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Diterpenoids. XXXVII.[*,1)] Rearrangement of Methyl 13-Isopropyl-7-oxo-podocarpa-5,8,11,13-tetraen-15-oate by Means of Aluminum Chloride[2)]

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The phenacylidene ester 2, methyl 13-isopropyl-7-oxo-podocarpa-5,8,11,13-tetraen-15-oate, underwent novel rearrangements on refluxing with an excess of aluminum chloride to afford 13-isopropyl-1α-methyl-1β-methoxycarbonyl-7-oxo-15,16-bisnor-10α-podocarpa-5,8,11,13-tetraene (7) and 10α-hydroxy-13-isopropyl-7-oxo-1,10-seco-spiro(1.5)-podocarpa-8,11,13-trien-15-oic acid 15→10 lactone (8) in 57 and 5% yields, respectively. Their structures were unequivocally established by chemical conversions and spectral examinations. The reaction courses (a) and (b) through 6 were proposed for the mechanisms of these rearrangements which somewhat differ from the rearrangement of 2 by means of protonic acid. It was further found that boron trifluoride etherate promoted also these rearrangement, but was less effective as catalyst, and treatment of 7 with aluminum chloride under the same condition led to the formation of 2 and 8 though in respective small yields.

It has been recently found that methyl 13-isopropyl-7-oxo-podocarpa-5,8,11,13-tetraen-15-oate[4)] (phenacylidene ester,[5)] 2) derived from dehydroabietic acid (1) undergoes interesting reversible methyl migrations ($2 \rightleftharpoons 3$)[6)] under acidic conditions as illustrated in Chart 1. Further similar treatment of 2 in the presence of an additional electrophile such as acetyl[6)] or bromo cation[7)] was found to give 1-acetyl- or 1-bromo-phenacylidene derivative (4 or 5) by analogous two-step courses *via* 3.

We were interested in the behavior of 2 in the presence of Lewis acid instead of protonic acid. The present paper deals mainly with another novel rearrangement of 2 promoted by aluminum chloride.

Whereas no reaction was observed when 2 was stirred at room temperatures for 24 hours with a large excess of aluminum chloride in anhydrous benzene, the reaction under reflux and stirring for 12 hours caused novel rearrangements, and 13-isopropyl-1α-methyl-1β-methoxycarbonyl-7-oxo-15,16-bisnor-10α-podocarpa-5,8,11,13-tetraene (7), colorless prisms, mp 113—113.5°, as a main product (57%) and 10α-hydroxy-13-isopropyl-7-oxo-1.10-seco-spiro(1.5)-podocarpa-8,11,13-trien-15-oic acid 15→10 lactone (8), colorless plates, mp 225—226.5°, as a minor one (5%) were obtained accompanied by 15% recovery of 2 (Chart 2).

The structure elucidation of the main product (7) was successfully achieved by the chemical transformations as well as spectral examinations.

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[*] Dedicated to the memory of Prof. Eiji Ochiai

1) Part XXXVI: A. Tahara (the late), M. Shimagaki, S. Ohara, T. Tanaka, and T. Nakata, *Chem. Pharm. Bull.* (Tokyo), 23, 2329 (1975).

2) A part of the work has been published as a preliminary communication: A. Tahara, H. Akita, T. Takizawa, and H. Mizuno, *Tetrahedron Letters*, 1974, 2837.

3) Location: *Wako-shi, Saitama-ken, 351, Japan.*

4) E. Wenkert, R.W.J. Carney, and C. Kaneko, *J. Am. Chem. Soc.*, 83, 4440 (1961).

5) The abbreviation "benzonidene" has been formerly used for 7-oxo-podocarpa-5,8,11,13-tetraene derivatives in the series of work, however, phenacylidene is apparently more appropriate one and will be used from now.

6) A. Tahara, H. Mizuno, and T. Ohsawa, *Chemistry Letters*, 1972, 1163.

7) A. Tahara and H. Mizuno, *Tetrahedron Letters*, 1974, 523.

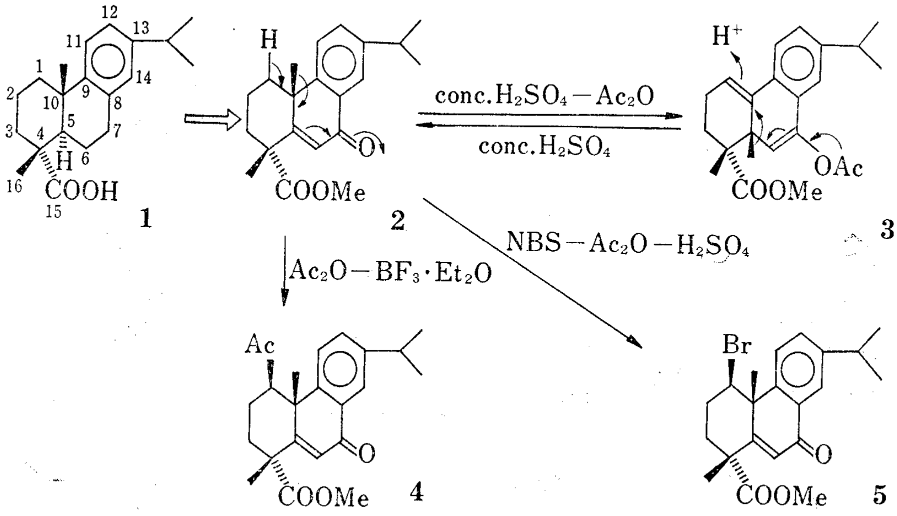

Chart 1

At first, in order to clarify the mother skeleton, the following sequence of degradative transformations of **7** were carried out (Chart 2). Catalytic hydrogenation of **7** over palladium-charcoal gave the dihydro derivative (**9**), which was converted to the free carboxylic acid (**10**) by alkaline hydrolysis and then to the de-oxo compound (**11**) by catalytic hydrogenolysis in the presence of palladium-charcoal under pressure (H_2-3 kg/cm^2); **11** was purified and characterized as the methyl ester (**12**), mp 79—79.5°. The stereochemistry of **9**, **11**, and **12** will be later discussed in detail. The acid (**11**) was then oxidatively decarboxylated with lead-tetraacetate[8] to give a mixture of exo- (**13**) and endo-olefinic compounds (**14**) in the ratio 7:3 by gas–liquid chromatography (GLC) analysis. The mixture was ozonolyzed in dichloromethane with dry ice-acetone cooling followed by treating with 30% hydrogen peroxide to afford the 1-oxo derivative (**15**) from the neutral fraction of the reaction mixture. Finally **15** was converted into the corresponding 1-de-oxo phenacylidene compound, 13-isopropyl-7-oxo-15,16-bisnor-10α-podocarpa-5,8,11,13-tetraene (**19**), through the hydrocarbon (**16**), its 7-oxo (**17**) and 6-bromo-7-oxo derivatives (**18**) successively by the Huang-Minlon reduction of **15**, chromic anhydride-oxidation of **16** in acetic anhydride, bromination of **17** and dehydrobromination of **18** with 1,5-diazabicyclo[5.4.0] undecene-5 (DBU).[9] The phenacylidene compound (**19**) thus obtained showed negative Cotton effect in the optical rotatory dispersion (ORD) spectrum, suggesting that **19** has 10α-methyl group.

For the sake of direct comparison, the corresponding phenacylidene compound having 10β-methyl group (**20**) was unambiguously synthesized from a mixture of isomeric 4-oxo derivative (**23**)[10] through **24**, **25**, and **26** by practically the same procedures as those used in the conversion of **15** to **19**. The requisite (**23**) was prepared from 4-dimethylamino-derivative (**21**) by the route reported by Zeiss and Martin[10]; however, treatment of **21** in dichloromethane with *m*-chloroperbenzoic acid was found to be more convenient for the preparation of **22** than the procedure of Zeiss and Martin[10] which involves the isolation of 4-trimethylammonium salt or the corresponding amine oxide because of the one-step formation of **22** (Chart 3).

Both **19** and **20** have completely the same physical properties (IR, NMR, Mass spectra and retention time in GLC) only with the exception of the ORD spectrum. As shown in Fig. 1, their signs of Cotten effect are opposite and the shapes of curves are completely antipodal

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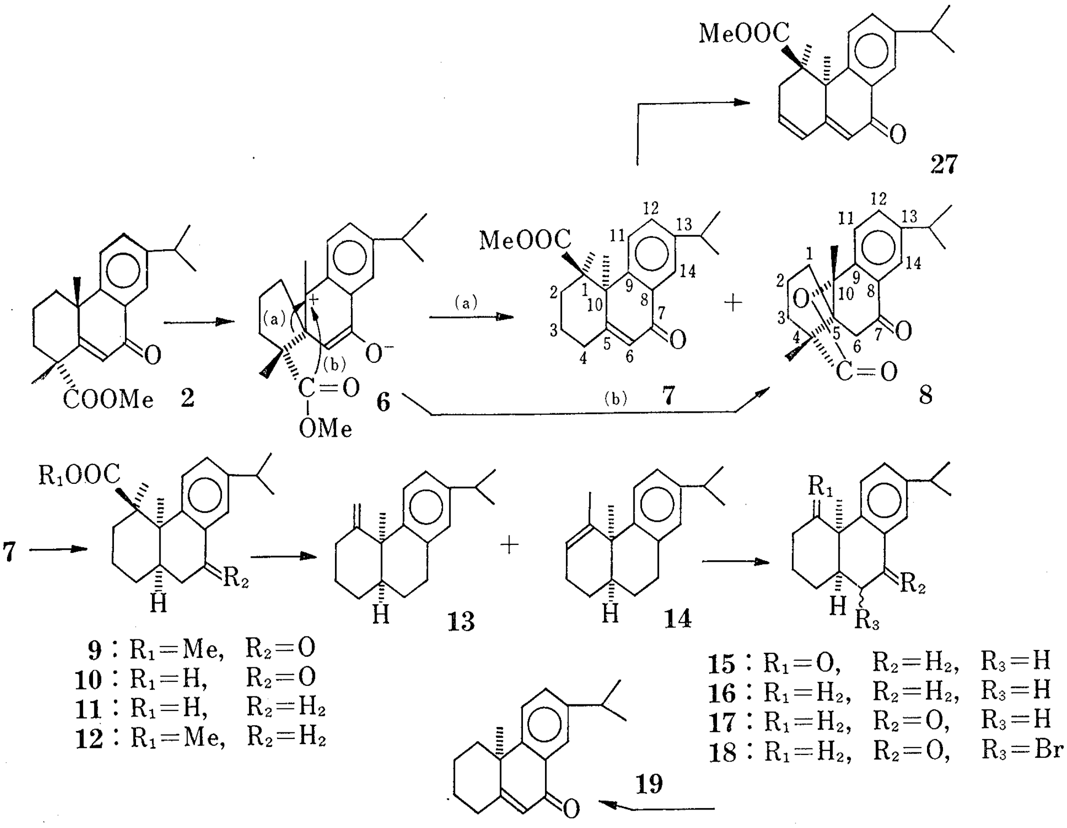
8) *a*) J.W. Huffman and P.G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965); *b*) C.R. Bennett, R.C. Cambie, R.A. Franich, and T.J. Fullerton, *Aust. J. Chem.*, **22**, 1711 (1969).

9) M. Fieser and L. Fieser, "Reagents for Organic Synthesis," Vol. 2, John Wiley and Sons, Inc., New York, 1969, p. 101.

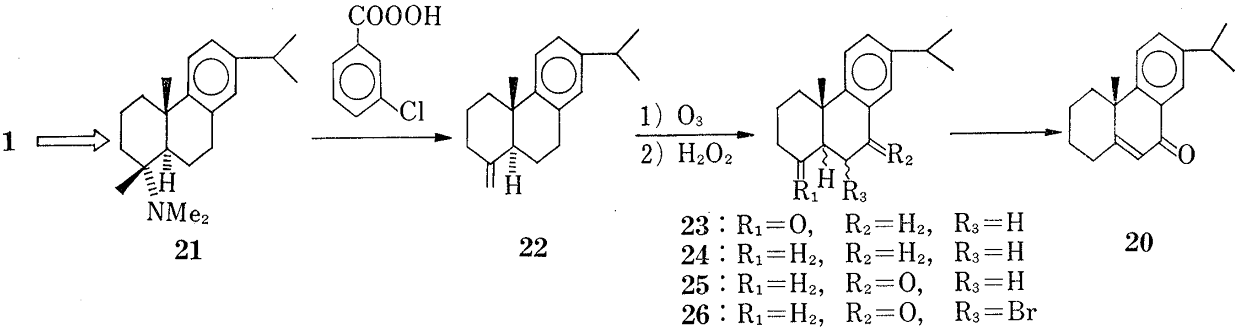
10) H.H. Zeiss and W.B. Martin, *J. Am. Chem. Soc.*, **75**, 5935 (1953).



9 : $R_1=Me$, $R_2=O$
10 : $R_1=H$, $R_2=O$
11 : $R_1=H$, $R_2=H_2$
12 : $R_1=Me$, $R_2=H_2$

15 : $R_1=O$, $R_2=H_2$, $R_3=H$
16 : $R_1=H_2$, $R_2=H_2$, $R_3=H$
17 : $R_1=H_2$, $R_2=O$, $R_3=H$
18 : $R_1=H_2$, $R_2=O$, $R_3=Br$

Chart 2



23 : $R_1=O$, $R_2=H_2$, $R_3=H$
24 : $R_1=H_2$, $R_2=H_2$, $R_3=H$
25 : $R_1=H_2$, $R_2=O$, $R_3=H$
26 : $R_1=H_2$, $R_2=O$, $R_3=Br$

Chart 3

in the ORD spectra. Thus it was established that **19** and **20** are mirror images of each other, and 10-methyl group of **19**, therefore that of **7**, has α-configuration.

Subsequently the proposed position and configuration of the *gem*-methyl-methoxycarbonyl group of **7** was elucidated by the nuclear magnetic resonance (NMR) spectral examination. The methyl protons of methoxycarbonyl group appeared as a singlet at higher field (δ 3.17) as compared with those of the starting material (**2**) (δ 3.71). Further, a nuclear Overhauser effect (NOE) was distinctly observed on 11-hydrogen[11] by irradiation at 1-methyl and

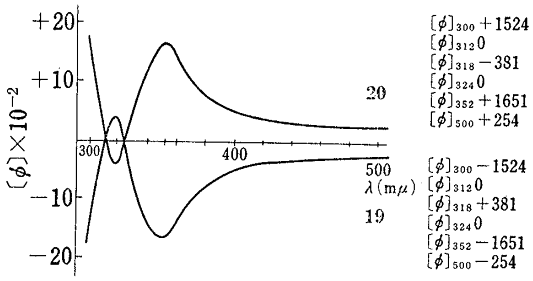


Fig. 1

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[11] The signal due to 11-hydrogen clearly appears when measured with 100 MHz NMR spectrometer.

10-methyl groups; 26.9 and 34.6% increases were noticed by irradiation at δ 1.53 and 1.62, respectively. These observation can be well explained by the fact assumption the methyl protons of 1β-methoxycarbonyl group is shifted upfield by the diamagnetic effect of the benzene ring and 1α-methyl is located near 11-hydrogen.

In order to ascertain the absence of substituent at the 4-position, **7** was treated with chloranil in the presence of *p*-toluenesulfonic acid to give a dehydrogenated compound (**27**) of the empirical formula $C_{21}H_{24}O_3$. Infrared absorption at 1605 cm^{-1} and chemical shifts at δ 5.96—6.43 in the NMR spectrum indicated that an additional olefinic bond was newly formed in **27**, and the extension of conjugated system, *e.q.*, the 3,5-diene structure of **27**, was evident from the observation that the ultra violet (UV) absorption at 253 nm (log ε=4.3027) of **7** was shifted to 294 nm (log ε=4.0774) in **27**.

Thus the structure of **7** was unequivocally established.

Further, **12** obtained in the course of conversion of **7** into **19** was reduced with lithium aluminum hydride to the corresponding alcohol (**28**), and comparison of their NMR spectra revealed that **12** had a *cis* A/B-ring junction of a nonsteroidal conformation. The resonance signals of **12** at δ 1.30 and 1.52 can be assigned to 1-methyl and 10-methyl protons respectively, since the conversion of methoxycarbonyl group to hydroxymethyl group caused a fairly upfield of the former (to δ 1.03) but only a slight one of the latter (to δ 1.45). Therefore chemical shifts due to 1- and 10-methyl groups of **9** are also assignable as shown Table I. In addition, the fact that 10-methyl signal of **12** appears at lower field as compared with the usual case is explicable by assuming that 10-methyl group is spatially held in the plane of benzene ring and deshielded by its anisotropic effect. Inspection of a molecular model indicates evidently that a *cis* A/B-junction of a nonsteroidal conformation is the correct configuration of **12** in full agreement with the above observations (Fig. 2).

Table I. Chemcial Shift due to 1- and 10-Methyl Groups of 7, 9, 12, and 28

	7	9	12	28
1-Me	1.53 (or 1.62)	1.27	1.30	1.03
10-Me	1.62 (or 1.53)	1.59	1.52	1.45

12 A/B-*cis* (nonsteroid) R=COOMe
28 A/B-*cis* (nonsteroid) R=CH_2OH

12 A/B-*cis* (steroid) R=COOMe
28 A/B-*cis* (steroid) R=CH_2OH

Fig. 2

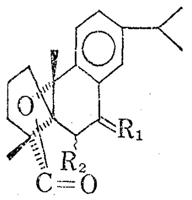
The structure of the minor product (**8**) was substantiated by its IR and NMR spectra.

Absorption in IR at 1692 and 1767 cm^{-1} shows the presence of the 7-oxo group and a 5-membered lactone, respectively.

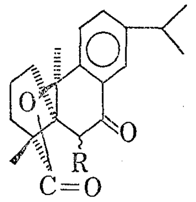
The singlet peak at δ 2.86 (A_2-pattern) due to 6-methylene group indicates that the 7-oxo function bisects the angle between 6α- and 6β-protons and no hydrogen is present at the adjacent 5-position. This was proved by the observation that a new singlet peak assignable to 6-hydrogen appeared in place of the above signal when **8** was brominated to the 6-bromo derivative (**29**). Two methyl singlets of **8** at δ 1.54 and 1.27 may be assigned to 4-methyl and

10-methyl protons, respectively, since the 4-methyl group can be considered to be spatially held in the plane of 7-oxo group and deshielded by its anisotropic effect; 10-methyl group should be equatorial in the B-ring. This assignment was supported by the fact that the signal at δ 1.54 was shifted upfield (δ 1.34) in the 7-hydroxy lactone (**30**) formed by reduction of **8** with sodium borohydride, and further NOE by 100 MHz was clearly observed on 11-hydrogen by irradiation at δ 1.27 (18.5% increase) but not observed at δ 1.54.

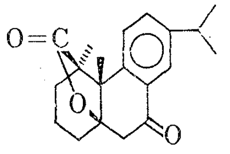
As for the structure of γ-lactone, **31**, **33**, and **34** shown below are formally conceivable in addition to **8**.



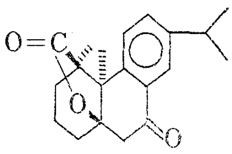
29 : R_1=O, R_2=Br
30 : $R_1={<}^{H}_{OH}$, R_2=H



31 : R=H
32 : R=Br



33



34

If the structure of the γ-lactone is either **33** or **34**, two methyl singlets at δ 1.54 and 1.27 should be assigned to 1-methyl and 10-methyl groups respectively, since 1-methyl resonance signal would be more strongly affected by the anisotropic effect of the benzene and the lactone carbonyl group. Close examination of molecular model shows that 11-hydrogen is spatially very near to 1-methyl group in these cases, so that NOE should be observed on 11-hydrogen by irradiation at 1-methyl group, but it was not noticed at all as described before. Thus the structures **33** and **34** were ruled out.

In the cases of both **8** and **31**, 4-methyl signal should appear at lower field (δ 1.54) by the anisotropic effect of the lactone carbonyl and 7-oxo groups, the signal at δ 1.27 being due to 10-methyl protons. To distinguish between **8** and **31**, the NMR spectrum of 6-bromo derivative (**29** or **32**) prepared from the lactone was examined, and the introduction of 6-bromo substituent was found to cause the down-field shift of the 4-methyl signal to δ 1.78. Inspection of molecular models demonstrated that the 4-methyl group in **29** derived from **8** might be fairly affected by 6-bromo substituent independent of the bromine's configuration, but on the contrary no magnetic interaction could be conceivable between these group in the **32** structure.

Thus, the structure of the γ-lactone (**8**) was proved beyond doubt.

For chemical proof of its structure, the following conversion of **8** was further tried (Chart 4). Reduction of **8** with lithium aluminum hydride gave the expected triol (**35**), which on treatment with acetic anhydride in pyridine afforded a diacetate (**36**) containing a free tertiary alcohol group. Hydrogenolysis of **36** over palladium-charcoal resulted in formation of a compound (**37**) having a primary acetoxy and a free tertiary alcohol functions. It is very noteworthy that the signal due to 11-hydrogen was found at δ 7.69 in fairly lowfield as compared with normal aromatic region; for example, aromatic protons of **30** appeared at δ 7.07—7.35. This observation may be accounted for in terms of van der Waals repulsion by the oxygen atom of 10-hydroxy substituent and 10-methyl group because 11-hydrogen is very close to them. These results provide further evidence for the proposed structure since skeleton coversion is not conceivable during the course from **8** to **37**.

The rearrangement of **2** to **7** and **8** is reasonably rationalized by the course (a) and (b) through **6** as illustrated in Chart 2.

As an extension of the above-mentioned study, the reaction of **2** using boron trifluoride etherate instead of aluminum chloride was carried out. Treatment of **2** with 11.5 equivalents of boron trifluoride etherate under reflux for 12 hr resulted in formation of **7** in 30% yield ac-

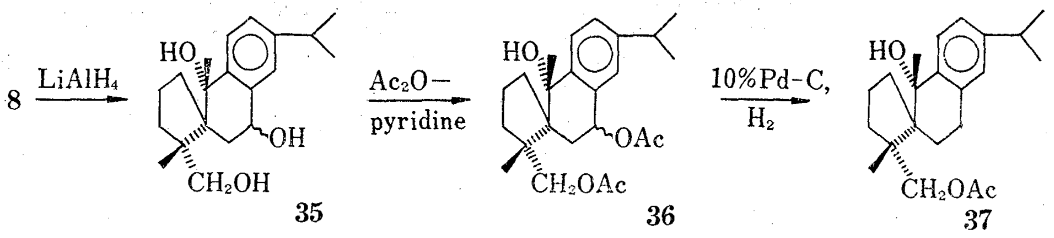


Chart 4

companied by 36% recovery of 2, the lactone (8) being not obtained. Apparently the reactivity of 2 toward Lewis acid depends upon the strength of the acid.

Finally, in order to examine the reversibility of these rearrangement the phenacylidene compound (7) was treated with aluminum chloride under the same condition as that applied to the rearrangement of 2. Although 7 was largely recovered (69%), the starting phenacylidene compound (2) and the γ-lactone (8) were isolated in respective yields of 18 and 7%.

Experimental[12]

Rearrangement of Methyl 13-Isopropyl-7-oxo-podocarpa-5,8,11,13-tetraen-15-oate (2) **to 13-Isopropyl-1α-methyl-1β-methoxycarbonyl-7-oxo-15,16-bisnor-10α-podocarpa-5,8,11,13-tetraene** (7) **and 10α-Hydroxy-13-isopropyl-7-oxo-1.10-seco-spiro (1.5)-podocarpa-8,11,13-trien-15-oic Acid 15→10 Lactone** (8)——A mixture of 2[4] (2.737 g) and $AlCl_3$ (27.37 g) in dry benzene (40 ml) was refluxed for 12 hr with stirring, poured into ice-water and extracted with ether. The extract was washed with 5% Na_2CO_3 aq., sat. NaCl aq., and dried over Na_2SO_4. Removal of the solvent gave a brown oil (3.312 g), which was chromatographed on silica gel (100 g) to be separated into three fractions. The first fraction (424 mg; 15% yield) eluted with petr. ether–ether (4: 1) was identified as the starting material (2) by GLC. The second one (1.576 g; 57% yield) subsequently obtained was recrystallized from MeOH–H_2O to give 7 (1.018 g), colorless prisms, mp 113—113.5°. *Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.30; H, 7.88. IR ν_{max}^{KBr} cm^{-1}: 1728, 1658. NMR δ: 1.27 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 1.53, 1.63 (each 3H, s; 1-, 10-Me), 3.17 (3H, s; COOMe), 6.39 (1H, s; 6-H), 7.30—7.65 (2H, m; 11-, 12-H), 8.08 (1H, d, $J=2$ Hz; 14-H). NOE (100 MHz). Irradiation at δ 1.53 and 1.62 increased the area peak due to 11-H by 26.9 and 34.6%, respectively. The third fraction (127 mg; 5% yield) eluted with petr. ether–ether (1: 1) was recrystallized from MeOH to give **8** (50 mg), colorless plates, mp 225—226.5°. *Anal.* Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.03; H, 7.73. IR ν_{max}^{KBr} cm^{-1}: 1767, 1692. NMR δ: 1.24 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 1.27 (3H, s; 10-Me), 1.54 (3H, s; 4-Me), 2.86 (2H, s; 6-H_2), 7.31—7.53 (2H, m; 11-, 12-H), 7.91 (1H, d, $J=2$ Hz; 14-H). NOE (100 MHz): Irradiation at δ 1.27 increased the area of peak due to 11-H by 18.5%.

Hydrogenation of 7 to 13-Isopropyl-1α-methyl-1β-methoxycarbonyl-7-oxo-15,16-bisnor-10α-podocarpa-8,11,13-triene (9)——A solution of 7 (500 mg) in MeOH (50 ml) was hydrogenated at ordinary temperature and pressure over 10% Pd-C (200 mg). After hydrogen absorption had ceased, the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The resulting residue was chromatographed on silica-gel (25 g) with petr. ether–ether (4: 1) to give 9 (387 mg), colorless oil, bp 150° (bath temp.)/10^{-2} mmHg. *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.69; H, 8.59. Found: C, 76.81; H, 8.56. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720, 1680. NMR δ: 1.25 (6H, d, $J=7.2$ Hz, iso-C_3H_7), 1.27 (3H, s; 1-Me), 1.59 (3H, s; 10-Me), 3.25 (3H, s; COOMe), 7.32 (2H, d; 11-, 12-H), 7.91 (1H, br. s, 14-H).

Hydrogenolysis of 9 to 13-Isopropyl-1α-methyl-1β-methoxycarbonyl-15,16-bisnor-10α-podocarpa-8,11,13-triene (12)——A solution of 9 (1.284 g) in AcOH (10 ml) -conc. H_2SO_4 (3 drops) was hydrogenated at room temperature over 10% Pd-C (400 mg) under hydrogen pressure (3 kg/cm^2). After hydrogen absorption had ceased, the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The ether extract of the resulting residue was washed with sat. Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave crystals (1.172 g), which were recrystallized from MeOH to give **12** (1.026 g), colorless prisms, mp 79—79.5°. *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.31; H, 9.53. IR ν_{max}^{KBr} cm^{-1}: 1710. NMR δ: 1.24 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 1.30 (3H, s; 1-Me), 1.52 (3H, s; 10-Me), 3.31 (3H, s; COOMe), 6.94—7.40 (3H, m; 11-, 12-, 14-H).

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12) All melting points were measured on the Kofler block and were uncorrected. NMR spectra were measured (δ) at 60 MHz in $CDCl_3$ *vs.* Me_4Si as internal reference. High-resolution mass spectra were taken with JMS-01SG spectrometer. GLC was measured under the column condition (2 m×4 mm, 1.5% OV-17 on Shimalite W (80—100 mesh)).

Conversion of 9 to 1β-Carboxy-13-isopropyl-1α-methyl-15,16-bisnor-10α-podocarpa-8,11,13-triene (11)——1) A solution of **9** (1.023 g) and KOH (5 g) in MeOH (50 ml)–H_2O (5 ml) was refluxed for 12 hr with stirring, and concentrated under reduced pressure. The residue was diluted with H_2O and extracted with ether (neutral fraction). The aqueous solution was acidified with conc. HCl and extracted with ether (acidic fraction). Both ether extracts were separately washed with sat. NaCl aq., dried over Na_2SO_4 and evaporated. The former gave no definite product, but the latter gave 957 mg of 1β-carboxy-13-isopropyl-1α-methyl-7-oxo-15,16-bisnor-10α-podocarpa-8,11,13-triene (**10**) as an oil.

2) The oil (**10**) was hydrogenolized over 10% Pd-C (400 mg) in AcOH (20 ml)–conc. H_2SO_4 (3 drops) under hydrogen pressure (3 kg/cm^2). The resulting mixture was treated as in the case of hydrogenolysis of **9** to give **11** (903 mg), an oil, which was used without further purification. The corresponding methyl ester (**12**) (CH_2N_2–ether) was proved identical with **12** obtained earlier.

Preparation of 13-Isopropyl-1-oxo-15,16-bisnor-10α-podocarpa-8,11,13-triene (15) from 11——1) A mixture of crude **11** (1.288 g) and $Pb(OAc)_4$ (2.5 g) in dry benzene (50 ml)–pyridine (0.5 ml) was refluxed for 4 hr under N_2 stream. The cooled mixture was filtered and the filtrate was washed with 10% KOH aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave an oil (1.224 g) which was chromatographed on basic alumina (70 g) with petr. ether (400 ml) to give a mixture (516 mg), gas chromatography of which indicated the presence of 13-isopropyl-1-methylene-15,16-bisnor-10α-podocarpa-8,11,13-triene (**13**) and 13-isopropyl-1-methyl-15,16-bisnor-10α-podocarpa-1,8,11,13-tetraene (**14**) in the ratio 7 : 3.

2) Ozone was passed through a solution of the oily mixture of **13** and **14** (916 mg) in CH_2Cl_2 (20 ml) with dry ice-acetone cooling for 10 min and then 30% H_2O_2 aq. (5 ml) was added at room temperature. The mixture was stirred for 30 min, and washed with 10% KOH aq., sat. NaCl aq., and then dried over Na_2SO_4. The CH_2Cl_2 solution was evaporated to give **15** (712 mg), an oil. *Anal.* High-resolution mass spectrum. Calcd. for $C_{18}H_{24}O$ (M^+; *m/e*): 256.1827. Found: 256.1836. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1703. The above alkaline washings were acidified with 10% HCl aq., and extracted with ether. The extract was washed with sat. NaCl aq., and then dried over Na_2SO_4. Removal of ether gave 199 mg of an acidic oil.

Preparation of 13-Isopropyl-7-oxo-15,16-bisnor-10α-podocarpa-5,8,11,13-tetraene (19) from 15——1) A solution of the crude **15** (712 mg), $NH_2NH_2 \cdot H_2O$ (1.6 ml) and KOH (1.6 g) in diethylene glycol (12 ml) was stirred and heated at 160—170° for 1 hr, and then excess hydrazine was distilled off. Another KOH (1.6 g) was added to the reactants which were heated at 220° for 2 hr, cooled, diluted with H_2O and extracted with ether. The ether extract was washed with sat. NaCl aq. and then dried over Na_2SO_4. Removal of the solvent gave an oil (578 mg), which was chromatographed on basic alumina (50 g) with petr. ether (500 ml) to give 215 mg of 13-isopropyl-15,16-bisnor-10α-podocarpa-8,11,13-triene (**16**).

2) The crude **16** was treated with CrO_3 (133 mg)–Ac_2O (4 ml) at room temperature for 3 hr, the whole was heated at 90° for 4 hr with stirring. After MeOH (2 ml) was added, the reaction mixture was evaporated under reduced pressure. The residue was diluted with H_2O and extracted with ether. The ether extract was washed with 5% Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave 13-isopropyl-7-oxo-15,16-bisnor-10α-podocarpa-8,11,13-triene (**17**), an oil (208 mg). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1682.

3) A mixture of the crude **17** in AcOH (1 ml), 13% (w/v) Br_2–AcOH (1.5 ml) and 13% (v/v) HBr–AcOH (2 drops) was stirred at room temperature for 2 hr. After red color disappeared, the reaction mixture was diluted with H_2O and extracted with ether. The ether extract was washed with 5% Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave 6ξ-bromo-13-isopropyl-7-oxo-15,16-bisnor-10α-podocarpa-8,11,13-triene (**18**), brown oil (270 mg).

4) The crude **18** was heated at 100° with DBU (10 ml) for 3 hr. After $CHCl_3$ was added to the cooled reaction mixture, $CHCl_3$ layer was separated, washed with 10% HCl aq., 5% Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave brown oil, which was chromatographed on silica-gel (40 g) in petr. ether–ether (9 : 1) to give **19** (80 mg), a homogeneous oil. *Anal.* High-resolution mass spectrum. Calcd. for $C_{18}H_{22}O$ (M^+; *m/e*): 254.1671. Found: 254.1682. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1660, 1610. NMR δ: 1.26 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 1.46 (3H, s; 10-Me), 6.28 (1H, s; 6-H), 7.41 (2H, d; 11-, 12-H), 8.06 (1H, br. s; 14-H). ORD ($c=0.1$, EtOH) $[\Phi]^{25}$ (mμ): -1524 (300), 0 (312), $+381$ (318), 0 (324), -1651 (352), -1016 (370), -508 (400), -254 (500).

Degradation of 4-Dimethylamino-13-isopropyl-15-nor-podocarpa-8,11,13-triene (21) to 13-Isopropyl-4-methylene-15,16-bisnor-podocarpa-8,11,13-triene (22)——To a solution of **21**[10] (2.533 g) in CH_2Cl_2 (15 ml) was added *m*-chloroperbenzoic acid (1.461 g) with ice-water cooling. After the solution was kept for 12 hr in a refrigerator, it was washed with 10% HCl aq., 10%, KOH aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave an oil (2.215 g), which was chromatographed on basic alumina (50 g) in petr. ether (500 ml) to give **22** (1.19 g), a colorless oil. NMR δ: 1.00 (3H, s; 10-Me), 1.22 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 4.62, 4.84 (each 1H br. s; $>C=CH_2$), 6.92—7.32 (3H, m; 11-, 12-, 14-H). Compound (22) was identified by IR and NMR spectral examination.

Preparation of 13-Isopropyl-7-oxo-15,16-bisnor-podocarpa-5,8,11,13-tetraene (20) from 22——1) Ozone was passed through a solution of 22 (564 mg) in CH_2Cl_2 (20 ml) under dry ice-acetone cooling for 10 min and then 30% H_2O_2 aq. (5 ml) was added at room temperature. After the reaction mixture was stirred for 30 min, it was treated as described above to give 13-isopropyl-4-oxo-15,16-bisnor-5ξ-podocarpa-8,11,13-triene (**23**), an oil (657 mg).

2) A solution of crude **23**, $NH_2NH_2 \cdot H_2O$ (1.6 ml) and KOH (1.6 g) in diethylene glycol (12 ml) was stirred and heated at 160—170° for 1 hr, and then excess hydrazine was distilled off. Another KOH (1.6 g) was added to the reactants which were heated at 220° for 2 hr. The cooled mixture was treated as described above to give an oil (510 mg), which was chromatographed on basic alumina (50 g) in petr. ether (500 ml) to give 13-isopropyl-15,16-bisnor-5ξ-podocarpa-8,11,13-triene (**24**) (218 mg) as an oil.

3) The crude **24** (398 mg) was treated with CrO_3 (247 mg) $-Ac_2O$ (8 ml) at room temperature for 3 hr and then heated at 90° for 4 hr with stirring. After MeOH (4 ml) was added, the reaction mixture was treated as described above to give 13-isopropyl-7-oxo-15,16-bisnor-5ξ-podocarpa-8,11,13-triene (**25**) (375 mg) as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1682.

4) A mixture of **25** in AcOH (2 ml), 13% (w/v) Br_2–AcOH (1.5 ml) and 13% (v/v) HBr–AcOH (2 drops) was stirred at room temperature. After red color disappeared, the reaction mixture was treated as described above to give 6ξ-bromo-13-isopropyl-7-oxo-15,16-bisnor-5ξ-podocarpa-8,11,13-triene (**26**) (567 mg) as a brown oil.

5) The crude **26** was heated at 100° with DBU (20 ml) for 3 hr. After $CHCl_3$ was added to the cooled reaction mixture, $CHCl_3$ layer was treated as described to give a brown oil (279 mg), which was chromatographed on silica-gel (40 g) in petr. ether–ether (9: 1) to give **20** (136 mg) as a homogeneous oil. A part of **20** was treated with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone, red needles, mp 185—187° (AcOEt–EtOH). *Anal.* Calcd. for $C_{24}H_{26}O_4N_4 \cdot H_2O$: C, 63.70; H, 6.24; N, 12.38. Found: C, 63.92; H, 5.76; N, 12.59. *Anal.* High-resolution mass spectrum. Calcd. for $C_{18}H_{22}O$ (M^+,; *m/e*): 254.1671. Found: 254.1667. ORD ($c=0.1$, EtOH) $[\Phi]^{25}$ (mμ): −1524 (300), 0 (312), +381(318), 0 (324), +1651 (352), +1016 (370), +508 (400), +254 (500).

13-Isopropyl-1α-methyl-1β-methoxycarbonyl-7-oxo-15,16-bisnor-10α-podocarpa-3,5,8,11,13-pentaene (**27**) **from 7**——A solution of **7** (200 mg), chloranil (300 mg) and *p*-TsOH (10 mg) in AcOH (10 ml) was refluxed for 22 hr with stirring. The cooled mixture was diluted with H_2O and extracted with ether. The ether extract was washed with 5% Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave an oil, which was chromatographed on basic alumina (30 g) in petr. ether–ether (1: 1) to give **27** (47 mg), a colorless oil, bp 150° (bath temp.)/10^{-2} mmHg. *Anal.* Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.27; H, 7.35. *Anal.* High-resolution mass spectrum. Calcd. for $C_{21}H_{24}O_3$ (M^+; *m/e*): 324.1725. Found: 324.1739. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1728, 1648, 1605. NMR δ: 1.29 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 1.55, 1.58 (each 3H, s; 1-, 10-Me), 3.23 (3H, s; COOMe), 5.96—6.43 (3H, m; 3-, 4-, 6-H) (6.28 (1H, s; 6-H)), 7.41—7.63 (2H, m; 11-, 12-H), 8.10 (1H, d, $J=2$ Hz; 14-H). UV λ_{max}^{EtOH} mμ (log ε): 294 (4.0774). *cf.* **7**: UV λ_{max}^{EtOH} mμ (log ε): 253 (4.3027).

Reduction of 12 to 1β-Hydroxymethyl-13-isopropyl-1α-methyl-15,16-bisnor-10α-podocarpa-8,11,13-triene (**28**)——A mixture of **12** (100 mg) and $LiAlH_4$ (200 mg) in dry ether (15 ml) was refluxed for 1 hr with stirring. The reaction mixture was diluted with H_2O, then acidified and extracted with ether. The ether extract was washed with sat. Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave **28** (100 mg), a homogeneous oil. *Anal.* High-resolution mass spectrum. Calcd. for $C_{20}H_{30}O$ (M^+; *m/e*): 286.2296. Found: 286.2306. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3665. NMR δ: 1.03 (3H, s; 1-Me), 1.21 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 1.45 (3H, s; 10-Me), 2.93, 3.57 (each 1H, d, $J=12$ Hz; 1-$\underline{CH_2}$OH), 6.78—7.48 (3H, m; 11-, 12-, 14-H).

Bromination of 8 to 6ξ-Bromo-10α-hydroxy-13-isopropyl-7-oxo-1.10-seco-spiro (1.5)-podocarpa-8,11,13-trien-15-oic Acid 15→10 Lactone (**29**)——A solution of **8** (100 mg) in AcOH (5 ml) was stirred with 14% (w/v) Br_2–AcOH (5 ml) and 18% (v/v) HBr–AcOH (2 drops) for 2 hr at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether extract was washed with 5% Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave crystals (127 mg), which were recrystallized from MeOH to give **29** (123 mg), colorless needles, mp 210—210.5°. *Anal.* Calcd. for $C_{20}H_{23}O_3Br$: C, 61.38; H, 5.88; Br, 20.46. Found: C, 61.13; H, 5.58; Br, 21.08. IR ν_{max}^{KBr} cm^{-1}: 1772, 1687. NMR δ: 1.20 (3H, s; 10-Me), 1.26 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 1.78 (3H, s; 4-Me), 4.44 (1H, s; 6-H), 7.24 (1H, d, $J=8$ Hz; 11-H), 7.48 (1H, dd, $J=8$, 2 Hz; 12-H), 7.96 (1H, d, $J=2$ Hz; 14-H).

Reduction of 8 to 7α, 10α-Dihydroxy-13-isopropyl-1.10-seco-spiro (1.5)-podocarpa-8,11,13-trien-15-oic Acid 15→10 Lactone (**30**)——An ice-cooled solution of **8** (200 mg) and $NaBH_4$ (220 mg) in MeOH (10 ml) was stirred for 3 hr. The reaction mixture was diluted with H_2O and extracted with ether. The ether extract was washed with sat. NaCl aq. and then dried over Na_2SO_4. Removal of the solvent gave crystals (198 mg), which were recrystallized from MeOH–H_2O to give **30** (185 mg), colorless prisms, mp 180.5—182°. *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.55; H, 8.12. IR ν_{max}^{KBr} cm^{-1}: 3580, 1777. NMR δ: 1.22 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 1.28 (3H, s; 10-Me), 1.34 (3H, s; 4-Me), 4.60 (1H, m, $W_{1/2}=12$ Hz; 7-H), 7.07—7.35 (3H, m; 11-, 12-, 14-H).

Preparation of 15-Acetoxy-10α-hydroxy-13-isopropyl-1.10-seco-spiro (1.5)-podocarpa-8,11,13-triene (**37**) **from 8**——1) A mixture of **8** (820 mg) and $LiAlH_4$ (1 g) in dry ether (60 ml) was refluxed for 6 hr with stirring. The reaction mixture was diluted with H_2O, then acidified and extracted with ether. The ether extract was washed with sat. Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave 13-isopropyl-7ξ,10α,15-trihydroxy-1.10-seco-spiro (1.5)-podocarpa-8,11,13-triene (**35**) (853 mg) as an oil.

2) A mixture of the crude **35** and pyridine (10 ml) in Ac_2O (10 ml) was allowed to stand for 12 hr in a refrigerator, diluted with H_2O and evaporated under reduced pressure. The residue was diluted with H_2O and extracted with ether. The ether extract was washed with 10% HCl aq., sat. Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave 7ξ,15-diacetoxy-10α-hydroxy-13-isopropyl-1.10-seco-spiro (1.5)-podocarpa-8,11,13-triene (**36**) (1.045 g) as an oil.

3) A solution of the crude **36** in AcOH (50 ml) was hydrogenated at ordinary temperature and pressure over 10% Pd-C (1 g). After hydrogen absorption had ceased, the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was diluted with H_2O and extracted with ether. The ether extract was washed with sat. Na_2CO_3 aq., sat. NaCl aq., and then dried over Na_2SO_4. Removal of the solvent gave an *oil* (914 mg), which was chromatographed on silica-gel (70 g) in petr. ether–ether (4: 1) to give **37** (160 mg), a homogeneous oil. *Anal.* High-resolution mass spectrum. Calcd. for $C_{22}H_{32}O_3$ (M^+; *m/e*): 344.2351. Found: 344.2378. Calcd. for $C_{22}H_{30}O_2$ (M^+-H_2O; *m/e*): 326.2245. Found: 326.2239. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 1735, 1235. NMR δ: 1.21 (6H, d, $J=7.2$ Hz; iso-C_3H_7), 1.27 (3H, s; 4-Me), 1.41 (3H, s; 10-Me), 2.00 (3H, s; 4-$CH_2OCO\underline{CH_3}$), 4.56, 4.94 (each 1H, d, $J=12$ Hz: 4-$\underline{CH_2}$OAc), 6.80—7.08 (2H, m; 12-, 14-H), 7.69 (1H, d, $J=9.6$ Hz; 11-H).

Reaction of 2 with BF_3·Ether——A mixture of **2** (1.152 g) and $BF_3 \cdot Et_2O$ (5.75 g) in dry benzene (20 ml) was refluxed for 12 hr with stirring. The reaction mixture was treated as described at first to give a brown oil (1.131 g), which was chromatographed on silica-gel (30 g) with petr. ether–ether (4: 1) to give two fractions. The first fraction (414 mg; 36% yield) was proved the starting material (**2**) (GLC). The second one (342 mg; 30% yield) was identified with **7** (IR, NMR, and GLC).

Reaction of 7 with $AlCl_3$——A mixture of **7** (3.243 g) and $AlCl_3$ (32.43 g) in dry benzene (60 ml) was refluxed for 12 hr with stirring. The reaction mixture was treated as described earlier to give a brown oil (3.736 g), which was chromatographed on silica-gel (100 g) to give three fractions. The first fraction (576 mg; 18% yield) eluted with petr. ether–ether (4: 1) was as with **2** (IR, NMR, and GLC). The second one (2.245 g; 69% yield) subsequently obtained was recrystallized from MeOH–H_2O to give **7** (1.770 g), colorless prisms, mp 114—114.5°. The third fraction (208 mg; 7% yield) obtained from petr. ether–ether (1: 1) was recrystallized from MeOH to give **8** (156 mg), colorless plates, mp 226.5 —228°.

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