 127.3, 127.1, 124.6, 118.7 (s), 117.8 (s), 60.1 (t), 13.9 (q), 10.8 (q). Anal. Calcd for $C_{20}H_{18}NO_2Cl$: C, 70.68; H, 5.34; N, 4.12. Found: C, 70.95, H, 5.07; N, 4.37.

Spectral data for the products **8** are given in Table II.

***N*-Cyclohexyl-3-[[(ethoxycarbonyl)methyl]imino]-2-methyl-1-phenyl-3-(*p*-tolyl)prop-1-enamine (4b, R^1 = c-C_6H_{11}).** A mixture of *N*-cyclohexyl-3-imino-2-methyl-1-phenyl-3-(*p*-tolyl)prop-1-enamine (**1b**, R^1 = c-C_6H_{11}; 3.32 g, 10 mmol) and glycine ethyl ester hydrochloride (1.4 g, 10 mmol) in pyridine (60 mL) was stirred at room temperature for 24 h. The solution was then acidified with 4 N H_2SO_4 (150 mL) and extracted with ether. The dry organic layer was evaporated and the residue recrystallized from hexane to afford 3.14 g (75%) of **4b** (R^1 = c-C_6H_{11}): mp 103–105 °C; IR (Nujol) ν_{max} 1745, 1195 cm^{-1}; ^1H NMR ($CDCl_3$, internal Me_4Si) δ 0.9-1.9 (16 H, m, CH_2CH_3, $=CCH_3$, $(CH_2)_5$), 2.2 (3 H, s, CH_3), 2.5–2.9 (1 H, m, NCH), 3.8 (2 H, s, NCH_2CO), 4.0–4.4 (2 H, q, $OCH2CH_3$), 6.9–7.6 (9 H, m, aromatic); ^{13}C NMR ($CDCl_3$, internal Me_4Si) δ 13.2 (q), 16.7 (q), 20.0 (q), 23.6 (t), 24.7 (t), 33.7 (t), 51.1 (d), 54.0 (t), 59.2 (t), 96.6 (s), 126.6, 127.0, 127.2, 127.6, 128.0, 134.5 (s), 136.4 (s), 137.3 (s), 170.5 (s); mass spectrum, m/e 418 (M^+). Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 77.48; H, 8.19, N, 6.69. Found: C, 77.72, H, 7.92, N, 6.78.

Conversion of 4b to 8b. A solution of **4b** (3 g, 7.1 mmol) in pyridine (50 mL) was heated at 80 °C for 4 h. The solution was poured into 150 mL of ice-cooled 4 N H_2SO_4, extracted with ether, dried over sodium sulfate, and concentrated. The residue was recrystallized from hexane to give 2.0 g (89%) of **8b**.

Registry No. 1b, 71115-26-9; **1e**, 71115-32-7; **1h**, 72923-06-9; **2**, 623-33-6; **4b**, 80765-52-2; **8a**, 80765-53-3; **8b**, 80765-54-4; **8c**, 80765-55-5; **8d**, 80765-56-6; **8e**, 80765-57-7; **8f**, 53778-26-0; **8g**, 80765-58-8; **8h**, 80765-59-9; **8i**, 80765-60-2; **9**, 105-39-5.

Retinoic Acid Metabolites. 1. Total Synthesis of 4-Hydroxy- and 4-Oxoretinoic Acid

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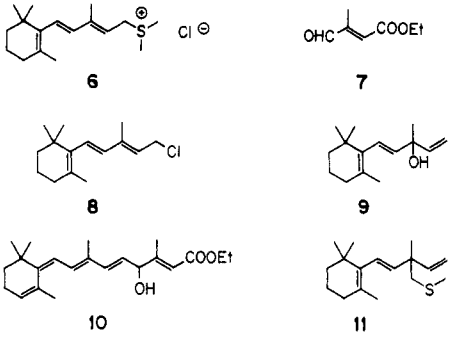
Two major metabolites of retinoic acid, 4-hydroxy- and 4-oxoretinoic acid, have been prepared by employing a polyene sulfonium salt and ethyl β-formylcrotonate.

Retinoic acid is a major metabolite of retinol, and like retinol it has several important functions in the body. It plays a key role in the maintenance and differentiation of epithelial tissue[1] and is essential for fetal development and growth promotion in general.[2]

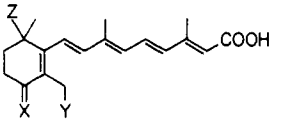
In animal tests, some striking effects have been demonstrated by retinoic acid and its derivatives in the inhibition and regression of precancerous[3] and cancerous conditions.[4] These exciting results coupled with the impressive effects demonstrated by 13-*cis*-retinoic acid in the treatment of cystic acne[5] have created a renewed interest in the area of retinoic acid and its metabolites.

The early literature[6] contains numerous reports of polar metabolites isolated from retinol which were inadequately characterized, possibly because of lack of material or suitable instrumentation. Some of the first well-characterized metabolites arising from retinoic acid were described by Rietz et al.,[7] who showed that the molecule

Chart I



underwent extensive oxidation to yield compounds such as **1–3**. Hänni et al.[8] continued in the footsteps of Rietz



1: Z = CH_3, Y = H, X = O
2: Z = CH_2OH, Y = H, X = O
3: Z = COOH, Y = H, X = O
4: Z = CH_3, Y = OH, X = H,H
5: Z = CH_3, Y = H, X = H,OH

and was able to isolate several new retinoic acid metabo-

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(3) Bollag, W. *Eur. J. Cancer* **1972**, *8*, 689.
(4) Trown, P. W.; Buck, M. L.; Hansen, R. *Cancer Treat. Rep.* **1976**, *60*, 1647.
(5) Peck, G. L.; Olsen, T. G.; Yoder, F. W.; Strauss, J. S.; Downing, D. T.; Pandya, M.; Butkus, D.; Arnaud-Battandier, J. *N. Engl. J. Med.* **1979**, *300*, 329.
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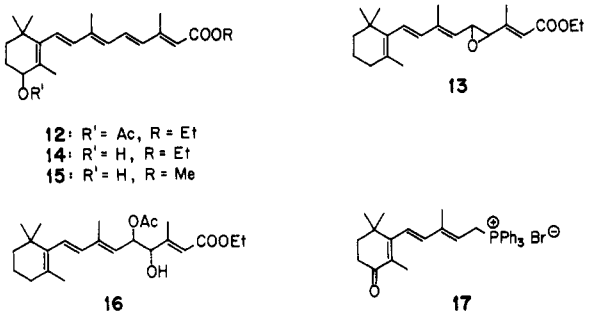
(7) Rietz, P. R.; Wiss, O.; Weber, F. *Vitam. Horm. (NY)* **1974**, *32*, 237.
(8) Hänni, R.; Bigler, F.; Meister, W.; Englert, G. *Helv. Chim. Acta* **1976**, *59*, 221. Hänni, R.; Bigler, F. *Ibid.* **1977**, *60*, 811.

0022-3263/82/1947-1698$01.25/0

Chart II



lites such as **4** from the urine and feces of rats. Other investigators[9,10] examining the fate of retinoic acid at physiological doses[11] recently identified the alcohol **5**.[10]

New syntheses for several of these metabolites have been developed to make sufficient material available for biological evaluation. This paper describes the synthesis of **1** and **5**, two major metabolites of retinoic acid.

Discussion

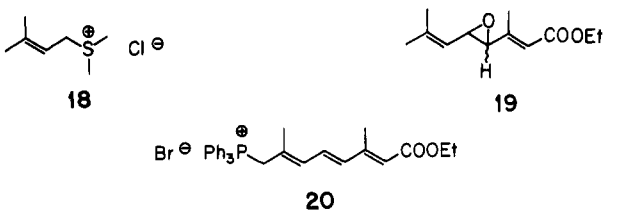
Several routes to 4-oxygenated retinoic acids have been described[1,12] but none of these methods proved practical for the preparation of up to 100 g amounts of material which would be needed for extensive biological evaluation.

In the past years we have been interested in the use of polyene sulfonium salts for the preparation of polyene epoxides, and it was in connection with these studies that we discovered a novel synthesis of 4-hydroxyretinoic acid.

Polyene sulfonium salts have found little use in the past[13] for the preparation of epoxides, because the ylides derived from them rapidly rearrange, by proton exchange and sigmatropic rearrangement, to form thioethers. However, when suitable reaction conditions are employed, these ylides can be used to give excellent yields of epoxides.

The route developed for compounds **1** and **5** involves the condensation of the key sulfonium salt **6** and the aldehyde **7** (Chart I). Initial attempts at preparing **6** from the chloride **8**[15] with dimethyl sulfide failed and yielded primarily the products of dehydrohalogenation. The salt could be prepared directly from vinyl-β-ionol **9** by exposure to a mixture of ethereal hydrogen chloride and dimethyl sulfide. In this way the crude sulfonium salt **6** separated as a semisolid product and could be used directly in the coupling reaction with **7**. Treatment of a mixture of **6** and **7** in dichloromethane with an aqueous solution of sodium hydroxide (5, 10, or 18 M) led to a rapid reaction and the formation of the alcohol **10** and the ylide rearrangement product **11**.

Chart III



Addition of acetic acid to the crude product from the above reaction resulted in the smooth transformation of **10** into **12** (Chart II). Hydrolysis with aqueous methanolic potassium hydroxide then gave the *all-trans*-retinoic acid **5** in 50% overall yield based on aldehyde **7**.

The epoxide **13** could be prepared in a crude form by employing short reaction times, low temperatures, and the tetrahydrothiophene sulfonium salt in place of the dimethylsulfonium salt. The product of such a reaction showed the expected spectral data (^{1}H NMR) but resisted all attempts at purification. Solutions of crude **13** in hexane containing triethylamine rapidly rearranged into mixtures of products while chromatography on silica gel, depending on the conditions, yielded either **10** or **14**. Further evidence for the formation of **13** in this sequence was obtained by the isolation of **16** after the acetic acid treatment of the crude epoxide mixture (see Experimental Section).

For formation of 4-oxoretinoic acid (**1**), compound **12** was treated with sodium methoxide in methanol which resulted in the formation of the hydroxy methyl ester **15**. Oxidation of this material with manganese dioxide then yielded the keto compound which on hydrolysis gave the metabolite **1**. Compound **1** was also prepared by the Wittig coupling of the phosphonium salt **17**[16] with **7**, which resulted in a mixture of isomers about the newly formed double bond. Hydrolysis and isomerization gave the pure metabolite **1**.

The methodology described above employing polyene sulfonium salts under aqueous conditions is quite general as long as a reactive carbonyl compound such as an aldehyde is used to trap the ylide.

For example, the sulfonium salt **18** (Chart III) is an isoprene equivalent useful in the formation of polyenes in carotenoid and vitamin A syntheses. Condensation of **18** with the aldehyde **7** in aqueous caustic soda solution yielded the mixture of epoxides **19** which, on exposure to triphenylphosphine hydrobromide, gave the important all-trans C_{10} phosphonium salt **20**[14] directly. The sulfonium salts themselves are quite stable as long as the molecule of water produced in their formation is retained. For example, attempts to dry the salts **6** and **18** resulted, primarily, in regeneration of the allylic halides (e.g., **8** from **6**).

In summary, the work described shows the potential for polyene sulfonium salts in synthesis. Already the method has found a use in the area of the leukotrienes,[17] and probably more applications of these useful reagents will appear in the future.

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(14) Isler, O., Ed. "Carotenoids"; Birkhauser Verlag: Basel and Stuttgart, 1971.

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Experimental Section[18,19]

***rac*-(2*E*,4*E*,6*E*,8*E*)-9-(3-Hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3,7-dimethyl-2,4,6,8-nonatetraenoic Acid (5).** Vinyl-β-ionol **9** (156 g, 0.75 mol, 92% pure by GLC) was dissolved in a mixture of ether (750 mL) and dimethyl sulfide (160 mL) and cooled to −50 °C. To this rapidly stirred solution, a solution of hydrogen chloride in ether (4.6 M, 270 mL) was added over 5–10 min. After most of the acid had been added, the salt separated as a gum, and stirring often becomes impossible. When the addition of the acid was complete, the mixture was warmed to −20 °C, the liquids were decanted, and the residue was washed twice with ether by decantation. The colorless semisolid residue **6** was dissolved in dichloromethane (500 mL), ethyl β-formylcrotonate (**7**; 53 g, 0.37 mol) and benzyltrimethylammonium chloride (2 g) were added, and the mixture was cooled to −20 °C. As rapidly as possible, a cooled (5 °C) solution of sodium hydroxide in water (5 M, 380 mL, temperature range −20 to −5 °C) was added to this mixture. The two-phase system was then warmed to room temperature and stirred for a further 30 min. Water was then added, and the products were isolated by extraction with ether. Removal of the solvents yielded an oil which was dissolved in acetic acid (200 mL) and kept at room temperature for 16 h. The solvents were removed in vacuo, and the residue was extracted into hexane and purified by preparative HPLC, employing a 5% ethyl acetate–hexane mixture, to yield **12** as an oil: 109 g (76%); UV max (ethanol) 351 nm (ε 43 800); ^{1}H NMR (CCl_4) δ 7.0 (dd, 1, J = 14, 10 Hz, H-5), 6.25 (d, 1, J = 10 Hz, H-6), 5.8 (s, 1, H-2), 5.2 (t, 1, J = 6 Hz, H-3), 4.1 (q, 2, J = 7 Hz, CH_2CH_3), 2.3 (s, 3, C-3 CH_3), 2.05 (s, 3, CO_2CH_3), 1.95 (s, 3, C-7 CH_3), 1.65 (s, 3, C-2 CH_3), 1.25 (t, 3, J = 7 Hz, CH_2CH_3), 1.0 (2 s, 6, C-6 CH_3). Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.34; H, 8.89. Crystallization from hexane yields material (mp 64–66 °C) with identical spectral features (UV and ^{1}H NMR). This material (109 g, 0.28 mol) was dissolved in methanol (550 mL) containing potassium hydroxide (75 g, 1.34 mol) and water (150 mL) and heated at reflux for 1 h. The cooled mixture was then poured into water (1.5 L) and acidified with acetic acid, and the solids were filtered off, dissolved in dichloromethane, and dried ($MgSO_4$). Removal of the solvents and crystallization of the residue from ethyl acetate yielded pure **5**: 57.6 g (65%); mp 178–81 °C; ^{1}H NMR ($CDCl_3$/Me_2SO-d_6) δ 6.96 (dd, 1, J = 15, 10 Hz, H-5), 6.29 (d, 1, J = 15 Hz, H-4), 6.18 (s, 2, H-8, H-9), 6.13 (d, 1, J = 10 Hz, H-6), 5.76 (s, 1, H-2), 3.96 (t, 1, $J \approx$ 5 Hz, H-4), 2.32 (s, 3, H-3 CH_3), 1.99 (s, 3, C-7 CH_3), 1.82 (s, 3, C-2 CH_3), 1.02 and 0.99 (2 s, 6, C-6 CH_3). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.62; H, 8.87. The methyl ester **15** prepared from this material with diazomethane had a melting point of 110–112 °C. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.64; H, 9.41.

The same methyl ester was formed from **14** *as follows.* A solution of the acetate **12** (21 g, 54 mmol, crystalline) in methanol (180 mL) containing sodium methoxide (3.55 M solution, 5 mL) was heated at reflux for 30 min, cooled, added to water, and extracted with ether. The extracts were washed (brine), dried ($MgSO_4$), concentrated, and dissolved in a 4:1 hexane–ethyl acetate mixture and stored at −20 °C for 16 h. The solids were filtered off and yielded pure **15** (3.8 g). The mother liquor material was purified by preparative HPLC (4:1 hexane–ethyl acetate) to yield more **15** (9.2 g; total yield 73%). Some 2-cis isomer is also formed in this reaction.

Compound 13. Vinyl-β-ionol **9** (4.5 g) was dissolved in ether (30 mL) containing tetrahydrothiophene (5 mL) and cooled to −60 °C. A solution of hydrogen chloride in ether (5 mL, 6.6 M) was then added, and the mixture was warmed to 0 °C. The solvents were decanted, and the colorless solid residue was washed twice with ether and dissolved in dichloromethane. This solution was then treated with **7** (2.5 g) and benzyltriethylammonium chloride (0.2 g) and cooled to −40 °C. Cold, aqueous sodium hydroxide solution (10 M, 10 mL) was then added rapidly, and the temperature rose to ∼−20 °C. The mixture was then stirred rapidly for 1 min at −20 °C and then cooled to −70 °C to freeze the aqueous base. The organic phase was poured off, the residue was washed with ether, and the combined organic extracts were washed (water) and dried ($MgSO_4$). Removal of the solvents yielded an oil; this was completely soluble in hexane unlike the rearrangement products. This material contained approximately 50% starting aldehyde, but it clearly showed the mixture of cis and trans epoxides in the ^{1}H NMR (CCl_4) spectrum: δ 3.8 (dd, J = 8, 4 Hz, *cis*-oxirane H-2), 3.6 (br d, J = 8 Hz, *cis*-oxirane H-3), 3.5 (dd, J = 8, 2 Hz, *trans*-oxirane H-2), 3.25 (d, J = 2 Hz, *trans*-oxirane H-3). This material is very delicate and spontaneously (exothermic) rearranges to the retro-alcohol **10**. Even dilute solutions in hexane containing triethylamine slowly rearrange.

Attempted Purification of 13. Isolation of Compounds 10, 14, and 16. From another experiment employing 18 M sodium hydroxide solution, the crude reaction product (from the vinyl-β-ionol, 4.4 g, 21 mmol) was chromatographed on silica gel (400 g, 25% ether–hexane, 20-mL fractions). Fractions 1–10 gave the ylide rearrangement product **11**: 0.9 g (17%); UV max (ethanol) 231 nm (ε 4700); ^{1}H NMR (CCl_4) δ 5.9 (dd, 1, J = 10, 18 Hz, H-4), 5.5 (dd, 2, J = 17 Hz, H-1, and H-2), 5.1 and 4.9 (2 m, 2, H-5), 2.55 (s, 2, CH_2S), 2.05 (s, 3, SCH_3), 1.6 (s, 3, C-2 CH_3), 1.2 (s, 3, C-3 CH_3), 1.0 (s, 6, C-6 CH_3). Anal. Calcd for $C_{17}H_{28}S$: C, 77.21; H, 10.67; S, 12.12. Found: C, 76.90; H, 10.75; S, 12.07.

Fractions 20–35 gave dehydroretinoic acid methyl ester (0.2 g) and fractions 55–110 contained the alcohol **10**: 1.3 g (18%): UV max (ethanol) 310 nm (ε 31 300), 323 (39100), 335 (32 200); ^{1}H NMR (CCl_4) δ 6–5.4 (m, 4, vinyl H), 5.95 (s, 1, H-2), 5.65 (t, 1, J = 6 Hz, H-3), 4.5 (m, 1, H-4), 4.05 (q, 2, J = 7 Hz, CH_2CH_3), 3.4 (s, 1, OH), 2.05 (s, 3, C-3 CH_3), 1.8 (br s, 6, C-2 and C-7 CH_3), 1.25 (s, 6, C-6 CH_3), 1.2 (t, 3, J = 7 Hz, CH_2CH_3). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.24; H, 9.30. Treatment of this material with acetic anhydride in pyridine did *not* give **14**, and the acetate formed showed the expected downfield shift of H-4 in the ^{1}H NMR spectrum.

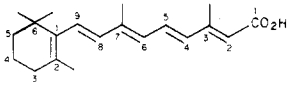
In another experiment on twice the scale, chromatography as before yielded none of **10** and only gave the alcohol **14**: 2.2 g (15%); UV max (ethanol) 354 nm (ε 39 800); ^{1}H NMR ($CDCl_3$) δ 7.1 and 6.9 (dd, 1, J = 14, 10 Hz, H-5), 6.25 (d, 1, J = 14 Hz, H-4), 6.15 (s, 2, H-8, H-9), 6.0 (d, 1, J = 10 Hz, H-6), 4.10 (q, 2, J = 7 Hz, CH_2CH_3), 3.95 (br s, 1, H-3), 2.70 (s, OH), 2.3 (s, 3, C-3, CH_3), 2.0 (s, 3, C-7 CH_3), 1.8 (s, 3, C-2 CH_3), 1.25 (t, 3, J = 7 Hz, CH_2CH_3), 1.0 (s, 6, C-6 CH_3). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 75.99; H, 9.48.

These materials are acid labile; for example, acidification with sulfuric acid of a base-hydrolysis reaction of **12** gave the 3-methoxy derivative: mp 176–78 °C; ^{1}H NMR ($CDCl_3$) δ 7.03 (dd, 1, J = 14, 10 Hz, H-5), 6.29 (d, 1, J = 14 Hz, H-4), 6.18 (s, 2, H-8, H-9), 6.13 (d, 1, J = 10 Hz, H-6), 5.79 (s, 1, H-2), 3.55 (t, 1, H-3), 3.26 (s, 3, OCH_3), 2.35 (s, 3, C-3 CH_3), 1.99 (s, 3, C-7 CH_3), 1.77 (s, 3, C-2 CH_3), 1.01 and 0.99 (2 s, 6, C-6 CH_3). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.22; H, 9.04.

Compound **16** was isolated as follows. After the desired material **12** had been eluted in the synthesis of **5** (preparative HPLC), the columns were stripped with ethyl acetate to yield the crude material **16** (43 g from 120 g of the vinyl-β-ionol) as an oil. This

(18) Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. All reactions were carried out under an atmosphere of argon under normal fluorescent lighting. The organic extracts were concentrated with a Buchi Rotavapor at 45 °C and 20 mm, and finally at 0.5 mm. Thin-layer chromatograms were run on Brinkmann silica gel G plates with a UV indicator, and the spots were made visible with UV light or by spraying with a 10% solution of phosphomolybdic acid in methanol and a 2% ceric sulfate solution in 5% aqueous sulfuric acid followed by heating to 120 °C. Preparative high-performance liquid chromatography (HPLC) was performed by using a Roche Prep LC MKI with a 4 ft × 1 in. steel column packed with silica gel (20–40 μm) and with a flow rate of 60 mL/min and a Waters LC Prep 500 employing one or two deactivated silica columns with a flow rate of 250 mL/min. The columns were deactivated with a methanol–acetone–ethyl acetate wash and stored in hexane under pressure. Waters LC Prep 500 silica columns after use have a longer life in a decompressed state if stored in ethyl acetate. Varian HA-100, T60, and XL-100 spectrometers were employed to record proton magnetic resonance spectra (^{1}H NMR), and the chemical shifts are relative to tetramethylsilane as an internal standard. Ultraviolet (UV) spectra were recorded on Cary Model 14M and Perkin-Elmer 202 spectrophotometers.

(19) Retinoic acid metabolites have been named as derivatives of nonatetraenoic acid, i.e.:



product was repurified (preparative HPLC, 4:1 hexane–ethyl acetate) to yield pure **16**: 26 g; UV max (ethanol) 218 nm (ϵ 21 600), 267 (13 100), 352 (6000); IR (film) 3500 (OH), 1740 and 1725 cm^{-1} (acetate and ethyl ester); ^1H NMR ($CDCl_3$) δ 6.4–5.6 (m, 4, H-2, H-6, H-8, H-9), 5.6 (dd, 1, J = 4, 8 Hz, H-5), 4.1 (m and q, 3, J = 7 Hz, H-4, OCH_2CH_3), 2.1 (s, 3, C-7 CH_3), 2.0 (s, 3, $OCOCH_3$), 1.9 (s, 3, C-3 CH_3), 1.65 (s, 3, C-2 CH_3), 1.2 (t, 3, J = 7 Hz, OCH_2CH_3), 1.0 (s, 6, C-6 CH_3). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.56; H, 9.16.

Oxidation of this material with MnO_2 in dichloromethane yielded a ketone confirming the position of the acetate at C-5: UV max (ethanol) 232 nm (ϵ 20 300), 275 (11 600), 350 (4400); ^1H NMR (CCl_4) δ 6.55 (m, 2, H-8, H-9), 6.3 (d, 1, J = 10 Hz, H-6), 6.2 (s, 1, H-2), 5.4 (d, 1, J = 10 Hz, H-5), 4.2 (q, 2, J = 7 Hz, OCH_2CH_3), 2.25 (s, 3, C-7 CH_3), 2.1 (s, 3, $OCOCH_3$), 2.0 (s, 3, C-3 CH_3), 1.7 (s, 3, C-2 CH_3), 1.3 (t, 3, J = 7 Hz, OCH_2CH_3), 1.0 (s, 6, C-6 CH_3). Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 72.11; H, 8.63.

The nature of chromatography products from **13** seemed to depend on the activity of the silica gel and the residence time on the adsorbent. Compound **10** was only isolated pure one time.

(2*E*,4*E*,6*E*,8*E*)-9-(3-Oxo-2,6,6-trimethyl-1-cyclohexen-1-yl)-3,7-dimethyl-2,4,6,8-nonatetraenoic Acid (1) and Its Methyl Ester. A slurry of manganese dioxide (100 g, Sterling Chemicals) in dichloromethane (450 mL) was cooled to 5 °C and over a period of 5 min treated with the alcohol **15** (10 g, 30.3 mmol) dissolved in more dichloromethane (50 mL). The mixture was then stirred for a further 1 h at room temperature and filtered, and the filtrate was concentrated. Crystallization of the residue from hexane yielded the keto acid methyl ester: 8.4 g (84%); mp 90–94 °C. This material (8 g, 24.4 mmol) was dissolved in methanol (90 mL) containing potassium hydroxide (4 g, 71.4 mmol) and water (10 mL) and heated at reflux for 20 min. Water (300 mL) was then added to the cooled reaction mixture followed by acetic acid (8 mL). The solids were filtered off, dissolved in ethyl acetate–tetrahydrofuran (50:1), washed (brine), dried ($MgSO_4$), and concentrated. Crystallization from an ethyl acetate–tetrahydrofuran–hexane mixture yielded the pure acid **1**: 5.5 g (72%); mp 186–89 °C; ^1H NMR ($CDCl_3$) δ 6.97 (dd, 1, J = 14, 12 Hz, H-5), 6.34, 6.30, 6.14 (m, 4, H-4, H-6, H-8, H-9), 5.79 (s, 1, H-2), 2.49 (t, 2, J = 6 Hz, H-4), 2.32 (s, 3, C-3 CH_3), 2.02 (s, 3, C-7 CH_3), 1.84 (s, 3, C-2 CH_3), 1.85 (t, 2, J = 6 Hz, H-5), 1.17 (s, 6, C-6 CH_3). Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 75.96; H, 8.32.

This material was also prepared from the phosphonium salt **17** as follows. A solution of **17** (224 g, 0.4 mol) in dichloromethane (1 L) containing the aldehyde **7** (52 g, 0.366 mol) was cooled to −10 °C and over a period of 25 min was treated with a methanolic solution of sodium methoxide (3.5 M, 121 mL). After the mixture was stirred for a further 90 min at 0 °C, acetic acid (10 mL) and water (300 mL) were added. The organic phase was then concentrated, and the residue was extracted with hexane (boiling, 2 × 1 L). The combined (cold) hexane extracts were then washed (75% methanol–water, 250 mL) and concentrated. The residue was dissolved in methanol (600 mL) containing potassium hydroxide (75 g, 1.34 mol) and water (100 mL) and heated at reflux for 45 min. After the mixture cooled to room temperature, water (1 L) and acetic acid (100 mL) were added, and the solids were filtered off. The solids were dissolved in dichloromethane, dried ($MgSO_4$), and concentrated. Crystallization from ethyl acetate yielded pure all-trans material: 28.3 g (25%); mp 187–90 °C. The mother liquor material was purified by preparative HPLC (2% acetic acid in 1:1 hexane–ethyl acetate) to yield the keto acid as a mixture of isomers (60 g). This material was dissolved in ethyl acetate (500 mL), treated with iodine (2.5 g), dissolved in more ethyl acetate (100 mL), seeded with pure **1**, and left at room temperature for 2 h with stirring. The solids were filtered off, washed (1:1 hexane–ethyl acetate), dissolved in dichloromethane, washed (0.1 M sodium thiosulfate), and concentrated. Crystallization of the residue from ethyl acetate yielded the pure material **1**: 18 g (16%); mp 186–89 °C.

A sample of this material on exposure to diazomethane yielded the methyl ester which, after crystallization from hexane, had a melting point of 93–95 °C.

(2*E*,4*E*,6*E*)-(7-Carbethoxy-2,6-dimethyl-2,4,6-heptatrien-1-yl)triphenylphosphonium Bromide (20). A solution of 3-hydroxy-3-methyl-1-butene (60 g, 0.7 mol) in dimethyl sulfide (80 mL) was treated, at room temperature, with a solution of methanolic hydrogen chloride (120 mL, 7.2 M) and left for 24 h. The solvents were then removed in vacuo [40 °C (0.1 mm)] to yield the sulfonium salt **18** as a solid: 81.8 g; ^1H NMR ($CDCl_3$) δ 8.15 (s, HO), 5.3 (t, 1, J = 8 Hz, H-2), 4.5 (d, 2, J = 8 Hz, H-1), 3.2 (s, SCH_3), 1.7 (s, C-3 CH_3). Anal. Calcd for $C_7H_{15}SCl$: S, 19.23. Found: S, 16.35. On the basis of the sulfur analysis and the ^1H NMR (water peak), the purity of the salt was between 85% and 90%. This crude salt (41 g) was dissolved in dichloromethane (150 mL) containing benzyltriethylammonium chloride (1 g) and ethyl β-formylcrotonate (30 g, 0.21 mol) and cooled to −10 °C. To the above solution, with rapid stirring, was added a cold (0 °C) solution of aqueous sodium hydroxide (84 g of NaOH in 84 mL of H_2O). After complete addition, the reaction mixture was stirred for a further 20 min at 0 °C and then treated with water and more dichloromethane. The organic phase was dried ($MgSO_4$) and concentrated to yield the epoxide mixture **19** (37.5 g). A portion of this material (30 g) was distilled to yield chemically pure epoxide: 26.1 g (74%); bp 104–106 °C (0.1 mm); ^1H NMR (CCl_4) δ 5.8 (m, 1, H-2), 4.8 (dm, 1, H-6), 4.1 (q, 2, J = 7 Hz, OCH_2CH_3), 3.8–3.0 (m, 2, H-5, H-6), 2.1 (br s, 3, C-3 CH_3), 1.75 (several s, C-7 CH_3), 1.2 (t, 3, J = 7 Hz, OCH_2CH_3). Decoupling the C-7 CH_3 resonance in the ^1H NMR spectrum resulted in a clear pair of doublets at δ 4.8 due to H-6 with relative intensities of 3:1. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.63; H, 8.57.

A solution of the epoxide mixture (5 g, 23.8 mmol) in dichloromethane (50 mL) was treated with triphenylphosphine hydrobromide (8.5 g, 54 mmol) and left at room temperature for 24 h. The solvents were then removed in vacuo, and the residue was crystallized from aqueous methanol to yield the salt **20**: 9.5 g; mp 155–65 °C. Recrystallization from water gave colorless crystals: 7.5 g (59%); mp 177–179 °C; ^1H NMR ($CDCl_3$) δ 7.8 (m, 15, phenyl H), 6.8–6.0 (m, 3, vinyl H), 5.65 (s, 1, H-7), 4.9 (d, 2, J = 15 Hz, H-1), 4.15 (q, 2, J = 7 Hz, OCH_2CH_3), 2.2 (s, 3, C-6 CH_3), 1.7 (d, 3, J = 4 Hz, C-2 CH_3), 1.2 (t, 3, J = 7 Hz, OCH_2CH_3).

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