[Chem. Pharm. Bull. 20(3) 459—468 (1972)]

UDC 547.92.057 : 547.914.2.04

Study on Synthesis of Antipodal Steroid[1]

AKIRA TAHARA,[2a] YOSHIHIRO HARIGAYA and MASAYUKI ONDA[2b]

The Institute of Physical and Chemical Research[2a] and School of Pharmaceutical Sciences, Kitasato University[2b]

(Received July 1, 1971)

Conversion of *l*-abietic acid, the main component of pine rosin, to steroids was planned, and syntheses of the ketone compounds (VI and VII), important intermediates in the synthesis of the skeleton of steroid antipodes, was successfully concluded in the present series of work. Since the conversion of these VI and VII to steroidal skeleton is already known in analogous compounds, availability of these intermediates has opened a way for the synthesis of steroid antipodes from diterpenes.

Various kinds of stereoid have been discovered in plants and animals, and they have drawn the attention of many chemists from olden times because of their characteristic physiological activity. Results of their work have made valuable contributions to chemistry, and many reports have appeared recently on total synthesis of steroids.

We have been working on the chemical development of pine resin from about 10 years ago and, as a part of such studies, work has been undertaken or is under way for conversion of resin acid, the main component of pine rosin, to some natural products with physiological activity.[3,4]

In the present series of work, we attempted the synthesis of steroids from pine rosin component (*l*-abietic acid) and, as the first step, important intermediates (VI and VII) were prepared for the synthesis of steroid antipodes.

Attempted conversion of *l*-abietic acid (I) to steroidal skeleton has been reported by a few workers. Zeiss and others[5] carried out the synthesis by taking the A,B, and C rings of the diterpene skeleton as the A, B, and C rings of the steroidal skeleton, and obtained an α,β-unsturated ketone compound (IV) *via* the ketone compound (III). Huffmann and others[6] attempted the synthesis by taking the A, B, and C rings in the diterpene skeleton as the D, C, and B rings of a steroid, and obtained V from the above-mentioned ketone compound (III) by conversion of the A ring into a five-membered ring. These plans, however, do not offer any concrete evidence for the final formation of a steroid.

Now, we planned the conversion by an idea different from the hitherto attempted syntheses. Dehydroabietic acid (II) derived from *l*-abietic acid (I) can be formulated as II′ and, con-

1) This paper constitutes Part XIX of "Diterpenoids" series by A. Tahara and co-workers. Part XVIII: A. Tahara and Y. Ohtsuka, *J. Chem. Soc.*, in press. This work was partly presented at the Annual Meeting of the Pharmaceutical Society of Japan, the 89th, Nagoya, April 1969 (Meeting Abstract, p. 230) and the 91st, Fukuoka, April 1971 (Meeting Abstract, p. 674). Melting points were determined on a micro hot-stage unless otherwise specified and were uncorrected. Nuclear magnetic resonance (NMR) spectra were measured in $CDCl_3$ (5—10% solution, tetramethylsilane as internal reference) with a JEOL's C-60 (60Mc) spectrometer. The following abbreviations were used to describe the signals: s, singlet; d, doublet. Mass spectra were determined on a JEOL's JMS-01S mass spectrometer with the direct sample inlet system (ionizing potential at 75eV). Optical rotatory dispersion (ORD) curves were measured in CH_3OH with JASCO ORD/UV-5 spectropolarimeter.

2) Location: *a) Wako-shi, Saitama*; *b) Shirokane, Minato-ku, Tokyo.*

3) A. Tahara and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **15**, 1934 (1967), and references cited therein.

4) A. Tahara and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **18**, 859 (1970), and references cited therein.

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

6) J.W. Huffmann and P.G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965).

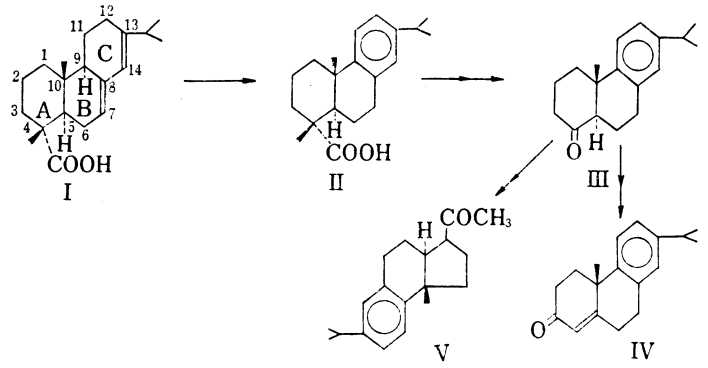


Chart 1

sequently, the C, B, and A rings in the diterpene skeleton can be considered respectively as the A, B, and C rings in steroids. According to the above idea, synthesis of the ketone compounds (VI and VII) from II′ was carried out. Further, conversion of these ketone compounds to the steroidal skeleton may follow the reported syntheses of steroids from analogous compounds.[7,8] The problems involved in the synthesis of these important intermediates (VI and VII) would be (i) the reduction of aromatic C ring in dehydroabietic acid (II′), (ii) transposition of the 10-methyl in II′ from A/B ring juncture to B/C ring juncture, and (iii) oxidation of the 4-*gem*-substituent in II′ to a ketone.

In order to examine the route of this synthesis, an intermediate (VI) still possessing an isopropyl group in 13-position of the diterpene (3-position in the steroid) was prepared, and then VII with an acetoxyl group in 13-position was synthesized.

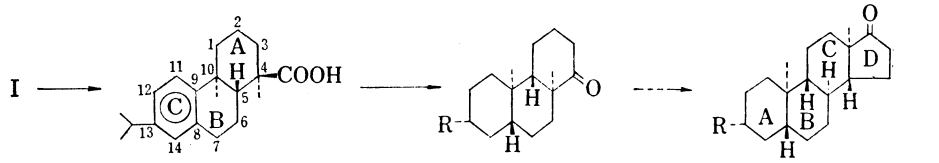
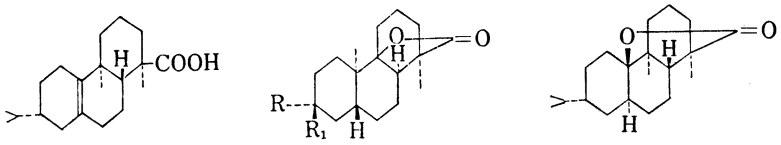


Chart 2

Reduction of dehydroabietic acid (II′) with metallic lithium-*tert*-amyl alcohol-ethylamine system and treatment of its product (X) with conc. sulfuric acid at a low temperature to obtain a lactone compound have already been reported. Fleck and Palkin[9] gave the structure of XI to this lactone and later workers[10] proved that it is a γ-lactone (XII) formed by rearrangement of the methyl group.

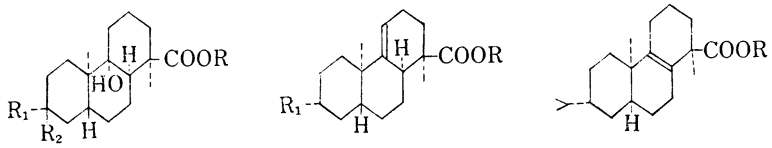
For the cleavage of the lactone ring, XII was boiled with 10% potassium hydroxide-methanol (or ethylene glycol) or with 2N hydrochloric acid-methanol, the latter being the conditions used for the cleavage of a γ-lactone in the rosanoic acid system,[11] but the reaction

7) W.E. Bachmann, S. Kushner and A.C. Stevenson, *J. Am. Chem. Soc.*, **64**, 974 (1942).
8) H.M.E. Cardwell, J.W. Cornforth, S.R. Duff, H. Holtermann and S.R. Robinson, *J. Chem. Soc.*, **1953**, 361.
9) E.E. Fleck and S. Palkin, *J. Am. Chem. Soc.*, **61**, 1230 (1939).
10) *a*) A.W. Burgstahler and L.R. Worden, *J. Am. Chem. Soc.*, **89**, 96 (1964); *b*) D.H.R. Barton, *Chem. Ind.*, **1948**, 638; *c*) L.J. Gough, T.F. Sanderson, V.I. Stenberg and E. Wenkert, *J. Org. Chem.*, **25**, 1269 (1960).
11) A. Harris, A. Robertson and W.B. Whalley, *J. Chem. Soc.*, **1958**, 1799.



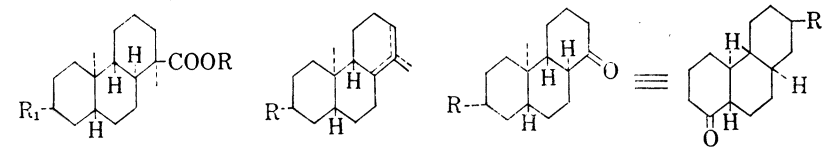
X XI

XII : $R=CH(CH_3)_2, R_1=H$
XXIV : $RR_1=O$
XXV : $R=C(CH_3)_2OH, R_1=H$
XXVI : $R=C(CH_3)_2OAc, R_1=H$
XXVII : $R=Ac, R_1=H$
XXVIII : $RR_1=$
XXXI : $R=OH, R_1=H$
XXXII : $R=OAc, R_1=H$



XIII : $RR_2=H, R_1=CH(CH_3)_2$
XIV : $R=CH_3, R_1=CH(CH_3)_2 R_2=H$
XXIX : $R=H, R_1R_2=$ 
XXX : $R=CH_3, R_1R_2=$ 

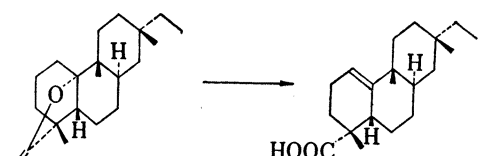
XVII : $R=H, R_1=CH(CH_3)_2$ XIX : $R=CH_3$
XVIII : $R=CH_3, R_1=CH(CH_3)_2$ XX : $R=H$
XXXIII : $R=H, R_1=OH$
XXXIV : $R=CH_3, R_1=OH$



XXI : $R=CH_3, R_1=CH(CH_3)_2$ XXIII : $R=CH(CH_3)_2$ VI : $R=CH(CH_3)_2$ VI' : $R=CH(CH_3)_2$
XXII : $R=H, R_1=CH(CH_3)_2$ XXXIX : $R=OAc$ VII : $R=OAc$ VII' : $R=OAc$
XXXV : $R=H, R_1=OH$
XXXVI : $R=CH_3, R_1=OH$
XXXVII : $R=H, R_1=OAc$
XXXVIII : $R=CH_3, R_1=OAc$

Chart 3

failed to progress. The condition was therefore changed to boiling with 10% potassium butoxide-dimethyl sulfoxide, and careful after-treatment afforded a hydroxy acid (XIII), which was found to be extremely labile and its purification was impossible to easily result in its reversion of the original γ-lactone (XII). Its corresponding ester (XIV) was in an only state and labile, and could not be purified, readily reverting to XII. Dehydration of this hydroxy ester (XIV) was tried under various conditions but did not materialize, and the best method was found to be the conditions used by Herz and Mirrington[12] for the one-step cleavage-dehydration of γ-lactone in pimaric acid system (XV—XVI). Refluxing of XIV (also of γ-lactone (XII)) in potassium hydroxide-diethylene glycol afford unstaturated



XV XVI

Chart 4

12) W. Herz and R.N. Mirrington, *J. Org. Chem.*, **30**, 3195 (1965).

acids (XVII and XX) in a good yield. This product was found to be a 10:1 mixture of XVII and XX by gas chromatographic analysis of their corresponding methyl esters. Recrystallization of the mixed product successfully afforded the main component (XVII) alone in a pure state. This compound melted at 166—168° and its structure was proved by the presence of carboxylic acid in its infrared (IR) spectrum ($\nu_{max}^{CCl_4}$ cm^{-1}: 3200—3400, 1700) and of a trisubstituted olefin in its NMR spectrum (τ=4.69 (broad, 1H)).

The minor component (XX) was not isolated in this case but it was synthesized from 1(10)-ene acid (XVII). Treatment of the corresponding oily methyl ester (XVIII) with acetic acid afforded an oily ester (XIX) whose NMR spectrum showed evidence for the absence of trisubstituted double-bond proton. Boiling of XIX with potassium hydroxide-diethylene glycol gave 5(10)-ene acid (XX) of mp 186—188°. Treatment of XVII and XX with mineral acid or *p*-toluenesulfonic acid easily reverted them to the original γ-lactone (XII).

Sanderson and others,[13] during structural studies on the γ-lactone (XII), found that XII was reacted with a Grignard reagent and gave the above 1(10)-ene acid structure, same as XVII, to its acid product of mp 147—148°. The melting points of these products are clearly different and, in order to prove their identity or difference, this Sanderson's reaction was reexamined. The obtained acid product was esterified and submitted to gas chromatography from which it was found that the product is a 1:5.3 mixture of XVII and XX. To make it certain, XX, mp 180—184°, and XVII, mp 167—169.5°, were separated by recrystallization and preparative gas chromatography, and were identified with the samples obtained in our experiments. Consequently, the product of mp 147—148° reported in Sanderson's literature is apparently a mixture of the two isomers.

Catalytic reduction of these unsaturated esters (XVIII and XIX) was then carried out. XIX failed to absorb hydrogen under any conditions but XVIII was reduced comparatively easily in acetic acid, in the presence of a platinum catalyst, and afforded an oily saturated ester (XXI) whose NMR spectrum showed evidence for the disappearance of a trisubstituted double-bond proton. Hydrolysis of XXI by boiling with potassium hydroxide–ethylene glycol gave the corresponding acid (XXII), mp 219°. In the hydrogenation of the double bond at 1-10 in XVIII, hydrogen would add to the double bond from the direction of least steric hindrance and product (XXI) was assumed to have anti-*trans* A/B ring juncture, which was confirmed from the ORD measurement of the oxidation product (VI) described later.

The next problem would be the conversion of a methyl and carboxyl group in 4-position in XXII to a ketone. Various processes have been tried in the past and, in the present work, the method adopted was the conversion of saturated acid (XXII) to an olefin with lead tetraacetate and then to a ketone by ozonolysis.[6,14] The resulted portion of the ozonolyzed product was treated with a Girard reagent and an oily ketone compound (VI), bp 96° (2.5×10^{-3} mmHg) was isolated in 32% yield. Its semicarbazone melted at 206—209°.

Thus, the synthesis of the objective compound (VI) having an isopropyl group in 13-position (3-position in the steroid) was successfully concluded. VII possessing a hydroxyl or acetoxyl in place of the isopropyl group is a more appropriate and important intermediate for obtaining the steroid antipode.

Sanderson and others[15] has already reported the oxidation of isopropyl group in 13-position of γ-lactone (XII) with chromium trioxide–acetic acid–acetic anhydride system to form XXIV with ketone group in 13-position (yield, 6.5%) (separation by Girard reagent), accompanied by XXV and XXVII. By our chromatographic separation, XXIV (increased yield, 18%) and XXVII were also obtained besides XXVI, mp 186—190.5° in palce of XXV. XXIV was chosen as the starting compound in the present work. After the ketone group in

13) L.A. Subluskey and T.F. Sanderson, *J. Am. Chem. Soc.*, **76**, 3512 (1954).
14) C.R. Bennet and R.C. Cambie, *Tetrahedron*, **23**, 927 (1967).
15) J. Minn, T.F. Sanderson and L.A. Subluskey, *J. Am. Chem. Soc.*, **78**, 630 (1956).

XXIV was protected as a thioketal (XXVIII), mp 163.5—167°, XXVIII was treated in the same way as the corresponding 13-isopropyl compound. Firstly, XXVIII was treated with potassium hydroxide-methanol to cleave the γ-lactone more easily than isopropyl derivative. However, the resulted hydroxy acid (XXIX) and its ester (XXX) failed to undergo dehydration by any of the procedures tried.

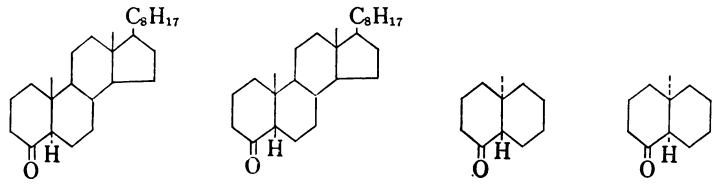
Therefore, an attempt was made to convert the ketone group in XXIV to a hydroxyl or an acetoxyl to attain the objective. Reduction of XXIV with sodium borohydride afforded a hydroxy-γ-lactone (XXXI), mp 141—142°. The 13-protons of XXXI and its acetate (XXXII), mp 174—175°, were assumed to be axial and therefore the substituent was thought to be equatorial from the width of half height (*ca.* 14 cps in XXXI, *ca.* 18 cps in XXXII)[16] of NMR-pattern.

Treatment of this 13-hydroxy-γ-lactone (XXXI) with potassium hydroxide–diethylene glycol, in the same way as XII, afforded a mixture of unsaturated acids (in 15:1 ratio, detected by gas chromatography after methylation) by cleavage of the lactone ring and its fractional recrystallization gave XXXIII, mp 200—207°, which formed a methyl ester (XXXIV) of mp 106—107.5°. Catalytic hydrogenation of XXXIII gave a saturated compound (XXXV), mp 283—286°, which formed a methyl ester (XXXVI), mp 118—119.5°. For the configuration of the 10-position in XXXV, it was considered that the A/B ring juncture would be anti-*trans*, same as in XII, which was proved later by ORD measurement.

Before oxidation of the 4-*gem*-substituent, the 13-hydroxyl was protected by acetylation. The acetate (XXXVII), mp 219—222.5°, so obtained formed an ester (XXXVIII), mp 149—150°.

Oxidation of the 13-acetoxy-acid compound (XXXVII) with lead tetraacetate in the same way as XXII afforded a mixture of olefins (XXXIX), whose NMR spectrum (τ=5.34 (broad, 1.5 H, *exo*-olefinic proton), τ=4.70 (broad, 0.5H, *endo*-olefinic proton)) showed to have an *endo* compound mixed in the *exo*-double bond compound. Ozonolysis of XXXIX at a low temperature and separation of the ketone compound with a Girard reagent, followed by purification of its product finally afforded the objective VII, mp 109—111°, (semicarbazone, mp 234—235°). The process for obtaining the acetoxy-ketone compound (VII) was shortened by a few steps from that of the isopropyl compound (VI).

Steric structure of these VI and VII especially that of the A/B ring juncture, was already assumed to be anti-*trans*. In order to confirm these structures, ORD measurements were carried out, centered on 4-ketone group. Taking ORD studies on the steric structure of steroids and bicyclic compounds into consideration, the ORD curves of VI and VII synthesized were compared with those of four compounds (XL(*trans*-5αH/10βMe), XLI (*cis*-5βH/10βMe), XLII (*trans*-5βH/10αMe), XLIII (*cis*-5αH/10αMe))[17] having possible steric structures on the A/B ring juncture (Fig. 1). The observation as shown in Fig. 2, indicate a positive Cotton effect and have a similar courve as that of XLII (*trans*-5βH/10αMe) among the four kinds of



XL XLI XLII XLIII

Chart 5

16) N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964, p. 77.

17) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).

curves shown in Fig. 1, while they are mirror image to the ORD curve of XL (*trans*-5α-H/10β-Me). Consequently, it is clear that the steric structure of the A/B ring juncture in VI and VII is *trans*-5β-H/10α-H.

This result is not inconsistent with the structure assumed from the direction of the introduction of hydrogen in catalytic reduction stated earlier.

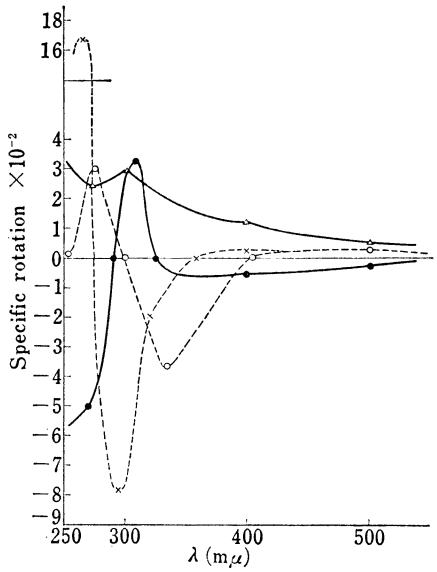


Fig. 1. Optical Rotatory Dispersion Curves

XL: ---×--- XLI: —△—
XLII: —●— XLIII: ---○---

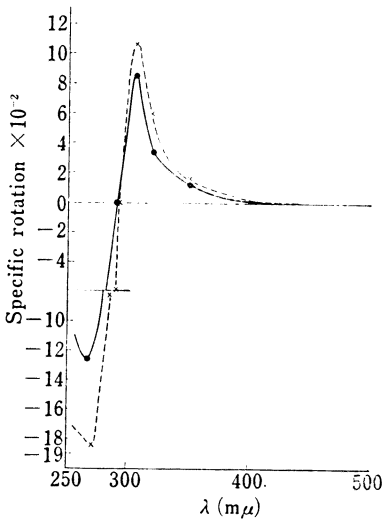
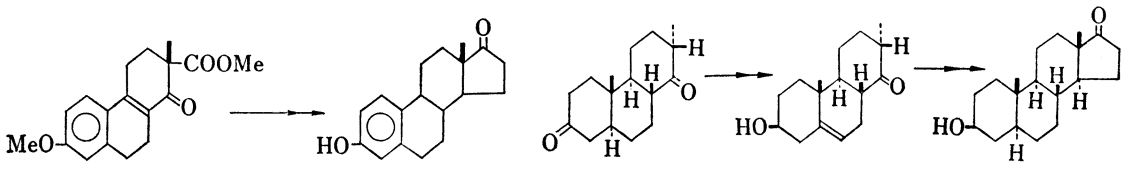


Fig. 2. Optical Rotatory Dispersion Curves

VI (VI'): ---×---
VII (VII'): —●—

Thus, the compounds (VI and VII), considered to be the important intermediates in the synthesis of steroid antipodes were synthesized and their structure was confirmed. Synthesis of steroids from these intermediates has already been completed in analogs and their conversion to steroid antipodes (VIII and IX) should not be difficult if a similar process is used. Examples of such a steroid synthesis would be that of estrone (XLIV→XLV) by Bachmann and others,[7] and that of epiandrosterone (XLVI→XLVII→XLVIII) by Robinson and others.[8]



XLIV XLV XLVI XLVII XLVIII

Chart 6

Experimental

10α-Hydroxy-13β-isopropyl-9β-methyl-17-nor-5β,8α-podocarpan-15-oic Acid 15→10α-lactone (XII)—— According to the method previously reported,[9,10] γ-lactone (XII) was synthesized from $\Delta^{8(9)}$-dihydroabietic acid (X). Its physical data were as follows. Colorless prisms, mp 130—131°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770. NMR τ: 9.12 (6H, d, J=4.5 cps, CH-Me$_2$), 9.17 (3H, s, 9-Me), 8.92 (3H, s, 4-Me).

Methyl 10α-Hydroxy-13β-isopropyl-9β-methyl-17-nor-5β,8α-podocarpan-15-oate (XIV) from XII *via* XIII——A solution of γ-lactone (XII) (50 mg) and *tert*-BuOK (300 mg) in dimethylsulfoxide (3.0 ml)–

H_2O (1 drop) was refluxed for 1 hr and then, the reaction mixture was diluted with H_2O and was washed with ether. The water layer was acidified under ice-cooling and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give a light yellow oil (XIII) (46.5 mg). The resulted oil (XIII) (20 mg) was methylated with CH_2N_2–ether solution in the usual manner to give the corresponding oily methyl ester (XIV) (20 mg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3420, 1710. The ester was too unstable to be further purified.

A solution of the ester (XIV) (20 mg) in MeOH (5.0 ml) containing conc. HCl (0.5 ml) was left standing for 1 hr at room temperature. After standing, it was diluted with H_2O and extracted with ether. The extract was washed with 5% KOH aq., with H_2O, then dried over Na_2SO_4 and the solvent was evaporated to give colorless crystals (18 mg), which were identical with the starting γ-lactone (XII) by comparison of their physical constants (IR and t_R).

13β-Isopropyl-9β-methyl-17-nor-5β,8α-podocarp-1(10)-en-15-oic Acid (XVII) from XII *via* XIV——i) After a solution of γ-lactone (XII) (8.0 g) and KOH (15 g) in diethylene glycol (50 ml) was refluxed for 9 hr, the reaction mixture was diluted with H_2O and washed with ether. The water layer was acidified with 10% HCl aq. and extracted with ether. The extract was washed with H_2O, then dried over Na_2SO_4 and evaporated to give crystals (XVII and XX) (7.62 g), a part of which was methylated with CH_2N_2–ether solution and examined by gas liquid chromatography (1.5% OV-17 on Shimalite W (80—100 mesh), 2 m×4 mm, 200°; t_R=8.5 min (XIX) and 9.9 min (XVIII) in ratio 1: 10). The mixed crystals were recrystallized three times from MeOH–H_2O to give colorless prisms (XVII), mp 166—168°. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.90; H, 10.70. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3200—3400, 1700. NMR τ: 9.13 (6H, d, J=6.0 cps, CH-Me_2), 9.08 (3H, s, 9-Me), 8.77 (3H, s, 4-Me), 4.69 (1H, broad, olefinic H).

ii) Hydroxy ester (XIV) (650 mg) was treated in the same way as in the dehydration of XII to give the crystals (XVII and XX in ratio of 1: 10; determination by gas liquid chromatography of the corresponding methyl ester) (643 mg).

Methyl 13β-Isopropyl-17-nor-5β,8α-podocarp-1(10)-en-15-oate (XVIII)——$\Delta^{1(10)}$-Acid (XVII) was methylated with CH_2N_2–ether solution as usual to give the corresponding methyl ester (XVIII), colorless oil. *Anal.* by high resolution mass-spectrometry. Calcd. for $C_{21}H_{34}O_2$ (M^+; m/e): 318.2559. Found: 318.2568. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. NMR τ: 9.14 (6H, d, J=6.0 cps, CH-Me_2), 9.10 (3H, s, 9-Me), 8.83 (3H, s, 4-Me), 6.32 (3H, s, COOMe), 4.70 (1H, broad, olefinic H). t_R=9.9 min (1.5% OV-17 on Shimalite W (80—100 mesh), 2 m×4 mm, 200°).

Methyl 13β-Isopropyl-9β-methyl-17-nor-8α-podocarp-5(10)-en-15-oate (XIX) from XVIII——After a solution of $\Delta^{1(10)}$-ester (XVIII) (226 mg) in AcOH (5.0 ml) was refluxed for 3 hr in the presence of p-TsOH (5.0mg), it was diluted with H_2O and extracted with ether. The extract was washed with H_2O, 5% KOH aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave a light yellow oil (XIX) (227 mg). *Anal.* by high resolution mass-spectrometry. Calcd. for $C_{21}H_{34}O_2$ (M^+; m/e): 318.2559. Found: 318.2546. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. NMR τ: 9.15 (6H, d, J=4.2 cps, CH-Me_2), 9.18 (3H, s, 9-Me), 8.74 (3H, s, 4-Me), 6.36 (3H, s, COOMe). t_R=8.5 min (1.5% OV-17 on Shimalite W (80—100 mesh), 2 m×4 mm, 200°).

13β-Isopropyl-9β-methyl-17-nor-8α-podocarp-5(10)-en-15-oic Acid (XX) from XIX——A solution of $\Delta^{5(10)}$-ester (XIX) (227 mg) and KOH (1.5 g) in diethylene glycol (15 ml) was refluxed for 5 hr. The reaction mixture was diluted with H_2O, washed with ether, acidified and then extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give light yellow oil (210 mg), which was recrystallized four times from MeOH–H_2O to give colorless prisms, mp 186—188°. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.72; H, 10.44. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2400—3500 (broad), 1695.

Lactonization of $\Delta^{1(10)}$-Acid (XVII) and $\Delta^{5(10)}$-Acid (XX)——i) A solution of $\Delta^{1(10)}$-acid (XVII) (100 mg) in conc. HCl (1.5 ml) and MeOH (10 ml) was refluxed for 1 hr. The reaction mixture was diluted with H_2O and extracted with ether. The extract was washed with 5% KOH aq., then with H_2O and evaporated to give crystals (70 mg) after dryness on Na_2SO_4. They were recrystallized from MeOH–H_2O to colorless prisms, mp 132°, whose physical constants (mixed mp and IR spectrum) were identical with those of γ-lactone (XII).

ii) A solution of $\Delta^{5(10)}$-acid (XX) (118 mg) and p-TsOH (38 mg) in AcOH (1 ml) was heated in water bath for 4.5 hr. After cooling the reaction mixture was diluted with benzene and the solution was washed with H_2O, 5% KOH aq. and then H_2O. Benzene solution was dried over Na_2SO_4 and evaporated to give crystals (33.6 mg). They were recrystallized from MeOH–H_2O to give colorless prisms, mp 129.5—131°, whose physical constants (mixed mp and IR-spectrum) were identical with those of γ-lactone (XII). While, alkaline extract was acidified and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give crystals (60 mg), which were recrystallized from acetone–H_2O to give colorless prisms, mp 163—170°. Rf value of the crystals on the TLC (benzene: AcOEt=8: 1, silica gel) was identical with that of starting $\Delta^{5(10)}$-acid (XX).

Abnormal Reaction of γ-Lactone (XII) with Methylmagnesium Iodide[13]——To a solution of γ-lactone (XII) (1.0 g) in benzene (20 ml), Grignard reagent ether solution (Mg (70 mg), MeI (0.2 ml) and I_2 (trace) in absolute ether (15 ml)) was added with stirring under ice-cooling.[13] After the reaction mixture was refluxed for 16 hr, it was poured into ice–water containing NH_4Cl (0.75 g) and the separated benzene layer was extracted with 2% NaOH aq. The benzene layer was washed with H_2O, dried over Na_2SO_4 and evapo-

rated to give colorless crystals (501 mg), whose IR-spectrum and t_R (1.5% OV-17 on Shimalite W (80—100 mesh), 2 m×4 mm, 205°) were identical with those of γ-lactone (XII). While, alkaline extract was acidified and then extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give colorless crystals (412 mg), whose component ((XVIII) and (XIX) in ratio of 1: 5.3) was shown by peak area in gas liquid chromatogram (1.5% OV-17 on Shimalite W (80—100 mesh), 2 m×4 mm, 205°) of the methylated product. The mixture crystals were purified by recrystallization from acetone, AcOEt and MeOH-H_2O, successively. The obtained colorless prisms, mp 180—184°, were identical with the sample (XX) obtained by alkaline hydrolysis and successive isomerisation of γ-lactone (XII) by comparison of IR-spectra. The corresponding methyl ester was identical with $\Delta^{5(10)}$-ester (XIX) by comparison of IR-spectra and retention time of gas liquid chromatography.

Mother liquid of recrystallization from acetone was treated with CH_2N_2-ether solution. The methylated mixture ((XIX) t_R=2.7 min and (XVIII) t_R=3.5 min in ratio of 2.4: 1 on gas liquid chromatogram (1.5% SE-30 on Chromosorb W (60—80 mesh), 2 m×4 mm, 202°) was preparatively separated by gas liquid chromatography (1.5% OV-17 on Shimalite W (80—100 mesh), 1.8 m×4 mm, 170°) to give an oil (XVIII) (6.3 mg). The oil was hydrolyzed by reflux in 10% KOH-ethylene glycol (1 ml) for 8 hr and then the mixture was diluted with H_2O. It was washed with ether, acidified and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give colorless crystals (3.3 mg), which were further purified by preparative TLC (silica gel; benzene: AcOEt=6: 1) and then recrystallized from MeOH-H_2O to give colorless prisms, mp 167—169.5°. They were identical with (XVII) by comparison of melting points (mixed mp) and IR-spectra (as the corresponding mthyl ester (XVIII)).

Methyl 13β-Isopropyl-9β-methyl-17-nor-5β,8α,10α-podocarpan-15-oate (XXI) from XVIII——A solution of $\Delta^{1(10)}$-ester (XVIII) (1.3 g) in AcOH (40 ml) was shaken in the presence of platinum (1.2 g as PtO_2) under hydrogen stream. After hydrogen absorption was ceased (5.5 hr), the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The resulted residue (colorless oil) was dissolved in ether. The extract was washed with H_2O, 5% KOH aq. and H_2O and dried over Na_2SO_4. Removal of the solvent gave a colorless oil (XXI) (1.25 g). *Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.75; H, 11.25. Found: C, 78.40; H, 11.11. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. NMR τ: 9.34 (3H, s, 9-Me), 9.15 (6H, d, J=6 cps, CH-Me_2), 8.82 (3H, s, 4-Me), 6.35 (3H, s, COOMe). t_R=8.5 min (1.5% OV-17 on Shimalite W (80—100 mesh), 2 m×4 mm, 200°).

13β-Isopropyl-9β-methyl-17-nor-5β,8α,10α-podocarpan-15-oic Acid (XXII) from XXI——A solution of ester (XXI) (300 mg) and KOH (300 mg) in ethylene glycol (3 ml) was refluxed for 8 hr and then, the reaction mixture was diluted with H_2O. The water layer was washed with ether, acidified and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give crystals (263 mg), mp 140—160°, which were recrystallized from MeOH to give colorless needles (XXII) (133 mg), mp 219° (in sealed tube). *Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 78.30; H, 11.18. Found: C, 78.26; H, 11.06. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2350—3600, 1690. NMR τ: 9.33 (3H, s, 9-Me), 9.19 (6H, d, J=6 cps, CH-Me_2), 8.80 (3H, s, 4-Me).

13β-Isopropyl-9β-methyl-15,16,17-trinor-5β,8α,10α-podocarpan-4-one (VI) from XXII *via* XXIII——$Pb(OAc)_4$ (900 mg) and absolute pyridine (1.4 ml) were added to a solution of acid (XXII) (565 mg) in dry benzene (30 ml). After the reaction mixture was stirring for 1 hr at room temperature and then refluxed for 8 hr, the precipitate was filtered off and the filtrate was washed with 10% HCl aq., 5% KOH aq. and H_2O. The benzene layer was dried over Na_2SO_4 and evaporated to give a colorless oil (XXIII) (516 mg).

Ozone gas was passed through a solution of the mixed oil (XXIII) (1.75 g) in CH_2Cl_2 (40 ml) under dry ice-acetone cooling for 4.5 hr. To the reaction mixture, AcOH (1 ml) and sat. KI aq. was added, then strongly shaken and left standing for 15 min. The CH_2Cl_2 layer was washed with sat. $Na_2S_2O_3$ aq., 5% KOH aq. and H_2O. After dryness, it was evaporated to give an oil (1.34 g), which was usually treated with Girard reagent to isolate a fraction having carbonyl group as follows. Namely, Girard reagent P (3 g) and AcOH (1 ml) was added to a solution of the oil in absolute EtOH (15 ml). The reaction mixture was refluxed for 1.5 hr and was poured into 1.5% $NaHCO_3$ aq. (100 ml). The solution was once washed with ether, acidified and refluxed for 2 hr. After it was extracted with ether, the extract was washed with 5% KOH aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave a colorless oil (VI) (557 mg) (32%), bp 96° (2.5×10^{-3} mmHg). *Anal.* Calcd. for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.52; H, 11.52. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1715. NMR τ: 9.20 (3H, s, 9-Me), 9.15 (6H, d, J=6.6 cps, CH-Me_2). t_R=6.2 min (1.5% OV-1 on Shimalite W (80—100 mesh), 2 m×4 mm, 190°). ORD (c=0.084, MeOH) $[\alpha]_D^{25}$(mμ): 0 (400), +172 (350), +702 (320) +1059 (306) (peak), 0 (294), −1860 (270) (trough), −345 (240), −246 (230).

Semicarbazone of VI——Semicarbazone usually obtained, was recrystallized from MeOH to give colorless prisms, mp 206—209°. *Anal.* Calcd. for $C_{19}H_{33}ON_3$: C, 71.43; H, 10.41; N, 13.15. Found: C, 71.82; H, 10.42; N, 13.12. IR ν_{max}^{KBr} cm^{-1}: 3470, 3200, 1695, 1583. Ketone (VI) was readily regenerated from the semicarbazone by reflux with 50% pyruvic acid and AcONa-AcOH.

Oxidation of γ-Lactone (XII) with Chromic Anhydride. 10α-Hydroxy-9β-methyl-13-oxo-17-nor-5β,8α-podocarpan-15-oic Acid 15→10α-Lactone (XXIV)——γ-Lactone (XII) (1.0 g) was oxidized as reported by Sanderson, *et al.*[15] Unlike the literature,[15] the resulted oil (700 mg) was directly chromatographed on alumina (100 g). Firstly, the starting γ-lactone (XII) (95.9 mg) was recollected from benzene elution. Then, two kinds of crystals (94 mg) (7.9%) and (130 mg) (12%) were successively obtained from benzene-AcOEt (99: 1) elution. The former crystals were recrystallized from MeOH-H_2O to give colorless needles

(XXVI), mp 186—190.5°. *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.26; H, 9.34. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1775, 1730, 1250. NMR τ: 9.16 (3H, s, 9-Me), 8.92 (3H, s, 4-Me), 8.59 (6H, s, C-Me_2), 8.04 (3H, s, C-OCOMe_2). In the previous literature,[15] hydroxy γ-lactone (XXV) was reported to separate in place of the acetoxy γ-lactone (XXVI). The latter crystals were recrystallized from MeOH–H_2O to give colorless needles, mp 135—137.5°, which were identical with the reported acetyl γ-lactone (XXVII) (lit[15]; mp 138—139°). At last, the aimed keto γ-lactone (XXIV) (161 mg) (18%) was eluted from benzene–AcOEt (94: 6) fraction and then was recrystallized from hexane–ether to give colorless needles, mp 150—152° (lit[15]: mp 150—152°).

Methyl 13-Ethylenedithio-10α-hydroxy-9β-methyl-17-nor-5β,8α-podocarpan-15-oate (XXX) from XXIV *via* XXVIII——Keto γ-lactone (XXIV) (30 mg) in benzene was usually reacted with ethane dithiol (0.1 ml), $ZnCl_2$ (100 mg) and Na_2SO_4 (100 mg) for 2 days at room temperature. The resulted crystals were recrystallized from MeOH to give colorless prisms (XXVIII) (14.1 mg), mp 161—165° and mp 163.5—167° for microanalysis. *Anal.* Calcd. for $C_{19}H_{28}O_2S_2$: C, 64.71; H, 8.00. Found: C, 64.55; H, 8.16. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780. NMR τ: 9.06 (3H, s, 9-Me), 8.85 (3H, s, 4-Me), 6.66 (4H, s, ).

A solution of thioketal (XXVIII) (24.5 mg) and KOH (200 mg) in MeOH (or EtOH) (2 ml) was refluxed for 22—24 hr. After the reaction mixture was diluted with H_2O and then washed with benzene, the water layer was acidified and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give crystals (XXIX) (11.4 mg), which were instantly methylated by usual CH_2N_2–method. Methyl ester (XXX) was oily compound. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1700. NMR τ: 9.13 (3H, s, 9-Me), 8.80 (3H, s, 4-Me), 6.75 (4H, s, ), 6.35 (3H, s, COOMe), 5.19 (1H, s, 10-OH, disappearance by D_2O treatment).

10α,13β-Dihydroxy-9β-methyl-17-nor-5β,8α-podocarpan-15-oic Acid 15→10α-lactone (XXXI) from XXIV——A methanol solution (8 ml) of keto γ-lactone (XXIV) (164 mg) was stirring with $NaBH_4$ (70 mg) at room temperature for 1 hr and then was evaporated. The resulted residure was dissolved in benzene containing H_2O and it was washed with 10% HCl aq., 5% KOH aq. and H_2O, and then dried over Na_2SO_4. Removal of the solvent gave crystals (160 mg), which were recrystallized from hexane–benzene to give colorless needles (XXXI), mp 141—142°. *Anal.* by high resulution mass-spectrometry. Calcd. for $C_{17}H_{26}O_3$ (M^+; *m/e*): 278, 1882. Found: 278.1896. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3500, 1760. NMR τ: 9.11 (3H, s, 9-Me), 8.92 (3H, s, 4-Me), 8.05 (1H, s, 13-OH: disappearance by D_2O treatment), 6.40 (1H, broad (width at half height=*ca.* 14 cps, 13-H).

13β-Acetoxy-10α-hydroxy-9β-methyl-17-nor-5β,8α-podocarpan-15-oic acid 15→10α-lactone (XXXII) from XXXI——Hydroxy γ-lactone (XXXI) (126.3 mg) was usually acetylated with Ac_2O (1 ml)–absolute pyridine (1 ml). The resulted crystals (133 mg) were recrystallized from isopropyl ether and then ether to give colorless needles (XXXII), mp 174—175°. *Anal.* by high resolution mass-spectrometry. Calcd. for $C_{19}H_{28}O_4$ (M^+; *m/e*): 320.1988. Found: 320.1997. IR ν_{max}^{KBr} cm^{-1}: 1765, 1730, 1245. NMR τ: 9.10 (3H, s, 9-Me), 8.92 (3H, s, 4-Me), 8.01 (3H, s, 13-OCOMe), 6.40 (1H, broad (width of half height=*ca.* 18 cps, 13-H).

13β-Hydroxy-9β-methyl-17-nor-5β,8α-podocarp-1(10)-en-15-oic Acid (XXXIII) from XXXI——Hydroxy γ-lactone (XXXI) (2.0 g) was hydrolysed under the same condition (refluxed with KOH–diethylene glycol) as in the case of XII. The resulted crystals (1.9 g), a part of which was methylated and examined by gas liquid chromatography (1.5% OV-17 on Shimalite W, 2 m×4 mm, 220°; t_R=8.4 min (uncertain compound) and 9.4 min (XXXIV) in ratio of 1: 15), were recrystallized twice from AcOEt to give colorless needles (XXXIII), mp 200—207°. *Anal.* Calcd. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.38; H, 9.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3500—2400, 1695, 1655 (weak). $\Delta^{1(10)}$-Hydroxy acid (XXXIII) was treated with conc. HCl–MeOH as in the case of $\Delta^{1(10)}$-acid (XVII). The quantitatively obtained crystals were recrystallized from benzene–hexane to give colorless needles, mp 145—146°, whose physical constants (mixed mp and IR-spectrum) were identical with those of hydroxy γ-lactone (XXXI).

Methyl 13β-Hydroxy-9β-methyl-17-nor-5β,8α-podocarp-1(10)-en-15oate (XXXIV)——$\Delta^{1(10)}$-Hydroxy acid (XXXIII) was usually methylated by CH_2N_2–ether solution to give crystals, which were recrystallized from ether–hexane to give colorless needles (XXXIV), mp 106—107.5°. *Anal.* by high resolution mass spectrometry. Calcd. for $C_{18}H_{28}O_3$ (M^+; *m/e*): 292.2038. Found: 292.2009. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3650, 1730, 1650 (weak). NMR τ: 9.02 (3H, s, 9-Me), 8.83 (3H, s, 4-Me), 8.25 (1H, s, 13-OH, disappeareance by D_2O treatment), 6.33 (3H, s, COOMe), 6.40 (1H, broad (width of half height=*ca.* 15 cps); 13-H), 4.70 (1H, broad, olefinic H).

13β-Hydroxy-9β-methyl-17-nor-5β,8α,10α-podocarpan-15-oic Acid (XXXV) from XXXIII——$\Delta^{1(10)}$-Hydroxy acid (XXXIII) (200 mg) was catalytically hydrogenated in AcOH (9 ml) in the presence of platinum (200 mg as PtO_2) as in the case of the hydrogenation of ester (XVIII). The resulted crystals (144.3 mg) were recrystallized twice from MeOH to give colorless prisms (XXXV), mp 283—286° (in sealed tube). *Anal.* Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.64; H, 10.30. IR ν_{max}^{KBr} cm^{-1}: 3380, 3200—2380, 1680.

Methyl 13-Hydroxy-9β-methyl-17-nor-5β,8α,10α-podocarpan-15-oate (XXXVI)——The acid (XXXV) was usually methylated with CH_2N_2–ether solution to give crystals, which were recrystallized from benzene–hexane to give colorless powder (XXXVI), mp 118—119.5°. *Anal.* Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.37; H, 10.56. IR ν_{max}^{KBr} cm^{-1}: 3400, 1725. NMR τ: 9.27 (3H, s, 9-Me), 8.81 (3H, s, 4-Me), 8.27 (1H, s, 13-OH, disappearance by D_2O treatment), 6.37 (3H, s, COOMe), 6.40 (1H, broad (width of half height= *ca.* 17 cps); 13-H). t_R=10.2 min (1.5% OV-17 on Shimalite W (80—100 mesh), 2 m×4 mm, 200°).

13β-Acetoxy-9β-methyl-17-nor-5β,8α,10α-podocarpan-15-oic Acid (XXXVII) from XXXV——A solution of hydroxy acid (XXXV) (104 mg) in Ac_2O (0.5 ml)–absolute pyridine (0.5 ml) was left standing at room temperature for 24 hr, then 5% AcONa aq. (10 ml) was added and it was stirred for 2 more hr. Thereafter, it was diluted with H_2O, extracted with benzene. After dryness of the extract, removal of the solvent gave crystals (118 mg), which were recrystallized twice from benzene–hexane to give colorless prisms (XXXVII), mp 219—222.5°. *Anal.* by high resolution mass-spectrometry. Calcd. for $C_{19}H_{30}O_4$ (M^+; *m/e*): 322.2144. Found: 322.2193. IR ν_{max}^{KBr} cm^{-1}: 2400—3450, 1735, 1685, 1240. NMR τ: 9.25 (3H, s, 9-Me), 8.79 (3H, s, 4-Me), 7.99 (3H, s, 13-OCOMe), 5.30 (1H, broad (width of half height=*ca.* 19 cps), 13-H).

Methyl 13β-Acetoxy-9β-methyl-17-nor-5β,8α,10α-podocarpan-15-oate (XXXVIII)——Acetoxy acid (XXXVII) was usually methylated by CH_2N_2–ether solution to give crystals, which were recrystallized from ether–hexane to give colorless prisms (XXXVIII), mp 149—150°. *Anal.* by high resolution mass-spectrometry. Calcd. for $C_{20}H_{32}O_4$ (M^+; *m/e*): 336.2301. Found: 336.2267. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730, 1240. NMR τ: 9.25 (3H, s, 9-Me), 8.82 (3H, s, 4-Me), 7.99 (3H, s, 13-OCOMe), 6.36 (3H, s, 4-COOMe), 5.30 (1H, broad (width of half height=*ca.* 16 cps); 13-H). t_R=14.7 min (1.5% OV-17 on Shimalite W (80—100 mesh), 2 m×4 mm, 200°).

13β-Acetoxy-9β-methyl-15,16,17-trinor-5β,8α,10α-podocarpan-4-one (VII) from XXXVII *via* XXXIX——The process was carried out in the case of (XXII). Namely, a solution of acetoxy acid (XXXVII) (200 mg) in dry benzene (5 ml) was treated with Pb $(OAc)_4$ (500 mg) in absolute pyridine (0.5 ml) to give a yellow oil (XXXIX) (202 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1655 (weak), 1240. NMR τ: 9.20 (3H, s, 9-Me), 7.99 (3H, s, 13-OCOMe), 5.34 (1.5H, broad; *exo*-olefinic H), 4.70 (0.5H, broad; *endo*-olefinic H).

The oil (870 mg) was ozonized for 3 hr in CH_2Cl_2 (30 ml) under dry ice–acetone cooling (−70° below). Oily compound (630 mg) was resulted. Absolute EtOH solution (6 ml) of the oil was refluxed for 1 hr 20 min with Girard reagent P (500 mg) and AcOH (0.6 ml). As in treatment of (XXIII), ketone part was regenerated with mineral acid from the water soluble adduct of Girard reagent. The obtained light yellow oil (115 mg), bp 160° (1×10^{-2} mmHg), was chromatographed on neutral alumina to elute colorless oil in benzene–hexane (1: 9) elution. The oil crystallized and was recrystallized from Petr. ether to give colorless powder (VII), mp 109—111°. *Anal.* by high resolution mass-spectrometry. Calcd. for $C_{17}H_{26}O_3$ (M^+; *m/e*): 278.1882. Found: 278.1876. IR ν_{max}^{KBr} cm^{-1}: 1735, 1700, 1240. ORD (*c*=0.142, MeOH) $[a]_D^{25}$ (mμ): 0 (400), +125 (350), +360 (320), +880 (305) (peak), 0 (292), −1260 (269) (trough), −900 (250).

Semicarbazone of VII——Semicarbazone, synthesized by usual method, was recrystallized from MeOH and then MeOH-isopropyl ether to give colorless powder, mp 234—235°. *Anal.* Calcd. for $C_{18}H_{29}O_3N_3$: C, 64.45; H, 8.72; N, 12.53. Found: C, 64.54; H, 8.71; N, 12.78.

Acknowledgement The authors are indebted to financial support from the Ministry of Education (Grantin-Aid for Scientific Research, No. 38745 (1970)).