Synthetic Studies toward Complex Diterpenoids. IX.[1,2] A New Stereocontrolled Synthetic Route to Some Intermediates for Diterpenoid Alkaloids and C_{20} Gibberellins

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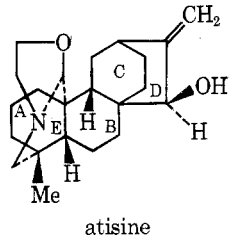
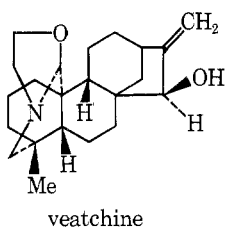
Received July 8, 1975

Stereocontrolled syntheses of (±)-*N*-acetyl-19,20-imino-13-methoxypodocarpa-8,11,13-triene (**1b**) and the corresponding demethoxy compound (**1a**), established synthetic intermediates for diterpenoid alkaloids and C_{20} gibberellins, are reported. The synthetic approach contains a novel method of angular alkylation based upon a regioselective intramolecular α-oxocarbenoid insertion across the benzylic C–H (at C-10) bond in the copper-catalyzed carbenoid decomposition of the easily accessible α-diazomethyl ketones **6a** and **6b** to the corresponding bridged tetracyclic ketones **8a** and **8b.** These have been converted, in high yields, to the respective dicarboxylic acids **11a** and **11b** through oxidation of the corresponding hydroxymethylene derivatives **10a** and **10b,** which were finally transformed to **1a** and **1b** through an efficient route. The ketone **8a** has been converted to the C-10 homologous dicarboxylic acid **13a.**

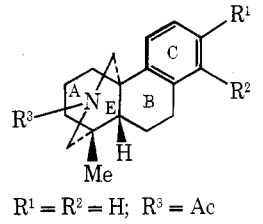
A great deal of attention in the past two decades toward complex diterpenoid alkaloids[3] has led to the total synthesis[4,5] of atisine, veatchine, synthetic intermediates, and related model compounds.[6,7] With a solitary exception,[4c] all the successful total synthetic approaches consist in the construction first of the heterocyclic E ring in an octahydrophenanthrene system such as **1c** or **1d** containing ring A, B, and C, followed by elaboration of the bridged-ring systems D through the aromatic moiety. The former syn-



atisine



veatchine



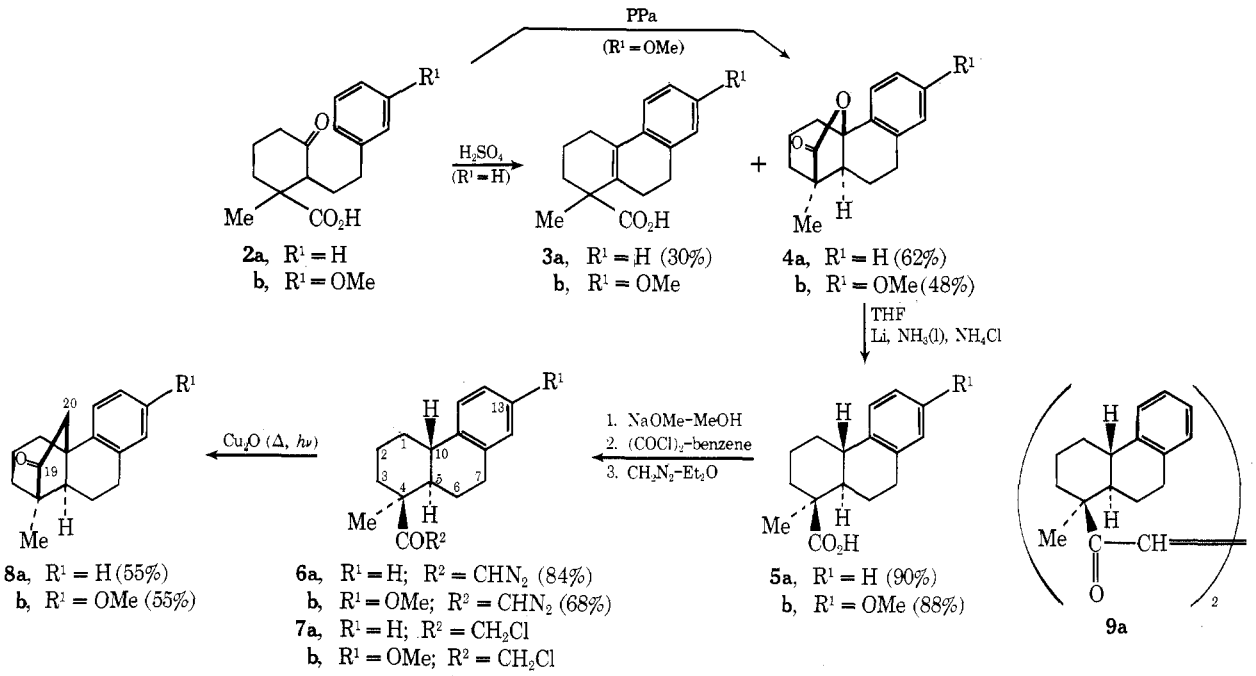
1a, $R^1 = R^2 = H$; $R^3 = Ac$
b, $R^1 = OMe$; $R^2 = H$; $R^3 = Ac$
c, $R^1 = OMe$; $R^2 = R^3 = H$
d, $R^1 = H$; $R^2 = OMe$; $R^3 = Ac$

thon has also been utilized in the solitary total synthesis of a C_{20} gibberellin, gibberellin A_{15}, by Nagata and his coworkers.[8] The crucial problem in the synthesis of the tetracyclic amine synthons lies in the introduction of the C-4, C-10 (diterpene numberings) functionalized carbon residues in a *trans*-hydrophenanthrene moiety. In spite of the notable achievements in the total synthesis of diterpene alkaloids, there are only a limited number of methods so far available for satisfactory realization of this objective. These can be classified only in three narrow groups, namely (1) intramolecular functionalization of C-4 or a C-10 angular methyl group in an appropriately constructed tri-[6a,d–f] or tetracyclic[4c,6l] system; (2) intramolecular alkylation[4d,6g,h] at C-4 in a tricyclic system through a functionalized C-10 angular methyl group; and (3) by conjugated addition of hydrocyanic acid.[4a] The methods included under 1 and 2 suffer not only from low yields and multiplicity in their reaction paths, but also from the synthetic problems associated with the starting materials containing at least two to three asymmetric centers. The hydrocyanation method[9] has so far been proved to be the best for allowing the synthesis of the tetracyclic synthon, e.g., **1c,** on a large scale; however, it is clearly necessary to pay great attention to the reaction conditions and reagents as well as the nature of the substrates.[10] Our long-range and comprehensive synthetic endeavors in this area[2] have culminated in a new simple synthetic method for stereospecific introductions of C-4 and C-10 functionalized carbon residues in a *trans*-hydrophenanthrene moiety leading to a few key intermediates for the synthesis of complex diterpenoids, including the tetracyclic acetylamine synthons **1a** and **1b.** The notable feature of this route lies in the angular alkylation at a classically nonreactive center through the C-4 diazoacetyl group via long-range regioselective intramolecular α-oxocarbenoid insertion[11] across the C-10 benzylic C-H σ bond in copper-catalyzed carbenoid decompositions in the diazo ketones **6a** and **6b** in which the stereochemistry of all the three asymmetric centers is already fixed at the early stage of the synthesis.

Simple stereospecific syntheses of the parent carboxylic acids **5a**[12] and **5b**[13] of the requisite diazo ketones were developed in this laboratory from the readily accessible starting materials through the respective unsaturated acids **3a** and **3b** and the lactones **4a** and **4b.** This two-step sequence for the synthesis of the lactones has been further simplified in the present study. While cyclization of the keto acid **2a**[14] with polyphosphoric acid (PPA), according to Mori et al.,[15] gave the lactone **4a** only in 30–35% yield in our hands (reported[15] yield 53%), repeating the reaction using H_2SO_4 at low temperature afforded the desired lactone **4a** in 62% yield along with the unsaturated acid **3a** in 30% yield. Attempted H_2SO_4-catalyzed cyclization of the methoxy keto acid **2b** did not give satisfactory results. However, PPA-induced reaction of **2b**[13] yielded the lactone **4b** in 48% yield. In the present studies reductive cleavages of the lactones **4a** and **4b** have been modified[12,13] by using lesser amounts of lithium metal without any detrimental effect on the yields of the corresponding acids **5a** and **5b.**

The crude acid chlorides obtained from the reactions of the dry sodium salts of the acids **5a** and **5b** were treated with an excess of ethereal diazomethane solution in the presence of triethylamine. The crystalline diazo ketones **6a** and **6b** were obtained in good yields. The required transformations of the diazo ketones **6a** and **6b** to the corresponding tetracyclic ketones **8a** and **8b** were achieved in a satis-

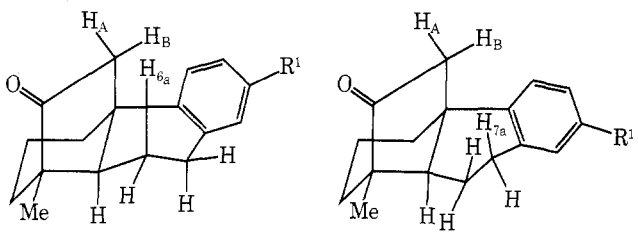
Scheme I



factory yield after extensive experimentations.[16] Best results were obtained when intramolecular alkylation was effected by thermal decomposition of dilute solutions of the crystalline diazo ketones in THF–cyclohexane in the presence of freshly prepared Cu_2O under irradiation[11d,17] with tungsten lamps. Under these conditions decomposition of the diazo ketone **6a** afforded the known tetracyclic ketone **8a** in 53–55% yield along with the dimeric compound **9a** in 5–10% yield as the only isolable crystalline products after chromatography on alumina. The ketone **8a** is identical with an authentic sample[6h] with respect to mixture melting point and ir comparisons.[18] The structure of the dimeric ketone **9a** has been assigned on the basis of ir and NMR spectral data (see Experimental Section). Thermal decomposition of the crystalline diazo ketone **6a** in THF–cyclohexane in the presence of anhydrous $CuSO_4$ gave the tetracyclic ketone **8a** in 50–54% yield as the only isolable crystalline product. However, using crude diazo ketone in the carbenoid decomposition under the above condition the desired ketone **8a** was isolated in 45–50% yield along with the chloro ketone **7a**, in variable yields (2–5%) after chromatography. The formation of the chloro ketone can be partly or completely supressed by using triethylamine in the conversion of acid chloride to diazo ketone. The structure of the chloro ketone **7a** has been assigned on the basis of ir, NMR, and elemental analyses (see Experimental Section).

The crystalline methoxy diazo ketone analogue **6b** on thermal decomposition under irradiation with a tungsten lamp in the presence of Cu_2O gave the desired tetracyclic ketone **8b** in 50–54% yield as the only isolable crystalline product after chromatography. Thermal decomposition of the diazo ketone **6b** in the presence of $CuSO_4$ gave the product **8b** in 38% yield. When the noncrystalline crude diazo ketone was used in the above reaction besides the tetracyclic ketone (20–25% yield), a small amount of chloro ketone **7b** (see Experimental Section) was also isolated after chromatography. The methoxy tetracyclic ketone **8b** showed a single strong five-membered ketone carbonyl band in the ir and a methoxyoctahydrophenanthrene chromophore in the uv. The final confirmation of the assigned structure for **8b** came from comparing a 220-MHz ^1H NMR spectrum of this ketone with that of the demethoxy analogue **8a** of established structure. In ^1H NMR (220 MHz in $CDCl_3$) spectra both the ketones **8a** and **8b** showed the C-4 Me singlet at δ 1.045; the OMe singlet in **8b** appeared at δ 3.78. The most important structural features common to **8a** and **8b** are the protons on the methylene bridge adjacent to the ketone carbonyl ($-COCH_2-$), which appeared as doublets and a pair of doublets centered at δ 2.32 and 2.47 (J_{AB} = 20 Hz), and δ 2.31 and 2.45 (J_{AB} = 20 Hz) in the ketones **8a** and **8b**, respectively. The small coupling (ca. 1.5 Hz) of the proton at higher fields, assigned to the H_B (shielded by aromatic ring), possibly arises with the proton H_{6a} or H_{7a} in the conformations **8A** and **8B**, respectively, in these compounds. The exact conformation of the B ring, however, could not be evaluated from these data.[19]

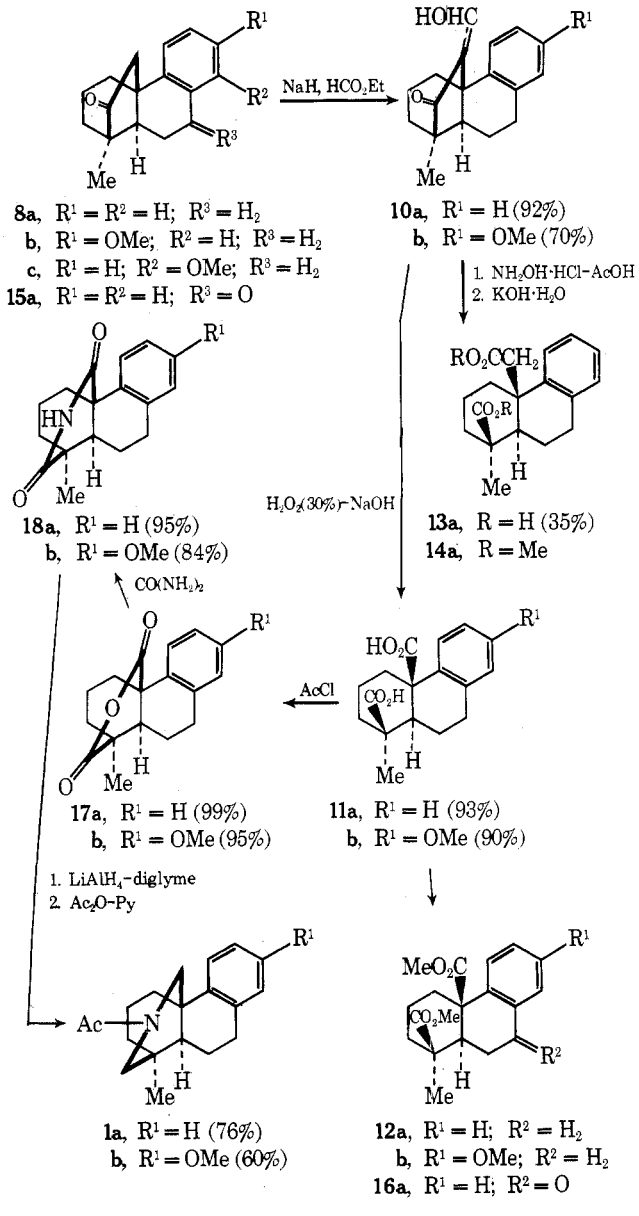
8A and **8B** ≡



With the establishment of the structures of the ketones **8a** and **8b**, it is clearly evident that the intramolecular oxocarbenoid insertion is highly regioselective[16] in the respective diazo ketones. Next, attention was devoted to the developments of the C-4, C-10 functionalities of the diterpenoids from the ketones **8a** and **8b**. Recently, Matsumoto et al.[6h] have reported conversions of **8a** and **8c** to the corresponding tetracyclic acetylamines **1a** and **1d**. Other approaches[4d,6g] toward similar transformations, developed earlier, are less satisfactory. We have now succeeded in elaborating an efficient sequence of reactions (Scheme II) which not only provides a route to the tetracyclic amine derivatives for the diterpenoid alkaloids, but also some intermediates **11a**, **11b**, and **13a** with C-4, C-10 functions suitable for preparation of C_{20} gibberellins[20] and other complex diterpenoids.[21]

Condensation of the ketone **8a** with ethyl formate in the presence of a large excess of sodium hydride under forcing

Scheme II



conditions[22] afforded the crystalline hydroxymethylene derivative **10a** in 92% yield. The same condensation using sodium methoxide gave only 19% of the desired product. On oxidation[23] with alkaline hydrogen peroxide, **10a** yielded the dicarboxylic acid **11a** in 93% yield; the dimethyl ester **12a** was obtained by esterification with diazomethane. Attempted ozonolysis of **10a** followed by in situ oxidation with hydrogen peroxide gave a complex mixture from which the diacid **11a** could be isolated in ca. 12% yield. Reaction of the hydroxymethylene ketone **10a** with hydroxylamine hydrochloride in acetic acid, followed by basic cleavage[24] of the resulting product, afforded the C-10 homologous dicarboxylic acid **13a** in 30% yield; dimethyl ester **14a,** mp 100 °C. The required transformation of the methoxy ketone **8b** to **11b** was satisfactorily achieved following the sequence developed for the demethoxy analogue and is summarized in Scheme II. The demethoxy ketone **8a** and the diester **12a** were also transformed to the corresponding 7-oxo compounds **15a** and **16a** by oxidation with chromic acid.

The final stage was now set for the development of the nitrogen containing hetereocyclic E ring of the diterpenoid alkaloids in the dicarboxylic acids **11a** and **11b** following the sequence developed by Tahara et al.[6e] for a similar transformation. The dicarboxylic acids **11a** and **11b** afforded the corresponding anhydrides **17a** and **17b** in 95–98% yield, which were converted to the respective imides **18a** and **18b** in 95 and 84% yield, respectively. The reduction of the imide **18a** under forcing conditions with lithium aluminum hydride in diglyme and subsequent acetylation of the crude amine furnished the tetracyclic acetylamine **1a** in 76% yield. It was proved to be identical with the sample derived through an independent synthetic route[6h] by mixture melting point and comparative ir spectrum.[18] In a similar sequence the methoxyimide **18b** was converted to the tetracyclic acetylamine **1b.** This was proved to be completely identical with a sample (prepared by Tahara[6e] from Nagata's[4a] racemic sample of the tetracyclic amine **1c**) of **1b** by mixture melting point, ir spectrum, and GLC retention times in two different columns.[25]

The tetracyclic base **1c** served as the key intermediate in the total synthesis of racemic atisine,[4a] veatchine,[4b] and gibberellin A_{15}.[8] Thus the stereospecific introduction of the C-4, C-10 cis dicarboxylic acid functionalities in a podocarpane (*trans*-hydrophenanthrene) moiety has been achieved through a new stereocontrolled intramolecular angular alkylation[26] reaction, thereby solving a crucial problem in the total syntheses of a large number of complex diterpenoids.

Experimental Section

The compounds described are all racemates. Melting points are uncorrected. Petroleum ether used in chromatography refers to the fraction of bp 60–80 °C and light petroleum refers to the fraction of bp 40–60 °C. Chromatography on neutral alumina was performed using aluminum oxide "standardized for chromatographic analysis acc. to Brockmann" purchased from M/S Sarabhai M. Chemicals. The homogeneity of all compounds was checked by TLC on silica gel G (200 mesh) plates of 0.2 mm thickness using benzene–ethyl acetate and benzene–methanol solvent systems. The spots were located by exposing the dried plates in iodine vapor. Uv spectra were determined in 95% ethanolic solution on a Beckman DU spectrophotometer and unless otherwise mentioned, ir spectra were determined in chloroform solution on a Perkin-Elmer Model 21 double beam recording spectrophotometer by Mr. A. Ghosal. NMR spectra were recorded on a Varian HA-60 spectrometer and Me_4Si as internal standard in $CDCl_3$; 220-MHz NMR spectra were obtained from the Varian Analytical Instrument Division, Palo Alto, Calif. Analyses were performed by Mrs. C. Dutta of this laboratory.

4aβ-Hydroxy-1α-methyl-1,2,3,4,4a,9,10,10a-*trans*-octahydrophenanthrene-1β-carboxylic Acid 1→4a Lactone (4a) and 1-Methyl-1-carboxy-1,2,3,4,9,10-hexahydrophenanthrene (3a).[27] a solution of the keto acid **2a** (26.0 g, 0.01 mol) in dry thiophene-free benzene (50 ml) was added to well-stirred concentrated sulfuric acid (350 ml), cooled in an ice–salt bath (ca. −10 to −5 °C), during 10–15 min and the stirring in the cold was continued for 2 h. The reaction mixture was poured onto crushed ice and extracted with ethyl acetate. The organic extract was thoroughly washed with 2% sodium hydroxide solution and water, dried (Na_2SO_4), and concentrated to afford 15.1 g (62%) of the lactone **4a,** mp 129–130 °C. A portion of this on recrystallization once from ethyl acetate–petroleum ether afforded **4a** in colorless prisms, mp and mmp 130–131 °C (lit.[12] 130–131 °C) (ir spectrum identical with that of an authentic sample). The combined aqueous alkaline extracts were acidified with 6 N hydrochloric acid and the separated white solid acid was extracted with ethyl acetate, washed with water, dried (Na_2SO_4), and evaporated. The residual product was recrystallized twice from CH_2Cl_2–methanol to give 7.3 g (30%) of **3a,** mp and mmp 180–181 °C (lit.[12] mp 180–181 °C) (ir spectrum identical with that of the previously prepared sample[12]).

(±)-20-Nordeoxypodocarpic Acid (5a). The lactone **4a** (3.5 g, 14.5 mmol) in anhydrous ether (40 ml) and dry tetrahydrofuran (40 ml) was subjected to reductive cleavage with liquid ammonia (ca. 350 ml) and lithium metal (400 mg, 57.6 mg-atoms) using solid ammonium chloride as proton donor, following exactly the method described earlier.[12] The crude product on recrystallization once from ethyl acetate–petroleum ether afforded 3.15 g (90%) of **5a:** mp and mmp 189–190 °C (lit.[12] 180–190 °C); ir spectrum identical with that of the previously prepared sample.[12]

4aβ-Hydroxy-1α-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-

***trans*-octahydrophenanthrene-1β-carboxylic Acid 1→4a Lactone (4b).** To a well-stirred mixture of PPA, prepared from phosphorus pentoxide (30 g) and orthophosphoric acid (24 ml, 85% w/w), at room temperature was added the keto acid **2b** (6.0 g, 22 mmol) in ether (10 ml) and the stirring was continued for 1 h. The temperature of the reaction mixture was then raised to 50 °C and the mixture was stirred for an additional 30 min. The cooled reaction mixture was poured onto crushed ice and the organic material was extracted with ethyl acetate, washed with 2% sodium hydroxide solution and water, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and crystallization from ethyl acetate–petroleum ether afforded the lactone **4b** (2.40 g), mp and mmp 171 °C (lit.[13] mp 171–172 °C) (ir spectrum identical with that of the previously prepared sample[13]). The alkaline washings on acidification and reextraction gave an acidic fraction (2.4 g) which on recyclization–lactonization under the above condition gave another crop of lactone **4b** (310 mg) (total yield 48%).

(±)-13-Methoxy-20-nordeoxypodocarpic Acid (5b). Reductive cleavage of the lactone **4b** (1.2 g, 4.4 mmol) using lithium metal (130 mg, 18.7 mg-atoms) in liquid ammonia (ca. 200 ml) according to the conditions described earlier[13] afforded the acid **5b** (950 mg, 88%), mp and mmp 165–166 °C (lit.[13] 165–166 °C) after recrystallization of the crude product from methanol. Ir spectrum was identical with that of the previously prepared sample.[13]

(±)-4β-Diazoacetyl-19,20-bisnorpodocarpa-8,11,13-triene (6a). The acid **5a** (4.0 g, 16.4 mmol) in benzene (100 ml) was titrated to neutrality with a solution of sodium methoxide in methanol (phenolphthalein indicator). After removal of the solvent, the residue was freed from traces of moisture and methanol by distillation with benzene. The dried sodium salt was suspended in anhydrous benzene (150 ml) containing pyridine (0.2 ml) and cooled in an ice bath and oxalyl chloride (5 ml, 58.6 mmol) was added. The mixture was stirred in the cold for 30 min and at 60 °C for 1 h, cooled, and filtered and the filtrate was evaporated under reduced pressure. An ethereal solution (200 ml) of the resulting crystalline acid chloride was added dropwise with stirring to an ice-cold ethereal diazomethane solution (generated from 10 g of *N*-methylnitrosourea) containing triethylamine (2.3 ml, 16.4 mmol) and left overnight. This was filtered and the filtrate evaporated to afford the crude diazo ketone **6a**, purified by filtering through a column of neutral alumina (30 g) and eluting with ether–petroleum ether (3:7). The diazo ketone **6a** was obtained as a pale yellow solid (3.75 g, 84%), mp 127–128 °C dec. Recrystallization from ether afforded the analytical sample, mp 127–128 °C dec, ir 2110 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.51. Found: C, 75.59; H, 7.42.

Intramolecular Insertion Reactions. Transformations of 6a to (±)-19,20-Cyclopodocarpa-19-oxo-8,11,13-triene (8a). Method A. With Cuprous Oxide under Thermal–Photochemical Decomposition.[27] A solution of the above diazo ketone **6a** (2.5 g, 9.3 mmol) in a mixture of anhydrous tetrahydrofuran–cyclohexane (400 ml, 1:1) was added during 5 h with stirring to a refluxing suspension of anhydrous cuprous oxide (8 g) in cyclohexane (300 ml) under irradiation with two 250-W tungsten lamps and the refluxing was continued for another 2 h (diazo ketone band in ir disappeared). The catalyst was filtered off and the solvent was evaporated under reduced pressure to afford a gummy solid which was chromatographed on neutral alumina (50 g) and eluted with petroleum ether to afford **8a** as a white solid (1.25 g, 55%), mp 116–117 °C. Recrystallization from light petroleum gave the analytical sample: mp and mmp 117–118 °C (lit.[6h] mp 118 °C); ir (KBr) spectrum was identical with that of the sample previously prepared by a different route;[6h,18] λ_{max} 266 nm (log ε 2.65), 274 (2.64); NMR (220 MHz) δ 1.045 (s, 3 H, $-CH_3$), 1.20–1.75 (complex m, 9 H, $-CH_2$ and –CH <), δ_A 2.32 (d, 1 H, J_{AB} = 20 Hz), δ_B 2.47 (dd, 1 H, J_{AB} = 20, J_B, H_{6a}, or J_B, H_{7a}, ≃ 1.5 Hz), 2.84 (m, 2 H, $-CH_2Ar$), 7.18 (m, 4 H, $-C_6H_4-$); mass spectrum (70 eV) *m/e* (rel intensity) 240 (M^+, 72), 224 (79), 205 (31), 195 (49), 180 (58), 165 (38), 150 (39), 130 (49), 120 (69), 90 (100).

Anal. Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.80; H, 8.39.

Petroleum ether–benzene (3:1) eluents gave a solid fraction contaminated with some oil, which on recrystallization yielded the dimeric product **9a** (220 mg, 10%): mp 153 °C; ir 1670 cm^{-1}; NMR δ 1.26 (s, 6 H, 2 CH_3), 1.42–2.71 (br m, 12 H, saturated $-CH_2-$), 2.67–3.44 (br m with two br s at 2.75 and 2.83, 12 H, remaining $-CH_2-$ and methine), 5.61 (br m, 2 H, –CH=CH–), 7.0–7.20 (br m, 8, 2 ArC_6H_4).

Anal. Calcd for $C_{34}H_{40}O_2$: C, 84.95; H, 8.39. Found: C, 84.85; H, 8.42.

Method B. Thermal Decomposition with Copper Sulfate. Thermal decomposition of the diazo ketone **6a** (2.0 g, 7.42 mmol) in a mixture of anhydrous cyclohexane (400 ml)–tetrahydrofuran (160 ml) in the presence of anhydrous copper sulfate (6 g) following the procedure described above required 8 h for complete reaction. After usual work-up and chromatography of the product on neutral alumina (60 g) using petroleum ether as eluent, there was obtained 970 mg (54%) of the bridged ketone **8a**, mp and mmp 117–118 °C.

Method C. Decomposition of Crude 6a with Copper Sulfate. When the crude diazo ketone **6a** prepared from the acid **5a** was used in the above reaction, the bridged ketone **8a** was isolated in variable yields ranging from 45 to 50%. In some cases, the chloro ketone **7a** could be separated in 2–5% yields, especially when triethylamine was not used during the preparation of the diazo ketone. The chloro ketone **7a** was obtained in the petroleum ether eluted fraction along with the bridged ketone **8a** during the chromatography of the insertion product and was separated by fractional crystallization from petroleum ether: mp 133 °C; ir 1715 cm^{-1}; λ_{max} 266 nm (log ε 2.72), 274 (2.69); NMR δ 1.33 (s, 3 H, CH_3), 1.83 (m, 6 H, saturated $-CH_2$ and CH<), 2.83 (m, 2 H, $-CH_2Ar$), 3.47 (br s, $-COCH_2Cl$), 7.17 (m, 4 H, $-C_6H_4-$).

Anal. Calcd for $C_{17}H_{21}OCl$: C, 73.79; H, 7.59. Found: C, 74.08; H, 7.62.

(±)-4β-Diazoacetyl-13-methoxy-19,20-bisnorpodocarpa-8,11,13-triene (6b). The diazo ketone **6b** was prepared from the acid **5b** (1.0 g, 3.6 mmol) in an exactly similar manner as described for its demethoxy analogue. The crude yellow semisolid product was purified by filtering through a short column of neutral alumina (15 g) and eluting with ether–petroleum ether (3:7) to afford the crystalline pale yellow diazo ketone **6b** (750 mg, 68%), mp 108–110 °C dec. Recrystallization from ether gave the analytical sample, mp 108–110 °C dec, ir 2115 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}O_2N_2$: C, 72.45; H, 7.43. Found: C, 72.01; H, 7.37.

Further elution with ether–petroleum ether (1:1) afforded a yellow gum which did not solidify.

Intramolecular Insertion Reaction. Transformation of 6b to (±)-19,20-Cyclopodocarpa-13-methoxy-19-oxo-8,11,13-triene (8b). Method A. With Cuprous Oxide under Thermal–Photochemical Decomposition. The diazo ketone **6b** (500 mg, 1.68 mmol) in anhydrous tetrahydrofuran (50 ml) and cyclohexane (50 ml) was added to a stirred refluxing suspension of cuprous oxide (2 g) in cyclohexane (100 ml) under irradiation with two 250-W tungsten lamps during 2 h and refluxed for another 2 h (disappearance of the diazo ketone band in ir). Removal of the solvent from the filtrate yielded a solid product which was dissolved in a minimum amount of benzene and chromatographed on neutral alumina (8 g). Elution with benzene–petroleum ether (1:3) afforded the desired ketone **8b** (250 mg, 55.5%), mp 129–130 °C. Recrystallization from light petroleum afforded the analytical sample: mp 130 °C; ir 1735 cm^{-1}; λ_{max} 276 nm (log ε 3.55); NMR (220 MHz) δ 1.045 (s, 3 H, CH_3), 1.20–1.75 (m, 9 H, $-CH_2-$ and –CH<), δ_A 2.31 (d, 1 H, J_{AB} = 20 Hz), δ_B 2.45 (dd, 1 H, J_{AB} = 20, J_B, H_{6a}, or J_B, H_{7a}, ≃ 1.5 Hz), 2.84 (m, 2 H, $-CH_2Ar$), 3.78 (s, 3 H, OCH_3), 6.90 (m, 3 H, $-C_6H_3-$); mass spectrum (70 eV) *m/e* (rel intensity) 270 (M^+, 100), 227 (64), 213 (70), 199 (67), 186 (56), 171 (89), 158 (64), 153 (56), 141 (94), 128 (100), 103 (61), 91 (100).

Anal. Calcd for $C_{18}H_{22}O_2$; C, 79.96; H, 8.20. Found: C, 79.75; H, 8.00.

No other crystalline compound could be isolated from 50–100% benzene and ether elutes.

Method B. Thermal Decomposition with Copper Sulfate. Thermal decomposition of the diazo ketone **6b** (500 mg, 1.68 mmol) in a mixture of anhydrous tetrahydrofuran (50 ml) and cyclohexane (150 ml) in the presence of anhydrous copper sulfate (2 g) afforded after chromatographic separation 175 mg (38.5%) of the bridged ketone **8b**.

Method C. Decomposition of Crude 6b with Copper Sulfate. When the insertion reaction was carried out with the crude semisolid diazo ketone **6b** in cyclohexane or tetrahydrofuran or a mixture of the two solvents in the presence of anhydrous copper sulfate, the bridged compound **8b** was formed in very low yield (20–25%). The chloro ketone **7b** was also isolated in variable yields (2–7%) from the earlier elutes with petroleum ether–benzene along with the bridged ketone and was separated by fractional crystallization. On recrystallization from ether, the chloro ketone **7b** melted at 151 °C, ir 1720 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}O_2Cl$: C, 70.47; H, 7.50. Found: C, 70.40; H, 7.55.

Hydroxymethylation of 8a. (±)-19,20-Cyclopodocarpa-8,11,13-triene-20-hydroxymethylen-19-one (10a). To an ice-cold stirred suspension of sodium hydride (4 g, 80 mmol of a 50% dispersion) in dry benzene (25 ml) under nitrogen was added a solution of the ketone **8a** (1.3 g, 5.4 mmol) in benzene dropwise followed by the addition of a drop of methanol. After addition of ethyl formate (2.2 ml, 27 mmol), the stirring was continued for an additional 2 h and the solution was left overnight. The excess of sodium hydride was decomposed with a small amount of methanol, diluted with water, acidified with 6 N hydrochloric acid, and extracted with ether. The ethereal layer was extracted with (2%) sodium hydroxide solution. The basic extract was acidified with hydrochloric acid (6 N) and extracted with ether. The ether layer was washed with brine and dried (Na_2SO_4). Evaporation of the solution afforded the hydroxymethylene derivative **10a** (1.2 g, 92%), mp 130–132 °C. Recrystallization from light petroleum furnished the analytical sample: mp 132 °C; ir 1670 and 1600 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.32; H, 7.46.

Oxidation of 10a. (±)-Podocarpa-8,11,13-triene-19,20-dioic Acid (11a). The hydroxymethylene ketone **10a** (1.2 g, 4.5 mmol) was dissolved in sodium hydroxide (100 ml, 10%) and cooled to ca. 10 °C and hydrogen peroxide solution (50 ml, 30%) was added. When the vigor of the reaction subsided, a second lot of alkali solution (50 ml, 10%) was added followed by 30 ml of hydrogen peroxide (30%) and allowed to stand overnight. The reaction mixture was diluted with water and extracted with ether. The aqueous layer was acidified with cold 6 N hydrochloric acid and extracted with ethyl acetate and methylene chloride. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded the dicarboxylic acid **11a** (1.2 g, 93%), mp 234–235 °C dec. The analytical sample was recrystallized from tetrahydrofuran–light petroleum, mp 234–235 °C dec, ir (Nujol) 1700 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.88; H, 7.13.

Methyl ester **12a** (diazomethane method) was recrystallized from light petroleum, mp 135 °C, ir 1725 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.05; H, 7.79.

(±)-20-Carboxypodocarpa-8,11,13-trien-19-oic Acid (13a). A mixture of the hydroxymethylene ketone **10a** (470 mg, 1.8 mmol), glacial acetic acid (7 ml), and powdered hydroxylamine hydrochloride (400 mg, 2.5 mmol) was heated under reflux for 10 min. After cooling to room temperature, a solution of KOH (100 ml, 30% aqueous) was added and refluxed for 60 h. The reaction mixture was diluted with water, acidified with cold 6 N HCl, and extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with $NaHCO_3$ solution and the basic extract was chilled and acidified with 6 N HCl. Extraction of the solid with ethyl acetate and evaporation of the solvent afforded the desired acid **13a** (200 mg, 35%), mp 229–230 °C. Recrystallization from ethyl acetate–petroleum ether furnished mp 233 °C, ir (Nujol) 1690 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.29; H, 7.03.

Dimethyl ester **14a** (diazomethane method) was recrystallized from light petroleum: mp 100 °C; ir 1720 cm^{-1}; NMR δ 1.25 (s, 3 H, CH_3), 1.5–2.2 (complex m, 9 H, $-CH_2$ and $-CH<$), 2.31 (br s, 2 H, $-CH_2CO_2Me$), 2.9 (m, 2 H, $-CH_2Ar$), 3.23 (s, 3 H, COOMe), 3.63 (s, 3 H, COOMe), 7.02 (br s, 4 H, ArH).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.81; H, 8.00.

Chromic Acid Oxidation of Bridged Ketone 8a. (±)-19,20-Cyclopodocarpa-8,11,13-triene-7,19-dione (15a). A solution of the ketone **8a** (450 mg, 1.9 mmol) in glacial acetic acid (6 ml) was mixed with a solution of CrO_3 (600 mg, 6 mmol) in water (2 ml) and acetic acid (2 ml) and shaken vigorously for 5–6 min. The reaction mixture was allowed to stand at room temperature overnight and finally heated to 60–65 °C for 2 h. The cooled reaction mixture was diluted with water, saturated with NaCl, and extracted with ether. The ethereal layer was washed with 2% NaOH solution and brine and dried (Na_2SO_4). Evaporation of the solvent left a crystalline residue (360 mg), mp 150–155 °C (ir 1730 and 1680 cm^{-1}), which was chromatographed on neutral alumina (20 g). Elution with petroleum ether afforded the recovered ketone **8a**, mp 114–116 °C (ir 1735 cm^{-1}) (150 mg). Elution with petroleum ether–benzene (1:1) gave the desired diketone **15a**, mp 160–162 °C (160 mg, 50% based on recovered ketone), purified by crystallization from ether–light petroleum: mp 164 °C; ir 1730 and 1680 cm^{-1}; λ_{max} 248 nm (log ϵ 3.98), 287 (3.15); NMR δ 1.08 (s, 3 H), 1.8–2.82 (complex m, 11 H), 7.44 (m, 3 H), 8.02 (m, 1 H).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.06; H, 7.13.

Chromic Acid Oxidation of Diester 12a. (±)-Dimethyl Podocarpa-8,11,13-triene-7-oxo-19,20-dioate (16a). The diester **12a** (400 mg, 1.26 mmol) was dissolved in glacial acetic acid (12 ml) and a solution of chromium trioxide (500 mg, 5 mmol) in water (1.5 ml) and glacial acetic acid (2 ml) was added with vigorous shaking. The reaction mixture was allowed to stand for 20 h with occasional swirling and then heated at 60–65 °C for 20 min. The cooled reaction mixture was diluted with water, saturated with sodium chloride, and extracted repeatedly with ether. The ether layer was washed with 2% sodium hydroxide solution followed by brine and dried (Na_2SO_4). Removal of the solvent afforded a solid (400 mg): mp 110–115 °C; ir 1730 and 1680 cm^{-1}. The material was subjected to chromatography on neutral alumina (15 g). First elution with benzene–petroleum ether (1:9) afforded the recovered diester **12a** (150 mg), mp and mmp 132–134 °C. Elution with benzene–petroleum ether (1:3) yielded the desired keto diester **16a** (200 mg, 77% based on recovered diester). Crystallization from ether–light petroleum afforded the analytical sample: mp 132 °C (mmp with the recovered diester 110–115 °C); ir 1730 and 1680 cm^{-1}; λ_{max} 248 nm (log ϵ 4.05), 285 (3.28).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.22; H, 6.90.

Preparation and Oxidation of 10b to (±)-Podocarpa-8,11,13-triene-13-methoxy-19,20-dioic Acid (11b). Treatment of the bridged ketone **8b** (300 mg, 1.1 mmol) with sodium hydride (1 g, 50%, 20 mmol) and ethyl formate (0.5 ml, 6.2 mmol) in benzene under identical reaction conditions afforded the hydroxymethylene derivative **10b** (235 mg, 70%) as a pink solid: mp 124–126 °C; ir 1670 and 1600 cm^{-1}. Oxidation of this hydroxymethylene derivative (230 mg, 0.77 mmol) with alkaline hydrogen peroxide, exactly under the condition described for the demethoxy analogue, afforded the dicarboxylic acid **11b** (200 mg, 90%), mp 228–230 °C dec, ir (Nujol) 1695 cm^{-1}. The analytical sample (from THF–light petroleum) melted at 232 °C dec.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.90; H, 7.21.

Dimethyl ester **12b** (diazomethane method) was recrystallized from light petroleum, mp 114 °C, ir 1730 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.12; H, 7.60.

Anhydride of 11a (17a). The diacid **11a** (1.2 g, 4.16 mmol) was refluxed with acetyl chloride (40 ml) for 2 h when it gradually went in solution. Removal of excess of the reagent under reduced pressure yielded the crystalline anhydride **17a** (1.10 g, 98%), mp 192–194 °C. Recrystallization from ethyl acetate–petroleum ether afforded the analytical sample: mp 194 °C; ir 1800 and 1760 cm^{-1}.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.28; H, 6.70.

Anhydride of 11b (17b). The methoxydicarboxylic acid **11b** (200 mg, 0.63 mmol) was refluxed with acetyl chloride (10 ml) for 2 h and then evaporated to dryness under reduced pressure to afford the crystalline anhydride **17b** (180 mg, 95%): mp 167–169 °C; ir 1800 and 1760 cm^{-1}. Recrystallization from ethyl acetate afforded the analytical sample, mp 170 °C.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.80; H, 6.50.

(±)-19,20-Dioxoiminopodocarpa-8,11,13-triene (18a). An intimate mixture of the anhydride **17a** (400 mg, 1.5 mmol) and urea (1 g, 16.7 mmol) was heated at 170–180 °C for 1 h. The solid mass after cooling was broken, treated with water, and filtered. The residue was thoroughly washed with water and dried. Recrystallization from ethyl acetate afforded the desired imide **18a** (380 mg, 95%): mp 248 °C; ir 1720 and 1705 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11. Found: C, 75.62; H, 7.41.

(±)-19,20-Dioxoimino-13-methoxypodocarpa-8,11,13-triene (18b). The anhydride **17b** (190 mg, 0.63 mmol) on treatment with urea (500 mg, 8.3 mmol) at 170–180 °C and subsequent purification by crystallization from ethyl acetate afforded the imide **18b** (160 mg, 84%): mp 255 °C; ir 1700 and 1715 cm^{-1}.

Anal. Calcd for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07. Found: C, 72.25; H, 7.22.

(±)-*N*-Acetyl-19,20-iminopodocarpa-8,11,13-triene (1a). To a solution of the imide **18a** (200 mg, 0.74 mmol) in anhydrous diglyme (15 ml) was added lithium aluminum hydride (300 mg, 7.8 mmol) and the mixture was stirred under nitrogen at 50 °C for 30 min and at 100–110 °C for 2 h. A second batch of lithium aluminum hydride (200 mg, 5.3 mmol) was added on cooling to room

temperature and the stirring was continued for another 4 h at 100–110 °C. After keeping overnight at room temperature, the excess of the reagent was destroyed carefully by addition of saturated sodium sulfate solution and then filtered under suction. The residue was thoroughly washed with ether. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of ether afforded a red oil (200 mg) which was immediately dissolved in dry pyridine (4 ml) and acetic anhydride (2 ml) and allowed to stand overnight. The cooled reaction mixture was diluted and acidified with ice-cold 6 N hydrochloric acid and extracted with ether. The ether layer was washed with 2% sodium hydroxide solution followed by brine and dried (Na_2SO_4). Removal of the solvent afforded a gummy solid (200 mg) which was chromatographed on acidic alumina (5 g). Elution with benzene–petroleum ether (3:7) yielded the acetyl derivative **1a**, mp 124–126 °C (160 mg, 76%). Recrystallization from light petroleum afforded the analytically pure specimen: mp and mmp[18] 125–126 °C (lit.[6h] mp 125–126 °C); ir (Nujol) 2920 (s), 2840 (sh), 1635 (s), 1493 (w), 1460 (s), 1440 (sh), 1380 (m), 1365 (m), 1320 (w), 1265 (m), 1050 (w), 1030 (w), 990 (w), and 740 cm^{-1} (m) (comparison[18] ir spectrum with an authentic sample was identical).

Anal. Calcd for $C_{19}H_{25}ON$: C, 80.52; H, 8.89. Found: C, 80.23; H, 8.67.

(±)-*N*-Acetyl-19,20-imino-13-methoxypodocarpa-8,11,13-triene (1b). The imide **18b** (120 mg, 0.4 mmol) in anhydrous diglyme (15 ml) was reduced with lithium aluminum hydride (250 mg, 6.6 mmol) and the product (102 mg) was acetylated with acetic anhydride (1 ml) and dry pyridine (2 ml). After usual work-up, the residue (100 mg) was chromatographed on acid-washed alumina (5 g). Elution with benzene afforded the desired *N*-acetylamine **1b** purified by recrystallization from ether–light petroleum: mp and mmp 165–166 °C (lit.[6e] mp 165–166 °C) (75 mg, 60%); ir (KBr) 1625 (s), 1575 (w), 1500 (m), 1440 (m, broad), 1370 (w), 1270 (s), 1250 (m), 1200 (m), 1160 (w), 1140 (m), 1045 (m), 985 (w), and 810 cm^{-1} (m); GLC on a 4 mm × 2.0 m 1.5% OV-1 on Shimalite W 80–100 mesh at 240 °C showed a single peak with retention time 10.6 min; on a 4 mm × 2.0 m 1.5% OV-17 on Shimalite W 80–100 mesh at 240 °C showed a single peak with retention time 11.7 min (comparative[25] ir spectrum and GLC analyses with an authentic sample[6e] were identical).

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68. Found: C, 76.38; H, 8.72.

Acknowledgment. We would like to express our sincere gratitude to Dr. L. F. Johnson, Varian Associates, for the 220-MHz NMR spectra and to Dr. C. R. Enzell, Swedish Tobacco Co., Stockholm, for the mass spectra. We graciously thank the C. S. I. R., New Delhi, for support of S.C.

Registry No.—**1a**, 38750-33-3; **1b**, 5550-67-4; **2a**, 57969-37-6; **2b**, 57969-38-7; **3a**, 21995-88-0; **4a**, 13936-31-7; **4b**, 33947-61-4; **5a**, 21995-83-5; **5b**, 33947-62-5; **6a**, 56846-72-1; **6b**, 56846-73-2; **7a**, 38750-21-9; **7b**, 38750-23-1; **8a**, 19772-92-0; **8b**, 38750-22-0; **9a**, 57969-39-8; **10a**, 38750-24-2; **10b**, 38750-27-5; **11a**, 38750-25-3; **11b**, 38750-28-6; **12a**, 38750-26-4; **12b**, 38750-29-7; **13a**, 38750-30-0; **14a**, 57969-40-1; **15a**, 57969-41-2; **16a**, 57969-42-3; **17a**, 38750-31-1; **17b**, 57969-43-4; **18a**, 38750-32-2; **18b**, 57969-44-5.

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