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Diterpenoids. XVII.¹⁾ Epimerization at Lactonization of 6 β -Hydroxy-*enantio*-podocarpan (and 8-monoen-)16-oic Acid (*cis*- and *trans*-B/C-ring Juncture) Syntheses of the Corresponding 6 α -Hydroxy Series

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Previously, it was found that a remarkable epimerization ($\beta\text{C}_6\text{-O} \rightarrow \alpha$) was occurred when 6 β -hydroxy acid (II) was lactonized. In order to further examine on the mechanism and the limitation of the epimerization, the corresponding hydrogenated 6 β -hydroxy acids (V, XIV and XXX) were chosen as model. One of them (XXX) was completely different, however the other (V and XIV) were epimerized as similar to (II).

During the synthetic investigation of diterpene alkaloid from *l*-abeitic acid (I), an attractive epimerization of hydroxyl group was found on the occasion of lactonization.³⁾ Namely, when 6 β -hydroxy-*enantio*-podocarpa-8,11,13-trien-16-oic acid (II) was treated with mineral acid, the acid (II) was converted to the corresponding 16 $\rightarrow$ 6 α -lactone (IV) with epimerization at C₆-configuration. Otherwise, the isomeric lactone (III) having a retained C₆-configuration was formed under thermal condition. The lactone (III) is so unstable that it would be impossible to purify and is readily converted to the stable lactone (IV) by further thermal or alumina treatment.³⁾

Analogous examples concerning with the epimerization in lactone ring and at lactonization were already known in the literatures as shown in Table I. However, our epimerization (II $\rightarrow$ IV) was caused in an usual lactonization between a simple hydroxyl- and carboxyl-group under acidic condition. Accordingly, our epimerization is fairly different from the many examples known as references, so it would be regarded as an unique reaction.

In general, it is believed that a configuration of hydroxyl group is not inverted under the usual condition of lactonization. On the above assumption, lactonization in a compound having a hydroxyl and carboxyl group is used to elucidate a stereochemistry of the hydroxyl group.

Accordingly, a detailed investigation on the relation between the exceptional epimerization and its structure (*e.g.* the effect of aromatic C-ring of II to the lactonization) is important, so 6 β -hydroxy-tetrahydro and -hexahydro acid series (*e.g.* V, XIV and XXX) are suitable for the examination of the structural boundary in the lactonization. In our last paper,¹⁾ preparative syntheses of 6 β -hydroxy-*enantio*-podocarpan-16-oic acid (*cis* and *trans*-B/C-ring juncture (XIV and XXX) and 8-monoen acid (V)) were achieved by hydrogenation of the aromatic ring of (II).

When C₆-epimerization was occurred at lactonization of the 6 β -hydroxy-tetrahydro and -hexahydro acids, the corresponding 6 α -hydroxy isomers were expected to be synthesized. The knowledge on these isomeric compounds would be served for the studies of diterpenoids

1) Preliminary Communication: A. Tahara and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **17**, 1529 (1969); Part XVI: A. Tahara, Y. Ohtsuka, N. Umino, K. Nagasawa and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **19**, 1756 (1971). All melting points were measured on Koflor block and were uncorrected. NMR spectra were measured at 60Mc in CDCl₃ vs. Me₄Si 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, *Tetrahedron*, **21**, 2133 (1965).

TABLE I

Epimerization of lactone	Epimerization at lactonization

a) D.H.R. Barton, *J. Org. Chem.*, **15**, 466 (1950)b) H. Ishikawa, *Yakugaku Zasshi*, **76**, 504 (1956)

c) H. Ogura and M. Yanagita, International Symposium on the Chem. of Natural Product (Kyoto), Abstract 31 (1964)

d) G. Lucius, *Chem. Ber.*, **93**, 2663 (1960)e) E.J. Corey and R.R. Sauer, *J. Am. Chem. Soc.*, **81**, 1739 (1959).f) H.H. Appel, J.D. Connolly, K.H. Overton and R.P.M. Bond, *J. Chem. Soc.*, **1960**, 4685g) A.A. Patchett and B. Witkop, *J. Am. Chem. Soc.*, **79**, 185 (1957).h) J. Meinwald and J.K. Crandall, *J. Am. Chem. Soc.*, **88**, 1292 (1966)i) J. Meinwald, J.C. Shelton, G.L. Buchanan and A. Courtin, *J. Org. Chem.*, **33**, 99 (1968)

having 6-hydroxyl group, which were recently advanced by several research groups.⁴⁾

Among the aimed compounds, chemical behavior at acidic lactonization of 6 β -hydroxy-podocarp-8-en-16-oic acid (V) was firstly examined. The acid (V) obtained by reduction (Li-*tert*-AmOH-EtNH₂) of the corresponding triene acid (II)³⁾ was refluxed with hydrochloric acid in *tert*-butanol to give a lactone (VI), mp 85–87°, whose physical data showed an absence of nuclear magnetic resonance (NMR)-signal due to ester and an existence of infrared (IR) absorption (1761 cm⁻¹) for lactone. *tert*-Butanol was used as solvent instead of methanol for prevention of esterification occurred in parallel with the lactonization. Alkaline hydrolysis of the lactone (VI) did not regenerate the original hydroxy acid (V), but gave a new hydroxy acid (VII). Although the physical constants of the new acid (VII), mp 206–207°, IR- and NMR-spectrum, were completely different from those of the original acid (V) (Table II), the both acids (V and VII) were readily lactonized to the same lactone (VI). α -Configuration of C₆-hydroxyl group of the acid (VII) was proved by chemical conversion (reduction by Li-EtNH₂-*tert*-AmOH) of the acid (VIII)³⁾ having a reliable α C₆-hydroxyl group into the acid (VII) in question.

Usual methylation (CH₂N₂) of the 6 α -hydroxy acid (VII) afforded the corresponding ester (IX), mp 91.5–93°, whose IR and NMR spectrum were also completely different from the isomeric 6 β -hydroxy ester (XII) reported in the last paper¹⁾ (Table II). The ester (IX) was easily hydrolyzed to the original hydroxy acid (VII) accompanied with the 6 α -lactone (VI). The lactone (VI) would be produced by heating of 6 α -hydroxy ester (IX) and remained itself under even the alkaline condition.

4) cf. reference 4) in the last paper (Part XVI).¹⁾

Chart 1

Besides the above lactone formation (V→VI) by acidic condition, 6β-hydroxy acid (V) was converted to the other type of unstable oily lactone (X) under the following mild condition: 1) thermal fusion (210°, 1 hr), 2) *p*-toluenesulfonic acid in benzene and 3) dicyclohexylcarbodiimide (DCC) in pyridine. NMR-analyses of these products showed that the lactone (X) obtained by thermal fusion was always contaminated with a small amount of the stable lactone (VI) and, otherwise, X yielded by two other ways was in almost pure state. Physical data of the unstable lactone (X), IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1770, 1107 and NMR τ : 8.97 8.74 (C₁₀- and C₄-Me), *ca.* 5.72 ($\text{H-C}_6\text{-OH}$) are quite distinct from those of the stable crystalline lactone (VI), IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1761, 1121, 1049 and NMR τ : 9.05 8.73 (C₁₀- and C₄-Me), *ca.* 5.02 ($\text{H-C}_6\text{-OH}$) (Table III). The lactone (X) was so unstable to readily epimerize to the stable lactone (VI) by 1) more drastic thermal fusion (260°, 5 hr), 2) alumina treatment (room temperature, 2 days) and 3) acidic condition as same as in the lactonization (V→VI). Since the unstable lactone (X) was easily converted to the stable lactone (VI) and the lactone (VI) was hydrolyzed to the different isomeric acid (VII) from the original one V, the unstable lactone (X) is presumably retained the same C₆-configuration as the original acid (V) and, therefore, the stable lactone (VI) would be formed from V and X through epimerization at C₆-configuration ($\beta \rightarrow \alpha$ -C-O bond).

Further confirmation of the structures of the above lactones, especially of C₆-configuration, was advanced as follows. Lithium aluminium hydride reduction of the lactones (VI) and (X) yielded the respective hydroxy alcohols (XI), mp 141–143° and XIII, mp 138–139°. Both alcohols (XI and XIII) were evidently different each other (Table II) and were respec-

tively identical with products obtained by LiAlH_4 -reduction of 6α -IX and 6β -hydroxy ester (XII), which had a reliable C_6 -hydroxyl configuration.

Subsequently, lactonization attitude of 6β -hydroxy-hexahydro acid having *anti-cis*-XIV¹⁾ and *anti-trans*-B/C-ring juncture (XXX)¹⁾ will be described. Lactonization of the *cis*-acid (XIV) was proceeded in the same behavior as the 6β -hydroxy acids (II and V) above mentioned. The 6β -hydroxy acid (*cis*-B/C-ring juncture) (XIV) was readily lactonized to XV, mp 159.5—161° under two acidic conditions (reflux with HCl aq.-*tert*-BuOH and -MeOH). Alkaline hydrolysis (reflux with KOH aq.-EtOH) of the lactone (XV) did not give the original acid (XIV), but afforded the isomeric new hydroxy acid (XVI), mp 187—188°, which returned to the original lactone (XV) under acidic condition (reflux with HCl aq.-MeOH). The corresponding hydroxy ester (XVII), mp 110—111.5° obtained by diazomethane-treatment of the acid (XVI), was completely different from the reported 6β -hydroxy ester (XVIII)¹⁾ by comparison with their physical constants (mp, IR and NMR spectrum) (Table II). Alkaline hydrolysis (reflux with KOH -EtOH- H_2O) and alumina treatment of the hydroxy ester (XVII) gave the starting hydroxy acid (XVI) and the lactone (XV), respectively.

Chart 2

TABLE II. Physical Constants

		R'=H	R'=βOH	R'=αOH	R'=H	R'=βOH	R'=αOH
R=COOMe	m.p.	140—141°	(XXXVIII) 79—80°	(XXXIX) 144—147°	(XL) 84—87°	(XII) bp 175°/ 0.003 mmHg	(IX) 91.5—93°
	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹	1727			1720	3545 1733 1710 1237 1170 (CCl ₄)	3460 1709 1159 1045
	NMR(τ) C ₁₀ -Me	8.97	8.98	8.63	9.23	9.20	8.94
	C ₄ -Me	8.73	8.54	8.70	8.79	8.53	8.68
	COOMe		6.25	6.63	6.33	6.26	6.20
	C ₆ -H				ca. 5.73	ca. 5.39	
R=COOH	mp		(II) 156—158°	(VIII) 163.5—165°		(V) oil	(VII) 206—207°
	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹		3580 3400 1726 1693 1240	3210 2360 1735 1675 1270		3430 1695	3270 2435 1682 1273
	NMR(τ) C ₁₀ -Me		8.88	8.63		9.09	8.88
	C ₄ -Me		8.44	8.72		8.48	8.67
	C ₆ -H				ca. 5.65	ca. 4.62	
R=CH ₂ OH	mp		163—164.5°	176—177.5°		(XIII) 138—139°	(XI) 141—143°
	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹		3310	3310		3275 1076 1017	3270 1097 1025
	NMR(τ) C ₁₀ -Me		8.71	8.45		8.90	8.64
	C ₄ -Me		8.71	8.90		8.80	8.94
	CH ₂ OH					6.64 5.75	6.79 5.70
						(J=10.5 cps)	(J=12 cps)

The stereochemistry on B/C-ring juncture of the C₆-epimerized compounds (XV, XVI and XVII) is certain to be *anti-cis*, because these compounds were converted from the reported 6 β -hydroxy acid (XIV)¹⁾ having secure *cis*-B/C-ring fusion *via* lactonization.

For further confirmation of the B/C-ring juncture of the above compounds, chemical relation of the hydroxy ester (XVII) with the authentic ester (XX) having a certain *cis*-B/C-ring juncture was carried out by dehydration and successive catalytic hydrogenation. The dehydration of 6 α -hydroxy ester (XVII) was performed by treatment with methanesulfonyl chloride- or phosphorous oxychloride-pyridine. The former method gave a chromatographically separable mixture consisting of Δ^5 -ester (XIX) and 6 α -lactone (XV) and, otherwise, the latter one yielded only pure Δ^5 -ester (XIX), mp 63—64°.¹⁾ The dehydration is different from the case of 6 β -hydroxy ester (XVIII) that the dehydrated mixture always consisted of Δ^6 -ester (XXII), Δ^5 -ester (XIX) and 6 α -lactone (XV), unsaturated part of which could not be separated in pure state as reported before.¹⁾ The specific formation of Δ^5 -ester (XIX) obtained from 6 α -hydroxy ester (XVII) can be reasoned by *trans*-diaxial elimination between 6 α -hydroxyl group and *tert*-5 β -hydrogen of XVII.

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		R'=H	R'=βOH	R'=αOH	R'=H	R'=βOH	R'=αOH
R=COOMe	mp	(XX) bp 120° 0.002 mmHg	(XVIII) 84 — 85°	(XVII) 110—111.5°	(XXI) 59—61°	(XXXI) oil	(XXXIV) 142.5—144.5°
	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹	1727	3525 1700	3430 1695 1232 1165	1727 1158 (film)	3535 1723 1157 1042 (film)	3440 1696 1167
	NMR(τ) C ₁₀ -Me	9.14	9.13	8.92	9.37	9.37	9.12
	C ₄ -Me	8.83	8.53	8.73	8.83	8.54	8.71
	COOMe	6.37	6.22	6.22	6.37	6.28	6.235
	C ₆ -H		ca. 5.8	ca. 5.45		ca. 5.93	ca. 5.58
R=COOH	mp		(XIV) 149.5—151°	(XVI) 187—188°		(XXX) 107.5—109°	(XXXV) 227.5—228.5°
	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹		3355 2710 1711	3220 2560		3423	3260 2425 1694 1682
	NMR(τ) C ₁₀ -Me		1266 9.02	1678 1270		1694	
	C ₄ -Me		8.51			9.26 8.50	
	C ₆ -H		ca. 5.76			ca. 5.84	
R=CH ₂ OH	mp		(XXIX) 152.5—155°	(XXVIII) 208—209.5°		(XXXVI) 141.5—143°	(XXXVII) 157.5—158.5°
	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹		3310 1087 1058	3190 1067 1023		3270 1450 1039	3150 1077 1016
	NMR(τ) C ₁₀ -Me		8.83	8.62		9.09	8.83
	C ₄ -Me		8.78	9.02		8.78	8.975
	CH ₂ OH		6.62 5.80	6.89 5.68		6.68 5.84	6.87 5.72
			(J=10.5 cps)	(J=12 cps)		(J=10.5 cps)	(J=10.5 cps)

The catalytic hydrogenation mode described in our last paper¹⁾ was that the configuration of B/C-ring juncture was retained in hydrogenation of mixture of Δ^5 - and Δ^6 -ester (XIX and XXII→XX or XXIII and XXIV→XXI) with platinum catalyst, but was inverted to more stable isomer having *trans*-B/C-ring juncture (XIX and XXII or XXIII and XXIV→XXI) in hydrogenation with palladium-charcoal. A similar behavior was shown in the hydrogenation of the pure Δ^5 -ester (XIX) obtained herein for the first time. In order to ascertain on B/C-ring juncture, Δ^5 -ester was hydrogenated with platinum catalyst to give only a saturated ester (XX), bp 120°/2 × 10⁻³ mmHg, which was compared with the authentic antipodal standard (XXV)^{1,5)} having *cis*-B/C-ring fusion. As the result, B/C-ring juncture of 6 α -hydroxy series that led to Δ^5 -ester was proved to be *cis*. In the other way, hydrogenation with palladium-charcoal of Δ^5 -ester (XIX) gave an inverted ester (XXI), mp 59—61°, having a stable *trans*-B/C-ring fusion, which was also proved by comparison with the authentic antipodal

5) cf. J.W. ApSimon, D.E. Edwards and R. Howe, *Can. J. Chem.*, **40**, 630 (1962).

standard (XXVI).^{1,6)} The saturated esters (XX and XXI) were firstly reported in pure state in this paper.

Synthesis of an unstable lactone (XXVII) with the same configuration of C₆-hydroxyl group as that of 6 β -hydroxy acid (XIV), was carried out by three kinds of condition: 1) thermal fusion, 2) *p*-toluenesulfonic acid in benzene and 3) DCC-pyridine treatment as in the case of II and V. An observation of its gas-liquid chromatography and NMR-spectrum indicated that the product obtained by the former two methods (thermal and *p*-TsOH treatment) consisted of 6 β -XXVII and 6 α -lactone (XV) in ratio of 12:5 and 7:3, respectively, whereas DCC-pyridine treatment afforded only pure 6 β -lactone (XXVII). The 6 β -lactone (XXVII) was furthermore heated (250° for 4 hr 10 min and 270° for 3 hr 45 min) to epimerize to the isomeric 6 α -lactone (XV). The conversion of the unstable lactone (XXVII) to the stable lactone (XV) was also performed by treatment with neutral alumina and by reflux with HCl aq.

According to the above chemical behavior on 6 α -XV and 6 β -lactone (XXVII), it become known that an epimerization occurs at C₆-position during acidic lactonization of 6 β -hydroxy acid (XIV) and chemical treatment of the unstable lactone (XXVII). Further evidence on the epimerization was given by chemical conversion of both 6 β - and 6 α -lactone (XXVII and XV) to the corresponding different 6 β - and 6 α -hydroxy alcohol (XXIX), mp 152.5–155° and (XXVIII), mp 208–209.5°. The structures of hydroxy alcohols (XXIX and XXVIII) were proved by identification with reduction products (LiAlH₄) of 6 β - and 6 α -hydroxy ester (XVIII and XVII) having the reliable C₆-configuration, respectively.

In contrast to the lactonization of 6 β -hydroxy acid series (II, V and XIV) described above, it is remarkable that chemical behavior of 6 β -hydroxy acid having *anti-trans*-B/C-ring fusion (XXX)¹⁾ was entirely different.

Chart 3

Many efforts of lactonization of the 6 β -hydroxy acid (XXX) under acidic condition (reflux for 2.5 hr with 10% HCl aq.-*tert*-BuOH and -MeOH) completely resulted in failure and only afforded the recovered acid (methyl ester (XXXI) was observed as additional product in using methanol as solvent). However, treatment of the acid (XXX) under the same condition (reflux for 10 min with *p*-toluenesulfonic acid in benzene) as used for the preparation of

6) cf. R.H. Bible and R.R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961).

unstable 6 β -lactones (III, X and XXVII) yielded a pure lactone (XXXII), mp 98—99.5°, IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1773, in quantitative yield. The lactone (XXXII) is unexpectedly stable and its sharp melting point, IR and NMR spectrum indicate to be not mingled with the epimerized 6 α -lactone (XXXIII), in contrast to the other mixed 6 β -lactones (III, X and XXVII) having unsharpened melting point. Unlike the other unstable 6 β -lactones, the pure 6 β -lactone (XXXII) was hydrolyzed to regenerate the starting 6 β -hydroxy acid (XXX) and was not converted to C₆-epimerized lactone under condition of thermal (265° for 2 hr), alumina (room temperature for 2 days)⁷⁾ and HCl aq. (reflux for 30 min) treatment.⁷⁾ Accordingly, the preparative method of 6 α -hydroxy derivatives having *anti-trans*-B/C-ring juncture was switched to another route.

6 α -Hydroxy-tetrahydro ester (IX) already elucidated as 6 α -hydroxyl configuration was catalytically hydrogenated in the presence of palladium-charcoal, which was specific catalyst for *trans*-addition of hydrogen to $\Delta^{8(9)}$ -double bond.¹⁾ Silica gel chromatography of the resulted product afforded the aimed 6 α -hydroxy ester (XXXIV), mp 142.5—144.5° and oily 6-deoxy ester (XXI) in ratio of 8.6:1, which were easily separable. Alumina treatment (room temperature for 40 hr) of the ester (XXXIV) readily lactonized to 6 α -lactone (XXXIII), mp 86—87°, which was different from the corresponding 6 β -lactone (XXXII) (Table III) and was identical with one of the dehydrated products (POCl₃-pyridine) of 6 β -hydroxy ester (XXXI) reported in our last paper.¹⁾

TABLE III. Physical Constants of Lactones

m.p.	174—176°	130—140°	85—87°	oil	159.5—161°	120—150°	86—87°	98—99.5°
IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹	1758	1774	1761	1770	1762	1766	1758	1773
	1110 (CCl ₄)	1090 (CCl ₄)	1121	1107	1050	1080	1202	1103
	1040 (CCl ₄)		1049	999	1003	1027	1153	1045
					932	990	1096	996
							997	
NMR (τ) C ₁₀ -Me	8.91	8.83	9.045	8.97	9.12	8.89	9.06	9.125
C ₄ -Me	8.75	8.70	8.73	8.74	8.72	8.74	8.73	8.74
C ₆ -H		ca. 5.37	ca. 5.02	ca. 5.72	ca. 5.05	ca. 5.83	ca. 5.25	ca. 5.92
GC (1.5% OV-17 on Shimadzu W, 4 mm $\times$ 2.0 m, 200°)					11.00	11.70	10.00	9.30

The 6 α -lactone (XXXIII) was hydrolyzed under alkaline condition (reflux with KOH-H₂O-EtOH for 2 hr) to 6 α -hydroxy acid (XXXV), mp 227.5—228.5°. Acid treatment (reflux with HCl aq.-MeOH for 30 min) and usual methylation (CH₂N₂) of the acid (XXXV) yielded the original lactone (XXXIII) and the corresponding ester (XXXIV), respectively.

Considering their synthetic route, the structures of both lactones (XXXII and XXXIII) were undeniably presumed. Additionally, further proof was adduced as in the other case mentioned above. The both lactones (XXXII and XXXIII) were reduced by LiAlH₄ to give the respective 6 β -hydroxy alcohol (XXXVI), mp 141.5—143° and 6 α -hydroxy alcohol (XXXVII), mp 157.5—158.5°, whose structures were reliably ascertained by identification with the corresponding hydroxy alcohols (XXXVI and XXXVII) led from 6 β -(XXXI) and

7) It was observed by gas-liquid chromatography that alumina and HCl aq. treatment of the 6 β -hydroxy acid (XXX) produced a small amount of epimerized lactone (XXXIII).

6 α -hydroxy esters (XXXIV) having certain C₆-configuration, respectively. The characteristic behavior of 6 β -hydroxy acid (XXX) and 6 β -lactone (XXXII) having *anti-trans*-B/C-ring juncture would be presumably affected by their structural feature, but the definite answer is not yet supplied.

Successively, the noticeable C₆-epimerization of 6 β -hydroxy acids (II, V and XIV) and 6 β -lactones (III, X and XXVII) will be examined in detail for a study of its mechanism. The comparative investigations of four pairs (II, III; V, X; XIV, XXVII and XXX, XXXII) of 6 β -hydroxy acids and 6 β -lactones were carried out under the same condition shown in Table IV. Besides, two solvent systems (MeOH and *tert*-BuOH) were used in these experiments, because *tert*-BuOH prevent from esterification of the used compounds (6 β -hydroxy acids and 6 β -lactones) unlike MeOH.

TABLE IV. Comparative Examination of Epimerization under the Acidic Condition.
Substance (0.1 mmole) in MeOH (or *tert*-BuOH) and 10% HCl aq.
(5:2.3 V/V). Reflux (bath temp., 110°) for 30 min

Starting material	Solvent	Product						Ratio of ester and 6 α -lactone
		Epimerized 16 $\rightarrow$ 6 α -lactone (%)	6 β -Hydroxy ester (%) (Methylation by solvent)	6 β -Hydroxy acid (%)	Total yield ^{a)} (%)			
II	MeOH	IV	29.5	XXXVIII 11.1	II	59.5	100.1	XXXVIII/IV=0.376
	<i>tert</i> -BuOH		32.8	—		64.0	99.8	
III ^{b)}	MeOH	IV	17.1	XXXVIII 53.0	II	30.0	100.1	XXXVIII/IV=3.1
	<i>tert</i> -BuOH		52.3	—		40.5	92.8	
V	MeOH	VI	10.8	XII <1.0	V	80.0	<i>ca.</i> 91	XII/VI=>0.01
	<i>tert</i> -BuOH		11.4	—		75.4	86.9	
X ^{b)}	MeOH	VI	23.0	XII 27.1	V	33.7	83.8	XII/VI=1.18
	<i>tert</i> -BuOH		11.6	—		44	55.6	
XIV	MeOH	XV	73.4	XVIII 1.6	XIV	12.6	87.6	XVIII/XV=0.022
	<i>tert</i> -BuOH		81.0	—		15	96	
XXVII	MeOH	XV	46.6	XVIII 34.3	XIV	0	80.9	XVIII/XV=1.36
	<i>tert</i> -BuOH		75.0	—		18.1	93	
XXX	MeOH	unepimerized 16 $\rightarrow$ 6 β -lactone XXXII	0.58	XXXI 2.02	XXX	94.0	96.6	
	<i>tert</i> -BuOH ^{c)}		3.84	—		87.0	90.8	
XXXII	MeOH	unepimerized 16 $\rightarrow$ 6 β -lactone XXXII	0.24	XXXI 83.0	XXX	15.2	98.44	
	<i>tert</i> -BuOH ^{c)}		1.0	—		93	94	

After the reaction was ceased, the resulted mixture itself (GLC -1) and its methylated product (CH₂N₂-treatment) (GLC -2) were analyzed by gas-liquid chromatography. Ratio of the produced components was estimated by peak area (height $\times$ width at half height) in the chromatogram. The gaschromatographic observation of reaction product itself (GLC -1) indicated only ratio of neutral product itself (lactone and ester, e.g. IV/XXXVIII=29.5%/11.1% in the case of II) and, otherwise, that of the methylated product (GLC -2) showed that acidic components were methylated and additionally appeared in the peaks of the corresponding esters (e.g. IV/XXXVIII=29.5%/70.6% in the case of II). Accordingly, the deducted value of the former chromatogram (GLC. -1) from the latter one (GLC -2) in the ester peak was equivalent to the value due to the acidic part (70.6—11.1=59.5%=II).

a) In case of less than 100% of total yield, the other undefined products were found as by-product.

b) The used 16 $\rightarrow$ 6 β -lactones (III and X) were contaminated with small amount of 16 $\rightarrow$ 6 α -lactones (IV and VI).

c) The reaction time was 2.5 hr instead of usual 30 min.

As a result, some workable suggestions were offered for the mechanism of the epimerized lactonization. Namely, two possible ways (route 1 and 2 in Chart 4) are reasonably considered for the mechanism. One of the routes (route 1) is the way that the epimerization (A $\rightarrow$ C) was occurred *via* 6 β -lactone formation (B). The other way (route 2) is suspected to be one step reaction that 4-carboxyl group attacks to the backside of 6-hydroxyl group to form the epimerized lactone (A $\rightarrow$ D $\rightarrow$ C),⁸⁾ just as S_N-2 reaction.

8) In the reaction intermediate (D), the 6-hydroxyl group may be axial in a boat form of B-ring.

Chart 4

If the reaction only proceeds through the route 1, yield ratios of 6β-hydroxy esters (methylation by solvent) and epimerized lactones obtained from 6β-hydroxy acids (in MeOH) should be equal to or be larger than those of the products yielded directly from the 6β-lactones. Because a direct route to 6β-hydroxy ester from 6β-hydroxy acid can be considered in addition to a route through 6β-lactone. In point of the fact, the observed ratios of products obtained from 6β-hydroxy acids ($\text{II} \rightarrow \text{XXXVIII}/\text{IV} = 0.376$; $\text{V} \rightarrow \text{XII}/\text{VI} < 0.01$ and $\text{XIV} \rightarrow \text{XVIII}/\text{XV} = 0.022$) are conversely smaller than that yielded from 6β-lactones ($\text{III} \rightarrow \text{XXXVIII}/\text{IV} = 3.1$; $\text{X} \rightarrow \text{XII}/\text{VI} = 1.18$ and $\text{XXVII} \rightarrow \text{XVIII}/\text{XV} = 1.36$) and, accordingly, acidic lactonization of 6β-hydroxy acids should proceed through only route 2 or competitive ways (route 1 and 2).

A few tendencies are shown from data in the Table IV.

i) Yields of epimerized 6α-lactone from 6β-hydroxy acid (HCl aq. in *tert*-BuOH) are in the following order: $(\text{XIV}) \rightarrow (\text{XV})$ (81%) $>$ $\text{II} \rightarrow \text{IV}$ (32.8%) $>$ $\text{V} \rightarrow \text{VI}$ (11.4%) $>$ $\text{XXX} \rightarrow \text{XXXII}$ (unepimerized lactone: 3.8%). Yield order of the recovered acid found in the lactonization is properly reversed: XXX (87%) $>$ V (75.4%) $>$ II (64%) $>$ XIV (15%).

ii) Yield of epimerization (HCl aq. in *tert*-BuOH) of 6β-lactone to 6α-lactone are in the following order: $\text{XXVII} \rightarrow \text{XV}$ (75%) $>$ $\text{III} \rightarrow \text{IV}$ (52.3%) $>$ $\text{X} \rightarrow \text{VI}$ (11.6%) $>$ XXXII (unepimerized). The facility orders of the lactonization (i) and the epimerization (ii) show the same tendency and depend on the structure of B/C-ring juncture.

iii) 6β-Hydroxy acids were not so easy to esterify at the epimerized lactonization (HCl aq. in MeOH), however, 6β-lactones was easier to convert to 6β-hydroxy ester under the same condition and the order is as follows: $\text{XXXII} \rightarrow \text{XXXI}$ (83%) $>$ $\text{III} \rightarrow \text{XXXVIII}$ (53%) $>$ $\text{XXVII} \rightarrow \text{XVIII}$ (34.3%) $>$ $\text{X} \rightarrow \text{XII}$ (27.1%).

iv) Acidic hydrolyses (HCl aq. in *tert*-BuOH) of 6β-lactones to 6β-hydroxy acids proceed in the following order: $\text{XXXII} \rightarrow \text{XXX}$ (93%) $>$ $\text{X} \rightarrow \text{V}$ (44%) $\approx$ $\text{III} \rightarrow \text{II}$ (40.5%) $>$ $\text{XXVII} \rightarrow \text{XIV}$ (18.1%). Conclusively, an accurate relation between the facility of lactonization and the structure is not yet obvious from these observations.

In the last¹⁾ and this papers, 6β- and 6α-hydroxy acid derivatives and 6β- and 6α-lactone series have been accomplished to synthesize. The physical data of these compounds were summarized in the Table II and III. NMR-analyses on methyl groups of 6-hydroxy-tetrahydro and -hexahydro esters were similarly argued as those of 6β-XXXVIII and 6α-hydroxy ester (XXXIX) in our previous paper.³⁾ It is generally known that NMR-signal of methyl group shifted 10 to 15 cps to lower magnetic field at 60Mc when a hydroxyl group was located

colse to methyl group in steroid series.⁹⁾ Analogous phenomenon was observed in our compounds. Namely, chemical shifts due to methyl groups nearly located to C₆-hydroxyl group; C₄-methyl of 6 β -hydroxy esters (XII: 8.53 τ , XVIII: 8.53 τ and XXXI: 8.54 τ) and C₁₀-methyl of 6 α -hydroxy esters (IX: 8.94 τ , XVII: 8.92 τ and XXXIV: 9.12 τ) are shifted to lower magnetic field than those of the deoxy standard (XL¹⁰⁾: 8.79 τ (C₄-Me), 9.23 τ (C₁₀-Me); XX¹⁾: 8.83 τ (C₄-Me), 9.14 τ (C₁₀-Me) and XXI¹⁾: 8.83 τ (C₄-Me), 9.37 τ (C₁₀-Me)).

Furthermore, NMR spectrum on proton attached to the same 6-position as hydroxyl function was examined. The chemical shifts of 6 α -hydrogens in 6 β -hydroxy esters (XII: *ca.* 5.73 τ , XVIII: *ca.* 5.8 τ and XXXI: *ca.* 5.93 τ) are appeared in higher magnetic field than those of 6 β -hydrogens in 6 α -hydroxy esters (IX: *ca.* 5.39 τ , XVII: *ca.* 5.45 τ and XXXIV: *ca.* 5.58 τ) respectively. This observation is consistent with their structural assignment of 6 β -hydroxy esters (ax. C₆-H and eq. C₆-OH) and 6 α -hydroxy esters (eq. C₆-H and ax. C₆-OH). In general, an ax.-proton in cyclohexane ring is expected to appear in higher magnetic field in relative to an eq. one.¹¹⁾

On investigation of their IR spectra, it is noticeable that carbonyl frequencies of the unstable 6 β -lactones ($\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: X: 1770; XXVII: 1766 and XXXII: 1773) are higher than those of stable 6 α -lactones ($\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: VI: 1761; XV: 1762 and XXXIII: 1758). The fact obviously shows that 6 β -lactones have larger strain of the lactone ring.

In conclusion, syntheses of 6 α -hydroxy derivatives were accomplished by the aid of epimerized lactonization of 6 β -hydroxy acid and properties of the both isomeric 6-hydroxy compounds were comparatively studied in this report.

Experimental

Epimerized Lactonization of 6 β -Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (V). 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oic Acid 16 $\rightarrow$ 6 α -Lactone (VI)—After a reaction mixture of 6 β -hydroxy acid (V) (200 mg)¹⁾ in *tert*-BuOH (25 ml) and 15% HCl aq. (30 ml) was refluxed for 3 hr, the solvent was evaporated and the resulted residue was extracted with ether. The extract was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄. Removal of the ether gave crystals (80 mg), which were recrystallized from MeOH-H₂O to colorless needles (VI), mp 85–87°. *Anal.* Calcd. for C₁₇H₂₄O₂: C, 78.42; H, 9.25. Found: C, 78.18; H, 8.95. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1761, 1121, 1049. NMR τ : 9.045 8.73 (s, 3H; C₁₀- and C₄-Me), *ca.* 5.02 (m, 1H; H-C₆-OH), t_R = 11.2 min (2% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 185°).

Alkaline Hydrolysis of 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oic Acid 16 $\rightarrow$ 6 α -Lactone (VI)—6 α -Lactone (VI) (22 mg) was hydrolyzed by reflux with KOH (180 mg) in MeOH (1.5 ml) and H₂O (0.1 ml) for 1.5 hr. After the solvent was removed under reduced pressure, the residue was diluted with H₂O and extracted with ether. The water layer was acidified, extracted with ether and the extract was washed with H₂O, then dried over Na₂SO₄. Removal of ether gave crystals (18 mg), which were recrystallized from MeOH-H₂O to colorless powder (VII), mp 203–208°. IR spectrum (KBr) and mp (mixed mp) of the acid were completely identical with those of 6 α -hydroxy acid (VII) prepared by reduction (Li-EtNH₂-*tert*-AmOH reduction) of 6 α -hydroxy acid having aromatic C-ring VIII as described later.

Lactonization of 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (VII)—A solution of 6 α -hydroxy acid (VII) (100 mg) in *tert*-BuOH (20 ml) and 10% HCl aq. (15 ml) was refluxed for 30 min. Then the solvent was removed and the resulted residue was extracted with ether. The extract was washed with 10% KOH aq., then H₂O and dried over Na₂SO₄. Removal of ether afforded crystals (70 mg) as neutral part, which were recrystallized from MeOH-H₂O to give colorless needles, mp 85–87°. The crystals were completely identical with the 6 α -lactone (VI) synthesized from 6 β -hydroxy acid (V) by comparison of mp, mixed mp and IR spectrum (KBr). On the other hand, the alkaline extract was acidified, extracted with ether and then dried over Na₂SO₄. Removal of the solvent gave the starting 6 α -hydroxy acid (VII) (30 mg).

Reduction (Li-EtNH₂-*tert*-AmOH) of 6 α -Hydroxy-*enantio*-podocarpa-8,11,13-trien-16-oic Acid (VIII). 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (VII)—To a solution of 6 α -hydroxy acid (VIII) (200 mg)³⁾ in dry EtNH₂ (15 ml)-*tert*-AmOH (1.0 g), granular Li-metal (250mg) was added. The reaction mixture was stirred

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at room temperature for 4 hr and then small amount of MeOH was added. The residue obtained by solvent evaporation, was diluted by H₂O, acidified and extracted with ether. The ether extract was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄ (neutral part). Removal of ether gave an oil (60 mg), which was identical with 6 α -hydroxy alcohol (XI) by comparison of IR spectrum (CCl₄) and gas-liquid chromatogram (t_R =11.1 min; 2.0% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 190°).

Otherwise, the alkaline extract was acidified and extracted with ether. The extract was washed with H₂O, then dried over Na₂SO₄ (acidic part) and evaporated to white powder (150 mg), which was recrystallized from MeOH-H₂O to give white powder VII, mp 206–207°. *Anal.* Calcd. for C₁₇H₂₆O₃: C, 73.34; H, 9.41. Found: C, 73.29; H, 9.27. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3270, 2435, 1682, 1273. NMR τ : 8.88 (s, 3H; C₁₀-Me), 8.67 (s, 3H; C₄-Me), *ca.* 4.62 (m (half band width=*ca.* 10.5 cps), 1H; H-C₆-OH).

Methylation of 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oic-Acid (VII). Methyl 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oate (IX)—Usual treatment of 6 α -hydroxy acid (VII) (70 mg) with excess CH₃N₂-ether solution quantitatively gave colorless crystals, which were recrystallized by H₂O addition to its MeOH-solution without heating to give colorless leaflets IX (40 mg), mp 91.5–93°. *Anal.* Calcd. for C₁₈H₂₈O₃: C, 73.93; H, 9.65. Found: C, 73.53; H, 9.59. IR $\nu_{\max}^{\text{CCl}_4}$ cm⁻¹: 3460, 1709, 1159, 1049. NMR τ : 8.94 (s, 3H; C₁₀-Me), 8.68 (s, 3H; C₄-Me), 6.20 (s, 3H; COOCH₃), *ca.* 5.39 (m (half band width=9 cps), 1H; H-C₆-OH). t_R =9.5 min (2% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 185°).

Alkaline Hydrolysis of Methyl 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oate (IX).—A solution of 6 α -hydroxy ester (IX) (50 mg) and KOH (700 mg) in MeOH (15 ml)-H₂O (1ml) was refluxed for 1 hr 20 min. After the solvent was evaporated and then H₂O was added, the reaction mixture was acidified under ice-cooling and was extracted with ether. The ether extract was washed with 10% KOH aq., with H₂O and dried over Na₂SO₄. Removal of ether gave colorless solid (34.5 mg), which was recrystallized from MeOH-H₂O to needles, mp 82–86°. The compound was completely identical with 6 α -lactone (VI) by comparison of their IR spectra (CCl₄).

On the other way, the alkaline extract above mentioned was acidified with HCl aq. and the appeared white precipitates were extracted with ether. The extract was washed with H₂O, dried over Na₂SO₄ and the solvent was removed. The resulted colorless crystals (10 mg) were recrystallized from MeOH-H₂O to fine needles, mp 198–198.5°, whose IR spectrum (KBr) and mixed mp were identical with those of 6 α -hydroxy acid (VII).

Lactonization of 6 β -Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (V). 6 β -Hydroxy-*enantio*-podocarp-8-en-16-oic-Acid 16 $\rightarrow$ 6 β Lactone (X)—1) Lactonization by Thermal Fusion: 6 β -Hydroxy acid (V)¹¹ (150 mg) was heated in sealed tube at oil bath (210°) for 1 hr. The reaction mixture was dissolved in ether and the extract was washed with sat. Na₂CO₃ aq., with H₂O, then dried over Na₂SO₄. Removal of the solvent gave a neutral oil (X) (73.5 mg), IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 1770, 1107, 999. NMR τ : 8.97 8.74 (s, 3H; C₁₀- and C₄-Me), *ca.* 5.72 (m, 1H; H-C₆-OH). *Anal.* by high resolution mass spectrometry. Calcd. for C₁₇H₂₄O₂ (M⁺; *m/e*): 260.1776. Found: 260.1785. The oil had lactone properties, but was completely different from 6 α -lactone (VI).¹²⁾

On the other hand, the alkaline (Na₂CO₃) extract was acidified, extracted with ether and dried over Na₂SO₄. The solvent was evaporate to acidic crystals (70 mg), which were identical with the starting material (V).

2) Lactonization with *p*-TsOH: A solution of 6 β -hydroxy acid (V) (50 mg) and *p*-TsOH (20 mg) in dry benzene (50 ml) was distilled under nitrogen atmosphere for 10 min until the distillate attained to *ca* 20 ml. The resulted residue was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄. Removal of the solvent gave an oily lactone (X) (45.5 mg), whose IR spectrum (CCl₄) was identical with that of 6 β -lactone (X) mentioned above.¹²⁾

3) Lactonization by Dicyclohexylcarbodiimide (DCC)-Pyridine: Reaction mixture of 6 β -hydroxy acid (V) (40 mg) and DCC (30 mg) in pyridine (3 ml) was heated at 100° for 60 min under nitrogen atmosphere. After cooling, the solvent was removed reduced pressure. Chloroform extract of the residue was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄. Ether solution of the residue obtained by removal of CHCl₃ was left standing overnight at -10°. The appeared precipitates were filtered off and the filtrate was condensed to give quantitatively the oily 6 β -lactone (X) (37 mg), which was identical with 6 β -lactone (X) by comparison of IR (CCl₄) and NMR spectrum.¹²⁾

Epimerization of 6 β -Hydroxy-*enantio*-podocarp-8-en-16-oic Acid 16 $\rightarrow$ 6 β -Lactone (X). 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oic-Acid 16 $\rightarrow$ 6 α -Lactone (VI)—1) Epimerization by Thermal Fusion: In a sealed tube, 6 β -hydroxy acid (V) (60 mg) was heated at 200–210° (oil bath temperature) for 1 hr 10 min in the same condition for a preparation of 6 β -lactone (X) from 6 β -hydroxy acid (V) and further at 265° (bath temperature) for 5 hr. Ether extract of the resulted brown solid was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄. Removal of ether gave light brown oil (38 mg), which as wrecrystallized from MeOH-H₂O to colorless needles VI (10 mg), mp 80–85°. IR spctum (CCl₄) and gas-liquid

12) IR- and NMR-analysis showed that DCC method gave a pure 6 β -lactone (X), but the other methods (thermal and *p*-TsOH method) afforded 6 β -lactone (X) including with small amount of 6 α -lactone (VI).

chromatogram ($t_R=6.3$ min; 1.5% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 210°) of the crystals were identical with those of 6 α -lactone (VI).

2) **Epimerization by Alumina Treatment:** A solution of 6 β -lactone (X) (*p*-TsOH preparation) (40 mg) in ether (20 ml) was treated with neutral alumina (8 g) at room temperature for 2 days. Alumina was filtered off and the filtrate was evaporated to give an oil, whose IR absorptions (CCl_4) at 1085, 990 cm^{-1} due to 6 β -lactone (X) were diminished and those at 1112, 1043 cm^{-1} due to 6 α -lactone (VI) were appeared. The oil was treated with CH_2N_2 -ether solution for esterification of acidic part. Gas-liquid chromatography of the resulted oil ($t_R=6.3$ min; 1.5% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 210°) showed it consisted of 6 α -lactone (VI) (46%) together with unidentified products, yields of which were measured by ratio of peak area (peakheight $\times$ width at half height).

3) **Epimerization by HCl aq. Treatment:** The experiment was described later.

LiAlH_4 -reduction of 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oic Acid 16 $\rightarrow$ 6 α -Lactone (VI). 6 α -Hydroxy-*enantio*-podocarp-8-en-16-ol (XI)—To a solution of 6 α -lactone (VI) (77 mg) in dry ether (40 ml), LiAlH_4 (100 mg) was added. The reaction mixture was refluxed for 3 hr and was left standing overnight at room temperature. It was diluted with H_2O , acidified and extracted with ether. The extract was washed with H_2O , dried over Na_2SO_4 and evaporated to crude crystals (90 mg), which were recrystallized from $\text{MeOH-H}_2\text{O}$ to colorless powder XI, mp 141–143°. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{28}\text{O}_2$: C, 77.22; H, 10.67. Found: C, 77.28; H, 10.51. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3270, 1097, 1025. NMR τ : 8.94 (s, 3H; $\text{C}_4\text{-Me}$), 8.64 (s, 3H; $\text{C}_{10}\text{-Me}$), 6.79 (d, 1H, $J=12$ cps; CH_2OH), 5.70 (d, 1H, $J=12$ cps; CH_2OH). $t_R=15.1$ min (1.5% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m 180°).

LiAlH_4 -reduction of Methyl 6 α -Hydroxy-*enantio*-podocarp-8-en-16-oate (IX)— LiAlH_4 (120 mg) was added to 6 α -hydroxy ester (IX) (73 mg) in dry ether (40 ml). The reaction mixture was refluxed for 3 hr and left standing overnight at room temperature. The same treatment of the reaction mixture as in case of VI gave crude crystals (40 mg), which were recrystallized from $\text{MeOH-H}_2\text{O}$ to colorless powder XI, mp 140–141°. The compound was identical with the 6 α -hydroxy alcohol (XI) obtained from 6 α -lactone (VI) by comparison of IR spectrum (KBr) and gas-liquid chromatogram ($t_R=10.8$ min; 1.5% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 190°).

LiAlH_4 -reduction of 6 β -Hydroxy-*enantio*-podocarp-8-en-16 $\rightarrow$ 6 β -Lactone (X)—To a solution of 6 β -lactone (X) (prepared by fusion method and mixed with small amount of 6 α -lactone (VI)) (24 mg) in dry ether (20 ml), LiAlH_4 (40 mg) was added and the reaction mixture was refluxed for 3 hr. Same treatment of the reaction mixture as in case of VI gave an oil (16.5 mg), whose IR absorption (CCl_4) at 3700, 3340 cm^{-1} was appeared instead of disappearance of absorption at 1780 cm^{-1} due to lactone group.

The oil was chromatographed on neutral alumina (10 g) to separate white powder (15 mg) in ether elution. Its gas liquid chromatogram ($t_R=14.7$ min; 1.5% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 180°) showed it consisted of β -hydroxy alcohol (XIII) together with small amount of α -hydroxy alcohol (XI) shown as shoulder in chromatogram. The compound was recrystallized twice from $\text{MeOH-H}_2\text{O}$ to colorless fine needles (2.0 mg), mp 132–135°, whose IR spectrum (KBr) was completely identical with that of 6 β -hydroxy alcohol (XIII) obtained by reduction of 6 β -hydroxy ester (XII).

LiAlH_4 -reduction of Methyl 6 β -Hydroxy-*enantio*-podocarp-8-en-16-oate (XII). 6 β -Hydroxy-*enantio*-podocarp-8-en-16-ol (XIII)—6 β -Hydroxy ester (XII)¹⁾ (110.5 mg) was reduced in dry ether (50 ml) by reflux with LiAlH_4 (200 mg). The same treatment of the reaction mixture as in case of (VI) gave crystals (80 mg), which were recrystallized from $\text{MeOH-H}_2\text{O}$ to colorless prisms (XIII), mp 138–139°. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{28}\text{O}_2$: C, 77.22; H, 10.67. Found C, 77.36; H, 10.85. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3275, 1075, 1017. NMR τ : 8.90, 8.80 (s, 3H; $\text{C}_4\text{-}$ or $\text{C}_{10}\text{-Me}$), 6.64 (d, 1H, $J=10.5$ cps; CH_2OH), 5.75 (d, 1H, $J=10.5$ cps; CH_2OH). $t_R=14.6$ min (1.5% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 180°).

Epimerized Lactonization of 6 β -Hydroxy-8 β H, 9 β H-*enantio*-podocarp-16-oic Acid (XIV) 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarp-16-oic Acid 16 $\rightarrow$ 6 α -Lactone (XV)—1) **Lactonization with HCl aq.-*tert*-BuOH:** A solution of 6 β -hydroxy acid (XIV)¹⁾ (476 mg) in 10% HCl aq. (10 ml) and *tert*-BuOH (40 ml) was refluxed for 2 hr. The reaction mixture was evaporated under reduced pressure and the resulted residue was extracted with ether after H_2O was added. The extract was washed with 10% KOH aq. (acidic part), then with H_2O and dried over Na_2SO_4 (neutral part). a) **Neutral Part:** The ether extract was evaporated to crude crystals (172 mg), which were recrystallized from $\text{MeOH-H}_2\text{O}$ to colorless needles XV, mp 159.5–161°. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_2$: C, 77.82; H, 9.99. Found: C, 77.54; H, 9.90. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1762, 1050, 1003, 932. NMR τ : 9.12, 8.72 (s, 3H; $\text{C}_{10}\text{-}$ and $\text{C}_4\text{-Me}$), *ca.* 5.05 (m (half band width=18 cps), 1H; H-C-OH). $t_R=10.4$ min (3.0% OV-17 on Shimalite W, 4 mm $\times$ 1.8 m, 230°). b) **Acidic Part:** The alkaline extract was acidified, extracted with ether and the ether extract was dried over Na_2SO_4 . Removal of the solvent gave a viscous oil (263 mg), which treated with excess CH_2N_2 -ether solution to give an oil. The compound was identical with 6 β -hydroxy ester (XVIII) by comparison of their IR spectra (CCl_4) and gas-liquid chromatogram ($t_R=7.7$ min; 3.0% OV-17 on Shimalite W, 4 mm $\times$ 1.8 m, 230°).

2) **Lactonization with HCl aq.-MeOH:** A solution of 6 β -hydroxy acid (XIV)¹⁾ (24.5 mg) in 10% HCl aq. (2.3 ml) and MeOH (5.0 ml) was refluxed for 2.5 hr. Removal of the solvent gave colorless needles, mp 156–159.5°, whose IR spectrum (CCl_4) was identical with that of 6 α -lactone (XV) mentioned above. Gas-

liquid chromatogram (t_R = 9.5 min (XV), 6.9 min (XVIII), 3.25 min (unknown part); 1.5% OV-17 on Gaschrom P, 4 mm $\times$ 2.0 m, 200°) of methylated product (CH_2N_2 -ether solution) of the crude needles showed it consisted of 6 α -lactone (XV), 6 β -hydroxy ester (XVIII)¹³ and unknown part in ratio (ratio of peak area: peak height $\times$ width at half height) of 93:3:4.

Alkaline Hydrolysis of 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oic Acid 16 $\rightarrow$ 6 α -Lactone (XV). 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oic Acid (XVI)—A reaction mixture of 6 α -lactone (XV) (85 mg) in 50% KOH aq. (3 ml) and EtOH (15 ml) was refluxed for 1 hr and then evaporated under reduced pressure. After H_2O was added to the resulted residue, it was extracted with ether and the extract was washed with H_2O , dried over Na_2SO_4 . a) Neutral Part: The ether extract was evaporated to give needles (16.5 mg), which were identical with the starting 6 α -lactone (XV) by comparison of IR-spectrum (CCl_4) and gas-liquid chromatogram (t_R = 14.6 min; 1.5% NGS on Shimalite W, 4 mm $\times$ 1.8 m, 220°). b) Acidic Part: The alkaline water layer was acidified with HCl aq. and the appeared precipitates were extracted with ether. The extract was washed with H_2O and dried over Na_2SO_4 . Removal of ether gave crude crystals (73.5 mg), which were recrystallized from MeOH- H_2O to give colorless prisms (XVI), mp 187–188°. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{28}\text{O}_3$: C, 72.82; H, 10.06. Found: C, 72.34; H, 9.95. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3220, 2560, 1678, 1270.

Lactonization of 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oic Acid (XVI)—A solution of 6 α -hydroxy acid (XVI) (30 mg) in 10% HCl aq. (5 ml) and MeOH (10 ml) was refluxed for 30 min. After the solvent was evaporated and H_2O was added, it was extracted with ether. The extract was washed with 10% KOH aq., then with H_2O and dried over Na_2SO_4 . The solvent was evaporated to colorless needles (32.5 mg), which were recrystallized from MeOH- H_2O to colorless needles (XV) (20 mg), mp 159–160.5°. Mixed mp, IR spectrum (KBr) and gas-liquid chromatogram (t_R = 7.8 min 1.5% OV-17 on Shimalite W, 4 mm $\times$ 2.0 m, 180°) of the crystals were identical with those of 6 α -lactone (XV).

Methylation of 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oic Acid (XVI). Methyl 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oate (XVII)—Usual treatment of 6 α -hydroxy acid (XVI) (100 mg) with excess CH_2N_2 -ether solution quantitatively gave the corresponding ester, which was recrystallized from MeOH- H_2O without heating¹³) to colorless plates XVII (80 mg), mp 110–111.5° (drying below 40°). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{30}\text{O}_3$: C, 73.43; H, 10.27. Found: C, 73.49; H, 10.12. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3430, 1695, 1237, 1165. NMR τ : 8.92 (s, 3H; $\text{C}_{10}\text{-Me}$), 8.73 (s, 3H; $\text{C}_4\text{-Me}$), 6.22 (s, 3H; COOCH_3), *ca.* 5.45 (m (half band width = *ca.* 7.5 cps), 1H; $\text{H-C}_6\text{-OH}$).

Alkaline Hydrolysis of Methyl 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oate (XVII)—A reaction mixture of 6 α -hydroxy ester (XVII) (50 mg) and KOH (100 mg) in EtOH (15 ml)- H_2O (1.0 ml) was refluxed for 1.5 hr. After the solvent was removed and H_2O was added, it was acidified by HCl aq. under ice-cooling and extracted with ether. The ether extract was washed with 10% KOH aq. (acidic part), then with H_2O and dried over Na_2SO_4 (neutral part). a) Neutral Part: The ether extract was removed to needles (35 mg), which were identical with 6 α -lactone (XV) by comparison of their IR spectra (CCl_4) and gas-liquid chromatograms (t_R = 9.1 min; 1.5% OV-17 on Shimalite W, 4 mm $\times$ 2.0 m, 180°). The lactone (XV) would be produced by heating of ester (XVII)¹³) and then remained itself under alkaline condition. b) Acidic Part: The alkaline extract was acidified under ice-cooling and the appeared precipitates were extracted with ether. The extract was washed with H_2O , then dried over Na_2SO_4 and evaporated to crude crystals (18 mg), which were recrystallized from MeOH- H_2O to colorless needles, mp 187–189°. Mixed mp and IR spectrum (KBr) was identical with those of 6 α -hydroxy acid (XVI).

Alumina Treatment of Methyl 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oate (XVII)—Neutral alumina (2.5 g) was added to a ether solution of 6 α -hydroxy ester (XVII) (25 mg) and ether was evaporated. After the mixture was left standing for 40 hr at room temperature, it was extracted with ether (*ca.* 60 ml) and the solvent was removed to give colorless needles (22 mg). The crystals were recrystallized from MeOH- H_2O to colorless needles (18 mg), mp 158–160°, which was identical with 6 α -lactone (XV) by comparison of IR (CCl_4) and gas-liquid chromatography (t_R = 11.05 min; 1.5% OV-17 on Shimalite W, 4 mm $\times$ 2 m, 200°).

Dehydration of Methyl 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oate (XVII). Methyl 8 β H, 9 β H-*enantio*-Podocarp-5-en-16-oate (XIX)—1) Dehydration by MsCl-Pyridine: A solution of 6 α -hydroxy ester (XVII) (200 mg) and MsCl (350 mg) in dry pyridine (2.0 ml) was heated at 85–90° for 2 hr 15 min. The resulted reaction mixture was poured into ice-water, then it was acidified and extracted with ether. The extract was washed with H_2O , dried over Na_2SO_4 and evaporated to give an oil (197 mg), which was chromatographed on neutral alumina (10 g) to separate an oil (91.5 mg) in petr. ether-ether (40:1) elution and crystals (95 mg) in successive same fraction. The latter crystals were identical with 6 α -lactone (XV) by comparison of their IR spectra (CCl_4).

On the other way, the former oil was distilled at 80°/3 $\times$ 10⁻³ mmHg and then recrystallized from MeOH- H_2O to colorless needles XIX, mp 63–64°. *Anal.* Calcd. for $\text{C}_{18}\text{H}_{28}\text{O}_2$: C, 78.21; H, 10.21. Found: C, 78.44; H, 10.19. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1729, 1650. NMR (100 Mc) τ : 9.13 (s, 3H; $\text{C}_{10}\text{-Me}$), 8.74 (s, 3H; $\text{C}_4\text{-Me}$),

13) The 6 α -hydroxy ester (XVII) was readily lactonized to 6 α -lactone (XV) by i) heating in MeOH- H_2O at 60° and ii) treatment with neutral alumina in ether.

6.40 (s, 3H; COOCH₃), 4.37 (q, 1H, $J=1.75$, 6.50 cps; $>CH-CH_2$). As IR and NMR spectrum of the unsaturated ester (XIX) were superimposable before and after the chromatography, a concern of double bond migration on alumina was rule out.

2) Dehydration by POCl₃-Pyridine: To a solution of 6 α -hydroxy ester (XVII) (100 mg) in dry pyridine (4 ml), POCl₃ (1 ml) was added under ice-cooling and then it was left standing at room temperature for 22 hr. The resulted mixture was poured into ice-water and it was extracted with ether. The extract was washed with H₂O and dried over Na₂SO₄. Removal of ether gave an oil (86.5 mg), a part (66 mg) of which was chromatographed on neutral alumina (10 g) to give crystals (61 mg) in petr. ether-ether (19:1) elution. The crystals were recrystallized from MeOH-H₂O to colorless needles (45 mg), mp 63–64°, whose IR (CCl₄), NMR spectrum and gas-liquid chromatogram ($t_R=4.0$ min; 1.5% OV-17 on Gaschrom P, 4 mm $\times$ 2.0 m, 240°) were completely identical with those of Δ^5 -ester (XIX).

Catalytic Hydrogenation of Methyl 8 β H, 9 β H-*enantio*-Podocarp-5-en-16-oate (XIX)—1) Hydrogenation (platinum catalyst) of Δ^5 -Ester (XIX) to Methyl 8 β H, 9 β H-*enantio*-Podocarp-16-oate (XX): A solution of Δ^5 -ester (XIX) (34.5 mg) in AcOH (8.2 ml) was shaken in presence of platinum (82 mg as PtO₂) under H₂-gas pressure (100 kg/cm²) for 2.5 hr. After absorption of H₂-gas was ceased, the catalyst was filtered off and the filtrate was evaporated. Ether extract of the resulted residue was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄. Removal of ether gave colorless oil, which was chromatographed on alumina to give an oil (27 mg) in petr. ether elution. Distillate of the oil (XX) at 120°/2 $\times$ 10⁻³ mmHg was identical with the authentic sample XXV^{1,5)} having complete antipodal structure by comparison of their IR (film), NMR spectrum and gas-liquid chromatogram. *Anal.* Calcd. for C₁₈H₃₀O₂: C, 77.65; H, 10.86. Found: C, 77.87; H, 10.72. IR ν_{max}^{film} cm⁻¹: 1727, 1155. NMR τ : 9.14 (s, 3H; C₁₀-Me), 8.83 (s, 3H; C₄-Me), 6.37 (s, 3H; COOCH₃). $t_R=15.0$ min (1.5% OV-17 on Gaschrom P, 4 mm $\times$ 2.0 m, 190°).

2) Hydrogenation (Palladium-Charcoal Catalyst) of Δ^5 -Ester (XIX) to Methyl 8 α H, 9 β H-*enantio*-Podocarp-16-oate (XXI): Δ^5 -Ester (XIX) (84 mg) was hydrogenated in MeOH (25 ml) with 10% Pd-C (80 mg) for 14 hr under hydrogen atmosphere. After gas absorption was ceased, the catalyst was filtered off and the filtrate was evaporated to give colorless oil (78.5 mg). Distilled oil at 100–105°/3 $\times$ 10⁻³ mmHg was slowly crystallized and recrystallized from MeOH-H₂O to colorless needles (XXI), mp 59–61°. *Anal.* Calcd. for C₁₈H₃₀O₂: C, 77.65; H, 10.86. Found: C, 77.65; H, 10.54. IR ν_{max}^{film} cm⁻¹: 1727, 1158. NMR τ : 9.37 (s, 3H; C₁₀-Me), 8.83 (s, 3H; C₄-Me), 6.37 (s, 3H; COOCH₃). $t_R=11.15$ min (1.5% OV-17 on Shimalite W, 4 mm $\times$ 2.0 m, 180°). IR (film), NMR spectrum and gas-liquid chromatogram of the compound were identical with those of antipodal specimen XXVI^{1,6)} obtained from *d*-podocarpic acid *via* reliable route.

Lactonization of 6 β -Hydroxy-8 β H, 9 β H-*enantio*-podocarp-16-oic Acid (XIV). 6 β -Hydroxy-8 β H, 9 β H-*enantio*-podocarp-16-oic Acid 16 $\rightarrow$ 6 β -Lactone (XXVII)—1) Lactonization by Thermal Fusion: 6 β -Hydroxy acid (XIV)¹⁾ (50 mg) was heated at 200° for 1 hr in a sealed tube and the resulted oil was extracted with ether. The extract was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄. Removal of solvent gave crude crystals (48 mg), which were recrystallized from MeOH-H₂O without heating to mp 120–150°. Its gas-liquid chromatogram and NMR (Table III) showed so-called 6 β -lactone (XXVII) was contaminated with 6 α -lactone (XV) in a proportion of 5/12. *Anal.* Calcd. for C₁₇H₂₆O₂: C, 77.82; H, 9.99. Found: C, 77.34; H, 9.72. IR ν_{max}^{KBr} cm⁻¹: 1766, 1080, 1027, 990. NMR τ : 8.89, 8.74 (s, 3H; C₁₀- or C₄-Me), *ca* 5.84 (m, 1H; -C₆H-OH). $t_R=14.7$ min (*cf.* 6 α -lactone (XV): 13.7 min; 1.5% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 200°).

2) Lactonization with *p*-TsOH: A solution of 6 β -hydroxy acid (XIV)¹⁾ (47 mg) and *p*-TsOH (19 mg) in dry benzene (47 ml) was distilled for 10 min under N₂-gas stream until the distillate was come up to *ca.* 15–20 ml. The residue was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄. Removal of the solvent gave crystals (48 mg), whose gas-liquid chromatogram (respective peak area) showed it consisted of 6 β -(XXVII) and 6 α -lactone (XV) in ratio of 7:3.

3) Lactonization by DCC-Pyridine: A reaction mixture of 6 β -hydroxy acid (XIV)¹⁾ (40 mg) and DCC (30 mg) in pyridine (3 ml) was heated at 100° for 1 hr under N₂-gas stream. After the solvent was removed, the resulted residue was dissolved in CHCl₃ and then was filtered. The filtrate was washed with 10% KOH aq., then with H₂O and dried over CaCl₂. Removal of CHCl₃ gave crude crystals, which were dissolved in ether and it was left standing overnight at *ca.* -10°. The appeared precipitates were filtered off and the filtrate was evaporated to give crude product (39.5 mg), whose IR (CCl₄) and NMR spectrum indicated it mainly consisted of 6 β -hydroxy lactone (XXVII). However, it was difficult to separate the lactone (XXVII) off from DCC.

Epimerization of 6 β -Hydroxy-8 β H, 9 β H-*enantio*-podocarp-16-oic Acid 16 $\rightarrow$ 6 β -Lactone (XXVII). 6 α -Hydroxy 8 β H, 9 β H-*enantio*-podocarp-16-oic Acid 16 $\rightarrow$ 6 α -Lactone (XV)—1) Epimerization by Thermal Fusion: 6 β -Lactone (XXVII) (50 mg) obtained from 6 β -hydroxy acid (XIV) by thermal fusion method (a mixture of 6 β -(XXVII) and 6 α -lactone (XV) in ratio of 12:5), was heated at 250° for 4 hr 10 min (its IR spectrum (CCl₄) showed 6 β -lactone (XXVII) still remained) and, furthermore, at 270° for 3 hr 45 min. The resulted product was extracted with ether and the extract was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄. Removal of the solvent gave crude crystals (40 mg), which were recrystallized from MeOH-H₂O to give colorless needles, mp 152–153°, whose IR spectrum (KBr) was identical with 6 α -lactone (XV).

2) Epimerization by Neutral Alumina: In the presence of neutral alumina (2 g), a solution of 6 β -lactone (XXVII) (10 mg) (prepared by thermal fusion method) in ether (5 ml) was left standing at room temperature for 2 days. After alumina was filtered off, the filtrate was evaporated to crude crystals (10 mg), whose IR spectrum (CCl₄) indicated it mainly consisted of 6 α -lactone (XV) together with a small amounts of 6 β -lactone (XXVII). The crystals were chromatographed on neutral alumina to separate crystals (10 mg) in petr. ether-ether (3:1) elution and recrystallized from MeOH-H₂O to colorless needles, which were completely identical with 6 α -lactone (XV) by comparison of IR spectrum (KBr).

3) Epimerization by HCl aq.: The experiment will be described latter.

LiAlH₄-reduction of 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oic Acid 16 $\rightarrow$ 6 α -Lactone (XV). 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-ol (XXVIII)—6 α -Lactone (XV) (32 mg) was reduced by reflux with LiAlH₄ (50 mg) in dry ether (10 ml) for 5 hr. The resulted mixture was diluted with H₂O, acidified with HCl aq., then extracted with ether and the ether extract was dried over Na₂SO₄. Removal of the solvent gave crude crystals (36 mg), which were recrystallized from MeOH-H₂O to colorless prisms (XXVIII) (21 mg), mp 208—209.5°. *Anal.* Calcd. for C₁₇H₃₀O₂: C, 76.64; H, 11.35. Found: C, 76.51; H, 11.09. IR $\nu_{\text{max}}^{\text{KBr}}$: 3190, 1067, 1023. NMR τ : 9.02 (s, 3H; C₄-Me), 8.62 (s, 3H; C₁₀-Me), 6.89 (d, 1H, $J=12.0$ cps; CH₂OH), 5.68 (d, 1H, $J=12.0$ cps; CH₂OH). $t_R=11.1$ min (1.5% OV-17 on Shimalite W, 4 mm $\times$ 2.0 m, 180°).

LiAlH₄-reduction of Methyl 6 α -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oate (XVII)—6 α -Hydroxy ester (XVII) (20 mg) was refluxed with LiAlH₄ (50 mg) in dry ether (10 ml) for 5 hr. The same treatment of the reaction mixture as in case of (XV) gave crude crystals (23 mg), which were recrystallized from MeOH-H₂O to colorless prisms (XXVIII) (15.5 mg), mp 207—208°. Mixed mp, gas-liquid chromatogram and IR spectrum (KBr) showed the compound was identical with 6 α -hydroxy alcohol (XXVIII) obtained from 6 α -lactone (XV).

LiAlH₄-reduction of 6 β -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oic Acid 16 $\rightarrow$ 6 β -Lactone (XXVII)—6 β -Lactone (XXVII) (50 mg) prepared by thermal fusion method (a mixture of 6 β -XXVII and 6 α -lactone (XV) in ratio of 12:5) was refluxed with LiAlH₄ (75 mg) in dry ether (15 ml) for 4 hr. The same treatment of the reaction mixture as in case of (XV) gave crude crystals (45.5 mg), whose IR (KBr), NMR spectrum and gas-liquid chromatogram ($t_R=13.6$ min and 13.8 (shoulder); 3.0% OV-17 on Gaschrom P, 4 mm $\times$ 1.8 m, 230°) showed it consisted of 6 β -hydroxy alcohol (XXIX) as main product together with 6 α -hydroxy alcohol (XXVIII). The ratio (XXIX: XXVIII=*ca.* 2:1) of the product measured by NMR peak integral due to C₁₀- and C₄-methyl.

LiAlH₄-reduction of Methyl 6 β -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-oate (XVIII). 6 β -Hydroxy-8 β H, 9 β H-*enantio*-podocarpin-16-ol (XXIX)—6 β -Hydroxy ester (XVIII)¹⁾ (50 mg) was reduced by reflux with LiAlH₄ (75 mg) in dry ether (15 ml) for 4 hr. The same treatment of the reaction mixture as in case of (XV) gave crude crystals (42.5 mg), which were recrystallized from MeOH-H₂O to colorless needles (XXIX) (20 mg), mp 152.5—155°. *Anal.* Calcd. for C₁₇H₃₀O₂: C, 76.64; H, 11.35. Found: C, 76.78; H, 11.57. IR $\nu_{\text{max}}^{\text{KBr}}$: 3310, 1087, 1058. NMR τ : 8.83, 8.78 (s, 3H; C₄- and C₁₀-Me), 6.62 (d, 1H, $J=10.5$ cps; CH₂OH), 5.80 (d, 1H, $J=10.5$ cps; CH₂OH).

Attempt on Lactonization of 6 β -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid (XXX) under Acidic Condition—1) Lactonization in HCl aq. -*tert*-BuOH: A solution of 6 β -hydroxy acid (XXX)¹⁾ (24.5 mg) in 10% HCl aq. (2.3 ml) and *tert*-BuOH (5 ml) was refluxed for 2.5 hr. After the solvent was evaporated under reduced pressure, the resulted residue was diluted with H₂O and it was extracted with ether. The extract was washed with 10% KOH aq. (acidic part), then with H₂O and dried over Na₂SO₄ (neutral part). The ether extract (neutral part) was evaporated to give scarcely any residue. Otherwise, the alkaline extract (acidic part) was acidified, then extracted with ether and the extract was dried over Na₂SO₄. Removal of the ether gave an oil (23 mg), whose methyl ester (CH₂N₂-treatment) was identical with 6 β -hydroxy ester (XXXI) by comparison of IR spectrum (CCl₄) and gas-liquid chromatogram ($t_R=5.8$ min; 1.5% OV-17 on Gaschrom P, 4 mm $\times$ 2 m, 200°). Accordingly, the lactonization did not occur, but only starting compound was recollected.

2) Lactonization in HCl aq. -MeOH: A solution of 6 β -hydroxy acid (XXX)¹⁾ (46 mg) in 10% HCl aq. (4.3 ml) and MeOH (9.4 ml) was refluxed for 2.5 hr. The solvent was evaporated under reduced pressure and the resulted residue was extracted with ether. The extract was washed with 10% KOH aq. (acidic part), then with H₂O and dried over Na₂SO₄ (neutral part). a) Neutral Part: The solvent was evaporated to give an oil (37 mg), whose IR spectrum (CCl₄) and gas-liquid chromatogram ($t_R=6.80$ min; 1.5% OV-17 on Shimalite W, 4 mm $\times$ 2 m, 200°) were identical with those of 6 β -hydroxy ester (XXXI). b) Acidic Part: Alkaline extract was acidified and extracted with ether. After the extract was washed with H₂O and dried over Na₂SO₄, it was evaporated to give an oil (5.5 mg). The corresponding methyl ester (CH₂N₂ treatment), which was identical with 6 β -hydroxy ester (XXXI) by comparison of their IR spectrum and gas-liquid chromatogram. Accordingly, HCl-MeOH treatment of 6 β -hydroxy acid (XXX) gave the corresponding methyl ester (XXXI) and recollected acid (XXX).

Lactonization of 6 β -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid (XXX). 6 β -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid 16 $\rightarrow$ 6 β -Lactone (XXXII)—A reaction mixture of 6 β -hydroxy acid (XXIX)¹⁾ (50 mg) and *p*-TsOH (20 mg) in dry benzene (50 ml) was distilled for 10 min under N₂-gas stream until

the distillate reached to *ca.* 20 ml. The residue was washed with 10% KOH aq., then washed with H₂O and dried over Na₂SO₄. Removal of the solvent gave crude crystals (47.5 mg), which were recrystallized from MeOH-H₂O to colorless needles (XXXII) (23 mg), mp 98–99.5°. *Anal.* Calcd. for C₁₇H₂₆O₂: C, 77.82; H, 9.99. Found: C, 77.81; H, 9.71. IR $\nu_{\max}^{\text{film}}$ cm⁻¹: 1773, 1103, 1045, 996. NMR τ : 9.125, 8.74 (s, 3H; C₁₀- and C₄-Me), *ca.* 5.92 (m, 1H; H-C₆-OH). *t*_R=7.5 min (1.5% OV-17 on Gaschrom P, 4 mm×1.8 m, 200°).

Alkaline Hydrolysis of 6 β -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid 16→6 β -Lactone (XXXII)—A solution of 6 β -lactone (XXXII) (37 mg) in 10% KOH aq. (1.0 ml) and MeOH (5.0 ml) was refluxed for 30 min and evaporated under reduced pressure. The resulted alkaline residue was diluted with H₂O, then extracted with ether and the extract was washed with H₂O, then dried over Na₂SO₄. The ether extract (neutral part) was evaporated to remain nothing. Otherwise, the alkaline layer (acidic part) was acidified, extracted with ether and the extract was washed with H₂O, dried over Na₂SO₄. Removal of ether gave an oil (XXX) (36.5 mg), whose IR (KBr) and NMR spectrum were identical with those of 6 β -hydroxy acid (XXX).

Attempt on Epimerization of 6 β -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid 16→6 β -Lactone (XXXII)—1) Thermal Fusion Treatment: 6 β -Lactone (XXXII) (40 mg) was heated at 265° for 5 hr in sealed tube. The resulted oil was dissolved in ether and the ether solution was washed with 10% KOH aq., with H₂O, then dried over Na₂SO₄. Removal of the solvent gave colorless oil (38 mg), whose IR spectrum (CCl₄) was identical with that of starting 6 β -lactone (XXXII).

2) Alumina Treatment: After neutral alumina (5 g) was added to a solution of 6 β -lactone (XXXII) (25 mg) in ether (2 ml) and then the solvent was evaporated, the reaction mixture was left standing at room temperature for 2 days. The resulted alumina was extracted with ether (60 ml) and then with MeOH (10 ml)-AcOH (1 drop). The ether and MeOH-AcOH extract were evaporated to give colorless oil (5 mg) and (1 mg), respectively. Gas-liquid chromatogram (1.5% OV-17 on Shimalite W, 4 mm×2 m, 200°) of the ether extract itself and the methylated MeOH-AcOH extract (CH₂N₂ treatment) showed that the former one consisted of dehydrated product (*A*⁵ and *A*⁶) (*t*_R=3.35 min), unidentified product (*t*_R=8.00 min) and 6 α -Lactone (XXXIII) (*t*_R=10.27 min) in ratio of 1.0:76.2:13.5 and the latter one consisted of 6 β -hydroxy ester (XXXI) (*t*_R=7.00 min) and 6 β -lactone (XXXII) in ratio of 26.5:1.0.

3) HCl aq. Treatment: The experiment will be described latter.

Catalytic Hydrogenation of Methyl 6 α -Hydroxy-*enantio*-podocarpa-8-en-16-oate (IX). Methyl 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oate (XXXIV)—A solution of 6 α -hydroxy tetrahydro ester (IX) (270 mg) in MeOH (110 ml) was stirred in the presence of 10% Pd-C (550 mg) under hydrogen gas atmosphere for 24 hr. After hydrogen absorption was ceased, the catalyst was filtered off and the filtrate was evaporated under reduced pressure to give crude crystals (244 mg). The crystals were chromatographed on silica gel to give oil (22 mg) in petr. ether-ether (19:1) elution and crystals (189 mg) in petr. ether-ether (9:1) fraction. The latter crystals were recrystallized from MeOH-H₂O without heating to give colorless plates (XXXIV) (153 mg), mp 137–139°. Sample for elemental analysis was mp 142.5–144.5°. *Anal.* Calcd. for C₁₈H₃₀O₃: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.49. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3440, 1696. NMR τ : 9.12 (s, 3H; C₁₀-Me), 8.71 (s, 3H; C₄-Me), 6.235 (s, 3H; COOCH₃), 5.58 (m, (half band width=6.6 cps), 1H; H-C₆-OH).

On the other way, the former oil was identical with deoxy ester (XXI) by comparison of their IR-spectra (CCl₄).

Lactonization of Methyl 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oate (XXXIV). 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid 16→6 α -Lactone (XXXIII)—After neutral alumina (2.5 g) was added to an ether solution of 6 α -hydroxy ester (XXXIV) (25 mg), the solvent was evaporated off and then the mixture was left standing at room temperature for 40 hr. The resulted mixture was extracted with ether (*ca.* 60 ml) and the extract was evaporated to give colorless needles (20 mg), which were recrystallized from MeOH-H₂O to colorless needles (XXXIII) (11 mg), mp 78–80°. Sample for elemental analysis was mp 86–87°. *Anal.* Calcd. for C₁₇H₂₆O₂: C, 77.82; H, 9.99. Found: C, 77.45; H, 9.56. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 1758, 1202, 1153, 1096, 997. NMR τ : 9.06, 8.73 (s, 3H; C₁₀- and C₄-Me), *ca.* 5.25 (m, 1H; H-C₆-OH). *t*_R=10.00 min; 1.5% OV-17 on Shimalite W, 4 mm×2 m, 200°. By means of mp (mixed mp) and IR spectrum (KBr) comparison, the lactone (XXXIII) was identical with one of the products obtained by dehydration of 6 β -hydroxy ester (XXXI).¹⁾

Alkaline Hydrolysis of 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid 16→6 α -Lactone (XXXIII). 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid (XXXV)—After a solution of 6 α -lactone (XXXIII) (48 mg) in KOH (220 mg)-H₂O (1.0 ml)-EtOH (9.0 ml) was refluxed for 2 hr, the solvent was evaporated and the resulted residue was diluted with H₂O, extracted with ether. The alkaline layer was acidified and the appeared precipitates were extracted with ether. The extract was washed with H₂O, dried over Na₂SO₄ and evaporated to give white powder (46 mg), a part (20 mg) of which was recrystallized from MeOH-H₂O to colorless needles (XXXV) (15 mg), mp 227.5–228.5°. *Anal.* Calcd. for C₁₇H₁₈O₃: C, 72.82; H, 10.06. Found: C, 72.98; H, 10.30. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3260, 2425, 1694, 1682.

Lactonization of 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid (XXXV)—After a solution of 6 α -hydroxy acid (XXXV) (7 mg) in 10% HCl aq. (1.2 ml) and MeOH (2.5 ml) was refluxed for 30 min, the

solvent was evaporated under reduced pressure and the resulted residue was extracted with ether. The extract was washed with 10% KOH aq., then with H₂O and dried over Na₂SO₄. Removal of the solvent gave colorless needles (8.5 mg), which were recrystallized from MeOH-H₂O to colorless needles (XXXIII) (1.0 mg), mp 88–89.5°. mp (mixed mp) and IR spectrum of the compound was identical with those of the 6 α -lactone (XXXIII) obtained by alumina-treatment of 6 α -hydroxy ester (XXXIV).

Methylation of 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid (XXXV)—6 α -Hydroxy acid (XXXV) (40 mg) was methylated by CH₂N₂-treatment. Removal of the solvent gave white powder (45 mg), which was recrystallized from MeOH-H₂O to give colorless plates XXXIV (30 mg), mp 142.5–144.5°. IR (KBr) and NMR spectrum of the crystal were identical with those of the ester (XXXIV) obtained by catalytic hydrogenation of 6 α -hydroxy tetrahydro-ester (IX).

LiAlH₄-reduction of 6 β -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid 16 $\rightarrow$ 6 β -Lactone (XXXII).—6 β -Lactone (XXXII) (19.5 mg) was reduced in dry ether (15 ml) by reflux with LiAlH₄ (40 mg) for 3 hr. The resulted mixture was diluted with H₂O, then acidified and extracted with ether. After the extract was dried over Na₂SO₄, it was evaporated to give white powder (21 mg), which was recrystallized from MeOH-H₂O to colorless prisms (10 mg), mp 135–137°. Mixed mp and IR spectrum (KBr) of the compound were identical with those of 6 β -hydroxy alcohol (XXXVI) obtained by LiAlH₄-reduction of 6 β -hydroxy ester (XXXI).

LiAlH₄-reduction of Methyl 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oate (XXXI). 6 β -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-ol (XXXVI)—The reaction mixture of 6 β -hydroxy ester (XXXI) (51 mg) and LiAlH₄ (75 mg) in dry ether (20 ml) was refluxed for 3.5 hr. The same treatment of the reaction mixture as in the case of (XXXII) gave white powder (48 mg), which were recrystallized from MeOH-H₂O to colorless prisms (XXXVI) (35 mg), mp 141.5–143°. *Anal.* Calcd. for C₁₇H₃₀O₂: C, 76.64; H, 11.35. Found: C, 76.68; H, 11.11. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3270, 1452, 1035. NMR τ : 9.09 (s, 3H; C₁₀-Me), 8.78 (s, 3H; C₄-Me), 6.68, (d, 1H, *J* = 10.5 cps; CH₂OH), 5.84 (d, 1H, *J* = 10.5 cps; CH₂OH).

LiAlH₄-reduction of 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oic Acid 16 $\rightarrow$ 6 α -Lactone (XXXIII). 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-ol (XXXVII)—To a solution of 6 α -lactone (XXXIII) (20 mg) in dry ether (15 ml), LiAlH₄ (40 mg) was added under stirring. After the mixture was refluxed for 4 hr, the same treatment of the reaction mixture as in the case of XXXII gave crude crystals (25 mg), which were recrystallized from MeOH-H₂O to colorless needles XXXVII (14 mg), mp 157.5–158.5°. *Anal.* Calcd. for C₁₇H₃₀O₂: C, 76.64; H, 11.35. Found: C, 76.56; H, 11.23. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3150, 1077, 1016. NMR τ : 8.975 (s, 3H; C₄-Me), 8.83 (s, 3H; C₁₀-Me), 6.87 (d, 1H, *J* = 10.5 cps; CH₂OH), 5.72 (d, 1H, *J* = 10.5 cps; CH₂OH).

LiAlH₄-reduction of Methyl 6 α -Hydroxy-8 α H, 9 β H-*enantio*-podocarpin-16-oate (XXXIV)—To a solution of 6 α -hydroxy ester (XXXIV) (11 mg) in dry ether (10 ml), LiAlH₄ (25 mg) was added under stirring and the mixture was refluxed for 4 hr. The same treatment of the reaction mixture as in the case of XXXII gave an oil (11.5 mg), which was recrystallized from MeOH-H₂O to colorless needles XXXVII (2 mg), mp 156.5–159.5°. Mixed mp and IR spectrum (KBr) of this compound were identical with those of 6 α -hydroxy alcohol (XXXVII) obtained by LiAlH₄-reduction of 6 α -lactone (XXXIII).

C₆-Epimerization at Lactonization of 6 β -Hydroxy acids (II, V, XIV, XXX), and at 16 $\rightarrow$ 6 β -Lactones (III, X, XXVII, XXXII), by Acidic Treatment (Table IV)—1) General Procedure (Epimerization of XIV as Example): A solution of 6 β -hydroxy acid (*cis*-B/C-ring fusion) (XIV) (1.3×10^{-2} mole/liter: 28 mg) in 10% HCl aq. (2.7 ml)–MeOH (or *tert*-BuOH) (5.8 ml) was refluxed (oil bath temperature: 110°) for 30 min. After the reaction mixture was rapidly cooled for 10 min, it was evaporated under reduced pressure (water bath temperature: 40°) to give an oil. The oil (GLC-1) and its methylated product (GLC-2) obtained by CH₂N₂-treatment was examined by gas-liquid chromatography (Shimadzu 4A-PF, 1.5% OV-17 on Gaschrom P (80–100 mesh), 4 mm $\times$ 2 m, 200°, N₂). The ratio of the resulted components was measured by ratio of peak area (height $\times$ width at half height) in the chromatogram.

Gas-liquid chromatography of the oil (GLC-1) indicated peaks of neutral part (lactone and methyl ester). Otherwise, that of the methylated product (GLC-2) showed a peak due to 6 β -hydroxy methyl ester (XVIII) included additional methylated acid, so comparison of the both chromatogram (GLC-1 and GLC-2) lead to know a proportion of the 6 β -hydroxy acid (XIV).

In conclusion, the result obtained from this sample (XIV) was shown as follows (in MeOH as solvent): epimerized 6 α -lactone (XV) (73.4%), 6 β -hydroxy ester (XVIII) (1.6%), recollected 6 β -hydroxy acid (XIV) (12.6%) and unidentified product (12.4%).

2) Result: According to the above general procedure, acid treatment of four kinds of pair compounds (acids II, V, XIV, XXX, and lactones (III, X, XXVII, XXXII)) carried out. The results were shown as in Table IV.

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