Total Synthesis of Racemic Triptolide and Triptonide

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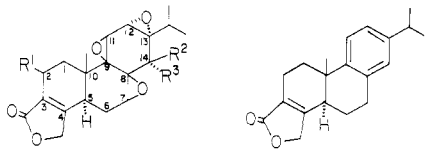
Received September 23, 1981

The total synthesis of (±)-triptolide (1) and (±)-triptonide (3) from tetralone 7 in 16 and 15 steps, respectively, is described.

The diterpenoid triepoxides triptolide (1), tripdiolide (2), and triptonide (3) were first isolated from extracts of



1, $R^1 = R^3 = H$, $R^2 = OH$
2, $R^1 = R^2 = OH$, $R^3 = H$
3, $R^1 = H$, R^2–$R^3 = O$
4, $R^1 = R^2 = H$, $R^3 = OH$

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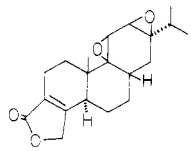

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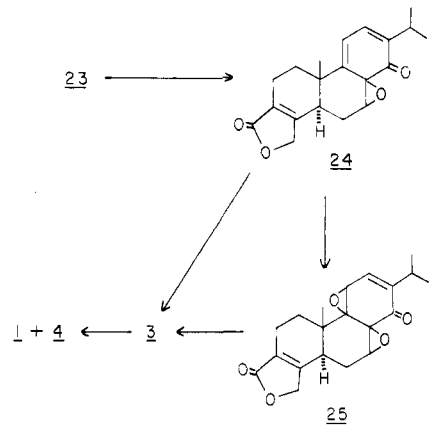
Tripterygium wilfordii by Kupchan and co-workers.[1] More recently the isolation of 1 and 3 has been reported by a Chinese group,[2] and Kutney and co-workers have reported a procedure for preparation of 2 from a tissue culture of *T. wilfordii*.[3] Structural data from X-ray crystallographic studies and from spectroscopic studies clearly indicate, as can be seen from molecular models, that the C-14 β-hydroxyl group of 1 and 2 is hydrogen bonded to the C-9,11 epoxide oxygen atom.[1] Both 1 and 2 suffer selective nucleophilic attack by propanethiol at C-9, while C-14 epitriptolide (4) is recovered unchanged under the same reaction conditions.[4] A proposal relating the hydrogen bonding observed in 1 and 2 to their chemical reactivity and biological activity has been presented.[4] Detailed toxicity studies of 1 in mice and dogs have been reported.[5]

The unique structural features of 1–3 and the biological activity of 1 and 2 have attracted the attention of synthetic chemists. Shortly after our preliminary report of the total synthesis of racemic 1 and 3,[6] van Tamelen and co-workers reported a synthesis of *l*-1 and *l*-3 from *l*-dehydroabietic acid,[7a,8] and recently they have reported a synthesis of racemic 1 and 3.[7b] Koike and Tokoroyama have developed an alternative approach to the C-ring functionality of 1,[9] and they report a synthesis of "isodehydroabietenolide" (5)[10] which, as pointed out earlier,[6,11] undoubtedly is the

Scheme I



$\Delta^{4,5}$ isomer rather than the $\Delta^{3,4}$ butenolide. Synthesis of 5 has been accomplished by van Tamelen's group.[11] Total synthesis of the diterpenoid diepoxide stemolide (6), isolated by Manchand and Blount,[12] was achieved by van Tamelen and Taylor.[8,13]

Our initial investigations established that the periodate route to epoxycyclohexadienones[14] proceeded smoothly with a tricyclic model system,[15] and procedures for the stereospecific construction of the C-ring functionality of 3 from the epoxy dienone precursor were developed in the model system.[16] In view of these preliminary results, the synthesis of 1 and 3 was undertaken.

Ketone 7, the synthesis of which was developed in our laboratory,[15] was a convenient starting material. Alkylation of the enolate of 7 with 8 (Scheme I) gave diastereomeric lactones 9 that reacted with dimethylamine to afford a 1:1 mixture of diastereomeric amides 10 in 94% yield from 7. Oxidation of 10 with Collins reagent provided aldehydes 11 for aldol condensation. After several failures to effect aldol condensation in good yield with various acidic and basic catalysts, we achieved success using a tenfold weight excess of neutral alumina in ethyl acetate at room temperature for 2 days. Products of the aldol condensation were 12 and 13; yields were quntitative in small-scale reactions but varied in large-scale reactions due to difficulty in extraction of products from the large quantity of alumina. Amides 12 and 13 were separated by crystallization for characterization. The mixture of 12 and 13 was heated

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(3) Kutney, J. P.; Beale, M. H.; Salisbury, P. J.; Sindelar, R. D.; Stuart, K. L.; Worth, B. R.; Townsley, P. M.; Chalmers, W. T.; Donnelly, D. J.; Nilsson, K.; Jacoli, G. G. *Heterocycles* **1980**, *14*, 1465–1467.
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(6) Buckanin, R. S.; Chen, S. J.; Frieze, D. M.; Sher, F. T.; Berchtold, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 1200–1201.
(7) (a) van Tamelen, E. E.; Demers, J. P.; Taylor, E. G.; Koller, K. *J. Am. Chem. Soc.* **1980**, *102*, 5424–5425. (b) Garver, L. C.; van Tamelen, E. E. *Ibid.* **1982**, *104*, 867–869.
(8) van Tamelen, E. E. *Pure Appl. Chem.* **1981**, *53*, 1259–1270.
(9) Koike, H.; Tokoroyama, T. *Tetrahedron Lett.* **1978**, 4531–4534.
(10) Koike, H.; Tokoroyama, T. *Chem. Lett.* **1979**, 333–336.
(11) van Tamelen, E. E.; Taylor, E. G.; Leiden, T. M.; Kreft, A. F., III. *J. Am. Chem. Soc.* **1979**, *101*, 7423–7424.
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(13) van Tamelen, E. E.; Taylor, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 1202–1203.
(14) Becker, H.-D.; Bremholt, T.; Alder, E. *Tetrahedron Lett.* **1972**, 4205–4208. Andersson, G. *Acta Chem. Scand., Ser. B* **1976**, *B30*, 403–406 and references cited therein.
(15) Sher, F. T.; Berchtold, G. A. *J. Org. Chem.* **1977**, *42*, 2569–2574.
(16) Frieze, D. M.; Berchtold, G. A.; Blount, J. F. *Tetrahedron Lett.* **1978**, 4607–4610.

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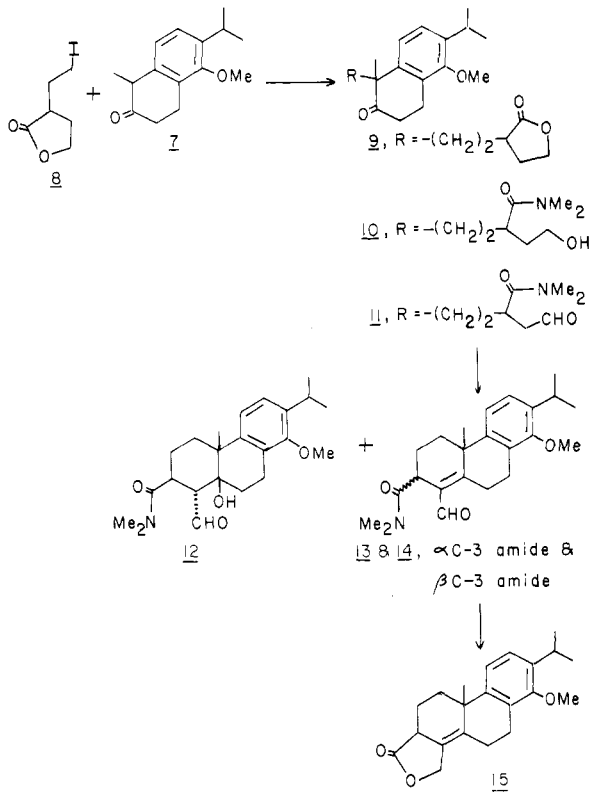
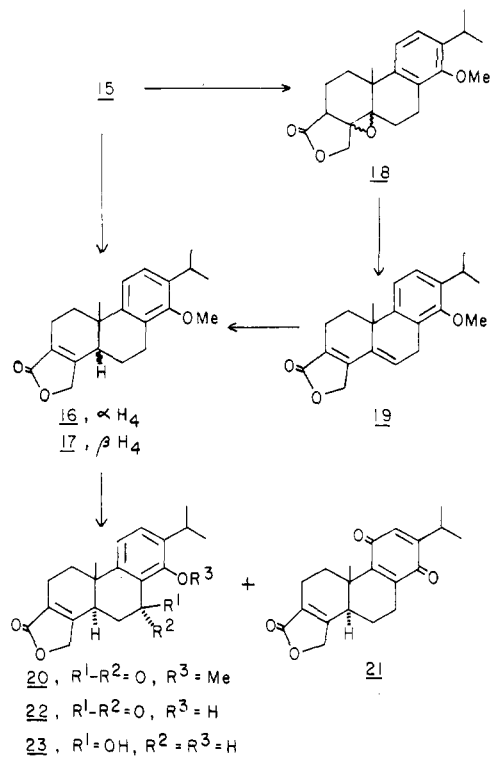
Scheme II



Scheme III



with *p*-toluenesulfonic acid in benzene to effect quantitative dehydration of **12** and afford a 1:2 mixture of **13** and **14**, respectively. Epimer **14** was separated by fractional crystallization for characterization. The ratio of **13** and **14** obtained represents the equilibrium mixture since heating either pure epimer with *p*-toluenesulfonic acid under the same conditions affords the same ratio of the two epimers. Unambiquous stereochemical assignments for **12–14** were not determined and, in fact, were unimportant in the synthesis because of subsequent transformations.

Reduction of the equilibrium mixture of **13** and **14** with sodium borohydride and subsequent treatment with 2 N HCl gave lactone **15**. Spectral data suggested **15** was essentially one epimer, and a single recrystallization from ethanol afforded sharp-melting material. Lactone **15** was recovered unchanged after treatment with 10% aqueous HCl/THF (1:1), but reaction with methoxide ion in methanol at room temperature for 15 min resulted in quantitative conversion to the trans (**16**, 40%) and cis (**17**, 60%) butenolides (Scheme II), of which **17** is the more stable isomer and is the sole product from the base-catalyzed reaction after 48 h. The product assigned the trans stereochemistry (**16**) in our original communication is, in fact, the cis isomer (**17**).[6,17] The two isomers are readily distinguished by the chemical shift position of the angular methyl group protons (**16**, δ 1.03; **17**, δ 1.33). The assignments are in agreement with results obtained by the van Tamelen group.[7,11]

A superior procedure for obtaining **16** was available through the following sequence. Peracid epoxidation of **15** gave epoxides **18**. Treatment with base isomerized **18** to the tertiary allylic alcohols which were dehydrated to diene **19**. Catalytic reduction of **19** with 10% Pd/C afforded **16** (70%) and **17** (30%) in an overall yield of ~90% from **15**, and **16** could be isolated (60%) by recrystallization from ether.

Benzylic oxidation (CrO_3/HOAc) of **16** gave **20** (45%) and a minor amount of quinone **21**, resulting from oxidation of the aromatic ring. Ether cleavage (BBr_3/CH_2Cl_2) gave phenol **22**, and subsequent borohydride reduction of the ketone afforded **23** in high yield from **20**. The stereochemistry of the benzylic hydroxyl group was established as described previously.[15]

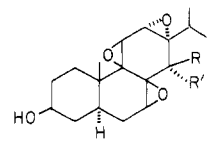
The Alder periodate reaction[14] converted **23** to epoxy dienone **24** (74%, Scheme III) as a relatively stable, pale yellow solid with the characteristic dienone UV absorption maximum at 343 nm (ϵ 4954) and an intense carbonyl absorption in the IR spectrum at 1660 cm^{-1}. Reaction of **24** with a large excess of MCPBA gave racemic **3** (41%). Alernatively, **24** could be oxidized to **25** (MCPBA) which reacted with H_2O_2/OH^- to afford **3**. Reduction of **3** ($NaBH_4$/EtOH) gave racemic **1** (21%) and **4** (68%) that were separated by preparative layer chromatography on silica gel. The ^1H NMR and IR spectra of racemic **1** and **3** were identical with the spectra of the natural products that were provided by the late Professor S. M. Kupchan.

Although undesired isomer **4** is the major product from borohydride reduction of **3**, **4** can be oxidized back to **3** in 77% yield with CrO_3·py complex in CH_2Cl_2.

In view of the suggestions of Kupchan and co-workers[4] concerning the chemical reactivity of the hydrogen-bonded 9,11-epoxy-14β-hydroxy system of **1** and **2** in relation to the antileukemic activity as described above, it was of interest to acquire information as to whether the butenolide moiety of **1** is necessary for the observed antileukemic activity.

Ketone **26**, described in previous model studies,[16] was reduced with sodium borohydride to afford **27** (27%) and **28** (58%). The structure of the epimeric alcohols was established by comparison of ^1H NMR data with those of **1** and **4**. The αC-14 carbinol hydrogen of **27** appears as a doublet (J = 11.6 Hz), confirming that the C-14 hydroxyl group is hydrogen bonded to the C-9,11 epoxide oxygen as is observed for **1** and **2**. Analogue **27** failed to show any

(17) The benzylic oxidation described previously[6] was perfomred on a mixture of **16** and **17** since isomerization of the A/B ring fusion does not occur during the oxidation.



26, R-R' = O
27, R = OH, R' = H
28, R = H, R' = OH

antileukemic activity against P388 lymphocytic leukemia.[18] From these results it is concluded that the butenolide moiety is necessary for the antileukemic activity observed for 1.

Experimental Section

Melting points were determined with a Thomas-Hoover Unimelt and are corrected. ^1H NMR spectra were recorded at 60 MHz (Perkin-Elmer R-24B or Varian T-60), 90 MHz (JEOL FX-90 Q), 250 MHz (Brucker WP 250 FT), or 270 MHz (Brucker HFX-270 FT). Unless other wise indicated, spectra were obtained at 60 MHz, and chemical shift values (δ) are reported in parts per million downfield from tetramethylsilane. ^{13}C NMR were recorded at 22.5 MHz (JEOL) or 62.83 MHz (Brucker WP). Chemical shift values (δ) are reported in parts per million downfield from tetramethylsilane. Mass spectra were determined with a Varian MAT 44 instrument. High-resolution mass spectra were provided by the facility supported by National Institutes of Health Grant RR00317 (principal investigator Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources. Infrared spectra were obtained with a Perkin-Elmer Model 567 grating spectrophotometer. Ultraviolet spectra were obtained with a Perkin-Elmer Model 552 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

2-(β-Iodoethyl)butyrolactone (8). To a mixture of 162 g of 48% aqueous hydrobromic acid and 47.6 g of concentrated sulfuric acid was added tetrahydropyran-4-carboxylic acid[19] (20 g), and the mixture was heated overnight at 140 °C. The mixture was cooled, neutralized (Na_2CO_3), and extracted with ether. The ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was distilled to give 20.6 g (70%) of 2-(β-bromoethyl)butyrolactone as a colorless oil: bp 97–99 °C (0.2 mm); IR ($CHCl_3$) 1764 cm^{-1}. Anal. Calcd for $C_6H_9BrO_2$: C, 37.33; H, 4.70; Br, 41.39. Found: C, 37.22; H, 4.69; Br, 41.37.

The bromolactone (193 g, 1.0 mol) was added to a solution of sodium iodide (176.2 g, 1.1 mol) in 1 L of acetone. A precipitate formed almost immediately. The mixture was stirred overnight, filtered, and concentrated under reduced pressure. The residue was dissolved in ether, washed with equal volumes of water and saturated sodium thiosulfate, dried ($MgSO_4$), and concentrated to give 240 g (100%) of crude 8 that was satisfactory for further reaction: IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–3.0 (5 H, m), 3.2–3.7 (2 H, m), 4.2–4.7 (2 H, m); MS m/e 240 (M^+).

(R*,R*)-(±)- and (R*,S*)-(±)-1,2,3,4-Tetrahydro-α-(2-hydroxyethyl)-5-methoxy-1-methyl-6-(1-methylethyl)-2-oxo-1-naphthalenecarboxylic Acid Lactone (9). A dispersion of 50% NaH in oil (5.72 g of NaH, 0.238 mol) was placed in a flask and washed with three 50-mL portions of petroleum ether. The flask was placed in an ice bath, and 250 mL of dry dimethylformamide was added. A solution of 7[15] (50.2 g, 0.21 mol) in 500 mL of dimethylformamide was added dropwise with stirring. The mixture was stirred for 20 min after the addition was complete, and a solution of 8 (57.2 g, 0.238 mol) in 500 mL of dimethylformamide was added dropwise with stirring. The ice bath was removed, and the solution was warmed to room temperature and stirred overnight. The solution was diluted with ether, washed with water and saturated aqueous NaCl solution, and dried ($MgSO_4$). Concentration under reduced pressure gave 69 g (94%) of lactones 9. An analytical sample was prepared by recrystallization from ethanol: mp 112–113 °C; IR ($CHCl_3$) 1764, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (6 H, d, J = 7 Hz), 1.40 (3 H, s), 1.5–2.8 (9 H, m), 2.8–3.6 (3 H, m), 3.70 (3 H, s), 4.0–4.4 (2 H, m), 6.97 (1 H, d, J = 10 Hz), 7.18 (1 H, d, J = 10 Hz); UV (ethanol) λ_{max} 267 nm (ϵ 475); MS m/e 344 (M^+). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.08; H, 8.13.

(R*,R*)-(±)- and (R*,S*)-(±)-1,2,3,4-Tetrahydro-α-(2-hydroxyethyl)-5-methoxy-N,N,1-trimethyl-6-(1-methylethyl)-2-oxo-1-naphthalenebutanamide (10). A mixture of 9 (12.0 g, 34.8 mmol) and 200 mL of anhdyrous dimethylamine was stirred overnight at room temperature. Excess amine was removed under reduced pressure to give 13.5 g (100%) of disasteromers 10 that were sufficiently pure for further use. Analytically pure 10 (colorless oil) was prepared by chromatography on silica gel (ethyl acetate): IR 3400 (br), 1706, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (6 H, d, J = 7 Hz), 1.37 (3 H, s), 1.5–3.2 (17 H, m), 3.50 (3 H, m), 3.70 (3 H, s), 6.8–7.4 (2 H, m). Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.92; H, 9.06; N, 3.60. Found: C, 70.61; H, 8.93; N, 3.61.

(R*,R*)-(±)- and (R*,S*)-(±)-1,2,3,4-Tetrahydro-α-(formylmethyl)-5-methoxy-N,N,1-trimethyl-6-(1-methylethyl)-2-oxo-1-naphthalenebutanamide (11). A solution of pyridine (18.6 g, 0.235 mol) in 100 mL of CH_2Cl_2 was cooled in an ice bath, and CrO_3 (11.7 g, 0.12 mol) was added in small portions over 20 min. The solution was warmed to room temperature and stirred for 15 min. A solution of 7.6 g (50 mmol) of 10 in 10 mL of CH_2Cl_2 was added, and the mixture was stirred for 15 min. The mixture was diluted with ether. The solution was decanted, and the residue was washed with a second portion of ether. The combined ether extracts were washed with an equal volume of water, with 2 N NaOH (3 × 250 mL), with 2 N HCl (3 × 250 mL), with saturated $NaHCO_3$ (3 × 250 mL), with water (2 × 250 mL), and with saturated NaCl solution (2 × 250 mL). The ether layer was dried ($MgSO_4$) and concentrated to give 6.27 g (83%) of 11 as a pale yellow oil that was sufficiently pure for further use. An analytical sample (colorless oil) was prepared by chromatography on silica gel (ethyl acetate): IR ($CHCl_3$) 2733, 1716, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (6 H, d, J = 7 Hz), 1.47 (3 H, s), 1.5–3.5 (18 H, m), 3.72 (3 H, s), 6.8–7.4 (2 H, m), 9.73 (1 H, s); MS m/e 387 (M^+). Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.33; H, 8.66; N, 3.42.

(4aβ,10aβ)-1-Formyl-1,2,3,4,4a,9,10,10a-octahydro-10a-hydroxy-8-methoxy-N,N,4a-trimethyl-7-(1-methylethyl)-2-phenanthrenecarboxamide (12) and 1-Formyl-2,3,4,4a,9,10-hexahydro-8-methoxy-N,N,4a-trimethyl-7-(1-methylethyl)-2-phenanthrenecarboxamide (13). A mixture of 11 (6.27 g, 16.2 mmol), 60 g of alumina (neutral alumina, Woelm TSC, activity III, ICN Pharmaceuticals), and 100 mL of ethyl acetate was stirred at room temperature for 2 days. The solution was filtered, and the alumina was washed with ethyl acetate. The combined ethyl acetate solutions were concentrated under reduced pressure to give 6.25 g (99%) of a 1:1 mixture (^1H NMR) of 12 and 13 as a pale yellow solid. (On a larger scale complete extraction of products from the alumina was more difficult, and yields were as low as 80%.) Repeated crystallization from ethyl acetate gave pure 12: mp 198.5–199.5 °C; IR ($CHCl_3$) 3500 (br), 2739, 1713, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (6 H, s), 1.28 (3 H, s), 1.4–2.7 (6 H, m), 2.82 (3 H, s), 3.05 (3 H, s), 2.8–3.3 (2 H, m), 3.3–3.5 (2 H, m), 3.72 (3 H, s), 7.02 (2 H, m), 10.07 (1 H, s); ^{13}C NMR ($CHCl_3$) δ 22.3, 23.9, 25.9, 27.6, 29.3, 31.7, 35.5, 36.9, 38.4, 43.0, 52.6, 60.4, 74.3, 119.2, 122.4, 127.3, 138.6, 141.0, 155.4, 174.2, 203.7; MS m/e 387 (M^+). Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.24; H, 8.57; N, 3.45.

Repeated crystallization from ethanol gave pure 13: mp 187–188 °C; IR ($CHCl_3$) 1661, 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (6 H, d, J = 7 Hz), 1.61 (3 H, s), 1.6–3.8 (9 H, m), 2.97 (3 H, s), 3.18 (3 H, s), 3.70 (3 H, s), 7.14 (2 H, m), 10.27 (1 H, s); ^{13}C NMR ($CHCl_3$) 22.6, 23.8, 26.3, 29.7, 36.2, 37.7, 40.3, 60.8, 122.3, 125.0, 128.4, 132.2, 138.6, 143.9, 154.2, 164.8, 175.3, 191.0; MS m/e 369 (M^+). Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.48; N, 3.79. Found: C, 74.58; H, 8.64; N, 3.73.

***cis*- and *trans*-1-Formyl-2,3,4,4a,9,10-hexahydro-8-methoxy-N,N,4a-trimethyl-7-(1-methylethyl)-2-phenanthrenecarboxamide (13 and 14).** A 1:1 mixture of 12 and 13 (3.16 g) and 3.6 mg of *p*-toluenesulfonic acid in 25 mL of benzene was heated under reflux for 2 h with removal of water in a Dean–Stark

(18) Sample submitted to the National Cancer Institute for biological evaluation.

(19) Thomas, J.; Clough, D. *J. Pharm. Pharmacol.* **1963**, *15*, 167–177.

trap. The solution was cooled, diluted with ether, and washed with 50 mL of 10% $NaHCO_3$, 50 mL of water, and 50 mL of saturated NaCl solution. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 3.0 g (95%) of a 1:2 mixture (^1H NMR) of **13** and **14**, respectively. Fractional crystallization from ethanol afforded pure **14**: mp 183–184 °C; IR ($CHCl_3$) 1661, 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (6 H, d, J = 7 Hz), 1.50 (3 H, s), 1.6–3.8 (10 H, m), 2.90 (3 H, s), 3.20 (3 H, s), 3.72 (3 H, s), 7.07 (2 H, m); ^{13}C NMR ($CHCl_3$) δ 21.5, 23.4, 23.8, 26.2, 26.5, 30.2, 33.0, 34.5, 35.7, 37.5, 40.2, 60.8, 122.3, 124.7, 128.5, 131.0, 138.5, 143.9, 154.2, 165.8, 173.8, 190.5; MS m/e 369 (M^+). Anal. Calcd for $C_{21}H_{31}NO_3$: C, 74.76; H, 8.48; N, 3.79. Found: C, 75.01; H, 8.41; N, 3.75.

4,5,9b,10,11,11a-Hexahydro-6-methoxy-9b-methyl-7-(1-methylethyl)phenanthro[1,2-*c*]furan-1(3*H*)-one (15). A 1:2 mixture of **13** and **14** (2.00 g, 5.4 mmol) was dissolved in 20 mL of absolute ethanol, and sodium borohydride (200 mg, 5.4 mmol) was added. The mixture was stirred at room temperature for 2 h. The solution was acidified with 2 N HCl and extracted with three 50-mL portions of ether. The combined ether extracts were washed with 100 mL of water and 100 mL of saturated NaCl solution. The organic layer was dried ($MgSO_4$) and concentrated to give 1.64 g (93%) of **15** as a pale yellow solid. Recrystallization from ethanol gave pure **22**: mp 159–160 °C; IR ($CHCl_3$) 1774, 1769, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.20 (6 H, d, J = 7 Hz), 1.39 (3 H, s), 1.5–3.2 (9 H, m), 3.34 (1 H, septet, J = 7 Hz), 3.67 (3 H, s), 4.85 (2 H, m), 7.04 (2 H, m); ^{13}C NMR ($CHCl_3$) δ 19.8, 23.8, 26.1, 30.8, 37.0, 38.1, 40.2, 60.6, 69.2, 121.8, 122.7, 124.8, 128.3, 136.9, 138.6, 144.9, 154.5, 176.8; MS m/e 326 (M^+). Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.18; H, 8.14.

Preparation of Epoxide Mixture 18. Olefin **15** (322 mg, 1.04 mmol) in CH_2Cl_2 (50 mL) was added to a solution of MCPBA (430 mg, 80%, 2 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred overnight at room temperature. The slurry was diluted with $CHCl_3$ (20 mL), and excess $Ca(OH)_2$ powder (1 g) was added. The mixture was stirred at room temperature for 0.5 h and filtered. The residue was washed with three 20-mL portions of $CHCl_3$. The combined organic layers were concentrated under reduced pressure to give 330 mg (98%) of epoxides **18** as white, crystalline material. The major isomer, assigned the α-epoxide structure, was isolated by recrystallization from 1% ether/ethanol: mp 188–190 °C; IR (KBr) 1780 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22 (6 H, d, J = 7 Hz), 1.34 (3 H, s), 3.73 (3 H, s), 4.35 (1 H, d, J = 10.3 Hz), 4.39 (1 H, d, J = 10.3 Hz), 6.98 (1 H, d, J = 8.5 Hz), 7.11 (1 H, d, J = 8.5 Hz); ^{13}C NMR ($CHCl_3$) δ 17.7, 21.1, 23.0, 23.9, 26.2, 28.5, 28.7, 36.7, 37.0, 60.6, 66.3, 66.9, 69.2, 120.8, 124.7, 127.6, 139.4, 142.9, 155.2, 176.0; high-resolution mass spectrum, calcd for $C_{21}H_{26}O_4$ m/e 342.181 60, found 342.181 60.

5,9b,10,11-Tetrahydro-6-methoxy-9b-methyl-7-(1-methylethyl)phenanthro[1,2-*c*]furan-1(3*H*)-one (19). Triethylamine (2 mL) was added to a solution of epoxides **18** (109 mg, 0.33 mmol) in 10 mL of CH_2Cl_2, and the solution was stirred overnight at room temperature under a nitrogen atmosphere. Volatile materials were removed in a rotary evaporator followed by high vacuum to yield the unsaturated C-3b alcohols (109 mg, 100%) as a white solid: IR (KBr) 3440, 1750 cm^{-1}. The mixture of alcohols in 2,4,6-trimethylpyridine (1 mL) and dimethylformamide (5 mL) was cooled to 10 °C. The cooling bath was removed, and, during the course of 1–2 min, methansulfonyl chloride (0.5 mL) containing 3.5% by weight of anhydrous SO_2 was added to the clear solution with stirring. The temperature was maintained at 25–35 °C during the addition and for 0.5 h after the addition was complete. Excess methanesulfonyl chloride was decomposed, with cooling, by slow addition of water until all the precipitate dissolved. The clear orange-red solution was added dropwise, with stirring, to water (50 mL) over a period of 10 min. The resulting slurry was stirred for 1 h at 20–25 °C and extracted with three 50 mL portions of ether. The combined ether extracts were worked up in the usual manner, and purification by preparative TLC (silica gel) gave **19** (95 mg, 92%) as pale yellow crystals that were recrystallized from ethanol: mp 148–150 °C; IR (KBr) 1750, 1660 cm^{-1}; UV (ethanol) λ_{max} 268 (ϵ 12 000), 205 (18 000); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.19 (3 H, s), 1.21 (3 H, d, J = 7 Hz), 1.27 (3 H, d, J = 7 Hz), 3.77 (3 H, s), 4.97 (2 H, m), 6.18 (1 H, dd, J = 5.7, 2.0 Hz), 7.20 (2 H, s); ^{13}C NMR ($CHCl_3$) δ 17.9, 23.6, 24.1, 25.0, 26.2, 27.2, 32.8, 36.9, 61.1, 69.2, 120.6, 123.8, 125.2, 125.9, 126.3, 135.3, 139.2, 142.4, 154.5, 155.0, 174.2; high-resolution mass spectrum, calcd for $C_{21}H_{24}O_3$ m/e 324.172 54, found 324.173 35.

***trans*- and *cis*-3b,4,5,9b,10,11-Hexahydro-6-methoxy-9b-methyl-7-(1-methylethyl)phenanthro[1,2-*c*]furan-1(3*H*)-one (16, 17).** Diene **19** (420 mg, 1.36 mmol) in anydrous ethyl acetate (20 mL) was reduced in a Parr hydrogenation apparatus with Pd/C (10%, 420 mg) and 50 psi of H_2 over a period of 1.5 h. The reaction mixture was suction filtered through a short solumn of Celite. The column was washed with ethyl acetate (2 × 20 mL). Removal of solvent under reduced pressure gave **16** (70%) and **17** (30%) (total yield 425 mg, 100%) as a white crystalline solid. The ratio of **16**/**17** was determined by integration of the methoxy signals in the ^1H NMR spectrum (250 MHz). The trans isomer (**16**) was selectively recrystallized from ether as colorless needles: mp 177–179 °C; IR (KBr) 1750, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.03 (3 H, s), 1.22 (3 H, d, J = 7 Hz), 1.24 (3 H, d, J = 7 Hz), 3.74 (3 H, s), 4.79 (2 H, m), 7.12 (2 H, s); ^{13}C NMR ($CHCl_3$) δ 17.7, 19,2, 21.8, 22.3, 23.4, 23.5, 25.7, 32.3, 35.9, 40.6, 60.0, 70.1, 119.8, 123.7, 124.4, 127.8, 138.7, 143.8, 155.2, 162.9, 173.8. Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.21; H, 7.95.

Removal of the solvent for recrystallization of **16** and recrystallization of the residue from ethanol gave pure cis isomer **17**: mp 162–162.5 °C; IR (KBr) 1755, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.21 (3 H, d, J = 7 Hz), 1.22 (3 H, d, J = 7 Hz), 1.33 (3 H, s), 3.69 (3 H, s), 4.72 (1 H, d, J = 17 Hz), 4.89 (1 H, d, J = 17 Hz), 7.11 (2 H, s); ^{13}C NMR ($CHCl_3$) δ 17.4, 19.2, 21.8, 22.3, 23.4, 23.5, 28.5, 34.0, 36.3, 41.1, 60.2, 70.5, 122.5, 124.1, 125.9, 128.6, 138.1, 141.0, 154.1, 162.9, 173.6; MS m/e 326 (M^+).

Base-catalyzed isomerization of **15** to **16** and **17** was effected in methanol containing 0.6 equiv of sodium methoxide. After 15 min at room temperature, the usual workup afforded a mixture of **16** (40%) and **17** (60%) as determined from the ^1H NMR spectrum (250 MHz). If the reaction was allowed to continue for 48 h, **17** was obtained in quantitative yield.

***trans*-3,3b,4,9b,10,11-Hexahydro-6-methoxy-9b-methyl-7-(1-methylethyl)phenanthro[1,2-*c*[furan-1,5-dione (20).** A solution of CrO_3 (740 mg, 7.4 mmol) in 90% acetic acid (10% water, 45 mL) was added over a 20-min period to a water-cooled solution of **16** (1.25 g, 3.83 mmol, 90% pure, contaminated with 10% **17**) in glacial acetic acid (56 mL). The reaction mixture was stirred at room temperature for 2 h. A solution of CrO_3 (740 mg) in 90% acetic acid (56 mL) was added, and the mixture was stirred for 2 h. A second portion of CrO_3 (550 mg) in 90% acetic acid (36 mL) was added, and the mixture was stirred for 2 h. The solution was diluted with an equal volume of water and extracted with $CHCl_3$ (3 × 100 mL). The combined $CHCl_3$ extracts were washed with water (2 × 100 mL) and saturated NaCl solution (50 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and purification by column chromatography gave pure **20**: 583 mg (45%); mp 181–183 °C; IR ($CHCl_3$) 1750, 1679 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.17 (3 H, s), 1.24 (3 H, d, J = 7 Hz), 1.26 (3 H, d, J = 7 Hz), 1.6–3.2 (7 H, m), 3.42 (1 H, septet, J = 7 Hz), 3.86 (3 H, s), 4.80 (2 H, m), 7.21 (1 H, d, J = 8 Hz), 7.52 (1 H, d, J = 8 Hz); ^{13}C NMR ($CHCl_3$) 17.8, 22.0, 23.3, 25.9, 32.0, 36.7, 37.7, 39.8, 62.7, 70.1, 118.8, 125.6, 132.0, 142.1, 150.7, 158.4, 160.3, 173.4, 195.1; high-resolution mass spectrum, calcd for $C_{21}H_{24}O_4$ m/e 340.1675, found 340.1673.

Quinone **21** (190 mg, 15%) was isolated as a byproduct during the chromatographic purification: IR ($CHCl_3$) 1751, 1679, 1650, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (6 H, d, J = 7 Hz), 1.20 (3 H, s), 4.70 (2 H, m), 6.33 (1 H, d, J = 1 Hz).

Benzylic ketone isomer with cis A/B ring fusion was isolated (4%) from oxidation of the minor amount of **17** present as an impurity: mp 172.5–173.5 °C; IR ($CHCl_3$) 1755, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (6 H, d, J = 6 Hz), 1.48 (3 H, s), 1.6–3.1 (7 H, m), 3.30 (1 H, septet, J = 7 Hz), 3.74 (3 H, s), 4.77 (2 H, m), 7.19 (1 H, d, J = 8 Hz), 7.50 (1 H, d, J = 8 Hz); high-resolution mass spectrum, calcd for $C_{21}H_{24}O_4$ m/e 340.1675, found 340.1669.

***trans*-3,3b,4,9b,10,11-Hexahydro-6-hydroxy-9b-methyl-7-(1-methylethyl)phenanthro[1,2-*c*]furan-1,5-dione (22).** To a solution of **20** (99.7 mg, 2.93 mmol) in 5 mL of CH_2Cl_2 at 0 °C under nitrogen was added boron tribromide (238 mg, 90 μL). After 10 min the ice bath was removed, and stirring was continued overnight at room temperature. Five milliliters of 2 N HCl were added, and the mixture was extracted with ether. The ether layer was washed with saturated NaCl solution and dried ($MgSO_4$).

Concentration under reduced pressure gave solid **22** (95 mg, 99%) that was recrystallized from ethyl acetate: mp 183–184 °C; IR ($CHCl_3$) 3500 (br), 1755, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3 H, s), 1.27 (6 H, d, J = 7 Hz), 1.6–3.7 (7 H, m), 4.79 (2 H, m), 6.89 (1 H, d, J = 8 Hz), 7.40 (1 H, d, J = 8 Hz); ^{13}C NMR ($CHCl_3$) δ 17.9, 22.2, 26.3, 31.7, 36.5, 40.5, 70.1, 113.6, 114.8, 126.1, 133.8, 136.1, 149.2, 159.9, 161.8, 173.4, 202.4; high-resolution mass spectrum, calcd for $C_{20}H_{22}O_4$ m/e 326.1518, found 326.1506.

3bα,4,5β,9bβ,10,11-Hexahydro-5,6-dihydroxy-9b-methyl-7-(1-methylethyl)phenanthro[1,2-*c*]furan-1(3*H*)-one (23). A solution of **22** (58.1 mg, 0.178 mmol) in ethanol (2 mL) was cooled in an ice bath, and sodium borohydride (15.0 mg, 0.39 mmol) was added. The solution was stirred at room temperature for 1 h and neutralized with saturated NH_4Cl solution. The mixture was diluted with water and extracted twice with ether. The combined ether extracts were washed with water, saturated NaCl solution, and dried ($MgSO_4$). Concentration under reduced pressure gave **23** (47.5 mg, 81%) as a pale yellow solid. Chromatography on silica gel (ether) gave colorless, crystalline **23**: mp 127–128 °C; IR ($CHCl_3$) 3580 (br), 3360 (br), 1753 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.13 (3 H, s), 1.23 (3 H, d, J = 7 Hz), 1.27 (3 H, d, J = 7 Hz), 1.5–3.2 (7 H, m), 3.33 (1 H, septet, J = 7 Hz), 4.78 (2 H, m), 5.18 (1 H, br t, J = 8 Hz, half band width = 16 Hz), 6.87 (1 H, d, J = 8 Hz), 7.17 (1 H, d, J = 8 Hz); UV (ethanol) λ_{max} 280 nm (ϵ 3280).

(5aα,9a*S*,10β,11aβ)-4,5,5a,10,11,11a-Hexahydro-5a-methyl-8-(1-methylethyl)-1*H*-oxireno[8a,9]phenanthro[1,2-*c*]furan-3,9-dione (24).** A solution of phenol **23** (45.0 mg, 0.14 mmol) in methanol (1 mL) was stirred while sodium metaperiodate (32.4 mg, 0.15 mmol) was added. A precipitate formed after 30 s. The mixture was stirred for 5 h at room temperature, filtered to remove the precipitate ($NaIO_3$), and partitioned between $CHCl_3$ and water. The $CHCl_3$ layer was washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure (without heating) to give 32.9 g (74%) of **24** as a yellow solid that was sufficiently pure for further use. Preparative layer chromatography on silica gel (1% $CH_3OH/CHCl_3$) gave pure **24**: mp 80–83 °C; IR ($CHCl_3$) 1755, 1680, 1660, 1637 cm^{-1}; UV (ethanol) λ_{max} 268 (ϵ 2393), 343 (4954); ^1H NMR ($CDCl_3$) δ 1.10 (6 H, d, J = 7 Hz), 1.15 (3 H, s), 1.5–2.6 (7 H, m), 2.93 (1 H, septet, J = 7 Hz), 4.07 (1 H, m), 4.70 (2 H, m), 6.42 (1 H, d, J = 7 Hz), 6.99 (1 H, d, J = 7 Hz); ^{13}C NMR ($CHCl_3$) δ 16.9, 17.6, 21.5, 21.7, 24.3, 26.3, 32.9, 38.3, 43.7, 57.2, 66.8, 70.0, 121.0, 125.3, 135.1, 142.2, 150.4, 160.3, 173.3, 194.1; high-resolution mass spectrum, calcd for $C_{20}H_{22}O_4$ m/e 326.1518, found 326.1516.

12,13-Deepoxytriptonide (25). A solution of **24** (33.0 mg, 0.1 mmol) and MCPBA (63.3 mg of 85% purity, 0.31 mmol) in 2.1 mL of CH_2Cl_2 was stirred for 20 h at 35 °C and for 18 h at room temperature. The mixture was diluted with ether, washed with saturated Na_2CO_3 solution and saturated NaCl solution, dried ($MgSO_4$), and concentrated to give a pale yellow solid. Preparative layer chromatography on silica gel (1% $CH_3OH/CHCl_3$) gave 15.6 mg (45%) of **25** as a white solid that was recrystallized from ethanol: mp 218–219 °C; IR ($CHCl_3$) 1759, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.00 (3 H, d, J = 7 Hz), 1.09 (3 H, d, J = 7 Hz), 1.13 (3 H, s), 1.5–2.5 (7 H, m), 2.70 (1 H, septet, J = 7 Hz), 3.57 (1 H, d, J = 3 Hz), 3.79 (1 H, d, J = 3 Hz), 4.68 (2 H, m), 6.90 (1 H, d, J = 5 Hz); ^{13}C NMR ($CHCl_3$) 13.7, 17.1, 21.5, 23.5, 27.2, 30.2, 35.2, 41.0, 51.6, 59.5, 62.0, 65.1, 69.9, 126.0, 136.4, 150.4, 159.5; high-resolution mass spectrum, calcd for $C_{20}H_{22}O_5$ m/e 342.146 72, found 342.146 19.

(±)-Triptonide (3). Method A (from 24). To epoxy dienone **24** (170 mg, 0.52 mmol) in CH_2Cl_2 (20 mL) was added MCPBA (440 mg of 85% purity, 2.5 mmol), and the mixture was stirred at 30–35 °C for 84 h during which time an additional 440 mg of MCPBA was added after 12 h and again after 36 h. The reaction mixture was diluted with $CHCl_3$ (20 mL), and $Ca(OH)_2$ powder (6 g) was added. The mixture was stirred for 0.5 h at room temperature. The solution was filtered, and the residue was washed with $CHCl_3$ (5 × 20 mL). The combined organic layers were concentrated to give a pale yellow solid. Preparative layer chromatography on silica gel (10% methanol/chloroform) gave white crystals of **3**: 75.7 mg (41%); mp 224–225 °C; IR (KBr) 1763, 1723, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.89 (3 H, d, J = 7 Hz), 0.98 (3 H, d, J = 7 Hz), 1.08 (3 H, s), 3.42 (1 H, d, J = 5 Hz), 3.85 (1 H, d, J = 3 Hz), 4.06 (1 H, d, J = 3 Hz), 4.71 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 13.7, 16.3, 17.1, 18.0, 23.2, 25.8, 30.5, 35.3, 40.5, 56.0, 58.9, 60.4, 60.9, 65.1, 66.5, 69.9, 125.8, 159.5, 173.1, 197.0; high-resolution mass spectrum, calcd for $C_{20}H_{22}O_6$ m/e 358.141 64, found 358.141 70.

Lower R_f fractions gave **25** (32.6 mg, 18%) as a white solid that was identical with **25** prepared as described earlier.

Method B (from 25). To a solution of **25** (50 mg, 0.15 mmol) in methanol (5.2 mL) were added 30% H_2O_2 (24.1 μL, 0.22 mmol) and NaOH (1 N, 73.0 μL, 0.18 mmol), and the solution was stirred for 20 h at room temperature. The methanol solution was diluted with water (4 volumes) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to give 30 mg (60%) of (±)-**3** that, after recrystallization from ethanol, was identical with (±)-**3** prepared by method A; mp 225–226 °C.

Method C (from 4). Chromium trioxide (23 mg, 0.23 mmol) was added to a solution of CH_2Cl_2 (1 mL) and pyridine (36.3 mg, 0.46 mmol). The mixture was stirred at room temperature for 15 min. A solution of (±)-**4** (13.8 mg, 0.038 mmol) in CH_2Cl_2 was added, and the mixture was stirred for 2 h. The mixture was diluted with ether. The organic layer was washed with 2 N NaOH, 2 N HCl, saturated $NaHCO_3$, and saturated NaCl solution and dried ($MgSO_4$). Concentration under reduced pressure gave 10.5 mg (77%) of (±)-**3** (mp 223–224 °C) that was identical with (±)-**3** prepared by method A.

(±)-Triptolide (1) and 14-Epitriptolide (4). To a solution of (±)-**3** (15.0 mg, 0.042 mmol) in ethanol (1 mL) was added sodium borohydride (3.0 mg). The reaction mixture was stirred at room temperature for 1 h. The solution was diluted with water (4 volumes) and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and concentrated. Preparative layer chromatography on silica gel (1% $CH_3OH/CHCl_3$) gave 3.2 mg (21%) of (±)-**1** and 10.2 mg (68%) of (±)-**4**. Recrystallization of (±)-**1** from ethanol gave colorless needles: mp 255–256 °C; IR ($CHCl_3$) 1755, 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.88 (3 H, d, J = 7 Hz), 1.01 (3 H, d, J = 7 Hz), 1.12 (3 H, s), 1.5–3.0 (8 H, m), 2.72 (1 H, d, J = 11 Hz), 3.40 (3 H, m), 3.90 (1 H, d, J = 3 Hz), 4.68 (2 H,m); high-resolution mass spectrum, calcd for $C_{20}H_{24}O_6$ m/e 360.157 29, found 360.156 95.

Recrystallization of (±)-**4** from ethanol gave colorless needles: mp 245–246 °C; IR ($CHCl_3$) 1755,1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 7 Hz), 1.09 (3 H, d, J = 7 Hz), 1.10 (3 H, s), 1.5–3.0 (8 H, m), 3.39 (1 H, d, J = 3 Hz), 3.72 (2 H, m), 4.50 (1 H, d, J = 2 Hz), 4.67 (2 H, m); high-resolution mass spectrum, calcd for $C_{20}H_{24}O_6$ m/e 360.157 29, found 360.156 72.

(1aα,2β,2a*S*,3aβ,6α,8aα,8b*R***,9aβ,9bα)-Dodecahydro-8a-methyl-1a-(1-methylethyl)phenanthro[2,3-*b*:4,4a-*b*′:10,10a-*b*′]trioxirene-2,6-diol (27) and (1aα,2α,2a*S***,3aβ,6α,8aα,8b*R***,9aβ,9bα)-Dodecahydro-8a-methyl-1a-(1-methylethyl)-phenanthro[2,3-*b*:4,4a-*b*′:10,10a-*b*′]trioxirene-2,6-diol (28).** A solution of **26**[16] (125 mg, 0.389 mmol) in absolute ethanol (10 mL) was treated with sodium borohydride (8.1 mg, 0.214 mmol) and stirred 1 h at room temperature. The solution was diluted with water (4 volumes) and extracted with CH_2Cl_2. The organic solutions were dried (Na_2SO_4) and concentrated to afford 123 mg of a mixtrue of **27** and **28**. Separation was accomplished by preparative layer chromatography on silica gel (4:1 CH_2Cl_2/five elutions) to give 34 mg (27%) of **27** and 73 mg (58%) of **28** as white, crystalline solid.

27: mp 167 °C dec; IR ($CHCl_3$) 3605, 3520; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (3 H, d, J = 7.3 Hz), 0.99 (3 H, d, J = 7.3 Hz), 1.16 (3 H, s), 1.18–1.54 (4 H, m), 1.54–1.83 (5 H, m, includes 6β-OH at 1.68), 1.84–1.98 (2 H, m), 2.25 (1 H, septet, J = 7.3 Hz), 2.80 (1 H, d, J = 10 Hz, 2β-OH, exchanges with D_2O), 3.22 (1 H, d, J = 5 Hz), 3.38 (1 H, d, J = 10 Hz, 2α-H, collapses to a singlet with D_2O), 3.49 (1 H, d, J = 3.8 Hz), 3.48–3.58 (1 H, m), 3.94 (1 H, d, J = 3 Hz); ^{13}C NMR ($CHCl_3$) δ 14.6, 17.1, 17.9, 28.5, 30.3, 32.1, 35.6, 37.6, 39.3, 55.0, 57.7, 61.1, 65.8, 68.3, 70.3, 74.1; high-resolution mass spectrum, calcd for $C_{18}H_{26}O_5$ m/e 322.178 02, found 322.179 88.

28: mp 206 °C dec; IR ($CHCl_3$) 3605, 3590, 3640–3320 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 1.14 (3 H, s), 1.18–1.54 (4 H, m), 1.54–1.83 (5 H, m, includes 6β-OH at 1.68), 1.84–1.98 (2 H, m, includes 2α-OH at 1.96 with J = 4 Hz), 2.34 (1 H, septet, J = 7 Hz), 3.37 (1 H, d, J = 3.2 Hz), 3.57 (1 H, d, J = 5 Hz), 3.48–3.58 (1 H, m), 3.81 (1 H, d, J = 3.2 Hz), 4.47 (1 H, br s, sharpens with D_2O); high-

resolution mass spectrum, calcd for $C_{18}H_{26}O_5$ m/e 322.178 02, found 322.178 99.

Acknowledgment. Financial support from the National Cancer Institute Grant No. 5-RO1-CA 18888 and 5-T32-CA 09112) is gratefully acknowledged.

Registry No. (±)-**1**, 73414-46-7; (±)-**3**, 73465-88-0; (±)-**4**, 73543-06-3; (±)-**7**, 81478-04-8; (±)-**8**, 73414-37-6; (*R**,*R**)-(±)-**9**, 81478-05-9; (*R**,*S**)-(±)-**9**, 81478-06-0; (*R**,*R**)-(±)-**10**, 73461-13-9; (*R**,*S**)-(±)-**10**, 73414-47-8; (*R**,*R**)-(±)-**11**, 81478-07-1; (*R**,*S**)-(±)-**11**, 81478-08-2; **12**, 81478-09-3; *cis*-(±)-**13**, 81478-10-6; *trans*-(±)-**14**, 73414-39-8; **15**, 73414-40-1; *trans*-(±)-**16**, 73414-41-2; *cis*-(±)-**17**, 81520-67-4; **18**, 81478-11-7; **18** C-3b allylic alcohol (isomer 1), 81478-12-8; **18** C-3b allylic alcohol (isomer 2), 81496-97-1; (±)-**19**, 81478-13-9; *trans*-(±)-**20**, 73414-42-3; *cis*-(±)-**20**, 81478-14-0; *trans*-(±)-**21**, 81478-15-1; *trans*-(±)-**22**, 73414-43-4; (±)-**23**, 73414-44-5; (±)-**24**, 73414-45-6; (±)-**25**, 81478-16-2; **26**, 70329-57-6; **27**, 81520-68-5; **28**, 81520-69-6; tetrahydropyran-4-carboxylic acid, 5337-03-1; (±)-2-(β-bromoethyl)butyrolactone, 81478-17-3.

Synthetic Studies of Fungal Metabolites: Ascofuranone and Colletochlorin D

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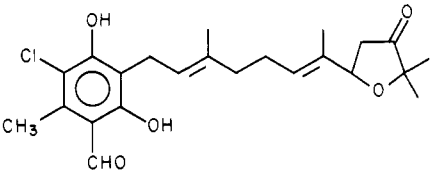
Received December 15, 1981

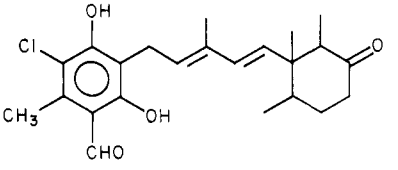
Procedures have been developed for the synthesis of hexasubstituted aromatic rings which are present in many fungal metabolites such as ascofuranone and colletochlorin D. (3-Bromo-5-chloro-2,6-dimethoxy-*p*-tolyl)acetaldehyde was synthesized from orcinol in eight steps. This aldehyde was converted to 2-bromo-6-chloro-3,5-dimethoxy-4-(3-methyl-2-butenyl)toluene which was subsequently formylated to afford 3-chloro-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)benzaldehyde. Although various demethylation procedures were tried, demethylation of both methoxy groups could not be accomplished. In our attempts to synthesize ascofuranone, (3-bromo-5-chloro-2,6-dimethoxy-*p*-tolyl)acetaldehyde was treated with isopropenylmagnesium bromide to afford an unstable allylic alcohol which was immediately subjected to the conditions of the "orthoacetate Claisen rearrangement" to give 2-bromo-6-chloro-4-[(*E*)-5-(ethoxycarbonyl)-3-methyl-2-pentenyl]-3,5-dimethoxytoluene. This compound was then converted to 2-bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-3-methyl-2-hexenyl-6-(triphenylphosphonio)-hex-2-enyl]toluene bromide in three steps. All attempts to carry out a Wittig reaction between this compound and 6,6-dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl methyl ketone failed. Other coupling methods were equally unsuccessful.

As part of our continuing interest in reduced furan natural products,[1-3] we have examined the synthesis of some fungal metabolites such as ascofuranone (**1**, Chart I). This compound has shown potent hypolipidemic and hypotensive activity,[4-14] and its biological properties have been studied extensively since it was isolated by Ando and co-workers in 1972.[4] An important feature of **1** is the hexasubstituted aromatic ring which is a common feature in several other fungal metabolites such as ascochlorin (**2**),[15-17] the LL-Z1272 series,[18,19] and the colletochlorins (**3**).[20-23] During the course of this investigation we also became interested in the synthesis of colletochlorin D, with

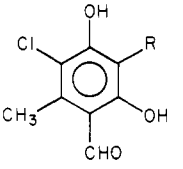
Chart I

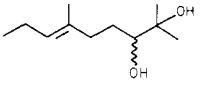


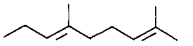
1

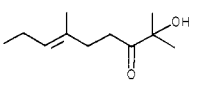


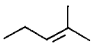
2



3a, R = 

b, R = 

c, R = 

d, R = 

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