The Total Synthesis of (±)-Royleanone[1,2]

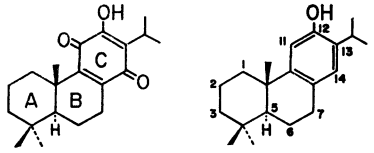
Yakudo TACHIBANA

Department of Chemistry, Faculty of Science, Hiroshima University, Higashisenda-machi, Hiroshima 730

(Received July 6, 1974)

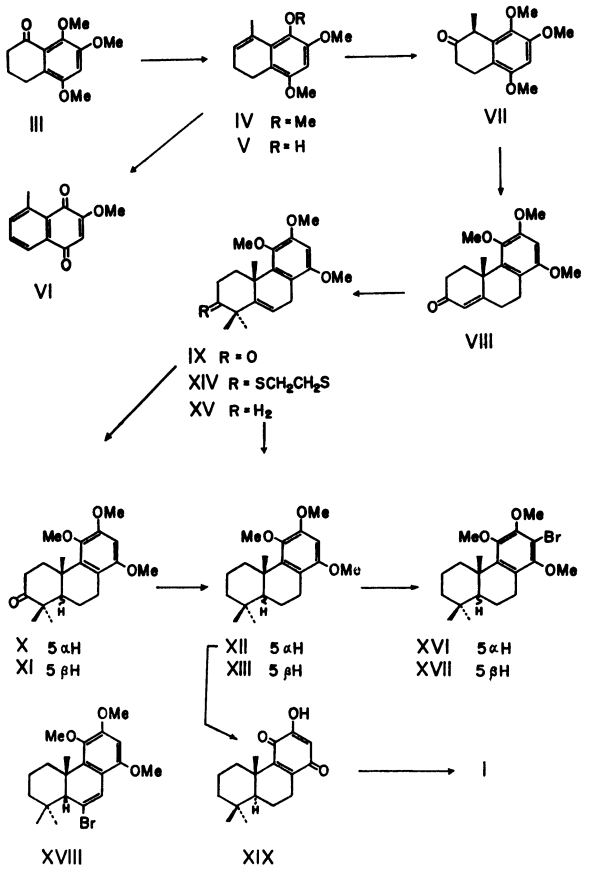
The total synthesis of (±)-royleanone (I) has been achieved. 5,7,8-Trimethoxy-1-tetralone (III) was converted into (±)-5,7,8-trimethoxy-1-methyl-2-tetralone (VII) *via* a dihydronaphthalene derivative (IV). The annelation of VII with methyl vinyl ketone gave a (±)-hexahydro-2-oxophenanthrene derivative (VIII), which was then further converted into (±)-11,12,14-trimethoxy-3-oxopodocarpa-5,8,11,13-tetraene (IX). The hydrogenation of IX over platinum oxide gave two dihydro derivatives, (X) and (XI), in a ratio of *ca.* 1: 7, these configurations in the A/B ring juncture were identified as *trans* and *cis* respectively. Therefore, IX was subjected to thioketalization, followed by desulfurization, to give (±)-11,12,14-trimethoxypodocarpa-5,8,11,13-tetraene (XV). The hydrogenation of XV over 10% palladium on carbon gave (±)-11,12,14-trimethoxypodocarpa-8,11,13-triene (XII), along with a small amount of its *cis* isomer (XIII). Finally, XII was converted into a hydroxy-1,4-quinone derivative (XIX), which was then treated with isobutyryl peroxide to give (±)-I, whose IR, UV, and NMR spectra were identical in every respect with those of natural royleanone.

Royleanone (I), a diterpenoid quinone, was isolated from the roots of *Inula royleana* D.C. by Edwards *et al.*[3] On the basis of chemical and spectral studies, they deduced its structure to be I. Kupchan *et al.*[4] also isolated royleanone from *Taxodium distichum* Rich (Taxodiaceae) and reported on its cytotoxity against Eagle's KB strain of human carcinoma of the nasopharynx. Although royleanone has been derived[3] from ferruginol (II)[5] in a 7% yield by oxidation with hydrogen peroxide, as a part of his own synthetic studies of quinone diterpenoids the present author attempted the total synthesis of (±)-royleanone (I) by the route of CB→A ring construction. The introduction of the isopropyl group at the C-13 position by using isobutyryl peroxide[6] was successfully carried out in the final step in the synthesis.



I II

5,7,8-Trimethoxy-1-tetralone (III),[7] which corresponds to the B and C rings in I, was chosen as the starting material. The Grignard reaction of III with methylmagnesium iodide and the subsequent dehydration of the resulting alcohol with dilute sulfuric acid gave 3,4-dihydro-5,7,8-trimethoxy-1-methylnaphthalene (IV), along with a small amount of a hydroxylic compound (IR 3530 cm^{-1}) (V). V showed a positive ferric chloride test, and the NMR spectrum in $CDCl_3$ showed a signal due to an aromatic proton at 6.45 ppm, while in Py-d_5 it shifted downfield to 6.68 ppm. Taking into account this pyridine-induced solvent shift and the ease of the cleavage of ether bonding *ortho* to a carbonyl group,[8] we tentatively identified V as 3,4-dihydro-8-hydroxy-5,7-dimethoxy-1-methylnaphthalene. With an intent to obtain (±)-5,7,8-trimethoxy-1-methyl-2-tetralone (VII), IV was treated with lead tetraacetate in acetic acid to give yellow crystals, whose structure was identified, on the basis of its spectral data (see Experimental section), as 2-methoxy-8-methyl-1,4-naphthoquinone (VI). Therefore, IV was oxidized with perbenzoic acid and then treated with dilute sulfuric acid to give VII. The construction of the A ring could be achieved by the annelation of VII with methyl vinyl ketone in the presence of sodium ethoxide in ethanol; after chromatographic purification, (±)-2,3,4,8,10,12-hexahydro-12-methyl-5,6,8-trimethoxy-2-oxophenanthrene (VIII) was obtained. This was further converted into (±)-11,12,14-trimethoxy-3-oxopodocarpa-5,8,11,13-tetraene (IX) with methyl iodide in the presence of potassium *t*-butoxide in *t*-butanol. Since the hydrogenation of IX over 10% palladium on carbon in acetic acid had not proceeded either at room temperature or at 50 °C, the catalyst was replaced by platinum oxide. After a smooth absorption of hydrogen, the crude product was separated by means of column chromatography on silica gel to give two corresponding dihydro derivatives, (X) and (XI), in a ratio of *ca.* 1: 7. In order to determine the configurations of the A/B ring juncture in X and XI, each of them was subjected to thioketalization with ethanedithiol in the presence of boron trifluoride etherate, followed by desulfurization with Raney nickel in boiling ethanol; after chromatographic purification (±)-11,12,14-trimethoxypodocarpa-8,11,13-triene (XII) and its *cis* isomer (XIII) were obtained respectively. The NMR spectrum of XII in CCl_4 showed signals due to three methyl groups at 0.89, 0.93, and 1.23 ppm,[9] while that of XIII showed corresponding signals at 0.51, 0.92, and 1.24 ppm. These NMR spectra, especially the signals of a significantly higher field at 0.51 ppm, strongly suggest the *cis* nature of the A/B ring juncture in XIII.[10] Therefore, the configurations of the A/B ring juncture in XII and XIII, also including those of X and XI, were identified as *trans* and *cis* respectively. Since natural royleanone possesses a *trans* A/B ring juncture, the above procedure was not effective for the preparation of the intermediate (X) because of its low yield. The desired *trans* compound (XII) could be effectively obtained by the following procedure. The ketone (IX) was first converted into its thioketal (XIV), which was then desulfurized with Raney nickel to give (±)-11,12,14-trimethoxypodocarpa-5,8,11,13-tetraene (XV). The hydrogenation of XV over 10% palladium on carbon in acetic acid afforded the requisite XII, along with a small amount of its *cis* isomer (XIII).



At this stage, some experiments regarding the introduction of isopropyl group at the C-13 position in XII and XIII were carried out.[11] The bromination of XII gave a bromide (XVI), while that of XIII under the same conditions gave two bromides, (XVII) and (XVIII). By the disappearance of the aromatic proton in the NMR spectrum the structure of XVI and XVII was determined to be nuclear-brominated (±)-13-bromo-11,12,14-trimethoxypodocarpa-8,11,13-triene and its *cis* isomer respectively. On the other hand, the NMR spectrum of XVIII showed three methyl signals, at 0.42, 1.06, and 1.21 ppm, together with three one-proton singlets attributable to the protons at the C-5, C-13, and C-7 positions at 1.89, 6.22, and 7.06 ppm respectively. Therefore, XVIII was identified as (±)-6-bromo-11,12,14-trimethoxy-5βH-podocarpa-6,8,11,13-tetra-ene. The treatment of XVI and XVII with so dium or phenylsodium in dry toluene, followed by the addition of either acetone or Dry Ice, resulted only in debromination giving XII and XIII respectively.

The final step of the present synthesis was carried out as follows; XII was demethylated with boron tribromide in methylene chloride, and the resulting hydroxylic product was oxidized in refluxing benzene with bubbling oxygen gas to give (±)-12-hydroxy-11,14-dioxopodocarpa-8,12-diene (XIX). This was then alkylated[6] with isobutyryl peroxide[12,13] in acetic acid at 100—105 °C to yield (±)-I as yellow crystals, whose IR, UV, and NMR spectra were found by a direct comparison to be identical in every respect with those of natural royleanone.

Experimental

The melting points are uncorrected. The NMR spectra were taken on a Hitachi Model R-20 spectrometer (60 MHz), with tetramethylsilane as the internal standard. The UV spectra were measured in ethanol, the IR spectra, in chloroform, and the NMR spectra, in carbon tetrachloride, unless otherwise stated. The chemical shifts are represented in terms of the δ values: s: singlet; bs: broad singlet; d: doublet; t: triplet; q: quartet; m: multiplet. Column chromatography was performed on Merck silica gel (0.08 mm).

3,4-Dihydro-5,7,8-trimethoxy-1-methylnaphthalene (IV). A solution of III (25 g) in dry benzene (250 ml) was dropped, over a period of 30 min, into a Grignard reagent (prepared from magnesium (3.1 g), methyl iodide (20 g) and dry ether (50 ml)) at room temperature. Stirring was continued at this temperature for 30 min, and then at 65 °C for 4 hr. The cooled mixture was poured into dilute hydrochloric acid (10%: 250 ml) and extracted with ether. The extract was washed with aqueous sodium thiosulfate and water and dried over sodium sulfate. After the removal of the solvent, the residue was refluxed for 4 hr in methanol containing dilute sulfuric acid (20%: 38 ml), cooled, and then extracted with ether. The extract was washed with saturated brine and dried over sodium sulfate. After the evaporation of the solvent, the crude product was chromatographed on silica gel (700 g), using benzene–hexane (7:3) as the eluent, to give IV (19.1 g: 76%) as an oil and V (2.1 g: 11%) as a solid, which was then recrystallized from petroleum ether–ether; mp 51.5—52.5 °C. IV; NMR 2.13 (d, J=1.5 Hz, =CC$\underline{H}_3$), 3.61, 3.70, 3.76 (each s, -OC$\underline{H}_3$), 5.77 (m, =C$\underline{H}$–), 6.30 (s, aromatic proton). Found: C, 71.92; H, 7.85%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%.

V; IR 3530 cm^{-1} (OH); NMR ($CDCl_3$) 2.28 (d, J=1.5 Hz, =CC$\underline{H}_3$), 3.76, 3.86 (each s, 2-OC$\underline{H}_3$), 5.56 (s, O$\underline{H}$), 5.84 (m, =C$\underline{H}$–), 6.45 (s, aromatic proton). NMR (Py-d_5) 2.59 (d, J=1.5 Hz, =CC$\underline{H}_3$), 3.71 (6H, s, 2-OC$\underline{H}_3$), 5.87 (m, =C$\underline{H}$–), 6.68 (s, aromatic proton). Found: C, 70.97; H, 7.39%. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

In another experiment, an azeotropic distillation of benzene solution of the crude Grignard reaction product containing two or three drops of concentrated hydrochloric acid, similar results were obtained.

2-Methoxy-8-methyl-1,4-naphthoquinone (VI). A mixture of IV (3.70 g), acetic acid (10 ml), and lead tetraacetate (freshly prepared from red lead oxide (11 g) and acetic acid (35 ml)) was stirred at room temperature for 2 hr; then ethylene glycol (4 ml) was added, and the mixture was stirred for an additional 30 min. The mixture was diluted with water and extracted with ether. The ether was washed with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, and then evaporated. The column chromatography and crystallization of the residue from methanol afforded VI (1.13 g: 35%); mp 151.5—152.5 °C; IR 1676, 1645, 1618 cm^{-1} (C=O); UV nm (ε): 243 (15700), 248.5 (15900), 276 (14700), 345 (3700); NMR ($CDCl_3$) 2.73 (s, =CC$\underline{H}_3$), 3.87 (s, -OC$\underline{H}_3$), 6.10 (s, =C$\underline{H}$–), 7.4—8.1 (3H, m, aromatic protons) and an unreacted starting material (1.16 g). Found: C, 71.28; H, 4.84%. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99%.

(±)-5,7,8-Trimethoxy-1-methyl-2-tetralone (VII). A solution of perbenzoic acid (19 g) in chloroform (450 ml) was added to a cooled solution of IV (20 g) in chloroform (600 ml) at below 10 °C. After storage overnight in a refrigerator, the red solution was washed with a sodium hydroxide solution and water, and evaporated. The residue was refluxed

for 1.5 hr in methanol (110 ml) containing sulfuric acid (17 ml) and water (90 ml), and the product was extracted with ether. After a usual work-up, the crude product was purified by column chromatography on silica gel (400 g), using benzene–ether (95: 5) as the eluent, to give VII (10.32 g: 48%), which was subsequently recrystallized from petroleum ether–ether; mp 90—91 °C; IR 1707 cm^{-1} (C=O); NMR ($CDCl_3$) 1.36 (d, J=7 Hz, $-\dot{C}H\underline{C}H_3$), 3.77, 3.78, 3.87 (each s, 3-$OC\underline{H}_3$), 6.44 (s, aromatic proton). Found: C, 67.31; H, 7.36%. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

(±)-2,3,4,9,10,12-Hexahydro-5,6,8-trimethoxy-12-methyl-2-oxophenanthrene (VIII). Under a stream of nitrogen, a solution of VII (6.9 g) in ethanol (150 ml) was added, by drop, to a solution of sodium ethoxide (prepared from sodium (1.32 g) and absolute ethanol (70 ml)) at room temperature. After stirring for 1 hr at room temperature, the mixture was cooled to −20—−30 °C, and then freshly-distilled methyl vinyl ketone (2.95 g) in absolute ethanol (5 ml) was added. Stirring was continued for 7 hr at this temperature, for 1.5 hr at room temperature and at reflux for 30 min. After cooling, the mixture was poured into dilute hydrochloric acid (10%: 200 ml) and extracted with ether. The extract was washed with saturated brine, dried, and evaporated. The residue was purified by column chromatography on silica gel (350 g), using benzene–ether (97: 3) as the eluent, to give VIII (5.34 g), which was then recrystallized from petroleum benzin–methylene chloride; mp 134.5—135.5 °C; IR 1660 cm^{-1} (C=O); NMR ($CDCl_3$) 1.69 (s, $-\dot{C}\underline{C}H_3$), 3.80, 3.85, 3.87 (each s, 3-$OC\underline{H}_3$), 5.84 (s, $=C\underline{H}-$), 6.46 (s, aromatic proton). UV nm (ε): 236 (24200), 290.5 (4500). Found: C, 71.75; H, 7.34%. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33%.

(±)-11,12,14-Trimethoxy-3-oxopodocarpa-5,8,11,13-tetraene (IX). Under a stream of nitrogen, a solution of VIII (4.15 g) in *t*-butanol (50 ml) was added, by drop, to a solution of potassium *t*-butoxide (5.6 g) in *t*-butanol (60 ml) at 10—15 °C. After stirring for 1.5 hr at this temperature, freshly-distilled methyl iodide (8.5 g) was added in one portion. The mixture was further stirred for 3.5 hr at room temperature and refluxed for 30 min. After cooling, the mixture was poured into dilute hydrochloric acid (10%: 160 ml) and extracted with ether. After a usual work-up, the crude product was purified by column chromatography on silica gel, using benzene–ether (97 :3) as the eluent; on recrystallization from petroleum ether–methylene chloride it gave IX (3.51 g: 77%) as colorless needles; mp 153—154 °C; IR 1700 cm^{-1} (C=O); NMR ($CDCl_3$) 1.32 (6H, s, 2-$\dot{C}\underline{C}H_3$), 1.35 (s, $-\dot{C}\underline{C}H_3$), 3.27 (m, $-C\underline{H}_2-$), 3.81, 3.83, 3.87 (each s, 3-$OC\underline{H}_3$), 5.83 (t, J=4 Hz, $=C\underline{H}-$), 6.47 (s, aromatic proton). Found: C, 72.90; H, 7.97%. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93%.

Hydrogenation of IX over Platinum Oxide. A solution of IX (3.3 g) in acetic acid (180 ml) was hydrogenated in the presence of platinum oxide (490 mg) at room temperature. After the absorption of hydrogen had ceased (after *ca.* 480 ml), the mixture was filtered, the filtrate was then evaporated under reduced pressure. The crude solid was separated (2.4 g) and chromatographed on silica gel (170 g), using benzene–ether (98: 2) as the eluent. The remaining oil was also chromatographed on silica gel (70 g) with the same eluent. X (0.225 g) (recrystallized from petroleum benzin–acetone; mp 156—158 °C; IR 1700 cm^{-1} (C=O); NMR 1.08 (9H, s, 3-$\dot{C}\underline{C}H_3$), 3.74 (6H, s, 2-$OC\underline{H}_3$), 3.78 (s, $-OC\underline{H}_3$), 6.28 (s, aromatic proton); Found: C, 72.50; H, 8.97%. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49%) and XI (1.64 g) (recrystallized from petroleum benzin–acetone; mp 141.5—142.5 °C; IR 1700 cm^{-1} (C=O); NMR 0.95, 1.08, 1.31 (each s, 3-$\dot{C}\underline{C}H_3$), 3.74 (6H, s, 2-$OC\underline{H}_3$), 3.79 (s, $-OC\underline{H}_3$), 6.28 (s, aromatic proton); Found: C, 72.27; H, 8.53%. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49%) were thus obtained.

(±)-11,12,14-Trimethoxypodocarpa-8,11,13-triene (XII) and Its cis *Isomer (XIII).* A mixture of X (100 mg), ethanedithiol (0.3 ml), freshly-distilled boron trifluoride etherate (1.0 ml), and benzene (5 ml) was allowed to stand 1 day at room temperature. The mixture was washed with a sodium hydroxide solution and water and then dried over sodium sulfate. After the removal of the solvent, the crude product was refluxed for 3 hr with Raney nickel (W-7, prepared from Raney alloy (5 g) in ethanol (50 ml)) and allowed to stand overnight at room temperature. The subsequent filtration and evaporation of the solvent gave an oil, which was chromatographed on silica gel (10 g), using benzene–petroleum ether (70: 30) as the eluent, to give XII (62 mg: 65%) as an oil. NMR 0.89, 0.93, 1.23 (each s, 3-$\dot{C}\underline{C}H_3$), 3.67 (6H, s, 2-$OC\underline{H}_3$), 3.73 (s, $-OC\underline{H}_3$), 6.31 (s, aromatic proton). Found: C, 75.59; H, 9.50%. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50%.

A similar treatment of XI (1.5 g) with ethanedithiol (1 ml), freshly-distilled boron trifluoride etherate (5 ml), and dry benzene (150 ml), followed by desulfurization with Raney nickel (W-7, prepared from Raney alloy (50 g)), gave XIII (1.09 g: 76%) after chromatographic purification on silica gel (150 g), using benzene–petroleum ether as the eluent. This was subsequently crystallized from petroleum ether; mp 69—72 °C; NMR 0.51, 0.92, 1.24 (each s, 3-$\dot{C}\underline{C}H_3$), 3.65, 3.68, 3.75 (each s, 3-$OC\underline{H}_3$), 6.24 (s, aromatic proton). Found: C, 75.22; H, 9.48%. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50%.

(±)-11,12,14-Trimethoxypodocarpa-5,8,11,13-tetraene (XV). A solution of IX (3.9 g), ethanedithiol (1.9 ml), freshly-distilled boron trifluoride etherate (11 ml), and dry benzene (60 ml) was allowed to stand 2 days at room temperature. After a usual work-up, the crude product was recrystallized from acetone to give a thioketal (XIV: 3.3 g 70%) as cubic crystals (mp 143—144 °C), which showed no carbonyl band in its IR spectrum. NMR ($CDCl_3$) 1.45, 1.46, 1.48 (each s, $-\dot{C}\underline{C}H_3$), 3.0—3.3 (6H, m, $-C\underline{H}_2-$), 3.75, 3.78, 3.83 (each s, 3-$OC\underline{H}_3$), 5.92 (m, $=C\underline{H}-$), 6.40 (s, aromatic proton). Found: C, 64.90; H, 7.54%. Calcd for $C_{22}H_{30}O_3S_2$: C, 65.01; H, 7.44%.

The above thioketal (3.2 g) was desulfurized with Raney nickel (W-7, prepared from Raney alloy (50 g)) in refluxing ethanol for 3 hr. After a usual work-up, the crude oil was purified by column chromatography on silica gel (150 g), using benzene–hexane (80: 20) as the eluent, to give XV (1.9 g: 76% from XIV) as an oil; NMR 1.17, 1.25, 1.45 (each s, 3-$\dot{C}\underline{C}H_3$), 3.72, 3.73, 3.78 (each s, 3-$OC\underline{H}_3$) 5.76 (m, $=C\underline{H}-$), 6.30 (s, aromatic proton). Found: C, 76.20; H, 8.76%. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%.

Hydrogenation of XV. A solution of XV (2.1 g) in acetic acid (50 ml) was hydrogenated in the presence of 10% palladium on carbon (550 mg) at room temperature, and then the mixture was filtered and evaporated. The crude oil was purified by means of column chromatography on silica gel (100 g), using benzene–petroleum ether (70: 30) as the eluent, to give XII (1.7 g: 81%). The NMR spectrum

of XII showed a small peak at 0.51 ppm, corresponding to the inseparable *cis* isomer (XIII). Its integration areas indicated the amount of XIII to be, at most, less than 15%.

Bromination of XII and XIII. A solution of bromine (290 mg) in carbon tetrachloride (5.8 ml) was stirred, drop by drop into a solution of XII (508 mg) in carbon tetrachloride (10 ml) over a period of 2.5 hr at 15—20 °C. After a usual work-up, the crude oil was chromatographed on silica gel, using benzene–petroleum ether as the eluent, to give XVI (533 mg: 84% as an oil; NMR 0.92, 0.95, 1.25 (each s, 3-$\overset{|}{\underset{|}{C}}CH_3$), 3.70, 3.73, 3.81 (each s, 3-OCH_3). Found: C, 60.75; H, 7.24%. Calcd for $C_{20}H_{29}O_3Br$: C, 60.45; H, 7.63%.

A similar treatment of XIII (420 mg) with bromine (230 mg) afforded XVII (293 mg: 53%) as an oil (NMR 0.56, 0.98, 1.25 (each s, 3-$\overset{|}{\underset{|}{C}}CH_3$), 3.70, 3.76, 3.80 (each s, 3-OCH_3); Found: C, 60.32; H, 7.48%. Calcd for $C_{20}H_{29}O_3Br$: C, 60.45; H, 7.36%) and XVIII (117 mg: 22%) as a solid, which was then recrystallized from petroleum benzin–methylene chloride (mp 142—143 °C; NMR 0.42, 1.06, 1.21 (each s, 3-$\overset{|}{\underset{|}{C}}CH_3$), 1.89 (s, -$\overset{|}{\underset{|}{C}}H$), 3.64, 3.73, 3.79 (each s, 3-OCH_3), 6.22 (s, aromatic proton), 7.06 (s, =CH–). Found: C, 60.77; H, 6.76%. Calcd for $C_{20}H_{27}O_3Br$: C, 60.76; H, 6.88%).

After a suspension of XVI (186 mg) and sodium (50 mg) in dry toluene (3.5 ml) had been stirred at room temperature for 4.5 hr, acetone (5 ml) was added. Stirring was continued for an additional hr; the mixture was then poured into dilute hydrochloric acid (10%: 5 ml) and extracted with ether. The chromatography of the crude product on silica gel gave an oil whose IR and NMR spectra were identical with those of XII. A similar treatment of XVII gave XIII. Such debromination phenomena were also observed on the treatment of XVI and XVII with either *n*-butyllithium or phenylsodium in dry toluene.

(±)-12-Hydroxy-11,14-dioxopodocarpa-8,12-diene (XIX). A solution of boron tribromide (1.6 ml) in methylene chloride (10 ml) was stirred at −60 °C into a solution of XII (279 mg) in methylene chloride (5 ml) over a period of 5 min. Stirring was continued at −30 °C for 1 hr, and then at room temperature for 30 min. After the excess reagent and the solvent had been removed under reduced pressure, ice was added and the mixture was extracted with ethyl acetate. The extract was washed with a sodium thiosulfate solution and saturated brine, and then dried over sodium sulfate. After the removal of the solvent, the crude solid was chromatographed on silica gel (20 g), using benzene–ethyl acetate (50: 50) as the eluent, to give a trihydroxy derivative. Without further purification, a part of this colorless solid (142 mg) was oxidized in refluxing benzene (10 ml) with bubbling oxygen gas for 4 hr. On recrystallization from acetone–benzene, XIX (60 mg: 31%) was obtained as yellow crystals; mp 195.5—197 °C decomp.; IR (KBr) 3235, 1655, 1625, 1595 cm^{-1}; NMR ($CDCl_3$) 0.89, 0.92, 1.24 (each s, 3-$\overset{|}{\underset{|}{C}}CH_3$), 5.95 (s, =CH–), 7.19 (s, OH); UV nm (ε): 276.5 (15400), 418 (600). Found: C, 74.53; H, 8.33%. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08%.

(±)-Royleanone (I). A solution of isobutyryl peroxide[13] (196 mg) in ether (2 ml) was added to a vigrously stirred solution of XIX (180 mg) in acetic acid (10 ml) at 110 °C, after which the mixture was stirred at 105 °C for 1 hr. After cooling, the mixture was diluted with water and extracted with ether. The ether was washed with a sodium hydrogen carbonate solution and saturated brine, and then dried over sodium sulfate. After the removal of the solvent, the crude solid (recovered starting material, XIX: 58 mg) was removed and the residual oil was chromatographed on silica gel (10 g), using benzene–chloroform (60: 40) as the eluent, to give (±)-I (107 mg: 76% based on the sample consumed) as yellow crystals, which were subsequently recrystallized from hexane; mp 153—154 °C; IR 3355, 1672, 1632, 1600 cm^{-1}, UV $\lambda_{max}^{CCl_4}$ nm(ε): 277(13800), 283(13400), 403(430); NMR ($CDCl_3$) 0.91, 0.94, 1.27 (each s, 3-$\overset{|}{\underset{|}{C}}CH_3$), 1.16, 1.27 (each s, -$CH(CH_3)_2$), 7.28 (s, OH); Mass *m/e* 316 (M^+). Found: C, 76.09; H, 8.97%. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%.

The identity of the synthetic I with natural royleanone was confirmed by direct comparisons of their IR and NMR spectra. The following spectral data have been reported for natural royleanone;[3] IR ($CHCl_3$) 3350, 1672, 1632, 1602 cm^{-1}; UV $\lambda_{max}^{CCl_4}$ nm(ε): 277(15900), 283(15200), 403 (510).

Thanks are due to Professor O. E. Edwards, National Research Council, Ottawa, and to Professor S. Morris Kupchan, University of Virginia, for their kind supply of the spectral copies of natural royleanone. The author also wishes to express his warm thanks to Professor Kenji Fukui and Dr. Takashi Matsumoto, Hiroshima University, for their useful suggestions and con tinual encouragement.

References

1) Most of these works have been reported in preliminary form; T. Matsumoto, Y. Tachibana, and K. Fukui, *Chem. Lett.*, **1972**, 321.

2) Although the formulas depicted represent only one enantiomer, they are taken to indicate a racemate.

3) a) O. E. Edwards, G. Feniak, and M. Los, *Can. J. Chem.*, **40**, 1540 (1962); b) J. H. Gough and M. D. Sutherland, *Aust. J. Chem.*, **19**, 329 (1966).

4) S. M. Kupchan, A. Karim, and C. Marcks, *J. Amer. Chem. Soc.*, **90**, 5923 (1968); *J. Org. Chem.*, **34**, 3912 (1969).

5) C. Brandt and L. G. Neubauer, *J. Chem. Soc.*, **1939**, 1031.

6) a) L. F. Fieser and A. E. Oxford, *J. Amer. Chem. Soc.*, **64**, 2060 (1942); L. F. Fieser and Coworkers, *ibid.*, **70**, 3174 (1948); b) A. C. Baillie and R. H. Thomson, *J. Chem. Soc., C*, **1968**, 48.

7) H. Kakisawa, M. Tateishi, and T. Kusumi, *Tetrahedron Lett.*, **1968**, 3787; *Tetrahedron*, **27**, 237 (1971).

8) a) V. Arkley, J. Attenburrow, G. I. Gregory, and T. Walker, *J. Chem. Soc.*, **1962**, 1260; b) Grignard, *C. R. Acad. Sci. Paris*, **151**, 322 (1910). c) A. Schönberg and R. Moubasher, *J. Chem. Soc.*, **1944**, 462.

9) M. Ribi, A. Chang Sin-Ren, H. P. Kung, C. H. Eugster, *Helv. Chim. Acta*, **52**, 1685 (1969); They reported that dihydroroyleanone trimethyl ether showed three methyl signals at 0.92, 0.95, and 1.26 ppm in its NMR spectrum (CCl_4).

10) a) M. Fetizon and G. Moreau, *Bull. Soc. Chim. Fr.*, **1965**, 3479; b) Y. Kondo and T. Ikenoue, *Chem. Pharm. Bull.* (Tokyo), **11**, 678 (1963).

11) Some of these results will be reported elsewhere.

12) M. S. Khrash, S. S. Kane, and H. C. Brown, *J. Amer. Chem. Soc.*, **63**, 526 (1941).

13) Isobutyryl peroxide was titrated before use according to the method cited in; V. R. Kokatanur and M. Jelling, *ibid.*, **63**, 1432 (1941).