these were not obtained when 6 and aromatic amines were heated alone in toluene.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Melting points over 300 °C were determined on a Mel-Temp capillary melting point apparatus. The infrared spectra were recorded on a Perkin-Elmer 467 grating spectrophotometer. The NMR spectra were obtained on a 60 MHz Hitachi Perkin-Elmer R20A high-resolution spectrometer using Me_4Si as an internal standard. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. TLC was performed on Eastman chromatogram sheets coated with silica gel.

8-(Carbomethoxy)-2,5,6-trimethyl-4*H*-3,1-benzoxazin-4-one (7). In a round-bottomed flask were placed 2.0 g (7.5 mmol) of 2-acetamido-3-(carbomethoxy)-5,6-dimethylbenzoic acid (**6**)[2] and 1.2 g of phosphorus oxychloride in 60 mL of toluene. The mixture was refluxed for 3 h. After concentration in vacuo, cold absolute methanol was added to the gummy residue. A solid precipitate was collected by filtration and recrystallized from acetonitrile to yield 0.5 g (27%) of **7**: mp 258–260 °C; IR (KBr) 2950, 1730, 1670, 1600 cm^{-1}; NMR (Me_2SO-d_6, acetone-d_6) δ 7.6 (s, 1 H), 3.75 (s, 3 H), 2.2–2.3 (3 s, 9 H).

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.12; H, 5.34; N, 5.62.

2,6,7-Trimethyl-3-*p*-tolyl-3,4-dihydro-4-oxoquinazoline-8-carboxylic Acid (10a). To a 100-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and heating mantle were added 2.6 g (9.8 mmol) of **6**, 1.5 g (14 mmol) of *p*-toluidine, and 0.5 g of phosphorus oxychloride in 60 mL of toluene. The mixture was refluxed for 3.5 h and concentrated in vacuo. Treating the gum with ether yielded a white solid. After recrystallization from methanol, 1.5 g (47%) of **10a** was obtained: mp 249.5–251 °C; IR (KBr) 3300, 2950, 1720, 1685, 1620 cm^{-1}; NMR ($CDCl_3$) δ 8.1 (s, 1 H), 7.1–7.5 (m, 4 H), 2.75 (s, 3 H), 2.45 (s, 3 H), 2.4 (s, 3 H), 2.3 (s, 3 H).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.57; H, 5.66; N, 8.65.

2,6,7-Trimethyl-3-(*m*-fluorophenyl)-3,4-dihydro-4-oxoquinazoline-8-carboxylic Acid (10b). The title compound was prepared as above from *m*-fluoroaniline and **6** in 32% yield (acetonitrile): mp 298–300 °C; IR (KBr) 3400, 1710, 1680, 1600 cm^{-1}; NMR (CD_3CN, TFA) δ 8.45 (s, 1 H), 7.2–7.5 (m, 4 H), 2.8 (s, 3 H), 2.6 (s, 3 H), 2.5 (s, 3 H).

Anal. Calcd for $C_{18}H_{15}N_2O_3F$: C, 66.25; H, 4.63; N, 8.58. Found: C, 66.21; H, 4.65; N, 8.58.

2,6,7-Trimethyl-3-(*p*-fluorophenyl)-3,4-dihydro-4-oxoquinazoline-8-carboxylic Acid (10c). The title compound was prepared as above from *p*-fluoroaniline and **6** in 37% yield (methanol): mp 311–313 °C; IR (KBr) 1710, 1680, 1610 cm^{-1}; NMR (pyridine-d_5, TFA) δ 8.7 (s, 1 H), 7.4–8.4 (m, 4 H), 2.7 (s, 3 H), 2.3 (s, 3 H), 2.25 (s, 3 H).

Anal. Calcd for $C_{18}H_{15}N_2O_3F$: C, 66.25; H, 4.63; N, 8.58. Found: C, 66.03; H, 4.68; N, 8.46.

2,6,7-Trimethyl-3-(*p*-fluorophenyl)-3,4-dihydro-4-oxo-8-(carbomethoxy)quinazoline (13). In a 250-mL Erlenmeyer flask was placed 3.5 g (0.01 mol) of **10c** dissolved in 50 mL of methylene chloride and 50 mL of absolute methanol. The flask was placed in an ice bath on a magnetic stirrer. The mixture was stirred as an excess of ethereal diazomethane solution was added. After 2 h the solvents were evaporated in vacuo. The solid residue was recrystallized from aqueous methanol to give 2.6 g (71%) of **13**: mp 237–239 °C; IR (KBr) 2980, 1730, 1690, 1620 cm^{-1}; NMR ($CDCl_3$, Me_2SO-d_6, TFA) δ 8.0 (s, 1 H), 7.2–7.5 (m, 4 H), 3.8 (s, 3 H), 2.8 (m, 6 H), 2.4 (s, 3 H).

Anal. Calcd for $C_{19}H_{17}N_2O_3F$: C, 67.05; H, 5.03; N, 8.23. Found: C, 66.94; H, 5.05; N, 8.18.

***N*-*p*-Tolyl-2-acetamido-3-carboxy-4,5-dimethylbenzamide (11a).** To a 250-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and heating mantle were added 2.6 g (9.8 mmol) of **6**, 1.5 g (14 mmol) of *p*-toluidine, 0.5 g of phosphorus oxychloride, and 0.5 mL of acetic acid in 60 mL of toluene. After refluxing the mixture for 3.5 h, the solvent was removed in vacuo. The white precipitate was recrystallized from acetonitrile to yield 1.7 g (51%) of **11a**: mp 253–255 °C; IR (KBr) 3280, 2940, 1710, 1660, 1640, 1600 cm^{-1}; NMR (TFA) δ 8.05 (s, 1 H), 7.25–7.60 (m, 4 H), 2.6 (s, 3 H), 2.4 (2 s, 6 H), 2.25 (s, 3 H).

Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.27; H, 6.00; N, 8.15.

***N*-(*m*-Fluorophenyl)-2-acetamido-3-(carbomethoxy)-4,5-dimethylbenzamide (12b).** To a 250-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and heating mantle were added 5.2 g (0.02 mol) of **6**, 2.0 mL of *m*-fluoroaniline, 1.0 g of phosphorus oxychloride, and 0.5 mL of acetic acid in 100 mL of toluene. The mixture was refluxed for 4 h, the solvent was removed in vacuo, and the solid residue was recrystallized from aqueous methanol to yield 2.3 g (34%) of **11b**: mp 219–221 °C; IR (KBr) 3240, 3020, 2940, 1725, 1640, 1600 cm^{-1}. This acid was treated with excess ethereal diazomethane in methylene chloride. The solvent was evaporated in vacuo, and the solid residue was recrystallized from absolute methanol to yield 2.1 g (87%) of **12b**: mp 209–211 °C; IR (KBr) 3260, 2960, 1730, 1660, 1600 cm^{-1}; NMR ($CDCl_3$, TFA) δ 9.4 (s, 1 H), 9.15 (s, 1 H), 8.0 (s, 1 H), 7.25–7.70 (m, 4 H), 4.0 (s, 3 H), 2.4 (2 s, 6 H), 2.3 (s, 3 H).

Anal. Calcd for $C_{19}H_{19}N_2O_4F$: C, 63.68; H, 5.34; N, 7.82. Found: C, 63.75; H, 5.38; N, 7.80.

***N*-(*p*-Fluorophenyl)-2-acetamido-3-(carbomethoxy)-4,5-dimethylbenzamide (12c).** The title compound was prepared as above from **6** and *p*-fluoroaniline. The intermediate acetamidobenzamido acid (**11c**) was obtained in 41% yield (acetonitrile): mp 224–226 °C; IR (KBr) 3280, 2960, 1710, 1660, 1650, 1610 cm^{-1}. Treatment of the acid with diazomethane gave an 88% yield (methanol–ether) of **12c**: mp 236–238 °C; IR (KBr) 3280, 2980, 1720, 1670, 1660, 1620 cm^{-1}; NMR ($CDCl_3$, Me_2SO-d_6, TFA) δ 9.4 (s, 1 H), 9.15 (s, 1 H), 8.0 (s, 1 H), 7.1–7.7 (m, 4 H), 3.95 (s, 3 H), 2.4 (2 s, 6 H), 2.3 (s, 3 H).

Anal. Calcd for $C_{19}H_{19}N_2O_4F$: C, 63.68; H, 5.34; N, 7.82. Found: C, 63.61; H, 5.40; N, 7.79.

Thermal Cyclodehydration in Diphenyl Ethers. (A) Preparation of 10a. In a 250-mL round-bottomed flask were heated 2.4 g (7 mmol) of **11a** and 40 mL of diphenyl ether in an oil bath at 230–40 °C for 15 min. The mixture was cooled, petroleum ether (bp 30–60 °C) was added, an the solid precipitate was collected by filtration. After recrystallization from methanol, **10a** was obtained: 2.0 g (88%); mp 249–251 °C. The IR and NMR spectra and R_f values were identical with those of **10a** obtained from the benzoxazinone (Scheme II).

(B) Preparation of 13. The acetamidobenzamide ester **12c** (2.0 g, 5.5 mmol) was taken up in 40 mL of diphenyl ether and heated in an oil bath at 230–240 °C with vigorous stirring for 25 min. The reaction mixture was cooled, and petroleum ether was added. Recrystallization of the solid precipitate from methyl acetate gave **13**: 1.2 (64%); mp 237–238 °C. The IR and NMR spectra and R_f values were identical with those of **13** obtained by esterification of **10c** (Scheme II).

Acknowledgment. This research was supported in part by National Institute of Neurological and Communicative Disorders and Stroke (Grant 5RO1NS16988).

Registry No. 6, 73318-18-0; **7**, 81045-03-6; **8** (R = *p*-Me), 106-49-0; **8** (R = *m*-F), 372-19-0; **8** (R = *p*-F), 371-40-4; **10a**, 81045-04-7; **10b**, 81045-05-8; **10c**, 81045-06-9; **11a**, 81045-07-0; **11b**, 81045-08-1; **11c**, 81045-09-2; **12b**, 81045-10-5; **12c**, 81045-11-6; **13**, 81045-12-7.

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

Michael Rosenberger* and Christian Neukom

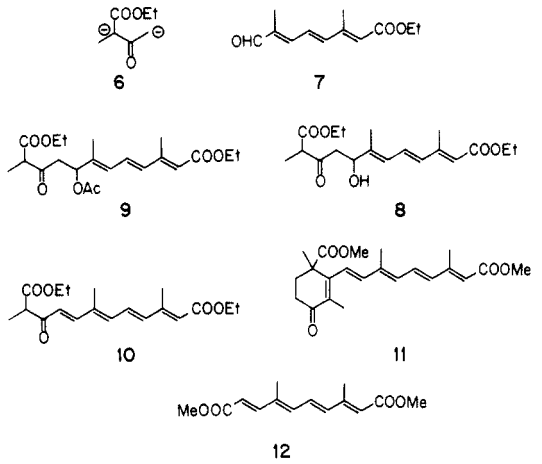
Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received November 23, 1981

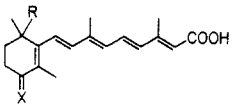
Retinoic acid has numerous essential functions in the body[2] and is very rapidly excreted from the system as the

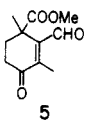
0022-3263/82/1947-1779$01.25/0

Chart I



glucuronide conjugate of the unchanged acid and as a host of metabolites in the nonconjugated form. Some of these metabolites are products of extensive oxidation in which the polyene side chain had been degraded and the ring system and one of the geminal methyl groups had also suffered oxidation.[3] Other metabolites retained the polyene chain and were identified as compounds 1, 2,[4] 3, and 4. The synthesis of 3 and 4 has been described previously;[1] the present work deals with the preparation of metabolites 1 and 2.





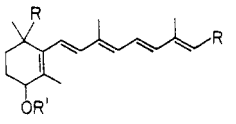
5

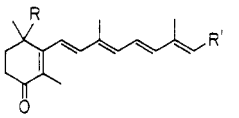
1: X = O, R = CH_2OH
2: X = O, R = COOH
3: X = O, R = CH_3
4: X = H, OH, R = CH_3

Results

At the outset of this work, the similarity of the ring system of 2 to trisporic acid[5] suggested that the same type of synthetic approach used in the construction of the trisporic acids could be employed for the metabolites 1 and 2. Our initial attempts to attach the polyene chain to the highly functionalized cyclohexenone 5,[6] as had been done successfully earlier in a trisporic acid synthesis, failed. However, building the elements of the ring system onto the polyene followed by cyclization, an approach which had also been successful in the area of trisporic acid synthesis,[6a,7] was highly rewarding.

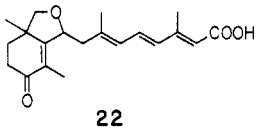
Chart II





13: R' = H, R = COOMe
14: R' = $CH(CH_3)OEt$, R = COOMe
15: R' = $CH(CH_3)OEt$, R = CH_2OH
16: R' = $CH(CH_3)OEt$, R = CH_2OAc
17: R' = H, R = CH_2OAc

18: R = R' = CH_2OAc
19: R = R' = CH_2OH
20: R = CH_2OH, R' = CHO
21: R = CH_2OH, R' = COOMe



22

Condensation of the dianion 6 (Chart I), formed with sodium hydride and subsequently *n*-butyllithium, with the aldehyde 7[8] gave the aldol 8 in 68% yield. Dehydration of this aldol was accomplished with methanesulfonic acid in glacial acetic acid to give a mixture of the deep red product 10 and the acetate 9. Condensation of 10 with ethyl vinyl ketone in methanolic sodium methoxide solution produced the desired product 11 as well as 12, the product of base-catalyzed cleavage of 10. The acetate 9 yielded the same result as 10 under identical reaction conditions, although the aldol 8 failed in this sequence. It was thus possible to employ the mixture of 9 and 10 to prepare 11; in this way the desired material 11 was available in 66% yield from the aldol 8. Hydrolysis of the product to the dicarboxylic acid, metabolite 2, proved straight forward and gave no detectable decarbomethoxylated products.[9]

With the diester 11 in hand, we felt that the preparation of 1 would present no problems. In theory all one has to do is reduce all the carbonyl functions to alcohols and then selectively oxidize the allylic alcohol groups to the respective ketone and carboxylic acid. This did not prove to be the case, and a more circuitous route had to be followed to reach 1.[10]

Reduction of 11 with sodium borohydride yielded a mixture of diastereoisomers 13 which, when treated with ethyl vinyl ether, gave the mixture of acetals 14 (Chart II). Further reduction of 14 with diisobutylaluminum hydride gave the diol 15[11] which was acetylated to furnish the diacetate 16. Acid hydrolysis of 16 then liberated the alcohol 17, which was oxidized to 18 with manganese dioxide and subsequently hydrolyzed to the diol 19. Further oxidation of 19 with manganese dioxide then afforded the aldehyde 20, which on treatment with more manganese dioxide and methanolic hydrogen cyanide[12-14] gave the methyl ester 21. Careful hydrolysis of 21 yielded the desired product 1 and the bicyclic material 22. If the hydrolysis is not followed carefully (thin-layer chromatog-

(1) Part 1: Rosenberger, M. *J. Org. Chem.*, accompanying paper is in this issue.

(2) (a) Moore, T. "The Vitamins"; Academic Press: New York and London, 1967. (b) Sporn, M. B.; Dunlop, N.; Newton, D.; Smith, J. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1976**, *35*, 1332. (c) Pitt, G. A. "Carotenoids"; Isler, O., Ed.; Birkhauser Verlag: Basel and Stuttgart, 1971.

(3) Hänni, R.; Bigler, F.; Meister, W.; Englert, G. *Helv. Chim. Acta* **1976**, *59*, 2221.

(4) Rietz, P. R., unpublished result.

(5) Bu'Lock, J. D.; Jones, B. E.; Winskill, N. *Pure Appl. Chem.*. **1976**, *47*, 191 and references cited therein.

(6) (a) Secrist, J. A., III; Hickey, C. J.; Norris, R. E. *J. Org. Chem.* **1977**, *42*, 525. (b) An approach based on the aldehyde 5 has recently been published: Yakovleva, I. M.; Vakulova, L. A.; Fillipova, T. M.; Bekker, A. R.; Samokhvalov, G. I. *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 1951. The method gave the retinyl methyl ethers in poor yields as mixtures of isomers.

(7) (a) Edwards, J. A.; Schwarz, V.; Fajkos, J.; Maddox, M. L.; Fried, J. H. *Chem. Commun.* **1971**, 292. (b) Isoe, S.; Huyase, Y.; Sakan, T. *Tetrahedron Lett.* **1971**, *40*, 3691. (c) Prisbylla, M. P.; Takabe, K.; White, J. D. *J. Am. Chem. Soc.* **1979**, *101*, 762.

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

(9) A feature of most trisporic acid syntheses is that they usually end at the methyl ester stage because of the problems associated with hydrolysis to the free acid. White's elegant approach to trisporic acids[7c] is one of the few publications in which the acid is described.

(10) None of the reduction conditions employed resulted in the isolation of the triol.

(11) Hydrolysis with acid, at this stage, gave a complex mixture of products, *none* of which corresponded to the triol 13 (R^1 = H, R = CH_2OH).

(12) A one-step oxidation of 17 to the ester 21 failed.

(13) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(14) Short reaction times with these substrates gave poor yields of esters but good yields of the methoxynitriles formed from the aldehydes.

raphy), the bicyclic compound **22** becomes the major product of the reaction. No loss of the hydroxymethyl group was ever observed.

Experimental Section[15,16]

Diethyl *rac*-(6*E*,8*E*,10*E*)-5-Hydroxy-3-oxo-2,6,10-trimethyl-6,8,10-dodecatrienedioate (8). A slurry of sodium hydride (5.76 g, 0.24 mol) in tetrahydrofuran (THF, 450 mL) was cooled to 0 °C and treated with ethyl 2-methylacetoacetate (34.6 g, 0.24 mol) dissolved in THF (270 mL). After complete addition, the ice bath was removed, and the mixture was stirred for a further 1.5 h. The mixture was then cooled to 0 °C and treated with *n*-butyllithium (100 mL, 2.4 M in hexane), and the clear solution was stirred for a further 0.75 h at 0 °C and 0.5 h without the ice bath. This clear solution was then cooled to −70 °C and treated dropwise with a solution of **7** (41.6 g, 0.2 mol) in THF (360 mL). After complete addition, the mixture was stirred a further 1 h at −70 °C and then warmed to 0 °c over 10 min. Excess aqueous sulfuric acid (1 N) was then added, the organic materials were extracted into ethyl acetate, and the extracts were washed (water, aqueous sodium bicarbonate solution, brine), dried ($MgSO_4$), and concentrated. The crude product (72 g) was then purified by HPLC (3:1 hexane–ethyl acetate) to give pure **8**: 48.4 g (69%); ^{1}H NMR ($CDCl_3$) δ 7.78 (dd, 1, *J* = 11, 15.5 Hz, H-8), 6.22 (d, 1, *J* = 11 Hz, H-7), 6.19 (d, 1, *J* = 15.5 Hz, H-9), 5.72 (s, 1, H-11), 4.58 (t, 1, *J* = 6Hz, H-5), 4.2 and 4.17 (2 q, 4, $CO_2CH_2CH_3$), 3.55 (q, 1, *J* = 7 Hz, H-2), 2.93 (br s, 1, OH), 2.78 (d, 2, *J* = 5 Hz, H-4), 2.3 (s, 3, C-10 CH_3), 1.83 (s, 3, C-6 CH_3), 1.3 and 1.26 (2 t, 6, $CO_2CH_2CH_3$), 1.23 (d, 3, *J* = 7 Hz, C-2 CH_3). Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.66; h, 8.18.

Diethyl *rac*-(4*E*,6*E*,8*E*,10*E*)-3-Oxo-2,6,10-trimethyl-4,6,8,10-dodecatetraenedioate (10). A solution of the aldol product **8** (5.28 g, 15 mmol) in acetic acid (100 mL), at room temperature, was treated with methanesulfonic acid (60 μL) and left for 5.5 h. Water was added to the solution, and the mixture was extracted with ethyl acetate. The combined extracts were washed (water, saturated aqueous sodium bicarbonate solution), dried ($MgSO_4$), and concentrated to approximately 50 mL. Storage of this solution at −20 °C for 72 h yielded pure **10**: 1.8 g; mp 117–119 °C; UV max (ethanol) 377 nm (ε 67 700); ^{1}H NMR ($CDCl_3$) δ 12.54 (d, 1, *J* = 3 Hz, OH), 7.11 (d, 1, *J* = 15 Hz, H-4), 6.92 (dd, 1, *J* = 11, 15.5 Hz, H-8), 6.37 (d, 1, *J* = 15 Hz, H-5), 6.36 (d, 1, *J* = 11 Hz, H-7), 6.32 (d, 1, *J* = 15.5 Hz, H-9), 4.24 and 4.16 (2 q, 4, $CO_2CH_2CH_3$), 2.37 (s, 3, C-10 CH_3), 2.0 (s, 3, C-6 CH_3), 1.88 (s, 3, C-2 CH_3), 1.3 and 1.27 (2 t, 6, $CO_2CH_2CH_3$). Anal. Calcd for $C_{19}H_{20}O_3$: C, 68.24; H, 7.84. Found: C, 68.32; H, 7.55.

Purification of the mother liquors by HPLC (4:1 heptane–ethyl acetate) yielded more of **10** (920 mg, total yield 54%) and the acetate **9**: 1.74 g (29%); UV max (ethanol) 304 nm (ε 38 700); IR (film) 1756 and 1722 (ester, β-keto ester), 1617 cm^{-1} (C=C); mass spectrum, *m/e* 394 (M^+); ^{1}H NMR ($CDCl_3$) δ 6.73 (dd, 1, *J* = 15, 11 Hz, H-8), 6.23 (d, 1, *J* = 15 Hz, H-9), 6.15 (d, 1, *J* = 11 Hz, H-7), 5.73 (s, 1, H-11), 5.61 (m, 1, H-2), 4.17 (m, 4, $CO_2CH_2CH_3$), 3.55 (m, 1, H-5), 2.9 (m, 2, H-4), 2.31 (s, 3, C-10 CH_3), 2.02 (s, 3, CO_2CH_3), 1.85 (s, 3, C-6 CH_3), 1.32 (d, 3, *J* = 7 Hz, C-2 CH_3), 1.28 (t, 6, $CO_2CH_2CH_3$).

Methyl *rac*-(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-[2,6-dimethyl-6-(methoxycarbonyl)-3-oxo-1-cyclohexen-1-yl]-2,4,6,8-nonatetraenoate (11). Powdered sodium methoxide (178 mg, 3.3 mmol) was dissolved in methanol (10 mL) and then treated with **10** (1.002 g, 3 mmol). To this mixture, over a period of 45 min at room temperature, was added a solution of ethyl vinyl ketone (378 mg, 4.5 mmol) dissolved in methanol (5 mL). After complete addition, the mixture was stirred for a further 18 h at room temperature, poured into aqueous sulfuric acid (1 N) and ice, and extracted with ethyl acetate. The extracts were then washed (water, sodium bicarbonate solution, brine), dried $MgSO_4$), and concentration to yield crude **11** (1.295 g). Crystallization from hexane–ethyl acetate (4:1) yielded pure material: 657 mg (59%); mp 105–107 °C; UV max (ethanol) 382 nm (ε 58 500); ^{1}H NMR ($CDCl_3$) δ 7.0 (dd, 1, *J* = 14, 12 Hz, H-5), 6.5 (s, 2, H-8, H-9), 6.4 (d, 1, *J* = 14 Hz, H-4) 6.3 (d, 1, *J* = 12 Hz, H-6), 5.85 (s, 1, H-2), 3.7 (2 s, 6, CO_2CH_3), 2.4 (s, 3, C-3 CH_3), 2.0 (2 s, 6, C-2 and C-7 CH_3), 1.55 (s, 3, C-6 CH_3). Anal. Calcd for $C_{22}H_{28}O_5$; C, 70.94; H, 7.58. Found: C, 71.12; H, 7.56.

The same material can be prepared from the aldol **8** as follows. A solution of the aldol **8** (48.35 g, 0.137 mol) in acetic acid (500 mL) was treated with methanesulfonic acid (0.2 mL) and left at room temperature for 21 h. The mixture was then poured into water, and the mixture of **9** and **10** (48 g) was isolated with ethyl acetate as before. This crude mixture was dissolved in methanol (600 mL) and treated with sodium methoxide (14.8 g, 0.274 mol) and then with a solution of ethyl vinyl ketone (17.3 g, 0.206 mol) in methanol (600 mL) over 5 h. After complete addition, the mixture was stirred at room temperature for 16 h and then worked up as before. The crude yellow solid (53 g) was crystallized from hexane–ether (1:4, 450 mL) at −20 °C, and the mother liquor materials were purified by HPLC (4:1 hexane–ethyl acetate) to give **11**: combined yield of 66% (33.88 g); mp 104–108 ° C.

Hydrolysis of 11. A solution of **11** (2 g, 5.38 mmol) in methanol (160 mL) was treated with aqueous sodium hydroxide solution (6 N, 40 mL) for 3.5 h at room temperatrue and then poured into cold aqueous sulfuric acid (500 mL, 1 N). Extraction with ethyl acetate followed by washing of the extracts (water, brine) and drying ($MgSO_4$) yielded the crude acid on removal of the solvents in vacuo. Crystallization from methanol–ethyl acetate (1:1, 250 mL) gave the pure metabolite **2**: 1.52 g (82%); mp 217–219 °C; UV max (ethanol) 382 nm (ε 52 800); ^{1}H NMR (Me_2SO–d_6) δ 12.13 (2 br s, 2, CO_2H) 6.97 (dd, 1, *J* = 14 Hz, H-11), 6.48 (2 s, 2, H-8, H-9), 6.43 (d, 1, *J* = 14 Hz, H-4), 6.29 (d, 1, *J* = 10 Hz, H-6), 5.75 (s, 1, H-2),2.45 (m, 2, H-4), 2.31 (s, 3, C-3 CH_3), 2.04 (s, 3, C-2 CH_3), 1.91 (s, 3, C-7 CH_3), 1.46 (s, 3, C-6 CH_3). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.80; H, 7.16.

Preparation of Isomer Mixture 13. A slurry of sodium borohydride (13.64 g, 0.359 mol) in methanol (400 mL) at 0 °C was treated dropwise with a solution of the dimethyl ester **11** (33.52 g, 0.09 mol) in methanol (600 mL) and then stirred for a further 3 h at room temperature. Cold aqueous sulfuric acid (1 N) was then added followed by an excess of water. The reaction products were extracted with ethyl acetate and the extracts were washed (water, asqueous sodium bicarbonate solution, brine), combined, dried ($MgSO_4$), and concentrated. The residue (33.8 g) was then crystallized from hexane–ethyl acetate (1:1) to yield the mixture of isomers: 23.16 g; mp 124–134 °C. The mother liquors on purification by HPLC (3:2 hexane–ethyl acetate) yielded more of the mixture (4.82 g, total yield 83%) which was combined with the above material and used in the next step. The cis and trans isomers can be separated by HPLC.

***rac*-3,7-Dimethyl-9-[6-(acetoxymethyl)-2,6-dimethyl-3-oxo-1-cyclohexen-1-yl]-2,4,6,8-nonatetraenyl Acetate (18).** The mixture of isomeric alcohols **13** (27.98 g, 74.8 mmol) was dissolved in a mixture of THF (300 mL) and ethyl vinyl ether (40 mL, 0.419 mol) at 0 °C and treated with *p*-toluenesulfonic acid (200 mg). The mixture was then stirred for 1 h at room temperature, treated with triethylamine (1 mL), and concentrated. The residue was dissolved in ethyl acetate, washed (aqueous sodium bicarbonate), dried ($MgSO_4$), and concentrated to yield the acetal **14** (35.1 g) as a pale yellow oil. This crude material was dissolved in THF (1.3 L), cooled to −20 °C, and treated dropwise with a solution of diisobutylaluminium hydride in hexane (560 mL, 1.225 M). The resulting mixture was then warmed to 0 °C over 90 min and stirred a further 30 min at 0 °C. Methanol was then carefully added followed by a saturated aqueous solution of sodium sulfate. After the exothermic reaction had ceased, the

(15) The metabolites are named and numbered as derivatives of 2,4,6,8-nonatetraenoic acid.

(16) Metlting 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 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.

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

Michael Rosenberger* and Christian Neukom

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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