mixture was stirred for a further 1 h at room temperature, treated with $MgSO_4$, filtered, and concentrated. Purification of the residue by HPLC (1:1 hexane–ethyl acetate) yielded chemically pure **15** (19.92 g, 68%). This product was dissolved in pyridine (150 mL) containing acetic anhydride (100 mL), and the mixture was left for 1 h at room temperature and then concentrated in vacuo to yield the crude diacetate (24 g). The crude diacetate **16** (41.4 g) was then dissolved in acetone (660 mL), treated with aqueous sulfuric acid (66 mL, 0.5 N), and stirred at room temperature for 90 min. The reaction mixture was then concentrated to half its original volume in vacuo, poured into water (1.5 L), and extracted with ethyl acetate. The extracts were washed (aqueous sodium bicarbonate, brine), dried ($MgSO_4$), and concentrated to give the crude alcohol **17** (37.24 g). Purification of HPLC (3:2 hexane–ethyl acetate) yielded chemically pure **17** (24.45 g, 72%). This material was dissolved in dichloromethane (1.2 L), treated with activated manganese dioxide (150 g, Sterwin Chemicals), and stirred at room temperature for 5 h. The mixture was then filtered through Celite and concentrated to yield the crude ketone. Purification by HPLC (2:1 hexane–ethyl acetate) yielded pure **18**: 17.2 g (70%); ^1H NMR ($CDCl_3$) δ 5.67 (t, 1, J = 7 Hz, H-2), 4.73 (d, 2, J = 7 Hz, H-1), 4.22 and 3.92 (2 d, 2, J = 12 Hz, CH_2OAc), 2.55 (m, 2, H-3), 2.08 and 2.05 (2 s, 6, $OCOCH_3$), 1.98 (s, 3, C-2 CH_3), 1.9 (2 s, 6, C-3 CH_3 and C-7 CH_3), 1.22 (s, 3, C-6 CH_3). All the above intermediates, which were mixtures of isomers, gave ^1H NMR spectra in accord with their structures.

***rac*-(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-[2,6-dimethyl-6-(hydroxymethyl)-3-oxo-1-cyclohexen-1-yl]-2,4,6,8-nonatetraenoic Acid (1).** A solution of **18** (17.2 g, 43 mmol) in methanol (380 mL) was treated with sodium hydroxide (10.32 g, 0.26 mol) in water (59 mL) and left at room temperature for 30 min. The dark colored reaction mixture was then poured into aqueous sulfuric acid (1.2 L, 1 N) and extracted with ethyl acetate. The organic extracts were washed (aqueous sodium bicarbonate, brine), combined, dried ($MgSO_4$), and concentrated. Purification of HPLC (ethyl acetate) gave pure material (9.47 g, 69%) as a yellow glass. This diol was dissolved in dichloromethane (500 mL), treated with manganese dioxide (75 g), and stirred at room temperature for 2 h. The mixture was then filtered through Celite and concentrated to yield a yellow glass: 6.56 g; ^1H NMR ($CDCl_3$) δ 10.13 (d, 1, J = 8 Hz, H-1), 7.10 (dd, 1, J = 11, 15 Hz, H-5), 6.4 (d, 1, J = 15 Hz, H-4), 6.37 (s, 2, H-8, H-9), 6.24 (d, 1, J = 11 Hz, H-6), 5.95 (d, 1, J = 8 Hz, H-2), 3.6 (m, 2, CH_2OH), 2.32 (s, 3, C-3 CH_3), 2.05 (s, 3, C-2 CH_3), 1.9 (s, 3, C-7 CH_3), 1.17 (s, 3, C-6 CH_3). A solution of this aldehyde (6.56 g, 20.9 mmol) in methanol (500 mL) was treated with acetic acid (1.95 g), sodium cyanide (5.34 g, 0.109 mol), and manganese dioxide (40 g) and then stirred at room temperature for 17 h. The reaction mixture was then filtered through Celite, concentrated (~200 mL), poured into water, and extracted with ethyl acetate. The organic extracts were washed (aqueous sodium bicarbonate, brine), dried ($MgSO_4$), and concentrated. Purification of the residue (7.16 g) by HPLC (1:1 hexane–ethyl acetate) gave the pure ester **21** as an oil: 5.13 g (34% from **18**); ^1H NMR ($CDCl_3$) δ 6.97 (dd, 1, J = 11, 15 Hz, H-5), 6.35 (d, 1, J = 15 Hz, H-4), 6.35 (s, 2, H-8, H-9), 6.25 (d, 1, J = 11 Hz, H-6), 5.82 (s, 1, H-2), 3.69 (s, 3, CO_2CH_3), 3.72, 3.44 (dd, 2, J = 10 Hz, CH_2OH), 2.55 (m, 2, H-4), 2.34 (s, 3, C-3 CH_3), 2.02 (s, 3, C-2 CH_3), 1.87 (s, 3, C-7 CH_3), 1.72 (s, 1, OH), 1.16 (s, 3, C-6 CH_3); mass spectrum, m/e 344 (M^+). A solution of the methyl ester **21** (4.11 g, 11.9 mmol) in methanol (400 mL) was treated with aqueous sodium hydroxide solution (100 mL, 3 N), stirred at room temperature for 2.7 h, and then quenched with aqueous sulfuric acid (1 L, 1 N). The organic products were estracted with ethyl acetate, and the extracts were washed (water, brine), combined, dried ($MgSO_4$), and concentrated. The solid residue (4.5 g) was dissolved in hot ethyl acetate (300 mL), treated with hexane (400 mL), and stored at 0 °C to yield the pure metabolite **1**: 2.15 g (54%); mg 203–205 °C; ^1H NMR (Me_2SO-d_6) δ 6.95 (dd, 1, J = 11, 15 Hz, H-5), 6.38 (d, 1, J = 15 Hz, H-4), 6.30 (s, 2, H-8, H-9), 6.24 (d, 1, J = 11 Hz, H-6), 5.73 (s, 1, H-2), 4.69 (s, 1, OH), 3.54 and 3.28 (dd, 2, J = 10 Hz, CH_2OH), 2.3 (s, 3, C-3 CH_3), 2.03 (s, 3, C-2 CH_3), 1.77 (s, 3, C-7 CH_3), 1.06 (s, 3, C-6 CH_3); mass spectrum, m/e 330 (M^+). Anal. Calcd for $C_{20}H_{26}O_4$: ,c, 72.80; H, 7.93. Found: C, 72.89; H, 8.05. Purification of the mother liquors by HPLC (1:1 hexane–ethyl acetate containing 1% acetic acid) yielded **22**: 283 mg (7%); mg 166–167 °C; UV max (ethanol) 258 nm (ϵ 20 600) 299 (31 000); ^1H NMR (Me_2SO-d_6) δ 11.8 (s, 1, CO_2H), 6.77 (dd, 1, J = 11, 15 Hz, H-5), 6.17 (d, 1, J = 15 Hz, H-4), 5.91 (d, 1, J = 11 Hz, H-6), 5.71 (s, 1, H-2), 4.52 (m, 1, H-9), 3.32 and 3.14 (dd, 2, J = 12 Hz, CH_2O), 2.25 (s, 3, C-3 CH_3), 1.84 (s, 3, C-2 CH_3), 1.77 (s, 3, C-7 CH_3), 1.32 (s, 3, C-6 CH_3); mass spectrum, m/e 330 (M^+). Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.52; H, 7.96.

Acknowledgment. We thank the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, NJ, for supplying most of the spectroscopic data and the microanalytical data. We also thank Dr. Beverly A. Pawson for her encouragement and continued support throughout this work.

Registry No. (±)-**1**, 81121-27-9; (±)-**2**, 81121-28-0; **5**, 60705-21-7; **7**, 63826-41-5; **8**, 81121-29-1; **9**, 81121-30-4; (±)-**10**, 81121-31-5; (±)-**11**, 81121-32-6; **12**, 81121-33-7; *cis*-**13**, 81141-16-4; *trans*-**13**, 81141-17-5; *cis*-**14**, 81141-18-6; *trans*-**14**, 81141-19-7; *cis*-**15**, 81141-20-0; *trans*-**15**, 81141-21-1; *cis*-**16**, 81141-22-2; *trans*-**16**, 81141-23-3; Cis-**17**, 81141-24-4; *trans*-**17**, 81141-25-5; (±)-**18**, 81121-34-8; (±)-**19**, 81132-93-6; (±)-**20**, 81121-35-9; (±)-**21**, 81121-36-0; **22**, 81121-37-1; ethyl 2-methylacetoacetate, 64854-05-3.

Retinoic Acid Metabolites. 3.[1] Total Synthesis of (2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-[6,6-dimethyl-2-(hydroxymethyl)-1-cyclohexen-1-yl]-2,4,6,8-nonatetraenoic Acid

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Received November 23, 1981

Among the numerous metabolites of retinoic acid,[1,2] one of the most recently identified products was isolated from the feces of rats which had been fed a diet containing added retinoic acid.[3] The structure of this product was clearly established as **1** (Chart I), the product of oxidation of a ring methyl group. As part of an extensive program in the area of retinoids,[4] several metabolites of retinoic acid were prepared in sufficient quantities for extensive biological evaluation.[1] This paper describes the work which culminated in the synthesis of **1**.

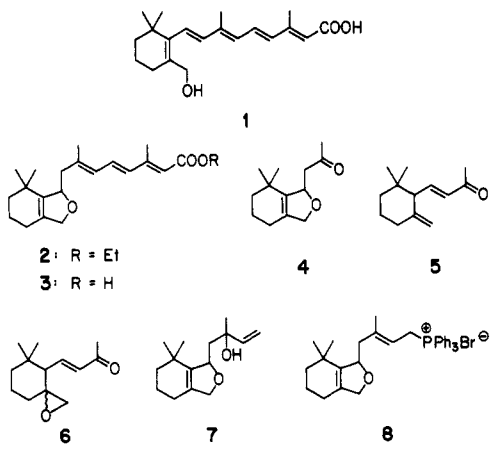
Results

An early attempt to prepare **1** was via the bicyclic dihydrofuran **2**, in which the hydroxymethyl group was masked by the formation of the cyclic ether. The molecule **2** had the potential of generating the fully conjugated polyene system of **1** by base treatment while at the same time releasing the hydroxy function. Fortunately, access to molecules such as **2** was readily available from the ketone **4**.[5] Epoxidation of γ-ionone[6] (**5**) yielded a mixture of epoxides **6**, which on exposure to base resulted directly in the formation of **4** in excellent overall yield (74%).

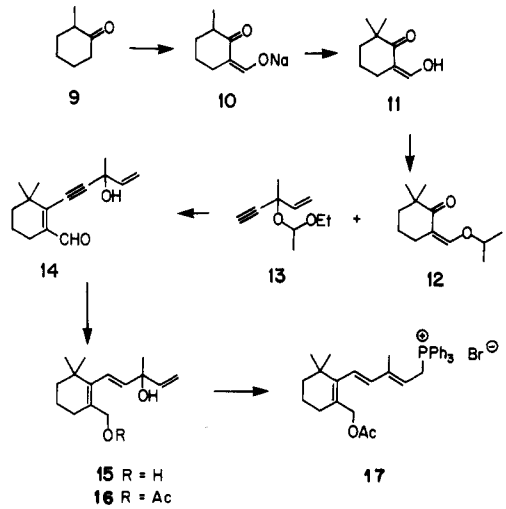
(1) Part 1: Rosenberger, M. *J. Org. Chem.*, accompanying paper in this issue. Part 2: Rosenberger, M.; Neukom, C., *J. Org. Chem.*, accompanying paper in this issue.
(2) Rietz, P. R.; Wiss, O.; Weber, F. *Vitam. Horm. (NY)* **1974**, *32*, 237.
(3) Hänni, R.; Bigler, F. *Helv. Chim. Acta* **1977**, *60*, 881.
(4) Mayer, H.; Bollag, W.; Hänni, R.; Ruegg, R. *Experientia* **1978**, *34*, 1105.
(5) Näf, F.; Decorzant, R.; Willhalm, B.; Valluz, A.; Winter, M. *Tetrahedron Lett.* **1977**, 1413.
(6) The authors are very grateful to Dr. F. Näf of Firmenich, Geneva, for a generous gift of the γ-ionone used in this work.

0022-3263/82/1947-1782$01.25/0

Chart I

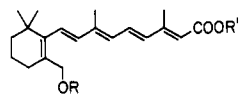


Scheme I

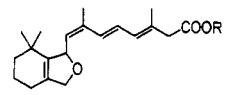


Addition of vinyl magnesium chloride to this product gave the vinyl alcohol **7**, which on reaction with triphenylphosphine hydrobromide furnished the salt **8** in high overall yield (71%). Wittig coupling of the phosphonium salt **8** with ethyl (*E*)-β-formylcrotonate gave a complex mixture of double bond isomers from which *all-trans*-**2** was isolated. Base treatment of **2** under a variety of conditions resulted in either recovered starting material, acid **3**, or total destruction of the material. Acid treatment led primarily to destruction of the substrate.

The above observations clearly showed that structures such as **2** had to be avoided. The approach, shown in Scheme I, eventually led to success. Condensation of 2-methylcyclohexanone (**9**) with methyl formate gave the sodium salt **10**;[7] alkylation via the dianion,[8] with potassium amide and methyl iodide, furnished an excellent overall yield of **11** (71%). Protection of the hydroxyl function with isopropyl iodide and potassium carbonate[9] gave the enol ether **12** which on condensation with the lithium salt of **13**[10] followed by acid hydrolysis yielded *only* **14**, the product of 1,2-addition.[11] Reduction of both the aldehyde and acetylene functions with lithium aluminum hydride furnished the highly crystalline but unstable diol **15**.[12] Exposure of the diol **15** to acetic anhydride in pyridine gave the monoacetate **16** which on treatment with triphenylphosphine hydrobromide yielded the trans phosphonium salt **17** in high overall yield (56% from 14). Condensation of this salt with ethyl (*E*)-β-formylcrotonate, by employing sodium methoxide as base, gave **18**, as a mixture of double



18: R = Ac, R' = Et
19: R = H, R' = Et
20: R = $CH(CH_3)OEt$, R' = Et
21: R = $CH(CH_3)OEt$, R' = H



22: R = H
23: R = CH_3

bond isomers, as well as the alcohol **19**. With an excess of sodium methoxide and an extended reaction time, **19** becomes the major product, and numerous other side products are seen.

Hydrolysis of **18** under the usual conditions (aqueous potassium hydroxide solution in refluxing methanol) yields very little of the metabolite **1** and gives primarily the "deconjugated" bicyclic material **22**. Clearly the thermodynamically more stable hexahydrobenzoisofuran system is manifesting itself again. To avoid this problem, the acetate grouping in **18** was first removed by mild hydrolysis with base, and the free hydroxyl function was then protected with ethyl vinyl ether to yield **20**. More vigorous basic hydrolysis now removed the ester group, and subsequent exposure of **21** to mild acid treatment liberated the desired metabolite **1**.

Experimental Section[13-15]

2-Formyl-6,6-dimethylcyclohexanone (11). A mixture of 2-methylcyclohexanone **9** (123 g, 1.1 mol) and ethyl formate (81.4 g, 1.1 mol) was added to a slurry of sodium methoxide (54 g, 1 mol) in ether (2 L) and the mixture was stirred for 18 h at room temperature. The solids were filtered off, washed with ether, and dried [70 °C (1 mm)] to yield the sodium salt (148 g, 91%).

The finely powdered salt (100 g, 0.617 mol) was added to a mixture of potassium amide (from potassium, 28 g, 0.718 mol) in liquid ammonia (2 L) and stirred at reflux for 1 h. To this mixture was added a solution of methyl iodide (104 g, 0.73 mol) in ether (200 mL); the ammonia was then slowly distilled off over a period of 3 h. The residue was carefully treated with water, and the aqueous phase was acidified (sulfuric acid, 3 M) and extracted with ether. Removal of the ether and distillation of the residue yielded the pure formyl derivative **11**: 68 g (71%);

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(8) Boatman, S.; Harris, T. M.; Hauser, C. R. *J. Am. Chem. Soc.* **1965**, *87*, 82.
(9) Johnson, W. S.; Posvic, H. *J. Am. Chem. Soc.* **1947**, *69*, 1361.
(10) Rosenberger, M.; McDougal, P.; Bahr, J., submitted for publication in *J. Org. Chem.*
(11) The five-membered-ring systems tend to give *only* the products of conjugate addition. Ferro, M. Ph.D. Dissertation, University of Michigan, Ann Arbor, MI, 1980.
(12) Simply heating this compound at 45 °C (0.005 mm) for 16 h resulted in extensive decomposition.
(13) Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. All reactions were carried out under an atmosphere of argon. 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.[14] Varian HA-100, T60, and XL-100 spectrometers were employed to record proton magnetic resonance spectra (^1H 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.
(14) Waters LC Prep 500 silica columns after use have a longer life in a decompressed state if stored in ethyl acetate.
(15) The metabolites are named as derivatives of 2,4,6,8-nonatetraenoic acid.

bp 54–55 °C (0.5 mm); ^{1}H NMR (CCl_4) δ 14.7 (s, 1, OH), 8.7 (s, 1, vinyl H), 2.3 (m, 2, H-3), 1.2 (s, 6, C-6 CH_3).

Isopropyl Ether 12. A solution of the formyl derivative 11 (68 g, 0.44 mol) in acetone (500 mL) was treated with isopropyl iodide (150 g, 0.88 mol) and potassium carbonate (120 g, 0.87 mol) and heated at reflux for 6 h. The mixture was cooled, the solids were filtered off, and the acetone was removed in vacuo. The residue was distilled to yield pure 12: 78 g (90%); bp 72–78 °C (0.2 mm); ^{1}H NMR (CCl_4) δ 7.3 (t, 1, J = 1 Hz, vinyl H), 4.2 (septet, 1, J = 6 Hz, $CH(CH_3)_2$), 2.7 (m, 2, H-3), 1.3 (d, 6, J = 6 Hz, $CH(CH_3)_2$), 1.05 (s, 6, C-6 CH_3). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.20; H, 10.40.

***rac*-5-(6,6-Dimethyl-2-formyl-1-cyclohexen-1-yl)-3-methyl-3-hydroxy-1-penten-4-yne (14).** A solution of *n*-butyllithium in hexane (125 mL, 2.4 M) was added to THF (750 mL) at −50 °C and then cooled to −65 °C. The acetylenic material 13 (51.1 g, 0.34 mol) in THF (100 mL) was added, and the mixture was then warmed to 0 °C and cooled back to −65 °C. A solution of the ketone 12 (50 g, 0.255 mol) in THF (100 mL) was then added at −65 °C, and after complete addition the clear reaction mixture was warmed to room temperature and stirred for a further 1 h. Brine and more ether were then added, and the ether layer was dried ($MgSO_4$) and concentrated. This crude adduct (100 g) showed *no* aldehyde carbonyl in the ^{1}H NMR spectrum and is probably the unrearranged adduct. This crude material was dissolved in acetone (800 mL) and treated with aqueous sulfuric acid (200 mL, 1 N) for 30 min. The reaction mixture was then washed (brine, saturated aqueous $NaHCO_3$), the aqueous extracts were back-extracted with ether, and the acetone–ether extracts were then concentrated and dried ($MgSO_4$). Removal of the solvents and purification of the residue by HPLC (15% ethyl acetate–hexane) gave pure 14: 47.2 g (79%); ^{1}H NMR (CCl_4) δ 10.17 (s, CHO), 6.2 (dd, 1, J = 10, 16 Hz, H-2), 5.45 (dd, J = 2, 16 Hz, trans H-1), 5.45 (dd, 1, J = 10, 2 Hz, cis H-1), 4.1 (s, 1, OH), 2.2 (m, 2, H-3), 1.6 (s, 3, C-3 CH_3), 1.2 (s, 6, C-6 CH_3); UV max (ethanol) 281 nm (ε 14100). Distillation of a sample yielded the analytical sample, bp 125 °C (0.005 mm). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.49; H, 8.93.

***rac*-(4*E*)-5-[2-(Acetoxymethyl)-6,6-dimethyl-1-cyclohexen-1-yl]-3-hydroxy-1,3-pentadiene (16).** A slurry of lithium aluminum hydride (12 g, 0.316 mol) in ether (800 mL) cooled to 0 °C was treated with a solution of 14 (46 g, 0.2 mol) in ether (200 mL) over a 20-min period. The mixture was then stirred for a further 3 h at room temperature, cooled to −10 °C, treated carefully with a saturated aqueous sodium sulfate solution (60 mL), and then stirred for a further 1 h at room temperature. The solids were then filtered off and washed with ether, and the combined extracts were concentrated to yield the crude diol 15 (46 g). This material was dissolved in ether (35 mL), cooled to 10 °C, treated with a mixture of acetic anhydride and pyridine (100 mL, 1:1) at 10–20 °C for 30 min, and allowed to stand at room temperature for a further 2 h. Concentration yielded the crude monoacetate (55 g). Purification by HPLC (10% ethyl acetate–hexane) yielded pure material: 32 g (57%); ^{1}H NMR (CCl_4) δ 6.1 (d, 1, J = 16 Hz, H-5), 6.1 and 5.85 (2 d, 1, J = 10, 18 Hz, H-2), 5.55 (d, 1, J = 16 Hz, H-4), 5.2 (dd, 1, J = 18, 2 Hz, trans H-1), 5.0 (dd, 1, J = 10, 2 Hz, cis H-1), 4.56 (s, 2, CH_2OAc), 2.85 (s, 1, OH), 2.05 (s, 3, $OCOCH_3$), 1.4 (s, 3, C-3 CH_3), 1.0 (s, 6, C-6 CH_3). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.51; H, 9.73.

In another experiment, the crude alcohol (5 g) was purified by HPLC (1:1 hexane–ethyl acetate). The pure 15 (2.9 g) obtained was crystallized from hexane to yield fine needles: 1.9 g; mp 68–69 °C. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.55; H, 9.83. Found: C, 76.74; H, 9.85.

Phosphonium Salt 17. The hydroxy acetate 16 (32 g, 0.115 mol) was dissolved in dichloromethane (100 mL) and added to a cold solution of triphenylphosphine hydrobromide (40 g, 0.117 mol) in dichloromethane (100 mL). The mixture was then kept at room temperature for 1 h and then poured slowly into ether (2 L). The precipitated salt was filtered off and dried to yield 17: 68.8 g (99%); ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 15, phenyl H), 5.9 (s, 2, H-4, H-5), 5.3 (m, 1, H-2), 4.75 (dd, 2, J = 16, 8 Hz, H-1), 4.45 (s, 2, CH_2OAc), 2.1 (s, 3, $OCOCH_3$), 1.85 (s, 3, C-3 CH_3), 1.0 (s, C-6 CH_3).

Ethyl (2*E*,4*E*,6*E*,8*E*)-9-[2-(Acetoxymethyl)-6,6-dimethyl-1-cyclohexen-1-yl]-3,7-dimethyl-2,4,6,8-nonatetraenoate (18). The phosphonium salt 17 (114 g, 0.189 mol) was dissolved in dichloromethane (750 mL) containing freshly distilled ethyl β-formylcrotonate (23.2 g, 0.163 mol) and cooled to −20 °C. A solution of sodium methoxide in methanol (76 mL, 3.2 M) was then added over ~15 min, and the resulting mixture was then stirred for a further 10 min at 0–5 °C. The reaction mixture was diluted with hexane–ethyl acetate (7:3, 2 L), washed (water), filtered, and concentrated. The residue was then extracted with the same hexane–ethyl acetate mixture (4 × 100 mL) and filtered through a column of silica gel (500 mL). Removal of the solvents and purification of the residue (70 g) by HPLC (95:5 hexane–ethyl acetate) yielded chemically pure 18 (51 g, 81%). Flushing the HPLC columns with ethyl acetate yielded the hydroxy compound 19 which was purified by HPLC (85:15 hexane–ethyl acetate) to yield chemically pure 19: ^{1}H NMR ($CDCl_3$) δ 7.0 (dd, *E* H-5), 6.2 (s, H-8 and H-9), 6.5 (m, H-4, H-5, H-6 of *E* and *Z* isomers), 4.2 (q, 2, J = 7 Hz, OCH_2CH_3), 4.1 (s, 2, CH_2OH), 2.5 (s, 1, OH), 2.35 (s, 3, C-3 CH_3), 2.0 (m, 3, C-7 CH_3), 1.3 (t, 3, J = 7 Hz, OCH_2CH_3), 1.0 (s, 6, C-6 CH_3). The major fraction (51 g) was crystallized from hexane to yield pure 18: 19 g; mp 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 6.92 (dd, 1, J = 10, 14 Hz, H-5), 6.22 (d, 1, J = 14 Hz, H-4), 6.2 (m, 2, H-8, H-9), 6.07 (d, 1, J = 10 Hz, H-6), 5.7 (s, 1, C-2 H), 4.6 (s, 2, CH_2OAc), 4.17 (q, 2, J = 6 Hz, OCH_2CH_3), 2.34 (s, 3, C-3 CH_3), 2.05 (s, 3, $OCOCH_3$), 1.97 (s, 3, C-7 CH_3), 1.27 (t, 3, OCH_2CH_3), 1.02 (s, 6, C-6 CH_3). Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.08; H, 8.83.

Purification of the mother liquors by HPLC (recycle) gave the pure 4,5-cis isomer of 18: ^{1}H NMR (CCl_4) δ 6.5 (m, 2, H-5, H-6), 6.15 (s, 2, H-8, H-9), 5.9 (m, 1, H-4), 5.75 (s, 1, H-2), 4.5 (s, 2, CH_2OAc), 4.1 (q, 2, J = 6 Hz, OCH_2CH_3), 2.3 (s, 3, C-3 CH_3), 2.0 (s, 3, $OCOCH_3$), 1.95 (s, 3, C-7 CH_3), 1.25 (t, 3, J = 6 Hz, OCH_2CH_3), 1.0 (s, 6, C-6 CH_3).

This cis isomer can be readily converted to the desired trans isomer as follows. A solution of the predominantly cis isomer (20 g) in acetonitrile (100 mL) containing triethylamine (2 mL) and water was treated with bis(benzonitrile)palladium dichloride (2 g) and left at room temperature for 1 h. Aqueous formaldehyde (2 mL) was then added followed by a mixture of hexane–ethyl acetate (200 mL), and the mixture was then washed (water, brine), dried ($MgSO_4$), and concentrated. Crystallization of the residue from hexane gave pure trans material (15 g). In this manner, an experiment employing ethyl β-formylcrotonate (48.2 g, 0.339 mol) yielded pure trans 18: 69.6 g (53%); mp 82–84 °C.

Base Hydrolysis of 18. The pure trans isomer 18 (1.8 g, 4.66 mmol) was dissolved in methanol (15 mL) containing potassium hydroxide (1.2 g, 21.4 mmol) and water (3 mL) and the mixture heated at reflux for 30 min. Aqueous acetic acid was then added; the acidic material was extracted into dichloromethane. Removal of the solvents yielded the crude product, which was crystallized from a hexane–ethyl acetate mixture to give pure 1: 230 mg (15%); mp 185–188 °C dec; UV max (ethanol) 342 nm (ε 49400); ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 6.97 (dd, 1 J = 15, 12 Hz, H-5), 6.29 (d, 1, J = 15 Hz, H-4), 6.21 (s, 2, H-8, H-9), 6.17 (d, 1, J = 12 Hz, H-6), 5.87 (s, 1, H-2), 4.11 (s, 2, CH_2OH), 2.34 (s, 3, C-3 CH_3), 2.0 (s, 3, C-7 CH_3), 1.04 (s, 6, C-6 CH_3). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.79; H, 8.94.

The mother liquor material was treated with an excess of diazomethane in ether and the crude methyl ester was purified by HPLC (90:10 hexane-ethyl acetate) to yield 23 (900 mg, 58%); UV max (ethanol) 271 nm (ε 39900), 281 (50800), 292 (38300); IR (film) 1740 (saturated ester) cm^{-1}; ^{1}H NMR (CCl_4) δ 6.5, 6.2, 5.9, 5.3 (m, 5, H-4, H-5, H-6, H-8, H-1), 4.3 (m, 2, H-3), 3.6 (s, 3, $OCOCH_3$), 3.0 (s, 2, H-2), 1.9, 1.85 (2 s, 6, C-3 CH_3, C-7 CH_3), 1.0, 0.95 (2 s, 6, C-7 CH_3). This material is a mixture of double bond isomers.

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-[6,6-dimethyl-2-(hydroxymethyl)-1-cyclohexen-1-yl]-2,4,6,8-nonatetraenoic Acid (1). The pure trans diester 18 (15.44 g, 0.04 mol) was dissolved in methanol (200 mL), treated with cold aqueous potassium hydroxide (5 g, 89 mmol, in 20 mL of H_2O), and after 10 min at room temperature quenched with acetic acid (5 mL). Most of the methanol was removed in vacuo, and the residue was extracted into ether. The ether layers were washed (brine), dried ($MgSO_4$), and concentrated to yield the alcohol 19 (13.4 g) as an oil: ^{1}H NMR ($CDCl_3$) δ 6.9 (dd, 1, J = 15, 11 Hz, H-5), 6.3 (d, 1, J = 15 Hz, H-4), 6.2 (d, 2, H-8, H-9), 6.15 (d, 1, J = 11 Hz, H-6), 5.8 (s,

1, H-2), 4.2 (q, 2, J = 7 Hz, OCH_2CH_3), 4.15 (s, 2, CH_2OH), 2.65 (s, 1, OH), 2.35 (s, 3. C-3 CH_3), 1.0 (s, 6, C-6 CH_3).

This material was dissolved in a mixture of ether (25 mL) and ethyl vinyl ether (25 mL); treated with *p*-toluenesulfonic acid (500 mg) with ice cooling, treated, after 10 min at room temperature, with more ether (500 mL), washed (saturated aqueous $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated. The crude product (18 g) was dissolved in a mixture of methanol (100 mL), water (100 mL), and potassium hydroxide (10 g, 0.179 mol) and heated at reflux for 10 min. The mixture was then cooled to 10 °C, poured onto ice (750 g), and acidified with acetic acid (10 mL). The organic materials were then extracted into ethyl acetate, and the extracts were washed (brine), dried ($MgSO_4$), and concentrated to yield the impure acid **21**. Crystallization from hexane furnished pure **21**: 9.4 g (60%); mp 118–119 °C; ^1H NMR ($CDCl_3$) δ 11.0 (s, 1, CO_2H), 7.0 (dd, 1, J = 15, 11 Hz, H-5), 6.3 (d, 1, J = 15 Hz, H-4), 6.2 (s, 2, H-8, H-9), 6.1 (d, 1, J = 11 Hz, H-6), 4.7 (q, 1, J = 6 Hz, $OCHCH_3$), 4.0 (s, 2, CH_2O), 3.55 (m, 2, OCH_2CH_3), 2.35 (s, 3, C-3 CH_3), 2.0 (s, 3, C-7 CH_3), 1.35, 1.25 (dd, 3, J = 6 Hz, $OCHCH_3$), 1.05 (s, 6, C-6 CH_3). Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.43; H, 9.32.

A solution of **21** (3.88 g, 10 mmol) in acetone (70 mL) was treated with aqueous sulfuric acid solution (10 mL, 1 M), treated, after 30 min at room temperature, with water until turbid, and then seeded with **1**. The solids were filtered off, dried (3.1 g, mp 179–85 °C), and recrystallized from aqueous acetone to yield pure **1**: 2.5 g (79%); mp 187–189 °C dec.

Acknowledgment. We thank the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, NJ, for supplying most of the spectroscopic data and all of the microanalytical data. We also thank Dr. Beverly A. Pawson for her continual support and encouragement throughout this work.

Registry No. **1**, 63531-93-1; **2**, 81121-38-2; **3**, 81121-39-3; **4**, 80704-19-4; **5**, 49816-69-5; **6**, 70143-17-8; **7**, 81121-40-6; **8**, 81121-41-7; (±)-**9**, 24965-84-2; (±)-**10**, 81121-42-8; (±)-**11**, 81121-43-9; **12**, 65519-73-5; **13**, 72008-25-4; (±)-**14**, 81121-44-0; (±)-**15**, 81121-45-1; (±)-**16**, 81121-46-2; **17**, 81121-47-3; 4-*cis*-**18**, 81121-48-4; 4-*trans*-**18**, 81176-71-8; (4*E*)-**19**, 81121-49-5; **20**, 81121-50-8; **21**, 81121-51-9; **22**, 81132-94-7; **23**, 81121-52-0; ethyl (*E*)-β-formylcrotonate, 62054-49-3; (4*Z*)-**19**, 81176-72-9.

Crystal Structure and Stereochemistry of Verbesindiol[1]

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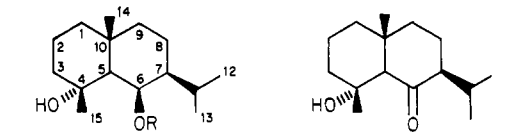
Received December 1, 1981

In the course of our search for biologically active lactones in Compositae, we recently described isolation from *Verbesina virginica* of the *p*-coumaryl ester **1a**.[2] The stereochemistry assigned to the parent diol **1d** which we named verbesindiol (4α,6β-dihydroxyeudesmane) was based primarily on ^1H NMR data. Coupling constants involving H-5 and H-6, chemical shift changes accompanying the conversion of **1a** to **1d** and thence to **2**, and the failure of **1d** to form an acetonide indicated that the isopropyl group was equatorial and that the C-6 hydroxyl and the two methyl groups were axial. This was supported by the demonstration of an appreciable NOE between the two methyl groups of **2** and Eu(fod)$_3$-induced shifts in the two methyl signals of **1d**. The absolute configuration was established by conversion of **1d** to (+)-selinene and (−)-selina-3,5-diene.



2

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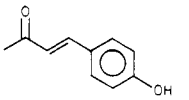

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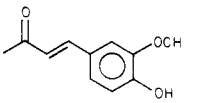

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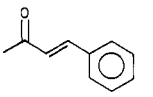

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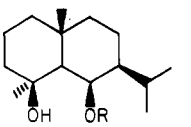
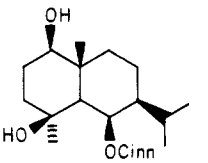
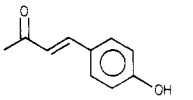




4

3a, R =



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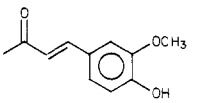

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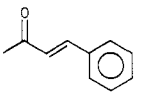

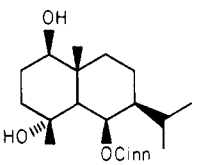

5

While our article was in press, Bohlmann and co workers[3] reported isolation of a substance **3a** and the corresponding ferulate **3b** from *Verbesina macrophylla*. The stereochemistry assigned by them to these compounds was based on the similarity of their ^1H NMR spectra to the spectrum of a cinnamate ester **3c**, earlier thought to be **1c**, from *V. eggersii* and *V. luetzelburgii*. The revision in stereochemistry from **1c** to **3c** hinged on a comparison[3] of its ^{13}C NMR spectrum with the ^{13}C NMR spectra of two related cinnamates ascribed formulas **4** (from *V. glabrata* and *V. luetzelburgii*)[3] and **5** (from *V. eggersii*).[4]

The ^1H NMR spectra of our **1a**[2] and the Berlin workers' **3a** and **3b**[3] were essentially superimposable as were the ^{13}C NMR spectra of our **1a**[2] and the presumed **3c**[3,5] if allowance is made for the extra aromatic hydroxyl in **1a**. This clearly indicated that the stereochemistries of all of these compounds were the same and required that our **1a** and the presumed **3a** were identical.

(1) Work at the Florida State University was supported in part by a grant from the U.S. Public Health Service (CA-13121) through the National Cancer Institute.

(2) Herz, W.; Kumar, N. *Phytochemistry* **1981**, *20*, 247.

(3) Bohlmann, F.; Grenz, M.; Gupta, R. K.; Dhar, A. K.; Ahmed, M.; King, R. M.; Robinson, H. *Phytochemistry* **1980**, *19*, 2391.

(4) Bohlmann, F.; Lonitz, F. *Chem. Ber.* **1978**, *111*, 254.

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