the filtrate concentrated in vacuo to give 5.0 g of crude product. Short-path distillation afforded 3.35 g (85%) of furan **6h:** bp 104–107 °C (10 mm); IR (neat) 1711 (ester C=O) and 1538 cm^{-1} (furan); NMR (CCl_4) δ 6.47 (1 H, s, furan **H**), 4.53 (2 H, q, J = 8 Hz, OCH_2CH_3), 3.05 (2 H, t, J = 8 Hz, CCH_2CH_2), 2.37 (3 H, s, CCH_3), 1.56–2.07 (2 H, m, $CH_2CH_2CH_3$), 1.38 (3 H, t, J = 8 Hz, OCH_2CH_3), 1.00 (3 H, t, J = 8 Hz, CH_2CH_3); mass spectrum (70 eV) m/e 196 (M^+). Redistillation afforded the analytical sample: bp 106.5 °C (11.5 mm).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.13; H, 8.09.

Ethyl 2-Methyl-3-furoate (6a). A. Preparation in the Absence of K_2CO_3. A solution of 3.124 g (20 mmol) of ethyl 2-acetyl-2-butenoate (**3a**) in 10 mL of carbon tetrachloride was added to a suspension of 3.559 g (20 mmol) of *N*-bromosuccinimide in 40 mL of carbon tetrachloride, and the resulting mixture was heated at reflux for 19 h. After cooling to room temperature, the insoluble succinimide byproduct was removed by filtration. Concentration of the filtrate in vacuo followed by short-path distillation afforded 0.4 g (13%) of **6a:** bp 87–89 °C (18 mm) [lit.[9] bp 81–84 °C (18 mm)]. A second fraction from the distillation was tentatively identified as ethyl 5-bromo-2-methyl-3-furoate, apparently formed by bromination of **6a:** bp 110–114 °C (20 mm); NMR (CCl_4) δ 6.88 (1 H, s, furan **H**), 4.46 (2 H, q, J = 8 Hz, OCH_2CH_3), 2.71 (3 H, s, CCH_3), and 1.39 (3 H, t, J = 8 Hz, OCH_2CH_3).

B. Preparation of 6a in the Presence of K_2CO_3. The reaction, as set forth above under **A**, was repeated using a Soxhlet extraction apparatus which contained a thimble loaded with 5.52 g (40 mmol) of anhydrous K_2CO_3. The reaction mixture was heated at reflux for 26 h during which the initially red mixture became pale yellow and the thimble became black. The resulting reaction mixture was workedup as described above under **A** to afford 0.73 g (24%) of furan **6a.**

Ethyl 2-Acetyl-4-bromo-2-pentenoate (5b). A mixture of 8.06 g (47 mmol) of ethyl 2-acetyl-2-pentenoate and 8.43 g (47 mmol) of *N*-bromosuccinimide in 50 mL of carbon tetrachloride was heated at reflux for 15 min. The mixture was then quickly cooled to room temperature, and the succinimide byproduct removed by filtration. Concentration of the filtrate in vacuo afforded 11.5 g (98%) of crude ethyl 2-acetyl-4-bromo-2-pentenoate (**5b**): NMR (CCl_4) δ 7.30 (0.44 H, d, J = 6 Hz, C=C**H**CHBr, *Z* isomer), 7.11 (0.47 H, d, J = 6 Hz, C=C**H**CHBr, *E* isomer), 6.63 (0.09H, s, CC**H**=CBr, dienol).

Registry No.—**1a,** 141-97-9; **1h,** 3249-68-1; **1i,** 94-02-0; **1j,** 123-54-6; **2a,** 75-07-0; **2b,** 123-38-6; **2c,** 123-72-8; **2d,** 78-84-2; **2e,** 111-71-7; **2f,** 112-45-8; **2g,** 124-25-4; (*Z*)-**3a,** 67556-07-4; (*E*)-**3a,** 67556-08-5; (*Z*)-**3b,** 67556-09-6; (*E*)-**3b,** 67556-10-9; (*Z*)-**3c,** 15802-68-3; (*E*)-**3c,** 15802-67-2; (*Z*)-**3d,** 67556-11-0; (*E*)-**3d,** 67556-12-1; (*Z*)-**3e,** 67556-13-2; (*E*)-**3e,** 67556-14-3; (*Z*)-**3f,** 67556-15-4; (*E*)-**3f,** 67556-16-5; (*Z*)-**3g,** 67556-17-6; (*E*)-**3g,** 67556-18-7; (*Z*)-**3h,** 67556-19-8; (*E*)-**3h,** 67556-20-1; (*Z*)-**3i,** 39626-67-0; (*E*)-**3i,** 39626-68-1; (*Z*)-**3j,** 67556-21-2; (*E*)-**3j,** 67556-22-3; (*Z*)-**3k,** 67556-23-4; (*E*)-**3k,** 67556-24-5; (*Z*)-**3l,** 67556-25-6; (*E*)-**3l,** 67556-26-7; (*Z*)-**5b,** 67556-27-8; (*E*)-**5b,** 67556-28-9; ethyl 5-bromo-2-methyl-3-furoate, 35304-35-9.

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Synthetic Studies toward Complex Diterpenoids. 10.[1] Stereocontrolled Total Synthesis of (±)-19α,20α-(Acetylimino)-12-hydroxy-5β,10α-podocarpa-8,11,13-triene, a Degradation Product of Atisine

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Received May 11, 1978

A stereocontrolled total synthesis of (±)-19α,20α-(acetylimino)-12-hydroxy-5β,10α-podocarpa-8,11,13-triene (**10**) through the tetracyclic ketone **11** and the dicarboxylic acid **28** is reported. The synthetic approach utilizes two stereoselective methods of angular alkylations. The first one is based upon a regioselective intramolecular α-oxocarbenoid insertion across the benzylic C–H (at C-10) bond in the copper-catalyzed carbenoid decomposition of α-diazomethyl ketone **23,** prepared from the tricyclic acid **22.** The second route consists of a stereospecific rearrangement of cyclobutanone **26,** easily accessible from the β,γ-unsaturated tricyclic acid **18** via the corresponding α-diazomethyl ketone **24** and the unsaturated cyclobutanone **25.** The starting tricyclic acids have been prepared by two alternate routes from Hagemann's ester (**12**) and 7-methoxy-1-tetralone (**19**).

The tetracyclic amines, such as **1** and **2,** are key intermediates in a number of total syntheses[2] of *Garrya* and *Atisine* groups of diterpene alkaloids. Any useful synthesis[1-3] of these compounds requires both stereochemical control of the C-1 and C-4a substituents in a *trans*-hydrophenanthrene moiety and an appropriate oxygen functionality in the aromatic ring for further elaborations. In our earlier papers[1,4] we reported two simple stereocontrolled synthetic approaches to the tetracyclic ketones **6** and **7** and illustrated their versatility[1] by total synthesis of the tetracyclic acetylamines **8** and **9.** We wish to report herein the details of the first stereocontrolled total synthesis of (±)-19α,20α-(acetylimino)-12-hydroxy-5β,10α-podocarpa-8,11,13-triene (**10**), a major degradation product[5] of atisine and a potential intermediate[6] toward the

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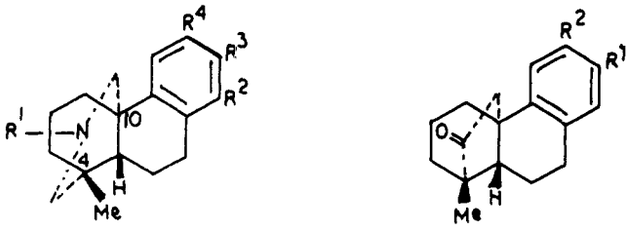
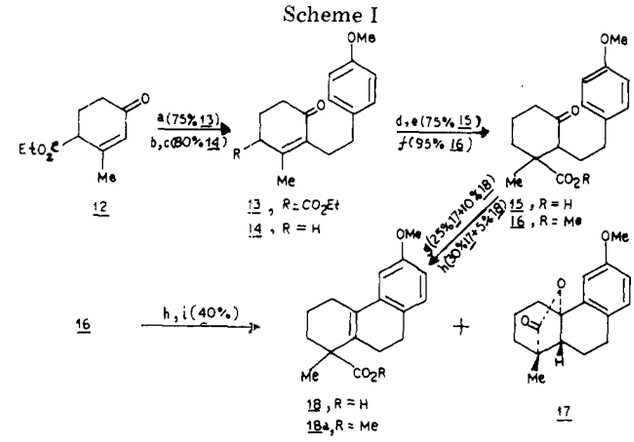


1, $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
2, $R^1 = R^3 = R^4 = H$; $R^2 = OMe$
8, $R^1 = Ac$; $R^2 = R^3 = R^4 = H$
9, $R^1 = Ac$; $R^2 = R^4 = H$; $R^3 = OMe$
10, $R^1 = Ac$; $R^2 = R^3 = H$; $R^4 = OH$
6, $R^1 = R^2 = H$
7, $R^1 = OMe$; $R^2 = H$
11, $R^1 = H$; $R^2 = OMe$

synthesis of ajaconine and atidine, through the tetracyclic ketone **11**.

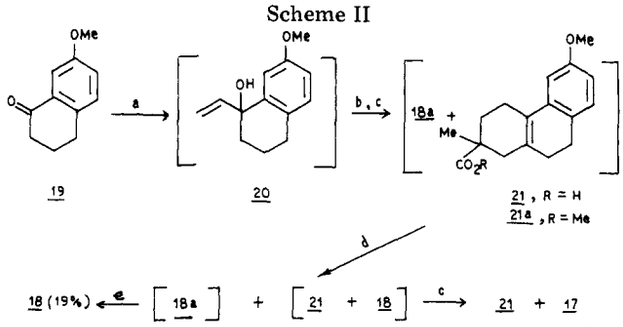
Preparation of Starting Tricyclic Acids 18 and 22. For synthesis of the tetracyclic ketone **11** following two alternate routes[1,4] (Schemes III and IV), we required the starting acids **22** and **18**. These were again prepared by two separate methods. In the first approach the desired starting acids were obtained by extension of the methods developed in this laboratory for the corresponding demethoxy[7] and 13-methoxy analogues.[8] Thus, alkylation[8,9] of ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate (**12**) (Hagemann's ester) with 2-(*p*-methoxyphenyl)ethyl bromide in the presence of potassium *tert*-butoxide afforded the desired condensation product **13** (Scheme I). This, on alkaline hydrolytic decarboxylation with boiling aqueous ethanolic potassium hydroxide solution followed by acidic treatment, afforded the α,β-unsaturated ketone **14** in good yields. Conjugate addition of a hydrogen cyanide residue to the unsaturated ketone with boiling aqueous ethanolic potassium cyanide in the presence of a catalytic amount of HMPA followed by alkaline hydrolysis in situ afforded the semisolid acid **15** as possibly a mixture of diastereoisomers which was used for cyclization reactions without further characterization. The corresponding methyl ester **16** was prepared by esterification with ethereal diazomethane. Unlike the corresponding demethoxy and *m*-methoxy analogues,[1] the keto acid **15** on attempted cyclization with PPA gave complex mixtures. Finally, a few acceptable, though not altogether ideal, cyclization conditions for the acid **15** and ester **16** were realized. Thus, treatment[1] of a cold benzene solution of **15** with a well-stirred benzene–concentrated sulfuric acid mixture at −15 to −5 °C formed the easily separable mixture of the γ-lactone **17**, mp 186–187 °C, and the unsaturated acid **18**, mp 188 °C, in 25 and 10% yields, respectively. Repeating the cyclization in anhydrous chloroform gave slightly more lactone **17** at the expense of unsaturated acid **18**

Scheme I



[a] *t*-BuOK–*t*-BuOH, *p*-$OMeC_6H_4CH_2CH_2Br$. [b] KOH–EtOH–H_2O. [c] Concentrated HCl. [d] KCN–EtOH–H_2O–HMPA. [e] KOH–H_2O. [f] CH_2N_2–Et_2O. [g] PhH–H_2SO_4. [h] $CHCl_3$–H_2SO_4. [i] KOH–$(CH_2OH)_2$–H_2O.

Scheme II



[a] CH_2=CHMgBr/THF. [b] $CH_3C(CO_2CH_3)$=CH_2/PhH–I_2–quinoline–hydroquinone. [c] Dry HCl (gas)–$CHCl_3$. [d] KOH–MeOH–H_2O. [e] KOH–$(CH_2OH)_2$–H_2O.

(see the Experimental Section). Cyclization[7] of the keto ester **16** with concentrated sulfuric acid in chloroform at ice–salt bath temperature gave the unsaturated ester **18a**, which on alkaline hydrolysis afforded the unsaturated acid **18** in 40% overall yield.

In the second route (Scheme II), the preparation of **18** has been based upon the previous observations in this[10] and other laboratories[11] that Diels–Alder cycloadditions of methyl 1-methacrylate to the dienes generated from 1-vinyltetrols and 1-vinylindanols are nonregioselective and result in the formation of both of the regioisomers in comparable yields.

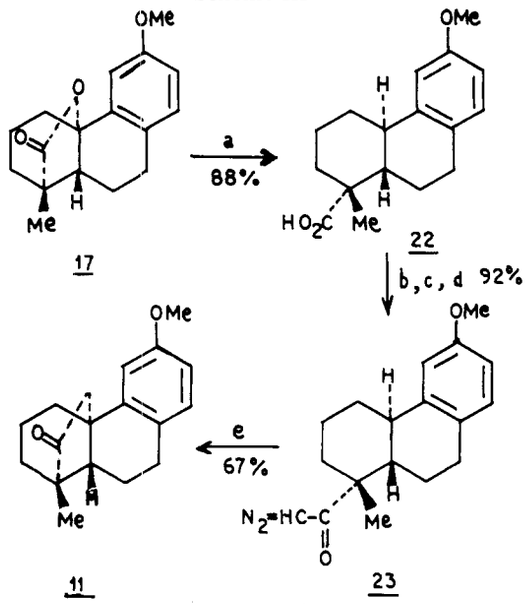
Accordingly, cycloaddition[10] of the diene generated in situ from the crude carbinol **20**, prepared by the reaction of vinylmagnesium bromide[12] with 7-methoxy-1-tetralone (**19**),[13] in refluxing benzene in the presence of catalytic amounts of iodine, quinoline, and hydroquinone and subsequent isomerization of the double bonds by treatment of the resulting product with dry HCl in chloroform afforded a mixture of the tricyclic esters **18a** and **21a** in 46% yield in a ratio of ca 1:1 as revealed from the ^1H NMR spectrum.

The controlled[10] alkaline hydrolysis of this mixture with 10% aqueous methanolic potassium hydroxide gave the relatively hindered unhydrolyzed ester **18a**. This was hydrolyzed to the acid **18** under more drastic conditions in an overall yield of 19%. The hydrolyzed acidic material consisting of the acids **18** and **21** on treatment with HCl in chloroform according to Mander et al.[11] gave a clean mixture of the γ-lactone **17** and the isomeric acid **21**, mp 153 °C, which was separated by the usual method.

Finally, hydrogenolysis[1,7] of the lactone **17** with lithium in liquid ammonia (Scheme III) in the presence of ammonium chloride afforded a single epimeric acid **22**, mp 180 °C, in 88% yield. The homogeneity of this acid was proved from the ^1H NMR spectrum of the corresponding methyl ester (diazomethane). This ester exhibited sharp methyl singlets at δ 1.23, 3.60, and 3.66 in the ^1H NMR spectrum, thereby revealing that the reductive cleavage of the lactone **17** had proceeded stereospecifically with complete retention of stereochemistry at the benzylic chiral center, in conformity with our earlier observations with other substrates.[7,8] The assigned stereochemistry of the acid **22** is in keeping with its subsequent transformation.

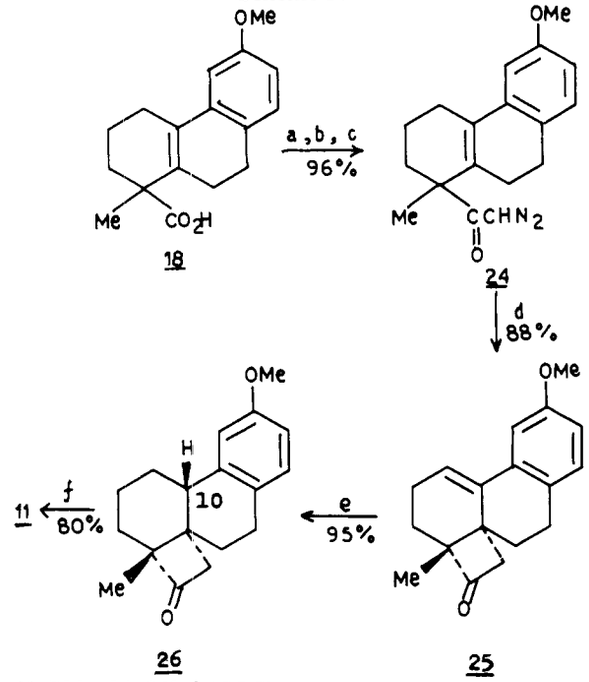
Synthesis of the Tetracyclic Ketone 11. In the first approach[1] toward the tetracyclic ketone **11**, the acid **22** was converted to the diazo ketone **23** through the corresponding acyl chloride in the usual procedure. Decomposition of the diazo ketone in dilute cyclohexane solution in the presence of anhydrous Cu_2O under irradiation with tungsten lamps and chromatographic purification of the crude product gave the tetracyclic ketone **11**, mp 130–131 °C, in 67% yield as the only isolable product (Scheme III). The structure of this ketone was established from its IR spectrum, which showed a five-membered saturated ketone band at 1735 cm^{-1}. The ^1H NMR spectrum (60 MHz in $CDCl_3$) exhibited a sharp quaternary

Scheme III



[a] Li–NH_3 (liquid)–THF, NH_4Cl. [b] NaOMe–MeOH. [c] $(COCl)_2$–PhH. [d] CH_2N_2–Et_2O–TEA. [e] Cu_2O–cyclohexane ($h\nu$, Δ).

Scheme IV

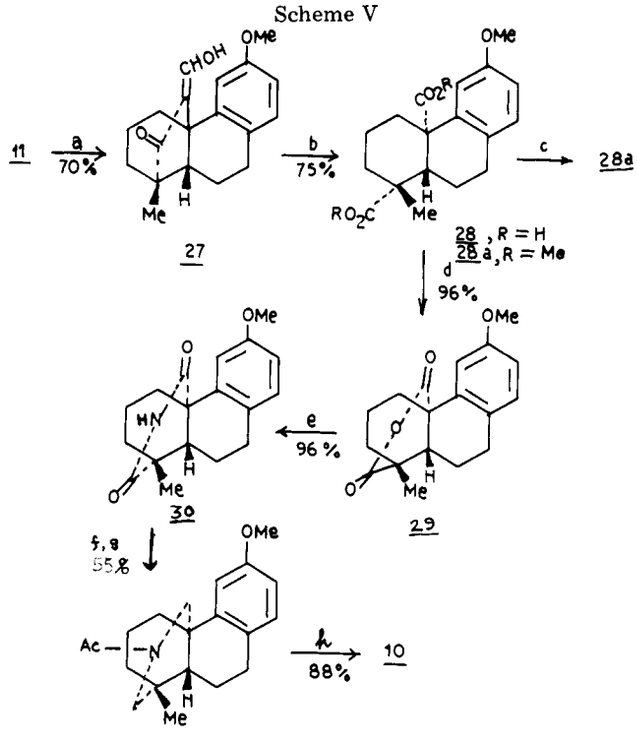


[a] NaOMe–MeOH. [b] $(COCl)_2$–PhH. [c] CH_2N_2–Et_2O–TEA. [d] $CHCl_3$–$HClO_4$ (70%). [e] 10% Pd-C, H_2–EtOH. [f] $Et_3O^+BF_4^-$–CH_2Cl_2.

methyl singlet and a methoxy singlet at δ 1.01 and 3.75. The $-CO-CH_2-$ protons appeared as a broad singlet at δ 2.35.

In the second route[4] (Scheme IV), the β,γ-unsaturated acid **18** was converted to the corresponding diazo ketone **24** in 98% yield through the usual method. Treatment of an ice-cold dilute solution of this diazo ketone with an excess of 70% perchloric acid[14] gave the desired unsaturated cyclobutanone **25**, mp 101 °C, in 88% yield after chromatography on neutral alumina. Catalytic hydrogenation of **25** in the presence of Pd–C (10%) catalyst in ethanol proceeded stereospecifically (as revealed in the ^1H NMR spectrum of the crude reduction product) to afford the saturated cyclobutanone **26**, mp 120 °C, in 95% yield. The stereochemical assignment of the newly generated C-10 chiral center was based on analogy[14] and has

Scheme V



[a] HCO_2Et–NaH–Et_2O. [b] NaOH–H_2O_2 (30%). [c] CH_2N_2–Et_2O. [d] CH_3COCl. [e] $CO(NH_2)_2$. [f] $LiAlH_4$–diglyme. [g] Ac_2O–pyridine. [h] BBr_3–CH_2Cl_2.

been confirmed from its further transformation to the bridged ketone **11** in 80% yield by treatment[4] with an excess of triethyloxonium tetrafluoroborate in anhydrous methylene chloride under a nitrogen atmosphere.

Transformation of 11 to the Racemic Acetylaminophenol 10. The required transformation of **11** to the tetracyclic acetylaminophenol **10** was satisfactorily achieved with some modifications of the sequence of reactons (Scheme V) developed for similar systems in our laboratory.[1]

Condensation of **11** with an excess of ethyl formate in the presence of a large excess of sodium hydride in ether under a nitrogen atmosphere afforded the crystalline hydroxymethylene ketone **27** in 70% yield. This, on oxidation with alkaline hydrogen peroxide (30%) at room temperature, yielded the dicarboxylic acid **28**, mp 217 °C, in 75% yield. This was also characterized through the corresponding dimethyl ester **28a**. The nitrogen-containing bridged E ring was finally generated in **28** by its conversion to the cyclic anhydride **29** in 96% yield followed by heating with urea to afford the imide **30**, mp 263 °C, in excellent yield. The reduction of the imide with lithium aluminum hydride in diglyme at elevated temperature and subsequent acetylation of the crude amine with acetic anhydride in pyridine gave the difficulty crystallizable acetylamine **31**, mp 93 °C, after chromatography on acid-washed alumina. The final stage of the synthesis of the racemic acetylaminophenol 10, mp 255 °C, was achieved in 80% yield through demethylation of **31** with boron tribromide[15] in methylene chloride.

The optically active acetylaminophenol **10** was obtained through degradation of atisine, and the enantiomer of this compound was synthesized by ApSimon and Edwards[5a] from (+)-podocarpic acid. Although a direct comparison of our synthetic sample with an authentic sample has not been possible,[16] the assigned structure of our synthetic compound is firmly based from the mode of its synthesis and the spectral data (see the Experimental Section).

The present work thus represents the first total synthesis of the racemic tetracyclic acetylamino phenol **10**.

Expermental Section

The compounds described are all racemates. Melting points are uncorrected. Petroleum ether used in chromatography refers to the fraction of bp 40–60 °C. UV spectra were determined in a 95% ethanolic solution on a Beckman DU spectrophotometer, and IR spectra were determined in $CHCl_3$ solutions on a Perkin-Elmer Model 21 double-beam recording spectrophotometer by Mr. A. Ghosal. NMR spectra were recorded on a Varian T60A spectrometer with Me_4Si as an internal standard by Mr. A. K. Mukherjee. Elemental analyses were performed by Mrs. C. Dutta of this laboratory. The general workup procedure was to extract the aqueous layer with ether or ethyl acetate (three to five times); and the combined extracts were washed with water (two times) and saturated sodium chloride (once), dried (Na_2SO_4), filtered, and concentrated in vacuo.

Preparation of the Tricyclic Unsaturated Acid 18 and the Lactone 17. Ethyl 3-(*p*-Methoxyphenylethyl)-2-methyl-4-oxocyclohex-2-enecarboxylate (13). Potassium (20.2 g) was dissolved in an excess of dry *tert*-butyl alcohol, and the latter was distilled off until a solid appeared in the flask. This was cooled at room temperature, and ethyl 2-methyl-4-oxocyclohex-2-enecarboxylate (Hagemann's ester) (**12**; 102 g, 0.55 mol) was added in one lot with shaking. The scarlet red color that formed initially turned into a straw-yellow solid mass in a few minutes. It was allowed to stand for 0.5 h, and (*p*-methoxyphenyl)-2-ethyl bromide 110 g, 0.5 mol) was added in one lot. The mixture was shaken vigorously for a few minutes and was finally heated under reflux for 16 h. The cooled product was poured on crushed ice (700 g), acidified with cold hydrochloric acid (6 N), and extracted with ether. The ethereal extract was washed with water and dried. Evaporation of solvent and subsequent distillation afforded a faintly yellow liquid (120.5 g, 75%): bp 184–190 °C (0.25 mm); UV λ_{max} 227 nm (log ϵ 4.38); IR 1725 (s), 1665 (s), 1625 (m), and 1610 (m) cm^{-1}; NMR (CCl_4) δ 1.25 (3 H, t, J = 7 Hz), 1.71 (s, 3 H), 1.87–2.38 (m, 4 H), 2.43 (br s, 4 H), 3.10 (1 H, t, J = 4.2 Hz), 3.67 (s, 3 H), 4.12 (2 H, q, J = 7 Hz), 6.76 (4 H, AB q, J = 9 Hz). The scarlet-red 2,4-dinitrophenylhydrazone was recrystallized from methanol, mp 142 °C.

Anal. Calcd for $C_{25}H_{28}O_7N_4$: C, 60.47; H, 5.68. Found: C, 60.46; H, 5.96.

2-(*p*-Methoxyphenylethyl)-3-methyl-1-oxocyclohex-2-ene (14). A solution of potassium hydroxide (92 g) in water (20 mL) and 90% ethanol (700 mL) was added to the aforementioned keto ester **13** (120 g, 0.38 mol). The reaction mixture was refluxed for 12 h under nitrogen. The cooled reaction mixture was slowly acidified with concentrated hydrochloric acid and left at room temperature for 15 min. The precipitated salt was filtered off, and then most of the alcohol was removed by distillation in vacuo. The residue was diluted with water (600 mL), the organic layer separated, and the aqueous layer was extracted with ether. The ethereal extract was mixed with the organic layer, and the combined organic layer was washed with sodium carbonate solution (5%) followed by water and dried. Evaporation of solvent left a thick brown liquid which on distillation afforded a light yellow liquid (72.3 g, 80%): bp 157–160 °C (0.2 mm); UV λ_{max} 227 nm (log ϵ 4.25); IR 1665 (s) and 1625 (m) cm^{-1}; NMR (CCl_4) δ 1.67 (s, 3 H), 1.8–2.45 (m, 6 H), 2.43 (br s, 4 H), 3.67 (s, 3 H), 6.76 (4 H, AB q, J = 9 Hz). The dark red 2,4-dinitrophenylhydrazone was recrystallized from methanol, mp 176 °C.

Anal. Calcd for $C_{22}H_{24}O_5N_4$: C, 62.25; H, 5.70. Found: C, 62.17; H, 5.77.

2-(*p*-Methoxyphenylethyl)-3-methyl-1-oxocyclohexane-3-carboxylic Acid (15). To a solution of the unsaturated ketone **14** (72 g, 0.3 mol) in ethanol (95%, 540 mL) and hexamethylphosphoramide (20 mL) was added a solution of potassium cyanide (72 g) in water (250 mL). The reaction mixture, which assumed a green color initially, was allowed to stand at room temperature for some time, when it turned to yellowish brown. It was finally heated under reflux for 16 h. On cooling, a solution of potassium hydroxide (108 g) in water (1080 mL) was added and the reaction mixture was heated under reflux for another 90 h. The cooled solution was poured into ice water, acidified carefully with concentrated hydrochloric acid, and saturated with sodium chloride, and the organic material was extracted with ether. The ethereal extract was washed thoroughly with sodium carbonate solution (5%) followed by water and was dried. Removal of solvent left a very little gummy material which was not characterized further. The alkaline and aqueous washings were combined and acidified with hydrochloric acid (6 N). The separated acid was extracted with ethyl acetate. The ethyl acetate extract was washed with water and dried. Removal of the solvent afforded the acid **15** as a semisolid light brown product (76 g, 75%): IR 1710 (s) and 1610 (m) cm^{-1}. The crude acid was used without further purification for the subsequent reactions.

2-(*p*-Methoxyphenylethyl)-3-methyl-3-carbomethoxy-1-oxocyclohexane (16). Methyl ester **16** was prepared by reacting the aforementioned acid **15** (5.1 g) with an excess of ice-cold ethereal diazomethane. After decomposition of excess diazomethane by acetic acid, the reaction mixture was washed with sodium hydroxide solution (1%) followed by water and was dried, and the solvent was removed. The residual liquid ester was filtered through a column of neutral alumina (20 g) and eluted with petroleum to afford a colorless mobile liquid (5 g, 95%): IR 1730 (s), 1705 (s), and 1615 (m) cm^{-1}; TLC in benzene–ethyl acetate (4:1) showed a single spot. The ester **16** gave a yellow 2,4-dinitrophenylhydrazone which was recrystallized from methanol, mp 168 °C.

Anal. Calcd for $C_{24}H_{28}O_7N_4$: C, 59.49; H, 5.83. Found: C, 59.19; H, 5.92.

(±)-*O*-Methyl-5(10)-dehydro-20-norpodocarpic Acid (18) and (±)-4aα-Hydroxy-1β-methyl-6-methoxy-1,2,3,4,4a,9,10,10a-*trans*-octahydrophenanthrene-1α-carboxylic Acid 1 → 4a Lactone (17). Cyclization of the Keto Acid 15. Method A: Using Benzene as Solvent. To a well-stirred solution of the aforementioned keto acid **15** (5.1 g, 17 mmol) in thiophene-free benzene (50 mL) cooled in an ice–salt bath (ca. −15 to −5 °C) was added cold concentrated sulfuric acid (75 mL) during 25 min, and stirring under these conditions was continued for another 30 min. The reaction mixture was poured into crushed ice (750 g) and extracted with ether. The ethereal extract was thoroughly washed with sodium hydroxide solution (2%) and water, dried, and concentrated to afford the lactone **17** (1.21 g, 25%), mp 187 °C. Recrystallization twice from ethyl acetate gave an analytical sample: mp 189 °C; IR 1770 (s) and 1610 (m) cm^{-1}; NMR ($CDCl_3$) δ 1.20 (s, 3 H, >CH_3), 1.46–2.82 (m, 11 H, methylene and methine), 3.63 (s, 3 H, –OCH_3), 6.93 (m, 3 H, Ar H).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.80; H, 7.21.

The combined aqueous alkaline washings were chilled, acidified with hydrochloric acid (6 N), and extracted with ethyl acetate after saturation with sodium chloride. The ethyl acetate extract was washed with brine and dried over anhydrous sodium sulfate. Evaporation of solvent afforded a gummy material (750 mg) which solidified on scratching. On recrystallization from ethyl acetate, the acid **18** (500 mg, 10%) was obtained: mp 187–188 °C; IR 1700 cm^{-1}; UV λ_{max} 273 nm (log ϵ 4.1).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.68; H, 7.47.

Method B: Using Chloroform as Solvent. To a well-stirred solution of the keto acid **15** (1.6 g) in dry chloroform (30 mL) cooled in an ice–salt mixture (ca. −15 to −5 °C) was added cold concentrated sulfuric acid (22 mL) during 15 min. Stirring in the cold was continued for another 45 min. Subsequent workup as described in method A afforded the lactone **17**, mp and mmp 187 °C (425 mg, 30%), and only 5% of the acid **18**, mp and mmp 188 °C.

Cyclization of the Keto Ester 16. To a well-stirred solution of the keto ester **16** (5.13 g, 18 mmol) in dry chloroform (55 mL) cooled in an ice–salt mixture (ca. −15 to −5 °C) was added cold concentrated sulfuric acid (75 mL) during 15 min, and stirring in the cold was continued for another 45 min. The reaction mixture was poured into crushed ice (ca. 700 g) and extracted with ether. The ethereal extract was thoroughly washed with sodium carbonate solution (5%) and water and dried. Removal of solvent afforded the unsaturated ester **18a** (2.7 g): UV λ_{max} 264 nm (log ϵ 3.98); IR 1725 (s) and 1610 (m) cm^{-1}; TLC in benzene–ethyl acetate (4:1) showed a single spot. This ester (2.65 g) was hydrolyzed in ethylene glycol (32 mL) with potassium hydroxide (4.2 g) and water (3.5 mL) by heating at reflux for 5 h under a nitrogen atmosphere. After cooling, the reaction mixture was diluted with water (100 mL) and the neutral portion was extracted with ether, washed with water, and dried. Removal of solvent afforded ca. 300 mg of neutral product, which was not investigated further. The basic portion was chilled and acidified with cold hydrochloric acid (6 N), and the precipitated acidic product was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried, and removal of the solvent afforded (1.8 g) the acid **18**; mp and mmp 188 °C in 40% overall yield based upon the starting keto ester **16**.

Preparation of 17, 18, and 1,2,3,4,9,10-Hexahydro-6-methoxy-2-methylphenanthrene-2-carboxylic Acid (21) from the Tetralone 19 by Diels–Alder Reaction. Vinylmagnesium bromide in dry THF, prepared from magnesium (7.5 g, 0.3 g-atom) and vinyl bromide (50 g, 0.45 mol) [generated[12] from 1,2-dibromoethane (97 mL, 0.51 mol) and potassium hydroxide (60 g, 1.07 mol) and collected in 60 mL of anhydrous THF], was reacted with a solution of 7-methoxy-1-tetralone (**19**; 25 g, 0.14 mol) in anhydrous THF (25 mL) according to the general procedure.[10,12] A benzene solution of the crude vinylcarbinol **20** thus obtained was subjected to Diels–Alder reaction with methyl 1-methacrylate (50 g, 0.5 mol) in the presence of I_2 (2 crystals), hydroquinone (30 mg), and quinoline (0.5 mL) using

a Dean-Stark water separator. The reaction product was worked up in the usual manner. Distillation of this product afforded the ester mixture as a light yellow liquid (18.7 g, 46%), bp 160–170 °C (0.2 mm). This was dissolved in 100 mL of dry chloroform, and dry HCl gas was passed through the ice-cooled solution until it was saturated. After keeping the mixture at room temperature for 1 h, the solvent and HCl were removed under a water aspirator below 40 °C. The residual oil was dissolved in ether, washed twice with water, thrice with 5% sodium carbonate solution, and water, and dried. The solvent was removed in vacuo, and the residue was distilled to afford a light yellow liquid (18.0 g): bp 160–170 °C (0.2 mm); UV λ_{max} 273 nm (log ϵ 4.1); IR 1725 cm^{-1}; NMR (CCl_4) showed the absence of a vinyl proton and the presence of **21a** and **18a** in a ratio of ca 1:1 from the relative integrations of the quaternary Me singlets at δ 1.21 and 1.33. The isomeric ester mixture was gently refluxed for 1 h under nitrogen with a solution of potassium hydroxide (18 g) in 90 mL of water and 90 mL of methanol. The solution was diluted with water and saturated with sodium chloride. The neutral fraction was extracted with ether and worked up in the usual way to give pure ester **18a** (8.12 g): IR 1725 (s) and 1600 (m) cm^{-1}; NMR (CCl_4) δ 1.33 (s, 3 H, $>CCH_3$), 1.66—2.46 (m, 10 H, methylene), 3.63 (s, 3 H, CO_2CH_3), 3.73 (s, 3 H, OCH_3), 6.66 (m, 3 H, Ar H).

The aqueous alkaline layer on acidification with 6 N hydrochloric acid and subsequent extraction with ethyl acetate afforded a solid (7.2 g) consisting of the acids **21** and **18** in a ratio of ca 4:1 as shown from the NMR spectrum of the crude methyl ester prepared by esterification of a sample of this mixture by ethereal diazomethane. This acid mixture was dissolved in 60 mL of chloroform, a stream of dry HCl was passed through the solution for 30 min at 0 °C, and the solution was allowed to stand at room temperature for 1 h. Chloroform was removed in vacuo, and the organic material was taken up in ethyl acetate, washed with water, 2% NaOH solution, and water, and dried. Removal of the solvent and one recrystallization from ethyl acetate of the residual solid product gave lactone **17** (1.12 g), mp and mmp 187 °C with the sample described above.

The basic aqueous washings were acidified with 6 N hydrochloric acid and extracted with ethyl acetate to afford 6.1 g of a solid product as flakes which on two recrystallizations from ethyl acetate afforded pure acid **21** (5.2 g, overall yield of 15% based on **19**): mp 153 °C; UV λ_{max} 273 nm (log ϵ 4.1); IR 1700 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.80; H, 7.21.

A small portion of this acid was converted to the corresponding methyl ester **21a** by treatment with ethereal diazomethane: IR 1725 cm^{-1}; NMR (CCl_4) δ 1.21 (s, 3 H, $>CCH_3$), 1.66–2.63 (m, 10 H, methylene), 3.61 (s, 3 H, CO_2CH_3), 3.71 (s, 3 H, OCH_3), 6.61 (m, 3 H, Ar H).

The aforementioned ester **18a** (8.0 g) was saponified under nitrogen by gently refluxing for 4 h with a solution of potassium hydroxide (9 g) dissolved in 5 mL of water and 85 mL of ethylene glycol. The reaction mixture was diluted with water and extracted with ether to afford a small amount of neutral product which was not characterized further. The aqueous basic portion was acidified with 6 N hydrochloric acid, and the liberated acid was extracted with ethyl acetate to afford the acid **18** (6.5g, 19% overall yield), mp and mmp 187–188 °C after one recrystallization from ethyl acetate.

(±)-O-Methyl-20-norpodocarpic Acid (22). To a stirred solution of the lactone **17** (2.5 g, 92 mmol) in anhydrous ether (10 mL) and anhydrous THF (10 mL) was added a solution of lithium wire (0.83 g, 0.12 g-atom) in anhydrous liquid ammonia (600 mL) in several lots during 3–5 min, and the blue color was discharged by the cautious addition of solid ammonium chloride. The ammonia was then allowed to evaporate completely at room temperature, 50 mL of moist ether was added, and the reaction mixture was carefully acidified with an excess of 6 N hydrochloric acid. The product was extracted with ethyl acetate and washed with water followed by 2% sodium hydroxide solution repeatedly. The trace of neutral product left after evaporation of ethyl acetate was discarded. The aqueous alkaline layer was acidified, and the liberated acid was extracted with ethyl acetate. After the usual workup, the acid **22** (2.25 g, 90%), mp 179–180 °C, was obtained. An analytical sample was prepared by one recrystallization from ethyl acetate: mp 180 °C; IR 1700 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.40; H, 8.20.

A small sample of the acid was esterified with ethereal diazomethane to afford a liquid methyl ester: IR 1725 cm^{-1}; NMR (CCl_4) δ 1.23 (s, 3 H, CH_3), 1.58–2.75 (m, 12 H, methylene and methine), 3.60 (s, 3 H, CO_2CH_3), 3.66 (s, 3 H, OCH_3), 6.66 (m, 3 H, Ar H).

(±)-19,20-Cyclopodocarpa-12-methoxy-19-oxo-8,11,13-triene (11). (i) Intramolecular Oxocarbenoid Insertion Reaction of the Diazo Ketone 24 under Thermal–Photochemical Decomposition with Cuprous Oxide Catalyst. The acid **22** (2.21 g, 0.08 mol) was neutralized with sodium methoxide in methanol (using phenolphthalein as indicator). The sodio salt thus obtained was dried, taken up in dry benzene (75 mL) and pyridine (0.2 mL), and converted to its acid chloride by reaction with oxalyl chloride (3 mL) in the usual way.[1] A solution of the crude acid chloride in dry ether (75 mL) was added to an excess of ice-cold ethereal diazomethane (generated from 10 g of *N*-methylnitrosourea) containing triethylamine (0.3 mL). After the usual workup, the crude diazo ketone was dissolved in ether (5 mL) and filtered through a column of neutral alumina (15 g). Elution with an ether–petroleum (1:1) mixture afforded low melting diazo ketone **23** (2.1 g, 92%): IR 2112 cm^{-1}.

The crude diazo ketone **23** (2.09 g, 7 mmol) in anhydrous cyclohexane (200 mL) was added dropwise to a stirred refluxing suspension of freshly prepared anhydrous cuprous oxide (4 g) in dry cyclohexane (400 mL) under irradiation with two 200-W tungsten lamps during 7 h. The reaction mixture was refluxed for another 3 h (until the IR band at 2115 cm^{-1} disappeared). The usual workup and chromatographic purification on neutral alumina (35 g) afforded the ketone **11** (1.3 g, 68%) (1:3 benzene–petroleum elution), mp 130–131 °C. An analytical sample was recrystallized once from ethyl acetate–light petroleum to afford colorless prisms: mp 132 °C; IR 1735 (s) and 1610 (m) cm^{-1}; NMR ($CDCl_3$) δ 1.01 (s, 3 H, CH_3), 1.25–1.95 (m, 9 H, methylene and methine), 2.35 (br s, 2 H, $CO-CH_2-$), 2.75 (m, 2 H, CH_2Ar), 3.75 (s, 3 H, OCH_3), 6.75 (m, 3 H, Ar H).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.68; H, 8.30.

(ii) Preparation of the Tetracyclic Ketone 11 from the Tricyclic Unsaturated Acid 18. Intramolecular Alkylation Reaction of Diazo Ketone 24: (±)-4α,5α-Ethano-18-oxo-12-methoxy-18,20-bisnorpodocarpa-1(10),8,11,13-tetraene (25). The diazo ketone **24** was prepared from the acid **18** (1.4 g, 0.005 mol) through the reaction of the corresponding sodium salt in dry benzene (75 mL) containing pyridine (4 drops) and oxalyl chloride (2.5 mL). The crude acid chloride was dissolved in dry ether (100 mL) and added dropwise to a magnetically stirred ice–salt cold ethereal diazomethane solution (generated from 5.5 g of *N*-methylnitrosourea) containing 0.2 mL of triethylamine. After keeping the mixture overnight at room temperature, the triethylamine hydrochloride was filtered off and the filtrate was evaporated under reduced pressure. The residual crude diazo ketone was dissolved in ether (25 mL) and filtered through a column of neutral alumina (20 g). Elution with ether–petroleum (1:1) afforded the diazo ketone **24** as a light yellow low melting solid (1.36 g, 96%): IR 2120 (s) and 1640 (m) cm^{-1}; NMR (CCl_4) δ 1.25 (s, 3 H, CH_3), 1.73–2.63 (m, 10 H, methylene), 3.73 (s, 3 H, OCH_3), 5.41 (s, 1 H, $COCHN_2$), 6.7 (m, 3 H, Ar H).

To an ice-cold solution of this diazo ketone (1.18 g, 4 mmol) in chloroform (200 mL) was added aqueous 70% perchloric acid (2 mL) in chloroform (20 mL) with stirring. After standing for 1 h in the cold, the reaction mixture was diluted with water (30 mL). The organic layer was separated, and the aqueous layer was extracted with chloroform. The chloroform extract and the separated organic layer were combined, washed with sodium carbonate solution (5%) followed by water, and dried. Removal of solvent under reduced pressure afforded a light yellow solid (ca. 1.17 g). This was dissolved in benzene (ca. 5 mL) and chromatographed on neutral alumina (30 g) to afford **25** as a colorless solid (0.89 g, 88%): mp 101 °C; IR 1775 (s), 1605 (m) cm^{-1}; UV λ_{max} 260 nm (log ϵ 4.24); NMR ($CDCl_3$) δ 1.20 (s, 3 H, CH_3), 1.36–2.87 (m, 10 H, methylene), 3.76 (s, 3 H, OCH_3), 6.35 (t, J = 4 Hz, 1 H, $>C=HC-$), 6.78 (m, 3 H, Ar H).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.72; H, 7.75.

Preparation of Saturated Cyclobutanone (26). The unsaturated cyclobutanone **25** (0.81 g, 3 mmol) in ethanol (70 mL) was hydrogenated catalytically in the presence of palladium on charcoal (250 mg, 10%). The usual workup afforded the saturated ketone **26** (0.8 g) as a white solid: mp 120 °C; TLC in benzene–ethyl acetate (1:1) showed a single spot; IR 1775 (s) and 1600 (m) cm^{-1}; UV λ_{max} 278 nm (log ϵ 3.4); NMR ($CDCl_3$) δ 1.10 (s, 3 H, CH_3), 1.2–3.2 (complex m, 13 H, methylene and methine), 3.76 (s, 3 H, OCH_3), 6.78 (m, 3 H, Ar H).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.77; H, 8.20.

Rearrangement of the Saturated Cyclobutanone 26 to the Bridged Cyclopentanone 11. Triethyloxonium tetrafluoroborate was prepared by adding epichlorohydrin (10 mL) dropwise to a magnetically stirred mixture of boron trifluoride etherate (20 mL, 0.16 mol) in dry ether (120 mL). The white crystalline solid thus obtained was dissolved in distilled methylene chloride (25 mL). To it was added the saturated cyclobutanone **26** (0.8 g, 3 mmol) in methylene chloride (100 mL) dropwise during 1 h at room temperature. The reaction mixture was stirred for another 24 h at room temperature, diluted with

water, and extracted with ether. The ethereal extract was washed with sodium carbonate solution (5%) and water and finally dried. Removal of solvent afforded a solid which was filtered through a column of neutral alumina (20 g). Petroleum elution afforded the bridged ketone **11** as cubes (0.64 g, 80%), mp 131–132 °C alone or mixed with the authentic sample described earlier.

Hydroxymethylation of the Bridged Ketone (11): (±)-20-Hydroxymethylene-19,20-cyclopodocarpa-12-methoxy-8,11,13-trien-19-one (27). To a magnetically stirred solution of the bridged ketone **11** (1.5 g, 6 mmol) in ethyl formate (27 mL, freshly distilled) immersed in an ice–salt bath under a nitrogen atmosphere was added sodium hydride (2.3 g, 96 mmol) and then absolute methanol (0.3 mL). The mixture was stirred in the cold until it became so thick that stirring was impeded, whereupon anhydrous ether (40 mL) was added and the mixture was stirred for 9 h at room temperature and left overnight. Ice was added, and the basic aqueous mixture was extracted with ether. The ethereal layer was washed with sodium hydroxide solution (2%) and water and dried. Removal of solvent afforded the recovered ketone (500 mg). The combined basic and aqueous washings were chilled, acidified with hydrochloric acid (6 N), and extracted with ether. The ethereal layer was washed with brine and dried. Removal of solvent afforded the hydroxymethylene derivative **27** (1.12 g, 70%) as a pink solid. An analytical sample was obtained after recrystallization from petroleum: mp 154–156 °C; IR 1670 and 1605 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.51; H, 7.38. Found: C, 76.23; H, 7.63.

(±)-Podocarpa-8,11,13-triene-12-methoxy-19,20-dioic Acid (28). To a stirred solution of sodium hydroxide (10%, 120 mL) in ethanol (50 mL) was added the formyl derivative **27** (1 g, 3.3 mmol). Then hydrogen peroxide (30%, 37 mL) was added dropwise, and the solution was stirred for 1 h. An additional amount of sodium hydroxide solution (10%, 120 mL) was added, and then hydrogen peroxide (30%, 75 mL) was added dropwise and the solution was allowed to stand at room temperature overnight. The mixture was extracted with ether. The ethereal layer was washed with water and dried over anhydrous sodium sulfate. Removal of solvent afforded the unreacted formyl derivative (100 mg).

The combined basic layer and aqueous washing were chilled, acidified with hydrochloric acid (6 N), and extracted with ethyl acetate after saturation with sodium chloride. The ethyl acetate layer was washed with brine and dried over anhydrous sodium sulfate. Removal of solvent afforded the diacid **28** (800 mg, 75%), mp 214–217 °C. An analytical sample was prepared by crystallization from acetone–light petroleum: mp 217 °C; IR 1700 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.92; H, 6.97. Found: C, 67.97; H, 7.00.

Methyl (±)-20α-Methoxycarbonyl-12-methoxy-20-nordeoxypodocarpate (28a). Dimethyl ester **28a** was prepared by reacting the diacid **28** (100 mg) with an excess of ice-cold ethereal diazomethane solution. After the usual workup, the residue was filtered through a column of neutral alumina (5 g) to afford the diester **28a** as a white solid, mp 120–122 °C. Recrystallization twice from petroleum furnished an analytically pure sample: mp 122 °C; IR 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (s, 3 H, CH_3), 3.56 (s, 3 H, CO_2CH_3), 3.63 (s, 3 H, CO_2CH_3), 3.76 (s, 3 H, OCH_3), 6.66–7.10 (m, 3 H, Ar H).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.26; H, 7.73.

Anhydride of (±)-Podocarpa-8,11,13-triene-12-methoxy-19,20-dioic Acid (29). The diacid **28** (660 mg, 2 mmol) was refluxed with acetyl chloride (26 mL) for 2 h when it gradually went into solution. Removal of excess acetyl chloride under reduced pressure yielded the anhydride **29.** Recrystallization from acetone furnished an analytically pure sample (590 mg, 96%): mp 170 °C; IR 1800 and 1760 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 72.00; H, 6.66. Found: C, 71.60; H, 6.43.

(±)-19,20-(Dioxoimino)podocarpa-12-methoxy-8,11,13-triene (30). An intimate mixture of the anhydride **29** (500 mg, 1.7 mmol) and urea (1.5 g, 25 mmol) was heated at 170–180 °C for 1 h. The solid mass, after cooling, was broken, treated with water (5 mL), and filtered. The residue was thoroughly washed with water and dried under suction and finally over phosphorus pentoxide. Crystallization from acetone afforded the imide **30** (480 mg, 96%): IR 1720 (sh) and 1705 cm^{-1}. An analytical sample obtained by two more recrystallizations from acetone melted at 263 °C.

Anal. Calcd for $C_{18}H_{21}O_3N$: C, 72.20; H, 7.07. Found: C, 72.17; H, 7.21.

Reduction of the Imide 30 and Subsequent Acetylation to (±)-N-Acetyl-19α,20α-imino-12-methoxy-5β,10α-podocarpa-8,11,13-triene (31). To a magnetically stirred suspension of the imide **30** (400 mg, 1.3 mmol) in anhydrous diglyme (25 mL) under nitrogen was added lithium aluminum hydride (600 mg, 16 mmol). After the mixture was stirred for 1 h at 60–65 °C, the temperature was gradually increased to 100–110 °C and stirring was continued for another 2 h at this temperature. The mixture was then cooled to room temperature, and a second batch of lithium aluminum hydride (600 mg) was added. Heating was continued at 100–110 °C for 2 h, and the mixture was left at room temperature overnight. Excess reagent was destroyed by moist ether and saturated sodium sulfate solution and filtered off. The residue was washed several times with ether, and the filtrate and washings were collected, extracted with ether, washed with brine, and dried. The red gum (380 mg) obtained after evaporation of ether was immediately mixed with dry pyridine (8 mL) and acetic anhydride (8 mL) and was allowed to stand overnight at room temperature.

The cooled reaction mixture was diluted with water, acidified with ice-cold hydrochloric acid (6 N), saturated with sodium chloride, and extracted with ether. The ethereal extract was washed with sodium hydroxide solution (2%) followed by brine and dried over sodium sulfate. Removal of solvent under reduced pressure afforded a gummy solid which was chromatographed on acidic alumina (10 g). Elution with benzene–petroleum (3:1) yielded the *N*-acetylamine **31,** which on recrystallization from ether–petroleum afforded (234 mg, 55%) mp 93 °C: IR 1625 (s) and 1430 (br) cm^{-1}; NMR ($CDCl_3$) δ (90 MHz) 0.96 (s, 3 H, CH_3), 1.25–2.0 (complex m, 9 H, saturated $-CH_2-$ and methine), 2.10 (s, 3 H, $OCOCH_3$), 2.4–3.55 (complex m, 6 H, benzylic and CH_2-N-CH_2), 3.82 (s, 3 H, OCH_3), 6.6–7.6 (m, 3 H, Ar H).

Anal. Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68. Found: C, 76.79; H, 8.50.

(±)-N-Acetyl-19α,20α-imino-12-hydroxy-5β,10α-podocarpa-8,11,13-triene (10). A solution of the *N*-acetyl derivative **31** (120 mg, 0.4 mmol) in dry methylene chloride (7 mL) was added at 0 °C to a stirred solution of boron tribromide (0.1 mL) in methylene chloride (2 mL), and the mixture was left overnight at room temperature. The mixture was then shaken with cold water, extracted with ether, washed with brine, and dried over anhydrous sodium sulfate. Removal of the solvent afforded the phenol (91 mg, 80%) as a white solid, mp 255 °C, after recrystallization from acetone–light petroleum [lit.[5a] mp ((+) form) 279–280 °C]; IR 3600 and 1625 cm^{-1}; UV λ_{max} 282 nm (log ε 3.48) [lit.[5b] λ_{max} 282 nm (log ε 3.22)]; NMR (80 MHz, $CDCl_3$) δ 1.05 (s, 3 H), 1.28–2.2 (br s and m, 9 H), 2.28 (s, 3 H), 2.5–4.8 (mm, 6 H), 6.75–7.1 (mm, 3 H), 8.63 (br s, 1 H).

Anal. Calcd for $C_{19}H_{25}O_2N$: C, 76.25; H, 8.36. Found: C, 76.04; H, 8.37.

Registry No.—10, 67661-63-6; **11,** 67661-64-7; **12,** 59323-55-6; **13,** 67661-65-8; **13** 2,4-DNP, 67661-66-9; **14,** 67661-67-0; **14** 2,4-DNP, 67661-68-1; **15,** 67661-69-2; **16,** 67661-70-5; **16** 2,4-DNP, 67661-71-6; **17,** 67661-72-7; **18,** 67661-73-8; **18** Na salt, 67661-75-0; **18** acid chloride, 67661-76-1; **18a,** 67661-74-9; **19,** 6836-19-7; **20,** 67661-77-2; **21,** 67661-78-3; **21a,** 67661-79-4; **22,** 67661-80-7; **22** Me ester, 67661-81-8; **22** Na salt, 67661-82-9; **22** acid chloride, 67661-83-0; **23,** 67661-84-1; **24,** 67661-85-2; **25,** 67661-86-3; **26,** 67661-87-4; **27,** 67661-88-5; **28,** 67661-89-6; **28a,** 67661-90-9; **29,** 67661-91-0; **30,** 67661-92-1; **31,** 67661-93-2; (±)-19α,20α-imino-12-methoxy-5β,10α-podocarpa-8,11,13-triene, 67661-94-3; *p*-methoxyphenylethyl bromide, 14425-64-0; vinyl bromide, 593-60-2; methyl methacrylate, 80-62-6; oxalyl chloride, 79-37-8.

References and Notes

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(16) We are deeply indebted to Professor J. W. ApSimon for kindly providing us with an 80 MHz NMR spectrum of our synthetic sample of **10**; however, no comparison data with their sample has been available.

Synthesis of *dl*-Epigriseofulvin

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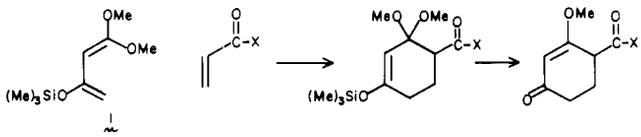
Received June 27, 1978

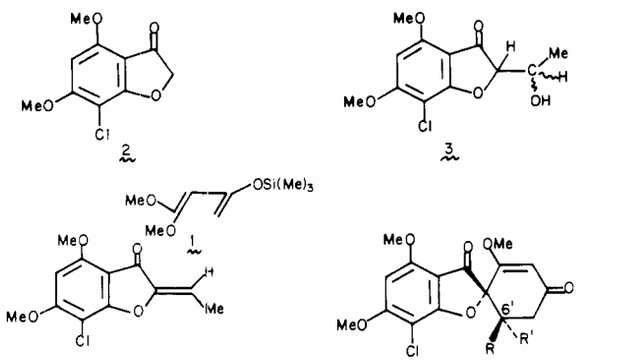
Diels–Alder reaction of (*Z*)-2-ethylidene-7-chloro-4,6-dimethoxycoumaran-3-one with 1,1-dimethoxy-3-(trimethylsilyloxy)-1,3-butadiene, followed by acidification, affords *dl*-epigriseofulvin.

Recently we described some cycloaddition reactions of the 1,1-disubstituted diene **1** with electrophilic dienophiles.[1,2]



Acid-catalyzed unraveling of the adducts of **1** with α,β-unsaturated carbonyl systems affords specific monoenol ethers of β-diketones.

It was of interest to examine the extension of this reaction to include α-alkylidinecycloalkanones as dienophiles, thereby providing a route to structurally defined spirocyclic β-methoxyenones. With this in mind, we addressed the synthesis of griseofulvin (**6**),[3,4] an antifungal agent of some importance. Our results are described herein.

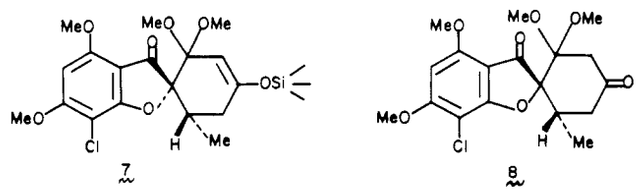


The known[4d] coumaranone (**2**) was treated with lithium diisopropylamide in tetrahydrofuran. The resultant enolate, at −78 °C, reacted instantaneously with acetaldehyde to afford a nearly quantitative yield of a stereoisomeric mixture of β-aldols **3** [($CDCl_3$) 2CHCH_3 doublets at δ 1.35 and 1.39].

While in some cases a given β-aldol can be converted to a geometrically defined alkylidenecycloalkanone by trans elimination of a suitably activated derivative of the alcohol,[5] a recent finding of Katzenellenbogen[6] suggests that such a stereospecific transformation is not always possible. Since chromatographic separation of **3** into its components appeared to be inconvenient, we first investigated the dehydration of the mixture. Treatment of a mixture **3** with methanesulfonyl chloride in pyridine containing 4-(dimethylamino)pyridine afforded an 89% yield of a single ethylidene ketone. Thus, even under these mild conditions, the presumed intermediate β-mesyloxy ketone was unstable to β elimination.

That **4** is, in fact, a single substance was suggested by its NMR spectrum [($CDCl_3$) δ 1.95 (3, d, J = 6 Hz), 5.98 (q, J = 6 Hz)]. Since only one isomer was available to us, we could not at this stage assign its configuration. This was ascertained through its cycloaddition with compound **1**.

Reaction of **4** with **1** was carried out in toluene at 115 °C. Two procedures were employed to convert the resultant adduct **7** into the desired β-methoxyenone. In method A the



residue, upon evaporation of the toluene, was directly chromatographed on silica gel. Elution with ethyl acetate–benzene afforded a mixture of *dl*-epigriseofulvin (**5**) and its β-methoxy derivative **8**. This mixture was treated with tosyl acid–benzene under reflux for 2 h to afford an 82% yield of essentially pure **5**.

Alternatively, the adduct was treated with aqueous HCl–THF. By this method, the adduct **7** suffered direct conversion to **5**, effectively bypassing the β-methoxy derivative **8**. Chromatography afforded **5** in 55% yield. An authentic sample of epigriseofulvin (**5**) was obtained by known procedures,[7] involving the base-catalyzed equilibration of griseofulvin (**6**)[8] with **5**. The spectral and chromatographic properties of the synthetic material were identical with those of the authentic, optically active sample. At no point, in either method of workup, was there any indication for the formation of griseofulvin (**6**) itself.

Assuming the stereochemical integrity of the ethylidene group under the conditions of the cycloaddition, it is surmised that **4** is of the *Z* configuration shown. Whether this is the result of equilibration of the hypothetical *E* isomer, formed from trans elimination of the erythro version of **3**, or whether **4** is the kinetic β-elimination product of both isomers of **3** can not be ascertained at this stage.

It will be noted that in light of the base-induced equilibration of **5** and **6**,[7] this work constitutes a formal total synthesis of griseofulvin (**6**) itself. Given the inefficiency of conducting this equilibration, separation, and recycling sequence, the method can not be regarded as an optimal path to griseofulvin.[9] However, in view of the excellent yields of Diels–Alder reactions of 2-alkylidenecoumaranones with diene **1**, several alternative routes to griseofulvin itself appear possible. These are now under active investigation in our laboratory.

0022-3263/78/1943-4604$01.00/0