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Diterpenoids. XVI.[1] Reduction of 6β-Hydroxy-*enantio*-podocarpa-8,11,13-trien-16-oic Acid Derivative

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Synthesis of 6β-hydroxy (acetoxy)-*enantio*-podocarpan-oic acid type compounds (*e.g.* V, VII; XIV, XVI and XV, XVIII) were herein accomplished.

These compounds are regarded as starting materials for examination of a notable epimerization at a lactonization. Furthermore, it is interesting that they have basic skeleton of many natural diterpenoids having C_6-oxygen function.

On the way of chemical conversion of *l*-abietic acid (I),[3] major component of rosin from Japanese pine trees, to the *aconitum* and *garrya* alkaloids, such as atisine, veatchine and garryine, an interesting epimerization at C_6-position in the acidic lactonization of 6β-hydroxy-*enantio*-podocarpa-8,11,13-trien-16-oic acid (II) to 16→6α-lactone (III) was found. Otherwise, the acid (II) was lactonized to the corresponding 16→6β-lactone (IV) under thermal condition and the unstable lactone (IV) could be readily converted to the epimerized lactone (III).

The epimerization is unique and, therefore, more elaborate investigation on the structural influence at the epimerization (*e.g.* influence of aromatic C-ring) should be carried out. The 6β-hydroxy-hexahydro and -tetrahydro acid obtained by reduction of the benzene ring of the acid (II) are suitable for the subjective compounds of the lactonization study.

On the other hand, there are many kinds of natural diterpenoid having oxygen function (as hydroxyl or lactone group) at C_6-position and most of their structures have been recently elucidated.[4] Since our 6β(α)-hydroxy acid (II and its isomer at C_6) and its hydrogenated derivative can be regarded as a basic skeleton of the above type of natural product, study on their synthesis and chemical behavior would be considered to give profitable suggestions for the natural chemistry.

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[1] Preliminary Communication: A. Tahara, Y. Ohtsuka, N. Umino, K. Nagasawa and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **17**, 1527 (1969); Part XV: K. Hirao, S. Mitsubayashi, J. Uzawa, A. Tahara, N. Mitomo and S. Hayashi, *ibid.*, **18**, 2169 (1970). All melting points were measured on Koflor block and were uncorrected. NMR spectra were measured at 60 Mc in $CDCl_3$ *vs.* Me_4Si as internal reference.

[2] Location: *Wako, Saitama.*

[3] A. Tahara and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **12**, 984 (1964); A Tahara, K. Hirao and Y. Hamazaki, *ibid.*, **12**, 1458 (1964); A. Tahara, K. Hirao and Y. Hamazaki, *Tetrahedron*, **21**, 2133 (1965); *cf.* A. Tahara and K. Hirao, *Tetrahedron Letters*, **1966**, 1453; A. Tahara, K. Hirao and Y. Hamazaki, *Chem. Pharm. Bull.* (Tokyo), **15**, 1785 (1967); A. Tahara and K. Hirao, *ibid.*, **15**, 1934 (1967).

[4] Literature since 1968; *a*) E.L. Ghisalberti and P.R. Jefferies, *Aust. J. Chem.*, **21**, 439 (1968); *b*) L. Mangoni and M. Adinolfi, *Tetrahedron Letters*, **1968**, 269; *c*) S. Itô, M. Kodama, M. Sunagawa, T. Takahashi, H. Imamura and O. Honda, *idid.*, **1968**, 2065; *d*) Y. Hayashi, S. Takahashi, H. Ona and T. Sakan, *ibid.*, **1968**, 2071; *e*) C. Tabacik-Wlotzka and Y. Laporthe, *idid.*, **1968**, 2531; *f*) L. Canonica, B. Rindone and C. Scolastico, *ibid.*, **1968**, 3149; *g*) G.A. Ellestad, R.H. Evans, Jr. and M.P. Kunstmann, *J. Am. Chem. Soc.*, **91**, 2134 (1969); *h*) S.M. Kupchan, A. Karim and C. Marcks, *J. Org. Chem.*, **34**, 3912 (1969); *i*) J.D. White and P.S. Muachand, *Chem. Commun.*, **1969**, 1315; *j*) T. Anthonsen and R. McCrindle, *Acta Chem. Scand.*, **23**, 1068 (1969); *k*) E. Fujita, T. Fujita and M. Shibuya, *Tetrahedron*, **25**, 2517 (1969); *l*) E. Fujita, T. Fujita, M. Taoka, H. Katayama and M. Shibuya, *Tetrahedron Letters*, **1970**, 421; *m*) M.N. Galbraith and D.H.S. Horn, *Chem. Commun.*, **1970**, 170; *n*) P. Sengupta, S. Roy and K.G. Das, *Chem. Ind.* (London), **1970**, 534.

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In view of the above two reasons, the syntheses of 6β-hydroxy-tetrahydro (V and VII) and -hexahydro acids (stereoisomer having *anti-cis*-B/C-ring fusion (XIV and XVI) and *anti-tans*-B/C-ring fusion (XV and XVII)) were attempted by hydrogenation of 6β-hydroxy acid (II).

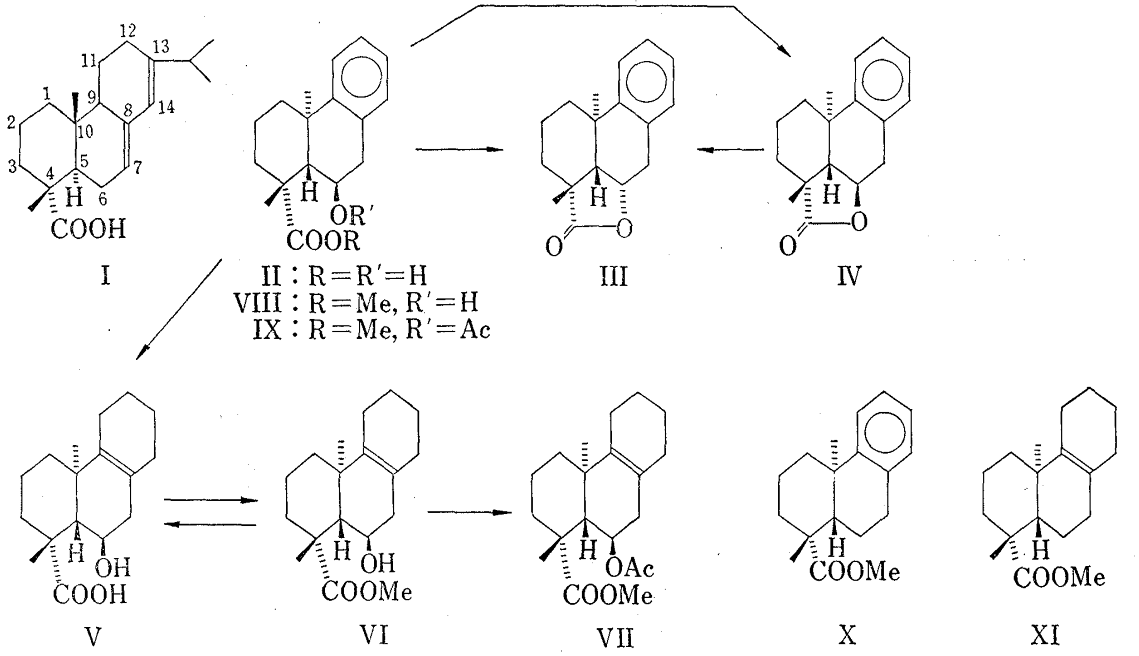

Chart 1

Firstly, it was found that reduction of the 6β-hydroxy acid (II) by lithium-ethylamine-*tert*-amyl alcohol system afforded a satisfactory result for synthesis of the aimed 6β-hydroxy-tetrahydro acid (V). The acid (V) was not successful to crystallize and to separate in pure state for elemental analysis by this procedure, but was pure enough to be used in our further experiments. While, the pure acid (V) could be obtained by following method. Usual methylation (CH_2N_2) of the acid (V) quantitatively afforded the corresponding ester (VI), bp 175°/ 3×10^{-3} mmHg, which was chromatographically purified and then hydrolyzed under alkaline condition ($KOH-MeOH-H_2O$)[5] to return to the original acid (V) in pure state. The ester was acetylated (AcCl–pyridine) to give an oily acetate (VII) after purification by alumina chromatography. The elemental analyses of V and VII were carried out by high resolution mass spectrometry.

For the purpose of a preparation of hexahydro-derivatives, an exhaustive hydrogenation of 6β-hydroxy compound having aromatic C-ring and 8,9-double bond (*e.g.*, II and V) was taken up. The ratio of produced stereoisomers on B/C-ring juncture (*anti-cis*- and *anti-trans*-fusion) would be depended on hydrogenation condition, so the reduction mode of 6β-hydroxy ester (VIII, IX[3]; VI, VII) were examined under some conditions and, for the sake of contrast, deoxy ester (X[6] and XI[7]) were also used for the hydrogenation. The reduction was undertaken in the presence of platinum as catalyst under three kinds of hydrogen pressure (1.0, 3.0 and 100 kg/cm^2). Ratio of the stereoisomers in the hydrogenated mixture was determined

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[5] In general, ester of podocarpic acid system was hard to hydrolyze, however the system having C_6-hydroxyl group was relatively easy to hydrolyze by anchimeric assistance of the hydroxyl group.

[6] E. Wenkert and A. Tahara, *J. Am. Chem. Soc.*, **82**, 3229 (1969); E. Wenkert, P. Beak, R.W.J. Corney, J.W. Chamberlin, D.B.R. Johnston, C.D. Roth and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963).

[7] A. Tahara and O. Hoshino, *Tetrahedron Letters*, **1966**, 3825; A. Tahara, O. Hoshino and T. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 54 (1969).

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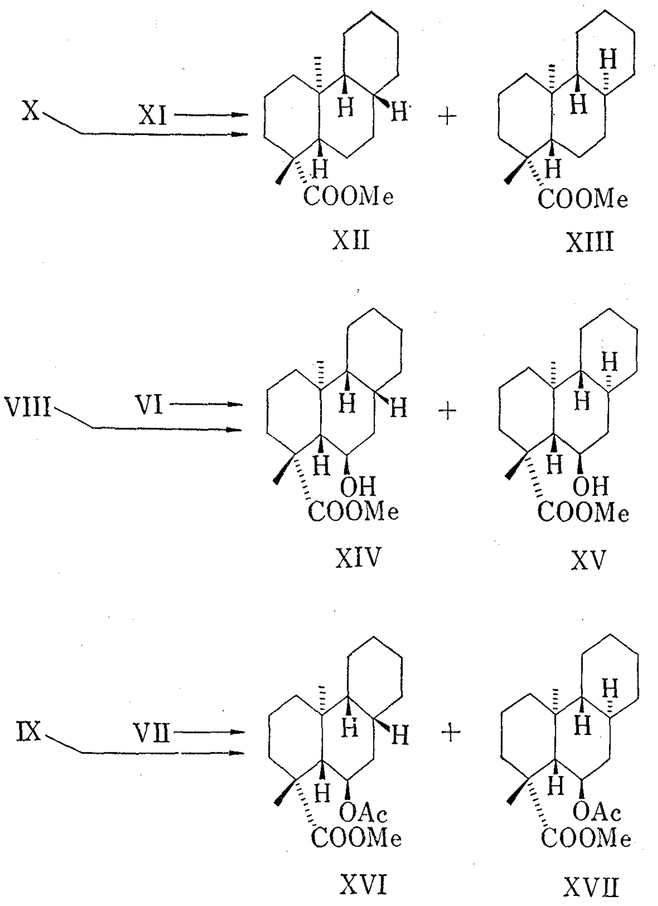

Chart 2

by the respective peak area (height × width at half height) of gas–liquid chromatogram (Table I).

As a general tendency shown in Table I, the higher the pressure was, the more amount of an isomer having *cis*-B/C-ring fusion was yielded. By contrast, the other isomer having *trans*-B/C-ring fusion was more yielded under the lower hydrogen pressure. Namely, in the presence of platinum catalyst, the hydrogenation of 6*β*-acetoxy ester (IX) under the higher hydrogen pressure (100 kg/cm^2) and of 6*β*-hydroxy ester (VI) under the lower hydrogen pressure (1.0 kg/cm^2) yielded stereoisomers on *anti-cis*-((IX)→*cis*-(XVI)/*trans*-isomer (XVII)=11.6/1) and *anti-trans*-B/C-ring fusion ((VI)→*cis*-(XIV)/*trans*-isomer (XV)=0.35/1) in higher ratio, respectively.

The former hydrogenated mixture mainly consisted of *cis*-isomer (XVI) was recrystallized to give pure 6*β*-acetoxy ester having *anti-cis*-B/C-ring fusion, mp 63.5—64°. But pure *trans*-isomer could not be isolated from the latter hydrogenated mixture.

A preparation of the *trans*-isomer in pure state was performed by the following method. Generally, *trans*-hydrogen addition to double bond by palladium-charcoal catalyst is more suitable than the case by platinum catalyst.[8] Taking the above fact into consideration, palladium-charcoal was used in place of platinum under the more favorable condition (hydrogenation of 6*β*-hydroxy ester (VI) under the lower hydrogen pressure, 1.0 kg/cm^2). Actually, the hydrogenation (Pd-C) of (VI) effectively gave the *trans*-isomer (XV) only mixed with a small amount of the deoxy compound (XIII) (XV/XIII=6/1). The pure *trans*-ester (XV),

TABLE I. Catalytic Hydrogenation (Pt-catalyst) of Methyl *enantio*-Podocarpa-8, 11, 13-trien-16-oate and Methyl *enantio*-Podocarp-8-en-16-oate type compounds

	Ratio (*cis*/*trans*) of stereoisomers (*anti-cis*- and *anti-trans*-B/C-ring fusion) in hydrogenated product						
	Starting material	X	VIII	IX	XI	VI	VII
	Product ratio	XII/XIII	XIV/XV	XVI/XVII	XII/XIII	XIV/XV	XVI/XVII
H_2-pressure (kg/cm^2)	1.0	1.75	1.82	3.14	0.35	0.35	0.66
	3.0	1.95	2.20	3.13	0.56	0.46	0.68
	100	2.80	2.67	11.6	1.40	0.66	1.90

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[8] *a)* J.W. ApSimon, P.V. Demarco and J. Lemke, *Can. J. Chem.*, **43**, 2793 (1965); O.E. Edwards and R. Howe, *ibid.*, **37**, 760 (1959); *b)* S. Siegel and G.V. Smith, *J. Am. Chem. Soc.*, **82**, 6087 (1960); S. Siegel, G.V. Smith, B. Dmuchovsky, D. Dubbell and W. Halpern, *ibid.*, **84**, 3136 (1962); A.W. Weitkamp, *J. Catalysis*, **6**, 431 (1966).

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colorless oil, could be isolated in petr. ether–ether (3:1) elution by alumina chromatography of a resulted mixture. Stereochemistry of *cis*-and *trans*- isomers on B/C-ring juncture will be fully discussed later.

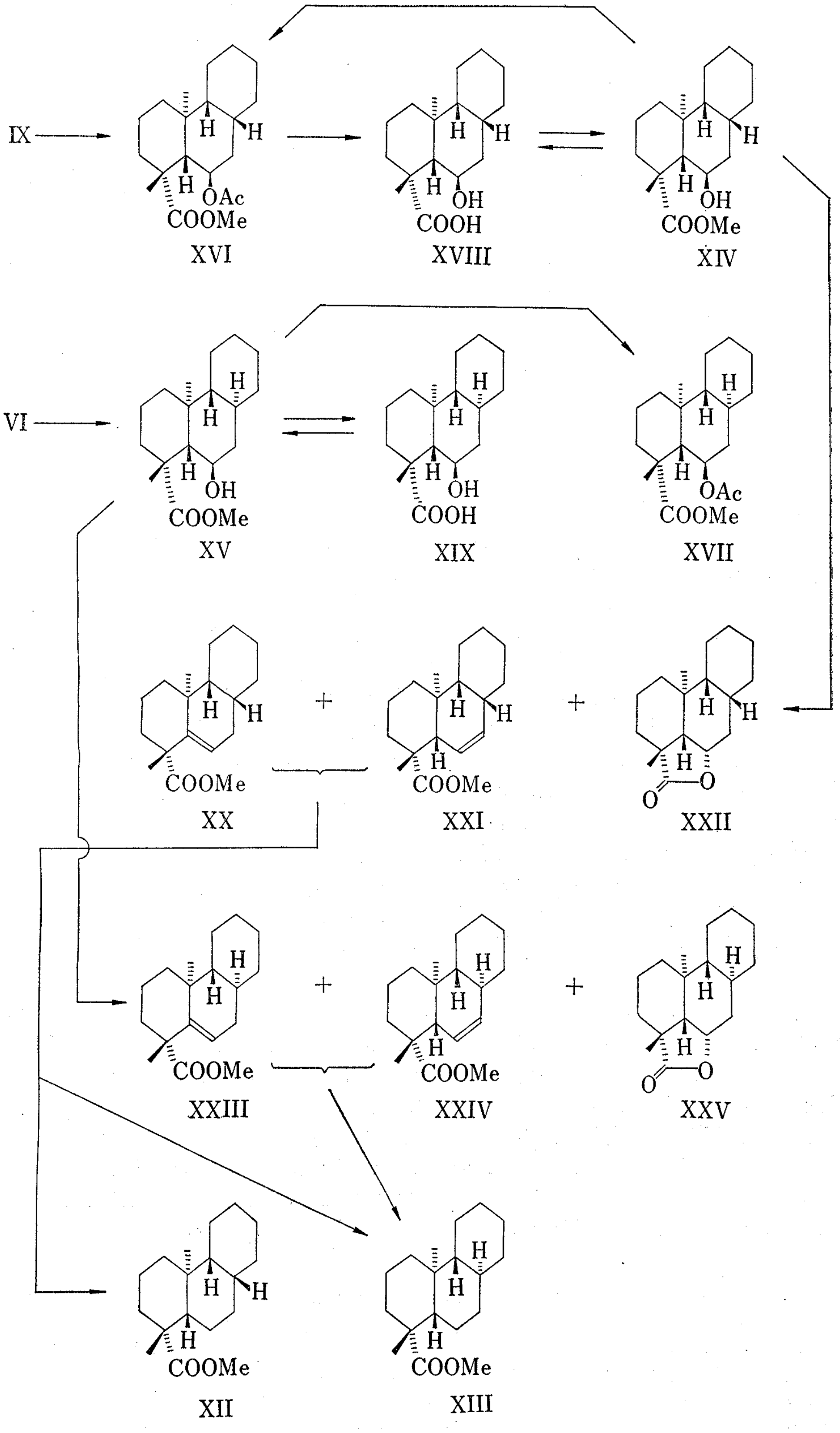

Chart 3

6β-Acetoxy ester (XVI) led by the profitable reduction of 6β-acetoxy ester (IX) having benzenoid C-ring, was available as a starting material for synthesis of *cis*-isomeric series. The acetoxy ester (XVI) was hydrolyzed under alkaline condition (KOH–ethylene glycol–H_2O) to 6β-hydroxy acid (XVIII), mp 149.5—151°, which was methylated (CH_2N_2) to 6β-hydroxy ester (XIV), mp 84—85°. The ester (XIV) could be returned to the original 6β-hydroxy acid (XVIII) and 6β-acetoxy ester (XVI) by the alkaline hydrolysis (KOH–MeOH–H_2O) and acetylation (AcCl–pyridine), respectively.

In the same manner as *cis*-isomer, preparation of another isomeric series having *anti-trans*-B/C-ring fusion was performed by using of 6β-hydroxy ester (XV) as starting material. Acetylation (AcCl–pyridine) and alkaline hydrolysis (KOH–MeOH–H_2O) of the ester (XV) afforded the corresponding oily acetate (XVII) and crystalline hydroxy acid (XIX), mp 107.5—109°, respectively. The acid (XIX) (elemental analysis was carried out by high resolution mass spectrometry) was readily methylated (CH_2N_2) to the original hydroxy ester (XV).

Considering the above chemical relation, the stereochemical structures of both isomeric series (*cis*- and *trans*-B/C-ring fusion) remain unchanged. The stereochemistry of the hexahydro compound on B/C-ring fusion was determined by the following proofs.

1) The proof was given by comparison of C_6-deoxo derivatives (XII and XIII) led from the corresponding 6β-hydroxy esters (XIV and XV) with authentic isomers (XXIX and XXXII) having antipodal structure, respectively.

Synthesis of the C_6-deoxo esters (XII and XIII) was accomplished by dehydration and successive hydrogenation of the respective hydroxy esters (XIV and XV). One of the isomeric 6β-hydroxy ester (*cis*-B/C-ring fusion) (XIV) was dehydrated by $POCl_3$– or MsCl–pyridine to give a mixed oil consisted of Δ^5-(XX), Δ^6-ester (XXI) and 6α-lactone (XXII).[9] Ratio of the mixed esters (XX and XXI, these esters were indivisible by gas-liquid chromatography) and the lactone (XXII) was measured from peak area in gas–liquid chromatogram and was 1.74:1 ($POCl_3$–pyridine) or 1.38:1 (MsCl–pyridine). By silica gel chromatography of the dehydrated mixture, the both esters (XX and XXI) were eluted together in petr. ether-ether (19:1) fraction and the pure lactone (XXII) was separated in the following petr. ether-ether (9:1) elution. However, pure Δ^5-ester (XX) was obtained through the other route as described in successive paper,[9] so the nuclear magnetic resonance (NMR) pattern of Δ^6-ester (XXI) could be distinguished by substruction of the pattern due to Δ^5-ester (XX) from that of the above resulted mixture (XX and XXI). The NMR spectrum of Δ^6-ester (XXI), NMR supported satisfactorily the 6.40 (COOMe), 4.22 (q, 2H, J=10.5, 32.7 cps; olefinic protons), τ: 9.22 (C_{10}-Me), 8.77 (C_4-Me), structure. The NMR analysis indicated the mixed ester was consisted of Δ^5-(XX) and Δ^6-ester (XXI) in ratio of 3:4 ($POCl_3$–pyridine) and 11:5 (MsCl–pyridine).

In the same way, dehydration of the other isomer (XV) having *trans*-B/C-ring fusion was also undertaken by $POCl_3$– and MsCl–pyridine. Chromatographic purification of the dehydrated mixture on silica gel afforded two fractions, unsaturated esters (XXIII and XXIV) in petr. ether–ether elution (19:1) and a crystalline 6α-lactone (XXV)[9] in petr. ether–ether (9:1) elution. The former mixture (XXIII and XXIV) was not separable at all, nevertheless NMR spectrum of the mixture could be devided to two kinds of patterns due to Δ^5-ester (XXIII), NMR τ: 9.25 (C_{10}-Me), 8.75 (C_4-Me), 6.40 (COOMe), 4.35 (q, 1H, J=1.50, 4.50 cps; olefinic proton) and Δ^6-ester (XXIV), NMR τ: 9.38 (C_{10}-Me), 8.77 (C_4-Me), 6.40 (COOMe), 4.33 (q,

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9) These compounds (XXII, XX, XXV, XII and XIII) will be described in the successive paper (A. Tahara and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **19**, 1768 (1971); The lactone (XXII) in pure state was mp 159.5—161°. The Δ^5-ester (XX) in pure state was mp 63—64°, NMR (100 Mc) τ: 9.16 (C_{10}-Me), 8.76 (C_4-Me), 6.40 (COOMe), 4.30 (q, 1H, J=1.75, 6.50 cps; olefinic proton). The lactone (XXV) in pure state was mp 86—87°. The saturated ester (*cis*-B/C-(XII) and *trans*-B/C-ester (XIII)) in pure state were bp 120°/2×10^{-3} mmHg, NMR τ: 9.14 (C_{10}-Me), 8.83 (C_4-Me), 6.37 (COOMe) and mp 59—61°, NMR τ: 9.37 (C_{10}-Me), 8.83 (C_4-Me), 6.37 (COOMe) respectively.

2H, J=10.0, 36.0 cps; olefinic protons) by difference of their relative integrated peak area and chemical shift. The result was that the both dehydrated mixture consisted of Δ^5-(XXIII) and Δ^6-ester (XXIV) in ratio of 1:2 ($POCl_3$–pyridine) and 6:5 (MsCl–pyridine), respectively.

Catalytic hydrogenation of the unsaturated ester having *cis*- or *trans*-B/C-ring fusion was carried out in the presence of two kinds of catalyst, platinum and palladium-charcoal, and the result was notable as follows. The mixed *cis*-esters (XX and XXI in ratio of 3:4) was reduced in the presence of platinum catalyst under higher hydrogen pressure (100 kg/cm^2) to yield a mixture of esters having *cis*-B/C-ring fusion (XII) and having *trans*-B/C-ring fusion (XIII) in ratio of 3.5:1. Similarly, catalytic hydrogenation of another mixed esters (XXIII and XXIV in ratio of 6:5) having *trans*-B/C-ring fusion under the same condition afforded only saturated ester having *trans*-B/C-ring fusion (XIII). Major products (XII and XIII) of the hydrogenations retained the same stereochemical structure on B/C-ring fusion as the starting materials (XX+XXI and XXIII+XXIV), respectively and, otherwise, minor one might be formed through the double bond migration discussed later.

In contrast, when palladium-charcoal was used as catalyst instead of platinum, the both hydrogenation of the mixed unsaturated *cis*-ester (XX and XXI in ratio of 2:1) and *trans*-ester (XXIII and XXIV in ratio of 1:2) only yielded the same product (XIII),[9] mp 59—61°, having *trans*-B/C-ring fusion. The experimental fact can be presumably explained by the general tendency that palladium catalyst more readily promote double bond migration than platinum in hydrogenation.[8b] Accordingly, the hydrogenated product in the presence of platinum catalyst only retains the stereo-structure on B/C-ring juncture of the original 6β-hydroxy ester (XIV and XV).

Successively, structural certification of the saturated esters (XII and XIII) was performed by comparison (gas–liquid chromatogram and NMR spectrum) with antipodal authentic samples (XXIX and XXXII) synthesized from *d*-podocarpic acid (XXVI) *via* the following reliable route.

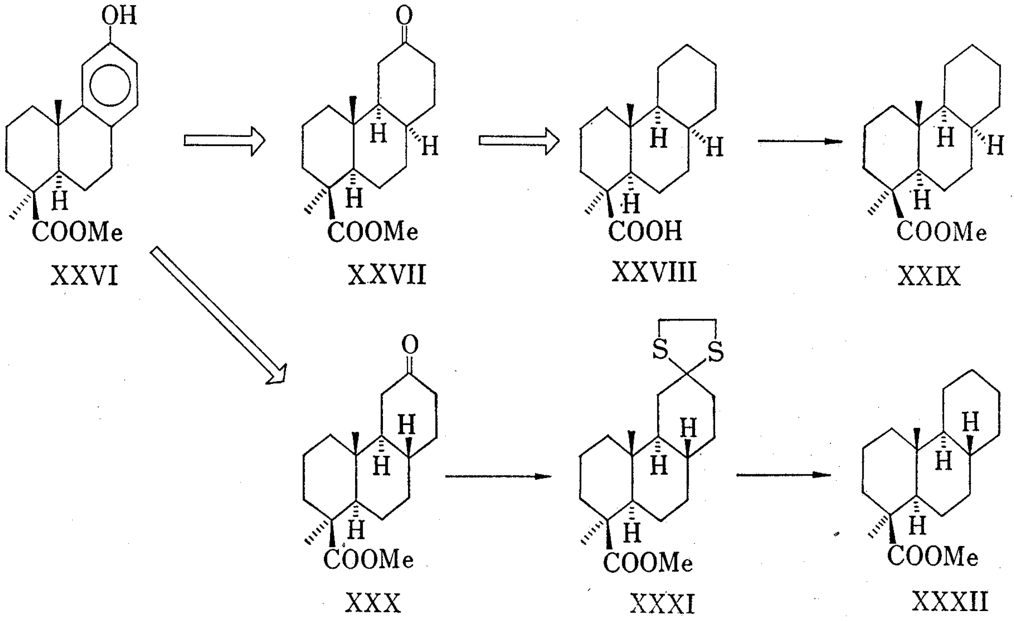

Chart 4

The standard ester having *cis*-B/C-ring fusion (XXIX), bp 120° (oil bath temp.)/2×10^{-3} mmHg, NMR τ:9.14 (C_{10}-Me), 8.83 (C_4-Me), 6.37 (COOMe), was readily obtained by only usual methylation of the corresponding acid (XXVIII) already synthesized from *d*-podocarpic acid (XXVI→XXVII→XXVIII).[10,11] On the other way, 12-keto ester (XXX) yielded also from *d*-podocarpic acid (XXVI) by Bible's method,[11] was used as starting material for a preparation of the other isomeric standard having *trans*-B/C-ring fusion (XXXII). The oxo group of the ester (XXX) was usually eliminated by thioketalization with ethane dithiol and the successive reduction with Raney nickel to give the standard (XXXII), mp 59—61°, NMR τ:9.38 (C_{10}-Me), 8.84 (C_4-Me), 6.38 (COOMe) *via* thioketal (XXXI), mp 141.5—143.5°.

2) The second evidence was adduced by comparison of chemical shifts due to methyl groups of the both isomers (hydroxy ester (XIV) and (XV), and acetoxy ester (XVI) and (XVII)) with those of the respective standard (XII and XIII) lacking of 6-hydroxy group. In general, when a hydroxyl group was located close to methyl group such as 1,3-diaxial relationship in the steroidal structure, the NMR signal of methyl group shifted 10 to 15 cps to lower magnetic field at 60 Mc.[12] In the diterpenoid field having similar structure, the same phenomenon was also observed between C_4-methyl and 6β-hydroxyl group and also between C_{10}-methyl and 6α-hydroxyl group and was reported in our previous work.[3]

From the stereochemical point of view, NMR signal due to C_{10}-methyl of the both hexahydro isomer (XIV and XV) must not be affected by its 6β-hydroxyl group, whereas that of C_4-methyl should be shifted to low magnetic field by the same hydroxyl group nearly located to the methyl group.

Taking it into account that the C_{10}-methyl is not located under the influence of 6β-hydroxyl group and, conversely, is more promptly affected by stereochemical difference of B/C-ring juncture than C_4-methyl, an NMR behavior of the C_{10}-methyl must be suitable for determination of the stereochemistry.

TABLE II. τ-Value of 4- and 10-Methyl of Hexahydro Esters

		10-Me (Shift (cps) from the respect standard)	4-Me (Shift (cps) from the respect standard)
cis-B/C ring juncture	hydroxy ester (XIV)	9.13 (−0.6)	8.53 (−17.4)
	acetoxy ester (XVI)	9.14 (±0)	8.70 (−7.2)
	standard (XII)	9.14	8.82
trans-B/C-ring juncture	hydroxy ester (XV)	9.37 (+0.6)	8.54 (−17.4)
	acetoxy ester (XVII)	9.32 (−2.4)	8.67 (−10.2)
	standard (XIII)	9.36	8.83

For the above reason, comparison of 6β-hydroxy esters (XIV and XV) with the respective standards (XII and XIII) was carried out as shown in Table II. Chemical shifts due to C_{10}-methyls of 6β-hydroxy esters (XIV:9.13 τ and XV:9.37 τ) are almost coincident with those of the standards (XII having *cis*-B/C-ring juncture: 9.14 τ and XIII having *trans*-B/C-ring juncture: 9.36 τ) respectively, whereas τ-values of C_4-methyls (XIV: 8.53 τ and XV: 8.54 τ) are mutually identical and are equally shifted 17.4 cps to lower magnetic field from the corresponding standards (XII: 8.82 τ and XIII: 8.83 τ) by the anisotropic effect of the 6β-hydroxyl group. The stereochemical assignment was proved by the fact that C_4-methyl signals of acetoxy esters (XVI: 8.70 τ and XVII: 8.67 τ) masking the effective hydroxyl group reverted to the higher magnetic field.[12]

3) The last evidence was given by hydrogenation mode. In the catalytic hydrogenation (platinum, AcOH) of the esters (X) having aromatic C-ring and XI having Δ^8-double bond,

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[10] J.W. ApSimon, O.E. Edwards and R. Howe, *Can. J. Chem.*, **40**, 630 (1962).

[11] R.H. Bible and R.R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961).

[12] Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

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it is noticeable that the isomer (XII) (*cis*-B/C-ring fusion) is more produced by reduction of benzene ring in X than by that of double bond in XI and also in proportion to increment of the hydrogen pressure. Similar hydrogenation of 6β-hydroxy (XIII and VI) and 6β-acetoxy ester (IX and VII) series was carried out and the result indicated the same tendency as in hydrogenation of the standards (X and XI) (Table I.)

In conclusion, the available synthetic method of 6β-hydroxy-tetrahydro ester and two kinds of stereoisomer (on B/C-ring fusion) of 6β-hydroxy-hexahydro ester derivative was established.

Experimental

Reduction of 6β-Hydroxy-*enantio*-podocarpa-8,11,13-trien-16-oic Acid (II) with Lithium-Ethylamine-*tert*-Amyl Alcohol. 6β-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (V)——A piece of lithium metal (884 mg) was added to a solution of acid (II)[3] (750 mg) in *tert* -amyl alcohol (3.68 g) and ethylamine (55 ml). The reaction mixture was stirred for 3 hr 50 min at room temperature and then was left standing overnight after *tert*-amyl alcohol (10 ml) and MeOH (8 ml) were carefully added. After the solvent was removed under reduced pressure, the reaction mixture was diluted with H_2O, acidified with conc. HCl aq. and then was extracted with ether. The extract was washed with 10% KOH aq., then the alkaline extract was acidified and extracted with ether. The ether extract was dried over Na_2SO_4 and then the solvent was removed to quantitatively give an oil (V), which was pure enough for the further experiment. A satisfactory sample for the elemental analysis was obtained by alkaline hydrolysis of the corresponding pure ester (VI) as described later.

Methylation of 6β-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (V). Methyl 6β-Hydroxy-*enantio*-podocarp-8-en-16-oate (VI)——Usual methylation of the tetrahydro acid (V) (389 mg) with excess CH_2N_2–ether solution gave an oil (VI) (394 mg), bp 175°/3×10^{-3} mmHg (bath temp.). *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.42; H, 9.33. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3545, 1733, 1710. NMR τ: 9.20 (s, 3H; C_{10}-Me), 8.53 (s, 3H; C_4-Me), 6.26 (s, 3H; COOC$\underline{H}_3$), *ca* 5.73 (m, (half band width=27 cps), 1H; $\underline{H}$-C-OH). t_R=6.1 min (1.5% OV-17 on Gaschrom P, 4 mm × 1.8 m, 230°).

Hydrolysis of Methyl 6β-Hydroxy-*enantio*-podocarp-8-en-16-oate (VI)——A solution of the tetrahydro ester (VI) (185 mg) and KOH (467 mg) in MeOH (15 ml) and H_2O (2.5 ml) was refluxed for 2 hr. After the solvent was evaporated under reduced pressure, the residue was diluted with H_2O, acidified and then extracted with ether. The extract was washed with 10% KOH aq., then H_2O and dried over Na_2SO_4 (neutral part). The alkaline extract was acidified, then extracted with ether and the ether extract was washed with H_2O and dried over Na_2SO_4 (acidic part). Evaporation of the both extract gave neutral (31 mg) and acidic fraction (123 mg), respectively. Infrared (IR) spectrum of the acid was identical with that of tetrahydro acid (V) obtained by lithium metal reduction of (II). *Anal.* by high resolution mass spectrometry. Calcd. for $C_{17}H_{26}O_3$ (M^+; *m/e*): 278.18820. Found: 278.18470. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3430, 1695. NMR τ: 9.09 (s, 3H; C_{10}-Me), 8.48 (s, 3H; C_4-Me), *ca* 5.65 (m, (half band width=21 cps), 1H; $\underline{H}$-C-OH).

Acetylation of Methyl 6β-Hydroxy-*enantio*-podocarp-8-en-16-oate (VI). Methyl 6β-Acetoxy-*enantio*-podocarp-8-en-16-oate (VII)——To a solution of tetrahydro ester (VI) (1.65 g) in pyridine (115 ml), acetyl chloride (5 ml) was dropped under ice-cooling. After the reaction mixture was left standing overnight at room temperature and then poured into ice-water, it was acidified and extracted with ether. The extract was washed with 10% KOH aq., then H_2O and dried over Na_2SO_4. Removal of ether gave an oil (1.69 g), which was purified by chromatography on neutral alumina to separate the acetate (VII) (580 mg) as an oil in petr. ether–ether (20:1) elution. *Anal.* by high resolution mass spectrometry. Calcd. for $C_{20}H_{30}O_4$ (M^+; *m/e*): 334.21441. Found: 334.21434. IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 1725, 1247. NMR τ: 9.17 (s, 3H; C_{10}-Me), 8.62 (s, 3H; C_4-Me), 7.96 (s, 3H; OCOC$\underline{H}_3$), 6.38 (s, 3H; COOC$\underline{H}_3$), *ca* 4.50 (m, 1H; $\underline{H}$-C-OH). t_R=9.0 min (1.5% OV-17 on Gaschrom P, 4 mm × 1.8 m, 230°).

Investigation on Condition of Catalytic Hydrogenation of Methyl *enantio*-Podocarpa-8,11,13-trien-16-oate (X) and Methyl *enantio*-Podocarp-8-en-16-oate (XI) Type Compounds. Relation between Hydrogen Gas Pressure and a Ratio of Stereoisomers on B/C-ring Fusion of the Resulted Products——General Procedure: The following compounds were carried out for the hydrogenated study: X, VIII, and IX; XI, VI, and VII. In autoclave, acetic acid solution (10 ml) of one of the above compounds (0.15 mmol) was hydrogenated in the presence of platinum (100 mg as PtO_2) at room temperature under 1.0, 3.0, and 100 kg/cm^2, respectively. After hydrogen absorption was ceased, the catalyst was filtered off and the solvent was evaporated to give the residue, which was extracted with ether. The ether extract was washed with 10% KOH aq., then H_2O and dried over Na_2SO_4. Removal of ether gave a mixture as colorless oil, whose components were examined by gas–liquid chromatography (X or XI→XII,[9] t_R=4.8 min and XIII,[9] t_R=3.9 min, 1.5% OV-17 on Shimalite W, 4 mm × 1.8 m, 190°. VIII or VI→XIV, t_R=8.5 min and XV, t_R=7.1 min; IX or VII→XVI, t_R=12.6 min and XVII, t_R=11.5 min, 1.5% OV-17 on Gaschrom P, 4 mm × 1.8 m, 210°). A ratio of the re-

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sulted isomers (*anti-cis-* and *anti-trans-*B/C-ring fusion) was calculated by peak area (height × width at half height) in the respective chromatogram.

Result: The result of the hydrogenation was as shown in Table I. As a general tendency, the higher the pressure was, the more amount of an isomer having *cis*-B/C-ring fusion was. For a preparation of B/C-*cis*- and -*trans*-isomer, catalytic hydrogenation (Pt-catalyst) of acetoxy ester (IX) under higher pressure (100 kg/cm^2) and, otherwise, of hydroxy ester (VI) under lower pressure (1.0 kg/cm^2) was more available respectively.

Furthermore, hydrogenolysis was simultaneously occurred with reduction of trien-esters (VIII and IX) and monoen-esters (VI and VII). Its facility was increased in the following order: VI>IX>VIII>VII and under the lower hydrogen pressure than higher one.

Methyl 6β-Acetoxy-8βH,9βH-*enantio*-podocarpan-16-oate (XVI) by Catalytic Reduction (Pt-catalyst) o Methyl 6β-Acetoxy-*enantio*-podocarpa-8,11,13-trien-16-oate (IX) (Available Preparation of *cis*-B/C-isomeric Series)——The following condition was best for preparation of the hexahydro-isomer series having *cis*-B/C-ring fusion. A solution of acetoxy ester (IX) (200 mg) in AcOH (50 ml) in the presence of platinum (400 mg as PtO_2) was shaken for 4 hr under hydrogen gas pressure (95—100 kg/cm^2) at room temperature. After hydrogen absorption was ceased, the catalyst was filtered off and the filtrate was condensed under reduced pressure. An ether-solution of the resulted residue was washed with 10% KOH aq., with sat. NaCl aq. and then dried over Na_2SO_4. Removal of ether gave crystals (201 mg), whose gas-liquid chromatogram showed that it consisted of *cis*-(XVI) and *trans*-hexahydro isomer (XVII) in ratio of 11:1 (t_R=14.7 min (XVI) and 13.6 min (XVII); 1.5% OV-17 on Shimalite W, 4 mm×1.8 m, 215°). The former crystals were recrystallized from MeOH-H_2O to colorless needles (167 mg), mp 63.5—64°. *Anal.* Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.50; H, 9.46. IR ν_{max}^{KBr} cm^{-1}: 1728, 1259, 1242. NMR τ: 9.14 (s, 3H; C_{10}-Me), 8.70 (s, 3H; C_4-Me), 7.99 (s, 3H; $OCOC\underline{H}_3$), 6.37 (s, 3H; $COOC\underline{H}_3$), *ca* 4.45 (m, half band width=24 cps), 1H; $\underline{H}$-C-OH).

Methyl 6β-Hydroxy-8αH,9βH-*enantio*-podocarpan-16-oate (XV) by Catalytic Reduction (Pd-C catalyst) of Methyl 6β-Hydroxy-*enantio*-podocarpan-8-en-16-oate (VI) (Available Preparation of *trans*-B/C-isomeric Series)——The following hydrogenated condition was best for preparation of the hexahydro-isomer series having *trans*-B/C-ring fusion. A solution of hydroxy-tetrahydro ester (VI) (84 mg) in MeOH (25 ml) was stirred for 52 hr in the presence of 10% Pd-C (100 mg) under hydrogen atmosphere. After the hydrogen absorption was ceased, the catalyst was filtered off and the solvent was evaporated. An ether extract of the resulted residue was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave colorless oil (82 mg), whose gas-liquid chromatogram showed it consisted of *trans*-hexahydro ester (XV) and the corresponding deoxy ester (XIII)$^{9)}$ in ratio of 6:1 (t_R=6.0 min (XV) and 2.7 min (XIII); 1.5% OV-17 on Gaschrom P, 4 mm×1.8 m, 200°).

The resulted oil (XV and XIII) was chromatographed on neutral alumina (10 g) to separate two fractions in petr. ether-ether (20:1) and successive petr. ether-ether (3:1) elution. The latter fraction (60 mg) was colorless oil (XV). *Anal.* Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.33; H, 10.27. IR ν_{max}^{film} cm^{-1}: 3535, 1723. NMR τ: 9.37 (s, 3H; C_{10}-Me), 8.54 (s, 3H; C_4-Me), 6.28 (s, 3H; $COOC\underline{H}_3$), *ca* 5.93 (m, 1H; H-C-OH).

On the other way, the crystals obtained from the former fraction were recrystallized from MeOH-H_2O to colorless needles (7 mg), mp 58—59°, which were identical with the standard deoxy ester having *trans*-B/C-ring fusion (XIII) by comparison of their IR spectrum (CCl_4).

Hydrolysis of Methyl 6β-Acetoxy-8βH,9βH-*enantio*-podocarpan-16-oate (XVI). 6β-Hydroxy-8βH,9βH-*enantio*-podocarpan-16-oic Acid (XVIII)——Acetoxy ester (XVI) (404 mg) was hydrolyzed by reflux with KOH (600 mg) in ethylene glycol (32 ml)-H_2O (1.6 ml) for 45 min. Subsequently, the reaction mixture was diluted with H_2O, acidified and then extracted with ether. The ether extract was washed with 10% KOH aq. and the alkaline extract was acidified, extracted with ether. After the extract was washed with sat. NaCl aq. and dried over Na_2SO_4, removal of the ether afforded colorless powder (336 mg), which was recrystallized from MeOH-H_2O to give colorless prisms (XVIII) (265 mg), mp 149.5—151°. *Anal.* Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.83; H, 10.22. IR ν_{max}^{KBr} cm^{-1}: 3355, 2710, 1711. NMR τ: 9.20 (s, 3H; C_{10}-Me), 8.51 (s, 3H; C_4-Me), 5.76 (m, (half band width=27 cps), 1H; $\underline{H}$-C-OH).

Methylation of 6β-Hydroxy-8βH,9βH-*enantio*-podocarpan-16-oic Acid (XVIII). Methyl 6β-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oate (XIV)——Hydroxy acid (XVIII) (203 mg) was methylated with excess CH_2N_2-ether solution in usual manner. The obtained crude crystals (215 mg) were recrystallized from MeOH-H_2O to colorless plates (XIV), mp 84—85°. *Anal.* Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.13; H, 10.39. IR ν_{max}^{KBr} cm^{-1}: 3525, 1700. NMR τ: 9.13 (s, 3H; C_{10}-Me), 8.53 (s, 3H; C_4-Me), 6.22 (s, 3H; $COOC\underline{H}_3$), *ca* 5.8 (m, 1H; $\underline{H}$-C-OH). t_R=7.5 min (1.5% OV-17 on Shimalite W, 4 mm×2.0 m, 230°).

Hydrolysis of Methyl 6β-Hydroxy-8βH,9βH-*enantio*-podocarpan-16-oate (XIV)——A solution of hydroxy ester (XIV) (30 mg) and KOH (210 mg) in MeOH (10 ml)-H_2O (0.8 ml) was refluxed for 1.5 hr. After the solvent was removed, the resulted residue was diluted with H_2O, acidified and extracted with ether. The ether extract was washed with 10% KOH aq. and the alkaline extract was acidified, then extracted with ether. After the extract was washed with H_2O and dried over Na_2SO_4, the solvent was evaporated to cry-

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stalline residue (23 mg), which was recrystallized from MeOH–H_2O to colorless prisms (XVIII), mp 150—151°. IR spectrum (KBr) of this compound was identical with that of the sample (XVIII) obtained by hydrolysis of acetoxy ester (XVI) as mentioned before.

Acetylation of Methyl 6β-Hydroxy-8βH,9βH-*enantio*-podocarpan-16-oate (XIV)——To a solution of hydroxy ester (XIV) (25 mg) in dry pyridine (4 ml), acetyl chloride (0.5 ml) was slowly added under ice-cooling. After the reaction mixture was left standing for 27 hr in refrigerator, it was poured into ice-water, acidified and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and then evaporated to give an oil (40 mg), which was purified by chromatography on neutral alumina (4.0 g). A colorless oil (15 mg) obtained from petr. ether–ether (3:1) elution was identical with the standard acetoxy ester (XVI) by comparison of retention time of its gas–liquid chromatography ($t_R = 12.7$ min, 1.5% OV-17 on Shimalite W, 4 mm × 1.8 m, 230°) and its IR spectra (CCl_4).

Acetylation of Methyl 6β-Hydroxy-8αH,9βH-*enantio*-podocarpan-16-oate (XV). Methyl 6β-Acetoxy-8αH,9βH-*enantio*-podocarpan-16-oate (XVII)——Acetyl chloride (0.5 ml) was slowly added to a solution of hydroxy ester (XV) (52 mg) in dry pyridine (2.0 ml) under ice-cooling. After the reaction mixture was left standing at room temperature for 0.5 hr and then in refrigerator for 4.5 hr, it was poured into ice-water, acidified and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give an oil (58.5 mg), which was purified by chromatography on neutral alumina (10 g). A colorless oil (XVII) (17.5 mg) was eluted from petr. ether–ether (10:1) fraction. *Anal.* Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.10; H, 9.57. IR ν_{max}^{film} cm^{-1}: 1729, 1249. NMR τ: 9.32 (s, 3H; C_{10}-Me), 8.67 (s, 3H; C_4-Me), 7.97 (s, 3H; OCOC$\underline{H}_3$), 6.34 (s, 3H; COOC$\underline{H}_3$), *ca* 4.9 (m, 1H; $\underline{H}$-C-OH). $t_R = 12.1$ min (1.5% OV-17 on Shimalite W, 4 mm × 1.8 m, 210°).

Hydrolysis of Methyl 6β-Hydroxy-8αH,9βH-*enantio*-podocarpan-16-oate (XV). 6β-Hydroxy-8αH,9βH-*enantio*-podocarpan-16-oic Acid (XIX)——A solution of hydroxy ester (XV) (830 mg) and KOH (3.19 g) in MeOH (150 ml)–H_2O (12 ml) was refluxed for 1 hr and then the solvent was removed under reduced pressure. The resulted residue was dissolved with H_2O, acidified and then extracted with ether. The extract was washed with 10% KOH aq. and the alkaline extract was acidified with HCl aq., then extracted with ether. After the extract was dried over Na_2SO_4, the solvent was removed to oily acidic fraction (XIX) (623 mg). A part (36 mg) of the fraction (XIX) was recrystallized from petr. ether–ether to give colorless fine cubics (9 mg), mp 107.5—109°. *Anal.* by high resoltuion mass spectrometry. Calcd. for $C_{17}H_{28}O_3$ (M^+; *m/e*): 280.20385. Found: 280.20249. IR ν_{max}^{KBr} cm^{-1}: 3423, 1694. NMR τ: 9.26 (s, 3H; C_{10}-Me), 8.50 (s, 3H; C_4-Me), *ca* 5.84 (m, (half band width = 27 cps), 1H; $\underline{H}$-C-OH).

Methylation of 6β-Hydroxy-8αH,9βH-*enantio*-podocarpan-16-oic Acid (XIX)——Hydroxy acid (XIX) (50 mg) was usually esterified by excess CH_2N_2–ether solution to quantitatively give an oil (51 mg), which was purified by chromatography on neutral alumina. A colorless oil obtained from petr. ether–ether (10:1) elution was identical with the standard hydroxy ester (XV) by comparison of their IR (film), NMR spectra and t_R.

Dehydration of Methyl 6β-Hydroxy-8βH,9βH-*enantio*-podocarpan-16-oate (XIV)——1) Dehydration by $POCl_3$–Pyridine: To a solution of hydroxy ester (XIV) (50 mg) in dry pyridine (4 ml), $POCl_3$ (1.3 ml) was slowly added under ice-cooling. The reaction mixture was left standing at room temperature for 23 hr, poured into ice-water and then extracted with ether. The extract was washed with 10% HCl aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave an oil (47 mg), whose gas–liquid chromatogram ($t_R = 8.2$ min (XX and XXI) and 23.2 min (XXII); 1.5% OV-17 on Shimalite W, 4 mm × 2.0 m, 180°) showed it was consisted of unsaturated esters (XX and XXI) and lactone (XXII)⁹⁾ in ratio of 1.74:1 (ratio of peak area: hight × width at half height). The oil was chromatographed on silica gel (15 g) to elute crystalline product (XX and XXI) (21 mg) in petr. ether–ether (19:1) fraction and then lactone (XXII) (22 mg) in the following petr. ether–ether (9:1) elution. Component ratio of the mixed unsaturated products (Δ^5-(XX) : Δ^6-ester (XXI) = 3:4) was determined by NMR analysis observed integral value of protons due to C_{10}-Me group (XX: 9.15; XXI: 9.22 τ).

The mixed oil (XX and XXI) was repeatedly chromatographed on alumina to separate the crystals, mp 62—83°, mainly consisted of XXI together with XX in ratio of 11 : 3 by determination of NMR analysis as above mentioned. No attempt for further purification made, so purity of the sample was not enough for elemental analysis. However, NMR information for pure Δ^6-ester (XXI) was acquired by deduction of NMR signal for pure Δ^5-component (XX)⁹⁾ from that of the mixed product (XX and XXI). The resulted NMR-pattern of Δ^6-ester (XXI), NMR τ: 9.22 (s, 3H; C_{10}-Me), 8.77 (s, 3H; C_4-Me), 4.22 (q, 2H, $J = 10.5$, 32.7 cps; CH-C$\underline{H}$=C$\underline{H}$-CH), 6.40 (s, 3H; COOC$\underline{H}_3$), was reasonable to support its structure.

2) Dehydration by MsCl–Pyridine: A solution of hydroxy ester (XIV) (35 mg) and MsCl (200 mg) in dry pyridine (1 ml) was heated at 100° for 2.5 hr. The reaction mixture was poured into ice-water, acidified and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give colorless oil (35 mg), whose components consisted of unsaturated products (Δ^5-(XX) and Δ^6-ester (XXI)) and lactone (XXII)⁹⁾ in ratio of 1.38:1. The ratio was measured by peak area (height × width at half height) in the gas–liquid chromatogram ($t_R = 7.8$ min (XX and XXI) and 22.9 min (XXII); 1.5% OV-17 on Shimalite W, 4 mm × 2.0 m, 180°). The mixed oil was chromatographed on silica gel (15 g) to separate the mixed ester (18 mg) (XX and XXI in ratio of 11:5) in petr. ether–ether (19:1) and the lactone (XXII) (17 mg) in

petr. ether–ether elution (9:1). A ratio of the mixed esters was measured by NMR analysis as mentioned in the case of dehydration by POCl$_3$–pyridine.

Catalytic Hydrogenation of Mixed Unsaturated Ester (XX and XXI) to Authentic Methyl 8βH,9βH-*enantio*-Podocarpan-16-oate (XII) and Methyl 8αH,9βH-enantio-Podocarpan-16-oate (XIII)——1) Hydogenation with Palatinum Catalyst: Mixed unsaturated ester (Δ^5-XX and Δ^6-ester (XXI)=3:4) (20 mg) obtained by POCl$_3$–dehydration of the hydroxy ester (XIV), was stirred in AcOH (10 ml) at room temaerature for 2.5 hr in the presence of platinum catalyst (100 mg as PtO$_2$) under hydrogen pressure (100 kg/cm^2). After the catalyst was filtered off, the solvent was removed under reduced pressure to give an oil (20 mg), whose gas–liquid chromatogram showed it was consisted of *cis*-B/C ester (XII)$^{9)}$ and *trans*-B/C ester (XIII)$^{9)}$ in ratio of 3.83:1 (t_R=4.8 min (XII) and 3.9 min (XIII); 1.5% OV-17 on Shimalite W, 180°). Further purification of the mixed oil by chromatography on silica gel (6 g) afforded an oil (7 mg) (XII: XIII=3.5:1) in petr. ether fraction. By comparison of their IR (film) (XII: 1379, 1125, 1043, 977, and XIII: 1018, 985 cm^{-1}), NMR spectrum (XII: 9.14 and XIII: 9.38 τ (C$_{10}$-Me)) and gas–liquid chromatogram, these components were respectively identical with the antipodal esters (XXIX and XXXII) synthesized *via* reliable route as described later.

2) Hydrogenation with Palladium–Charcoal Catalyst: Mixed unsaturated ester (Δ^5-(XX) and Δ^6-ester (XXI)=2:1) (27 mg) obtained by MsCl–dehydration of hydroxy ester (XIV), was stirred in MeOH (10 ml) at room temperature for 40 hr with Pd-C catalyst (50 mg) under hydrogen atmosphere. After the catalyst was filtered off, the solvent was removed under reduced pressure to give colorless oil, which was slowly crystallized and then recrystallized from MeOH–H$_2$O to colorless needles (XIII),$^{9)}$ mp 59—60°. By comparison of their IR (CCl$_4$), NMR spectra and retention time of gas–liquid chromatography (t_R=8.1 min; 1.5% OV-17 on Gaschrom P, 170°), the compound (XIII) was identical with the antipodal *trans*-B/C-standard (XXXII) synthesized *via* reliable route as described later.

Dehydration of Methyl 6β-Hydroxy-8αH,9βH-*enantio*-podocarpan-16-oate (XV)——1) Dehydration by POCl$_3$-Pyridine: Reaction mixture of hydroxy ester (XV) (45 mg) and POCl$_3$ (1.3 ml) in dry pyridine (4 ml) was treated as in the case of dehydration of isomeric hydroxy ester (XIV) having *cis*-B/C-ring fusion. The resulted colorless oil (42 mg) was chromatographed on silica gel (18 g) to separate an oil (34 mg) in petr. ether–ether (19:1) elution and then crystals (3 mg) in petr. ether–ether (9:1) elution. The latter crystals were recrystallized twice from MeOH–H$_2$O to colorless needles (XXV) (3 mg), mp 75—78°, whose mixed mp (75—81°), IR spectrum (CCl$_4$) and gas–liquid chromatogram (t_R=10.3 min; 1.5% OV-17 on Shimalite W, 4 mm × 2.0 m, 200°) was identical with those of 6α-lactone (XXV)$^{9)}$ having *trans*-B/C-ring fusion, mp 86—87°. The former mixed oil was indivisible each by gas–liquid chromatography, nevertheless NMR pattern due to the respective components (Δ^5-(XXIII) and Δ^6-ester (XXIV)) was disclosed by precise analysis; Δ^5-ester (XXIII), NMR τ: 9.25 (s, 3H; C$_{10}$-Me), 8.75 (s, 3H; C$_4$-Me), 6.40 (s, 3H; COOC$\underline{\text{H}}_3$), 4.35 (q, 1H, J=1.50, 4.50 cps; C=C$\underline{\text{H}}$-) and Δ^6-ester (XXIV), NMR τ: 9.38 (s, 3H; C$_{10}$-Me), 8.77 (s, 3H; C$_4$-Me), 6.40 (s, 3H; COOC$\underline{\text{H}}_3$), 4.33 (q, 2H, J=10.0, 36.0 cps; CH-C$\underline{\text{H}}$=C$\underline{\text{H}}$-CH) in ratio of 1:2. The ratio was measured by integral proton area due to the respective vinyl and C$_{10}$-methyl groups in the NMR spectrum of the mixture (XXIII and XXIV).

2) Dehydration by MsCl–Pyridine: A solution of β-hydroxy ester (XV) (35 mg) and MsCl (200 mg) in dry pyridine (1 ml) was treated as in the case of dehydration of isomeric hydroxy ester (XIV) having *cis*-B/C-ring fusion. The resulted brown oil (35 mg) was chromatographed on silica gel (15 g) to separate oily needles (25.5 mg) in petr. ether–ether (19:1) elution and then oil (5 mg) in petr. ether–ether (9:1) elution. The former oily crystals (XXIII and XXIV), mp 40—60°, were indistinguishable mixture by gas–liquid chromatography (t_R=6.65 min (single peak); 1.5% OV-17 on Shimalite W, 4 mm × 2.0 m, 180°), but were distinguished between the unsaturated esters (XXIII and XXIV) by NMR analysis. The ratio (XXIII: XXIV=5:6) was measured by integral proton area due to C$_{10}$-methyl group in the NMR spectrum.

Otherwise, two peaks in gas–liquid chromatogram (t_R=6.85 and 10.05 min; 1.5% OV-17 on Shimalite W, 4 mm × 2.0 m, 200°) of the latter oil corresponded to those of authentic samples (XV and XXV in ratio of 1:3.92).

Catalytic Hydrogenation of Mixed unsaturated Esters (XXIII and XXIV) to Authentic Methyl 8αH,9βH-*enantio*-Podocarpan-16-oate (XIII)——1) Hydrogenation with Platinum Catalyst: A solution of the mixed ester (XXIII and XXIV in ratio of 6:5; dehydration product by MsCl) (20 mg) in AcOH (10 ml) was stirred in presence of platinum (100 mg as PtO$_2$) under hydrogen pressure (100 kg/cm^2) at room temperature for 2.5 hr. After hydrogen absorption was ceased, the catalyst was filtered off and the solvent was removed to give colorless oil (XIII) (21 mg), t_R=7.6 min (1.5% OV-17 on Shimalite W, 4 mm × 2.0 m, 180°). Silica gel chromatography of the oil gave a crystalline compound (12 mg) in petr. ether elution. The crystals were recrystallized from MeOH–H$_2$O to give a colorless needles (XIII)$^{9)}$ (5.5 mg), mp 55—56.5°. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 1727, 1450, 1387, 1018, 985. NMR τ: 9.38 (s, 3H; C$_{10}$-Me), 8.84 (s, 3H; C$_4$-Me), 6.37 (s, 3H; COOC$\underline{\text{H}}_3$).

2) Hydrogenation with Palladium-Charcoal Catalyst: The mixed ester (XXIII and XXIV in ratio of 1:2; dehydration product by POCl$_3$) (10 mg) was hydrogenated in MeOH (3 ml) in the presence of 10% Pd-C (30 mg) under stirring for 23 hr. After hydrogen absorption was ceased, the catalyst was filtered off and the solvent was removed to give colorless oil. The oil was chromatographed on neutral alumina to

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isolate colorless needles (XIII) (5 mg), mp 59—61°, in petr. ether–ether (20:1) elution. By comparison of IR spectrum (CCl_4) and gas–liquid chromatogram ($t_R=11.1$ min; 1.5% OV-17 on Gaschrom P, 4 mm × 1.8 m, 170°), the crystal was identical with the standard antipodal ester (XXXII) synthesized *via* the reliable route.

Methylation of 8αH,9αH-Podocarpan-16-oic Acid (XXVIII). Methyl 8αH,9αH-Podocarpan-16-oate (XXIX)——According to J.W. ApSimon's method,[10] the acid (XXVIII) was synthesized from *d*-podocarpic acid (XXVI) *via* oxo-ester (XXVII).[11] Usual treatment of the acid (XXVIII) with excess CH_2N_2–ether solution quantitatively gave the corresponding ester (XXIX), colorless oil, bp 120°/2 × 10^{-3} mmHg (oil bath temp.). *Anal.* Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.91; H, 10.41. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1727. NMR τ: 9.14 (s, 3H; C_{10}-Me), 8.83 (s, 3H; C_4-Me), 6.37 (s, 3H; $COOC\underline{H}_3$).

Thioketalization of Methyl 12-Oxo-8βH, 9αH-podocarpan-16-oate (XXX). Methyl 12-Ethylene thioketal-8βH, 9αH-podocarpan-16-oate (XXXI)——Oxo ester (XXX) was obtained from *d*-podocarpic acid (XXVI) by R.H. Bible's method.[11] A solution of the oxo ester (XXX) (125 mg), ethane dithiol (0.15 ml) and *p*-TsOH (92 mg) in AcOH (3.0 ml) was left standing for 4 hr at room temperature. The reaction mixture was extracted with ether, the extract was washed with sat. Na_2CO_3 aq., H_2O and then dried over Na_2SO_4. Removal of the solvent gave crystals (150.5 mg), which were recrystallized from MeOH–H_2O to give colorless needles (XXXI), mp 141.5—143.5°. *Anal.* Calcd. for $C_{20}H_{32}O_2S_2$: C, 65.20; H, 8.75; S, 17.37. Found: C, 65.26; H, 8.69; S, 17.46. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1714. NMR τ: 9.38 (s, 3H; C_{10}-Me), 8.84 (s, 3H; C_4-Me), 6.74 (s, 4H; $-S-C\underline{H}_2-C\underline{H}_2-S-$), 6.38 (s, 3H; $COOC\underline{H}_3$).

Dethioketalization of Methyl 12-Ethylene thioketal-8βH,9αH-podocarpan-16-oate (XXXI). Methyl 8βH, 9αH-Podocarpan-16-oate (XXXII)——The ethylene thioketal (XXXI) (77 mg) was reduced by refluxing for 10 hr with Raney nickel W-7 (prepared from nickel alloy (2.1 g)) in distilled EtOH (15 ml). After the catalyst was filtered off, the solvent was removed to give colorless oil (54 mg), which was distilled, bp 105°/3 × 10^{-3} mmHg (oil bath temp.). The oil was recrystallized from MeOH–H_2O to colorless needles (XXXII), mp 59—61°. *Anal.* Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.48; H, 10.98. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1727, 1158. NMR τ: 9.38 (s, 3H; C_{10}-Me), 8.84 (s, 3H; C_4-Me), 6.38 (s, 3H; $COOC\underline{H}_3$). $t_R=11.2$ min (1.5% OV-17 on Gaschrom P, 4 mm × 1.8 m, 170°).

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