[Chem. Pharm. Bull. 19(9)1768—1785(1971)]

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

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Previously, it was found that a remarkable epimerization (βC_6-O→α) was occurred when 6β-hydroxy acid (II) was lactonized. In order to further examine on the mechanism and the limitation of the epimerization, the corresponding hydrogenated 6β-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 6β-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→6α-lactone (IV) with epimerization at C_6-configuration. Otherwise, the isomeric lactone (III) having a retained C_6-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→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 6β-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 6β-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 C_6-epimerization was occurred at lactonization of the 6β-hydroxy-tetrahydro and -hexahydro acids, the corresponding 6α-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. Tahasa 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 $CDCl_3$ *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, *Tetrahedron*, **21**, 2133 (1965).

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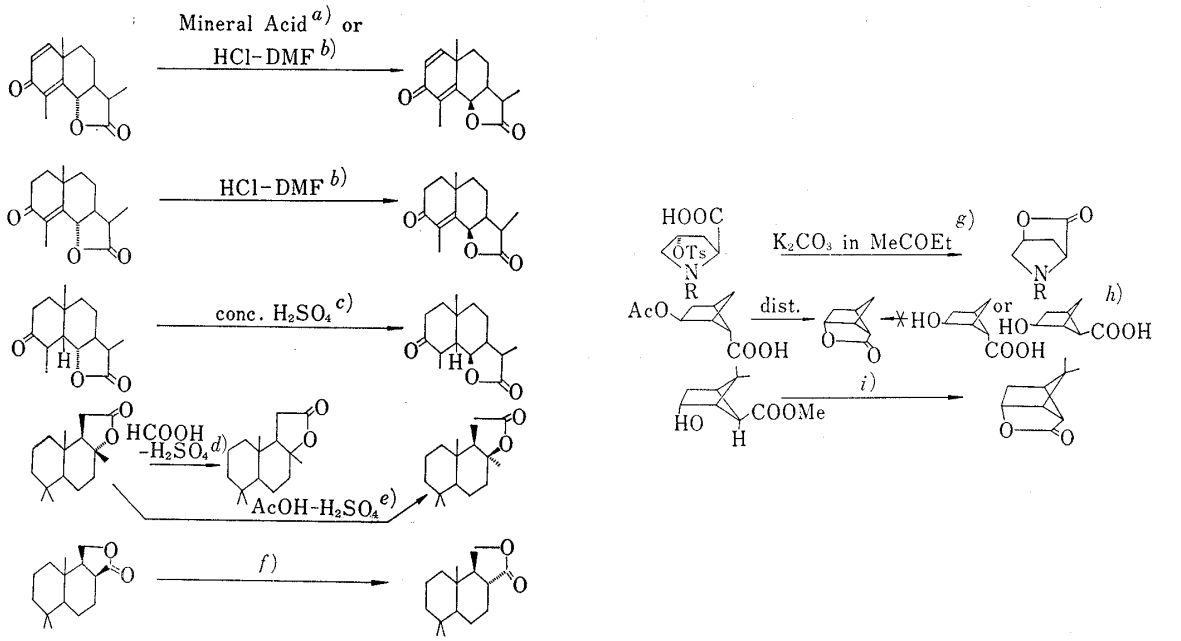
TABLE I



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. Sauers, *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**, 4685
g) 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 6β-hydroxypodocarp-8-en-16-oic acid (V) was firstly examined. The acid (V) obtained by reduction (Li-*tert*-AmOH-EtNH$_2$) 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 hydorxy 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 C$_6$-hydroxyl group of the acid (VII) was proved by chemical conversion (reduction by Li-EtNH$_2$-*tert*-AmOH) of the acid (VIII)[3)] having a reliable α C$_6$-hydroxyl group into the acid (VII) in question.

Usual methylation (CH_2N_2) of the 6α-hydroxy acid (VII) afforded the corresponding ester (IX), mp 91.5—93°, whose IR and NMR spectrum were also completely different from the isomeric 6β-hydroxy ester (XII) reported in the last paper[1)] (Table II). The ester (IX) was easily hydrolyzed to the original hydroxy acid (VII) accompanied with the 6α-lactone (VI). The lactone (VI) would be produced by heating of 6α-hydroxy ester (IX) and remained itself under even the alkaline condition.

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

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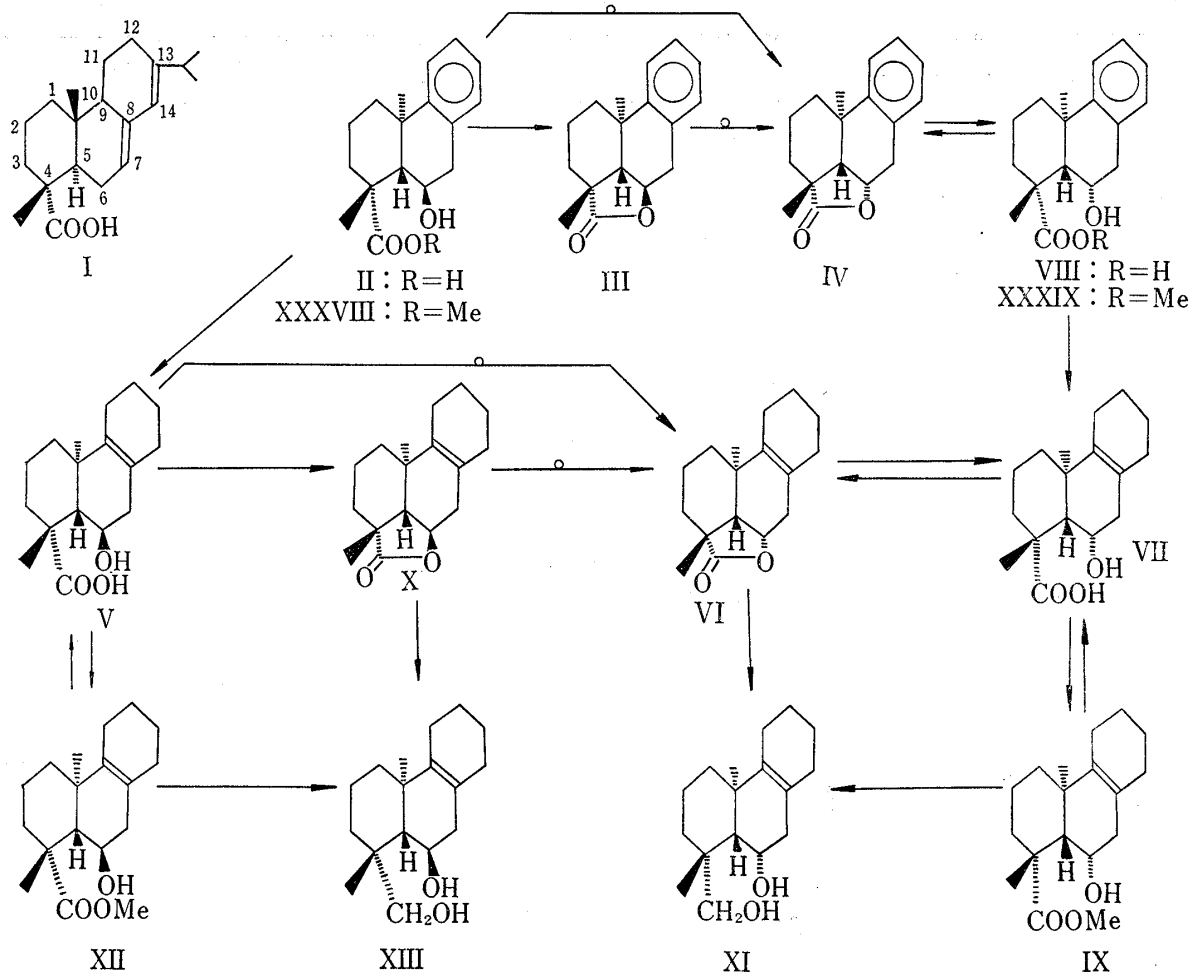

Chart 1

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) dicyclohexyl-carbodiimide (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 ν_{max}^{KBr} cm^{-1}: 1770, 1107 and NMR τ: 8.97 8.74 (C_{10}-and C_4-Me), *ca.* 5.72 (H-C_6-OH) are quite distinct from those of the stable crystalline lactone (VI), IR ν_{max}^{KBr} cm^{-1}: 1761, 1121, 1049 and NMR τ: 9.05 8.73 (C_{10}-and C_4-Me), *ca.* 5.02 (H-C_6-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 C_6-configuration as the original acid (V) and, therefore, the stable lactone (VI) would be formed from V and X through epimerization at C_6-configuration (β→α-C-O bond).

Further confirmation of the structures of the above lactones, especially of C_6-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-

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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*-XIV[1] 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.

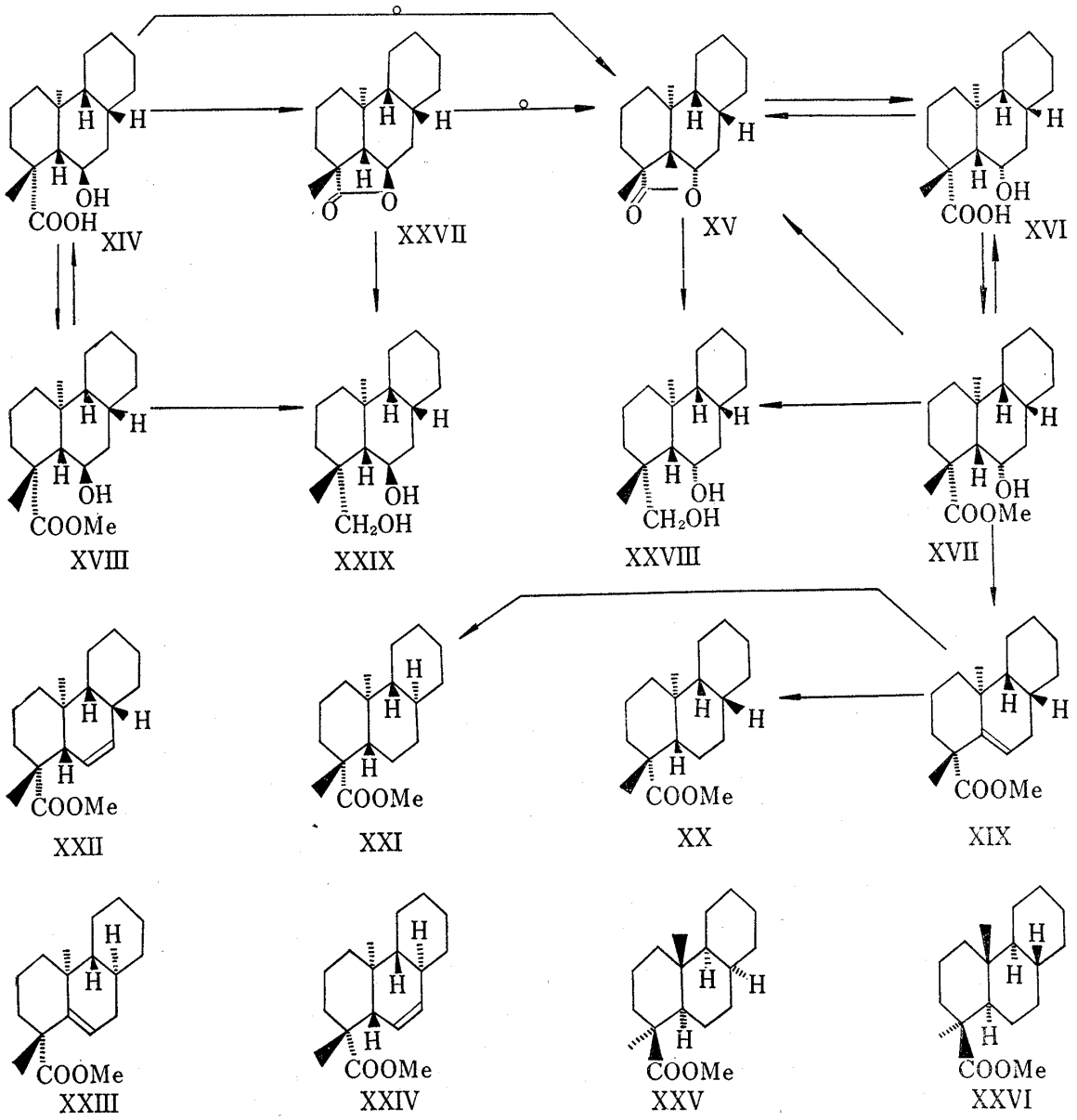

Chart 2

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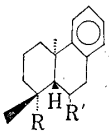
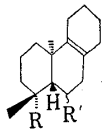
TABLE II. Physical Constants

		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 ν_{max}^{KBr} cm^{-1}	1727			1720	3545	3460
						1733	1709
						1710	
						1237	1159
						1170 (CCl_4)	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 ν_{max}^{KBr} cm^{-1}		3580	3210		3430	3270
			3400	2360			2435
			1726	1735			
			1693	1675		1695	1682
			1240	1270			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_2OH	mp		163—164.5°	176 —177.5°		(XIII) 138—139°	(XI) 141 —143°
	IR ν_{max}^{KBr} cm^{-1}		3310	3310		3275	3270
						1076	1097
						1017	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
	$C\underline{H}_2OH$					6.64	6.79
						5.75	5.70
						(J=10.5 cps)	(J=12 cps)

The stereochemistry on B/C-ring juncture of the C_6-epimerized compounds (XV, XVI and XVII) is certain to be *anti-cis*, because these compounds were converted from the reported 6β-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 6α-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 6α-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 6β-hydroxy ester (XVIII) that the dehydrated mixture always consisted of Δ^6-ester (XXII), Δ^5-ester (XIX) and 6α-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 6α-hydroxy ester (XVII) can be reasoned by *trans*-diaxial elimination between 6α-hydroxyl group and *tert*-5β-hydrogen of XVII.

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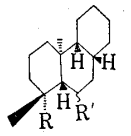
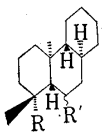
of 6-Hydroxy Esters

		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 ν_{max}^{KBr} cm^{-1}		3525	3430		3535	3440
		1727	1700	1695	1727	1723	1696
				1232	1158 (film)	1157	1167
		1155 (film)	1232	1165		1042 (film)	
			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 ν_{max}^{KBr} cm^{-1}		3355	3220		3423	3260
			2710	2560			2425
			1711				1694
				1678		1694	1682
			1266	1270			
	NMR(τ) C_{10}-Me		9.02			9.26	
	C_4-Me		8.51			8.50	
	C_6-H		*ca.* 5.76			*ca.* 5.84	
R=CH_2OH	mp		(XXIX) 152.5—155°	(XXVIII) 208—209.5°		(XXXVI) 141.5—143°	(XXXVII) 157.5—158.5°
	IR ν_{max}^{KBr} cm^{-1}		3310	3190		3270	3150
			1087	1067		1450	1077
			1058	1023		1039	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
	$C\underline{H_2}OH$		6.62	6.89		6.68	6.87
			5.80	5.68		5.84	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 paper[1] 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 6α-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).

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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 C_6-hydroxyl group as that of 6β-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 6β-XXVII and 6α-lactone (XV) in ratio of 12:5 and 7:3, respectively, whereas DCC-pyridine treatment afforded only pure 6β-lactone (XXVII). The 6β-lactone (XXVII) was furthermore heated (250° for 4 hr 10 min and 270° for 3 hr 45 min) to epimerize to the isomeric 6α-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 6α-XV and 6β-lactone (XXVII), it become known that an epimerization occurs at C_6-position during acidic lactonization of 6β-hydroxy acid (XIV) and chemical treatment of the unstable lactone (XXVII). Further evidence on the epimerization was given by chemical conversion of both 6β- and 6α-lactone (XXVII and XV) to the corresponding different 6β- and 6α-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 ($LiAlH_4$) of 6β- and 6α-hydroxy ester (XVIII and XVII) having the reliable C_6-configuration, respectively.

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

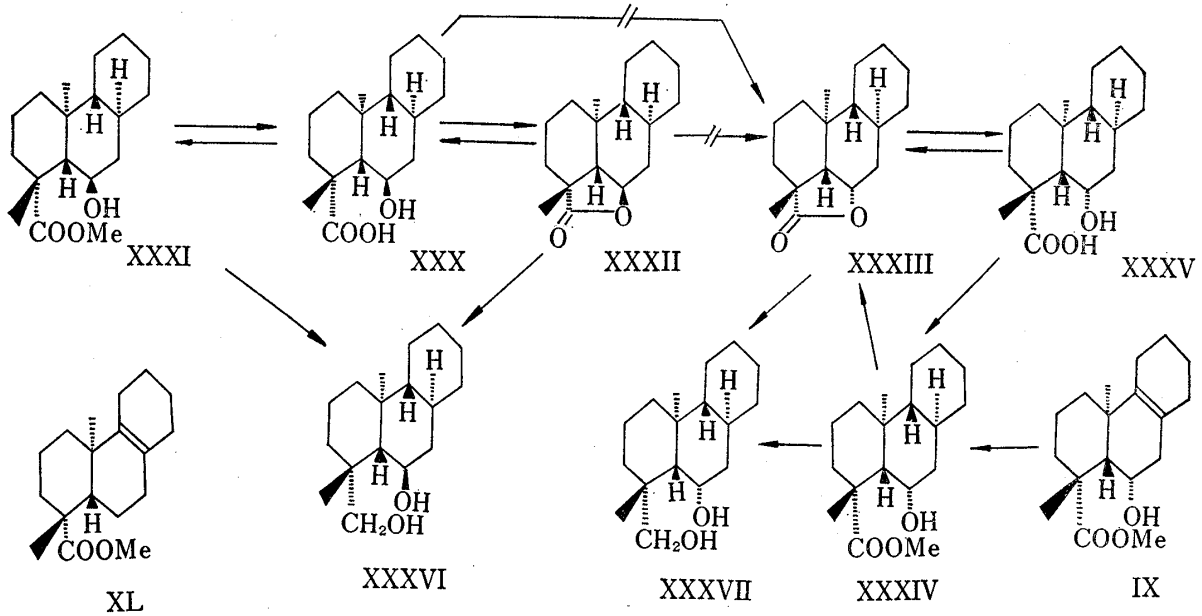

Chart 3

Many efforts of lactonization of the 6β-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).

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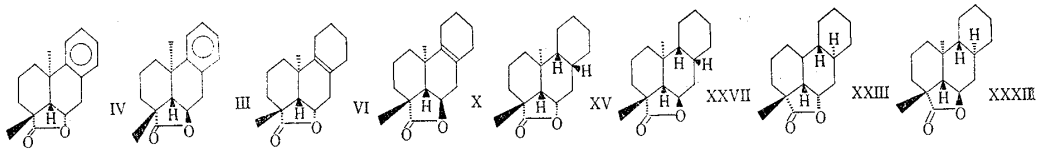
unstable 6β-lactones (III, X and XXVII) yielded a pure lactone (XXXII), mp 98—99.5°, IR ν_{max}^{film} cm^{-1}: 1773, in quantitative yield. The lactone (XXXII) is unexpectedly stable and its sharp melting point, IR and NMR spectrum indicate to be not mingled with the epimerized 6α-lactone (XXXIII), in contrast to the other mixed 6β-lactones (III, X and XXVII) having unsharpened melting point. Unlike the other unstable 6β-lactones, the pure 6β-lactone (XXXII) was hydrolyzed to regenerate the starting 6β-hydroxy acid (XXX) and was not converted to C_6-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 6α-hydroxy derivatives having *anti-trans*-B/C-ring juncture was switched to another route.

6α-Hydroxy-tetrahydro ester (IX) already elucidated as 6α-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 6α-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 6α-lactone (XXXIII), mp 86—87°, which was different from the corresponding 6β-lactone (XXXII) (Table III) and was identical with one of the dehydrated products ($POCl_3$-pyridine) of 6β-hydroxy ester (XXXI) reported in our last paper.[1]

Table III. Physical Constants of Lactones



	IV	III	VI	X	XV	XXVII	XXIII	XXXIII
m.p.	174—176°	130—140°	85—87°	oil	159.5—161°	120—150°	86—87°	98—99.5°
IR ν_{max}^{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 Shimalite W, 4 mm ×2.0 m, 200°)					11.00	11.70	10.00	9.30

The 6α-lactone (XXXIII) was hydrolyzed under alkaline condition (reflux with KOH–H_2O–EtOH for 2 hr) to 6α-hydroxy acid (XXXV), mp 227.5—228.5°. Acid treatment (reflux with HCl aq.-MeOH for 30 min) and usual methylation (CH_2N_2) 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 $LiAlH_4$ to give the respective 6β-hydroxy alcohol (XXXVI), mp 141.5—143° and 6α-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 6β-(XXXI) and

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

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6α-hydroxy esters (XXXIV) having certain C_6-configuration, respectively. The characteristic behavior of 6β-hydroxy acid (XXX) and 6β-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 C_6-epimerization of 6β-hydroxy acids (II, V and XIV) and 6β-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 6β-hydroxy acids and 6β-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 (6β-hydroxy acids and 6β-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: Epimerized 16→6α-lactone (%)		6β-Hydroxy ester (%) (Methylation by solvent)		6β-Hydroxy acid (%)		Total yield[a] (%)		Ratio of ester and 6α-lactone
II	MeOH	IV	29.5	XXXVIII	11.1	II		59.5	100.1	XXXVIII/IV=0.376
	tert-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
	tert-BuOH		52.3		—			40.5	92.8	
V	MeOH	VI	10.8	XII	<1.0	V		80.0	*ca.* 91	XII/VI=>0.01
	tert-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
	tert-BuOH		11.6		—			44	55.6	
XIV	MeOH	XV	73.4	XVIII	1.6	XIV		12.6	87.6	XVIII/XV=0.022
	tert-BuOH		81.0		—			15	96	
XXVII	MeOH	XV	46.6	XVIII	34.3	XIV		0	80.9	XVIII/XV=1.36
	tert-BuOH		75.0		—			18.1	93	
XXX	MeOH	unepimerized 16→6β-lactone XXXII	0.58	XXXI	2.02	XXX		94.0	96.6	
	tert-BuOH[c]		3.84		—			87.0	90.8	
XXXII	MeOH	unepimerized 16→6β-lactone XXXII	0.24	XXXI	83.0	XXX		15.2	98.44	
	tert-BuOH[c]		1.0		—			93	94	

After the reaction was ceased, the resulted mixture itself (GLC -1) and its methylated product (CH_2N_2-treatment) (GLC -2) were analyzed by gas-liquid chromatography. Ratio of the produced components was estimated by peak area (height × 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→6β-lactones (III and X) were contaminated with small amount of 16→6α-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→C) was occurred *via* 6β-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→D→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.

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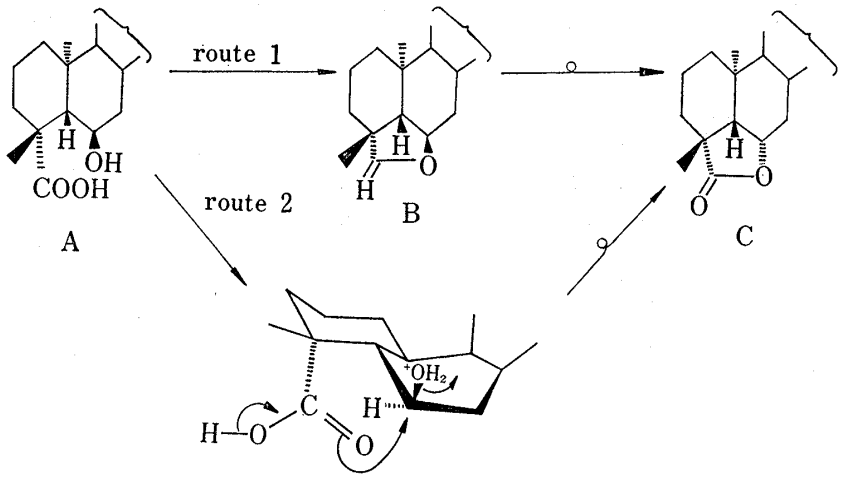

D

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 procucts obtained from 6β-hydroxy acids (II→XXXVIII/IV=0.376; V→XII/VI=<0.01 and XIV→XVIII /XV=0.022) are conversely smaller than that yielded from 6β-lactones (III→XXXVIII/IV =3.1; X→XII/VI=1.18 and XXVII→XVIII/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: (XIV)→(XV) (81%)>II→IV (32.8%)>V→VI (11.4%)>XXX→ 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: XXVII→XV (75%)>III→IV (52.3%)>X→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: XXXII→XXXI (83%)>III→XXXVIII(53%) >XXVII→XVIII (34.3%)>X→XII (27.1%).

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

In the last[1] and this papers, 6β- and 6α-hydroxy acid detivarives 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

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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 C_6-hydroxyl group; C_4-methyl of 6β-hydroxy esters (XII: 8.53τ, XVIII: 8.53τ and XXXI: 8.54τ) and C_{10}-methyl of 6α-hydroxy esters (IX: 8.94τ, XVII: 8.92τ and XXXIV: 9.12τ) are shifted to lower magnetic field than those of the deoxy standard (XL[10]: 8.79τ (C_4-Me), 9.23τ (C_{10}-Me); XX[1]: 8.83τ (C_4-Me), 9.14τ (C_{10}-Me) and XXI[1]: 8.83τ (C_4-Me), 9.37τ (C_{10}-Me)).

Furthermore, NMR spectrum on proton attached to the same 6-position as hydroxyl function was examined. The chemical shifts of 6α-hydrogens in 6β-hydroxy esters (XII: *ca.* 5.73τ, XVIII: *ca.* 5.8τ and XXXI: *ca.* 5.93τ) are appeared in higher magnetic field than those of 6β-hydrogens in 6α-hydroxy esters (IX: *ca.* 5.39τ, XVII: *ca.* 5.45τ and XXXIV: *ca.* 5.58τ) respectively. This observation is consistent with their structural assignment of 6β-hydroxy esters (ax. C_6-H and eq. C_6-OH) and 6α-hydroxy esters (eq. C_6-H and ax. C_6-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 6β-lactones (ν_{max}^{KBr} cm^{-1}: X: 1770; XXVII: 1766 and XXXII: 1773) are higher than those of stable 6α-lactones (ν_{max}^{KBr} cm^{-1}: VI: 1761; XV: 1762 and XXXIII: 1758). The fact obviously shows that 6β-lactones have larger strain of the lactone ring.

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

Experimental

Epimerized Lactonization of 6β-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (V). 6α-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid 16→6α-Lactone (VI)——After a reaction mixture of 6β-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 H_2O and dried over Na_2SO_4. Removal of the ether gave crystals (80 mg), which were recrystallized from MeOH–H_2O to colorless needles (VI), mp 85—87°. *Anal.* Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.25. Found: C, 78.18; H, 8.95. IR ν_{max}^{KBr} cm^{-1}: 1761, 1121, 1049. NMR τ: 9.045 8.73 (s, 3H; C_{10}-and C_4-Me), *ca.* 5.02 (m, 1H; H–C_6–OH), t_R=11.2 min (2% OV-17 on Gaschrom P, 4 mm×1.8 m, 185°).

Alkaline Hydrolysis of 6α-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid 16→6α-Lactone (VI)——6α-Lactone (VI) (22 mg) was hydrolyzed by reflux with KOH (180 mg) in MeOH (1.5 ml) and H_2O (0.1 ml) for 1.5 hr. After the solvent was removed under reduced pressure, the residue was diluted with H_2O and extracted with ether. The water layer was acidified, extracted with ether and the extract was washed with H_2O, then dried over Na_2SO_4. Removal of ether gave crystals (18 mg), which were recrystallized from MeOH–H_2O to colorless powder (VII), mp 203—208°. IR spectrum (KBr) and mp (mixed mp) of the acid were completely identical with those of 6α-hydroxy acid (VII) prepared by reduction (Li-$EtNH_2$-*tert*-AmOH reduction) of 6α-hydroxy acid having aromatic C-ring VIII as described later.

Lactonization of 6α-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (VII)——A solution of 6α-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 H_2O and dried over Na_2SO_4. Removal of ether afforded crystals (70 mg) as neutral part, which were recrystallized from MeOH–H_2O to give colorless needles, mp 85—87°. The crystals were completely identical with the 6α-lactone (VI) synthesized from 6β-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 Na_2SO_4. Removal of the solvent gave the starting 6α-hydroxy acid (VII) (30 mg).

Reduction (Li-$EtNH_2$-*tert*-AmOH) of 6α-Hydroxy-*enantio*-podocarpa-8,11,13-trien-16-oic Acid (VIII). 6α-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (VII)——To a solution of 6α-hydroxy acid (VIII) (200 mg)[3] in dry $EtNH_2$ (15 ml)-*tert*-AmOH (1.0 g), granular Li-metal(250mg) was added. The reaction mixture was stirred

9) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).
10) A. Tahara and O. Hoshino, *Tetrahedron Letters*, **1966** 3825; A. Tahara, O. Hoshino and T. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 54 (1969).
11) R.U. Lemieux, R.K. Kullnig, H.J. Bernstein and W.G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

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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 H_2O, acidified and extracted with ether. The ether extract was washed with 10% KOH aq., then with H_2O and dried over Na_2SO_4 (neutral part). Removal of ether gave an oil (60 mg), which was identical with 6α-hydroxy alcohol (XI) by comparison of IR spectrum (CCl_4) and gas-liquid chromatogram (t_R=11.1 min; 2.0% OV-17 on Gaschrom P, 4 mm×1.8 m, 190°).

Otherwise, the alkaline extract was acidified and extracted with ether. The extract was washed with H_2O, then dried over Na_2SO_4 (acidic part) and evaporated to white powder (150 mg), which was recrystallized from MeOH-H_2O to give white powder VII, mp 206—207°. *Anal.* Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.29; H, 9.27. IR ν_{max}^{KBr} cm^{-1}: 3270, 2435, 1682, 1273. NMR τ: 8.88 (s, 3H; C_{10}-Me), 8.67 (s, 3H; C_4-Me), *ca.* 4.62 (m (half band width=*ca.* 10.5 cps), 1H; H-C_6-OH).

Methylation of 6α-Hydroxy-*enantio*-podocarp-8-en-16-oic-Acid (VII). Methyl 6α-Hydroxy-*enantio*-podocarp-8-en-16-oate (IX)——Usual treatment of 6α-hydroxy acid (VII) (70 mg) with excess CH_2N_2–ether solution quantitatively gave colorless crystals, which were recrystallized by H_2O addition to its MeOH-solution without heating to give colorless leaflets IX (40 mg), mp 91.5—93°. *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.53; H, 9.59. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3460, 1709, 1159, 1049. NMR τ: 8.94 (s, 3H; C_{10}-Me), 8.68 (s, 3H; C_4-Me), 6.20 (s, 3H; $COOC\underline{H}_3$), *ca.* 5.39 (m(half band width=9 cps), 1H; $\underline{H}$-C_6-OH). t_R=9.5 min (2% OV-17 on Graschrom P, 4 mm ×1.8 m, 185°).

Alkaline Hydrolysis of Methyl 6α-Hydroxy-*enantio*-podocarp-8-en-16-oate (IX)——A solution of 6α-hydroxy ester (IX) (50 mg) and KOH (700 mg) in MeOH (15 ml)–H_2O (1ml) was refluxed for 1 hr 20 min. After the solvent was evaporated and then H_2O 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 H_2O and dried over Na_2SO_4. Removal of ether gave colorless solid (34.5 mg), which was recrystallized from MeOH–H_2O to needles, mp 82—86°. The compound was completely identical with 6α-lactone (VI) by comparison of their IR spectra (CCl_4).

On the other way, the alkaline extact above mentioned was acidified with HCl aq. and the appeared white precipitates were extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and the solvent was removed. The resulted colorless crystals (10 mg) were recrystallized from MeOH–H_2O to fine needles, mp 198—198.5°, whose IR spectrum (KBr) and mixed mp were identical with those of 6α-hydroxy acid (VII).

Lactonization of 6β-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid (V). 6β-Hydroxy-*enantio*-podocarp-8-en-16-oic-Acid 16→6β Lactone (X)——1) Lactonization by Thermal Fusion: 6β-Hydroxy acid (V)[1] (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. Na_2CO_3 aq., with H_2O, then dried over Na_2SO_4. Removal of the solvent gave a neutral oil (X) (73.5 mg), IR ν_{max}^{KBr} cm^{-1}: 1770, 1107, 999. NMR τ: 8.97 8.74 (s, 3H; C_{10}-and C_4-Me), *ca.* 5.72 (m, 1H; $\underline{H}$-C_6-O$\underline{H}$). *Anal.* by high resolution mass spectrometry. Calcd. for $C_{17}H_{24}O_2$ (M^+; *m/e*): 260.1776. Found: 260.1785. The oil had lactone properties, but was completely different from 6α-lactone (VI).[12]

On the other hand, the alkaline (Na_2CO_3) extract was acidified, extracted with ether and dried over Na_2SO_4. 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 6β-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 H_2O and dried over Na_2SO_4. Removal of the solvent gave an oily lactone (X) (45.5 mg), whose IR spectrum (CCl_4) was identical with that of 6β-lactone (X) mentioned above.[12]

3) Lactonization by Dicyclohexylcarbodiimide (DCC)-Pyridine: Reaction mixture of 6β-hydroxy acid (V) (40 mg) and DCC (30 mg) in pyridibe (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 H_2O and dried over Na_2SO_4. Ether solution of the residue obtained by removal of $CHCl_3$ was left standing overnight at −10°. The appeared precipitates were filtered off and the filtrate was condensed to give quantitatively the oily 6β-lactone (X) (37 mg), which was identical with 6β-lactone (X) by comparison of IR (CCl_4) and NMR spectrum.[12]

Epimerization of 6β-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid 16→6β-Lactone (X). 6α-Hydroxy-*enantio*-podocarp-8-en-16-oic-Acis 16→6α-Lactone (VI)——1) Epimerization by Thermal Fusion: In a sealed tube, 6β-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 6β-lactone (X) from 6β-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 H_2O and dried over Na_2SO_4. Removal of ether gave light brown oil (38 mg), which as wrecrystallized from MeOH–H_2O to colorless needles VI (10 mg), mp 80—85°. IR sptectrum (CCl_4) and gas–liquid

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

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

2) **Epimerization by Alumina Treatment**: A solution of 6β-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 6β-lactone (X) were diminished and those at 1112, 1043 cm^{-1} due to 6α-lacone (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×1.8 m, 210°) showed it consisted of 6α-lactone (VI) (46 %) together with unidentified products, yields of which were measured by ratio of peak area (peakheight × width at half height).

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

$LiAlH_4$-reduction of 6α-Hydroxy-*enantio*-podocarp-8-en-16-oic Acid 16→6α-Lactone (VI). 6α-Hydroxy-*enantio*-podocarp-8-en-16-ol (XI)——To a solution of 6α-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 MeOH–H_2O to colorless powder XI, mp 141—143°. *Anal.* Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.28; H, 10.51. IR ν_{max}^{KBr} cm^{-1}: 3270, 1097, 1025. NMR τ: 8.94 (s, 3H; C_4-Me), 8.64 (s, 3H; C_{10}-Me), 6.79 (d, 1H, J=12 cps; C$\underline{H}_2$OH), 5.70 (d, 1H, J=12 cps; C$\underline{H}_2$OH). t_R=15.1 min (1.5 % OV-17 on Gaschrom P, 4 mm× 1.8 m 180°).

$LiAlH_4$-reduction of Methyl 6α-Hydroxy-*enantio*-podocarp-8-en-16-oate (IX)—$LiAlH_4$ (120 mg) was added to 6α-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 reactuon mixture as in case of VI gave crude crystasl (40 mg), which were recrystallized from MeOH-H_2O to colorlese powder XI, mp 140—141°. The compound was identical with the 6α-hydroxy alcohol (XI) obtained from 6α-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×1.8 m, 190°).

$LiAlH_4$-reduction of 6β-Hydroxy-*enantio*-podocarp-8-en-16→6β-Lactone (X)——To a solution of 6β-lactone (X) (prepared by fusion method and mixed with small amount of 6α-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×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 MeOH–H_2O to colorless fine needles (2.0 mg), mp 132—135°, whose IR spectrum (KB_R) was completely identical with that of 6β-hydroxy alchol (XIII) obtained by reduction of 6β-hydroxy ester (XII).

$LiAlH_4$-reduction of Methyl 6β-Hydroxy-*enantio*-podocarp-8-en-16-oate (XII). 6β-Hydroxy-*enantio*-podoCarp-8-en-16-ol (XIII)——6β-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 MeOH–H_2O to colorless prisms (XIII), mp 138—139°. *Anal.* Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found C, 77.36; H, 10.85. IR ν_{max}^{KBr} cm^{-1}: 3275, 1075, 1017. NMR τ: 8.90, 8.80 (s, 3H; C_4– or C_{10}-Me), 6.64 (d, 1H, J=10.5 cps; C$\underline{H}_2$OH), 5.75 (d, 1H, J=10.5 cps; C$\underline{H}_2$OH). t_R=14.6 min (1.5% OV-17 on Gaschrom P, 4 mm×1.8 m, 180°).

Epimerized Lactonization of 6β-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid (XIV) 6α-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6α-Lactone (XV)——1) Lactonization with HCl aq.-*tert*-BuOH: A solution of 6β-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 MeOH–H_2O to colorless needles XV, mp 159.5—161°. *Anal.* Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.54; H, 9.90. IR ν_{max}^{KBr} cm^{-1}: 1762, 1050, 1003, 932. NMR τ: 9.12, 8.72 (s, 3H; C_{10}-and C_4-Me), *ca.* 5.05 (m (half band width=18 cps), 1H; $\underline{H}$–C_6–OH). t_R=10.4 min (3.0% OV-17 on Shimalite W, 4 mm×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 6β-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×1.8 m, 230°).

2) Lactonization with HCl aq. -MeOH: A solution of 6β-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 6α-lactone (XV) mentioned above. Gas-

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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×2.0 m, 200°) of methylated product (CH_2N_2–ether solution) of the crude needles showed it consisted of 6α-lactone (XV), 6β-hydroxy ester (XVIII)[1] and unknown part in ratio (ratio of peak area: peak height × width at half height) of 93:3:4.

Alkaline Hydrolysis of 6α-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6α-Lactone (XV). 6α-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid (XVI)——A reaction mixture of 6α-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 6α-lactone (XV) by comparison of IR-spectrum (CCl_4) and gas–liquid chromatogram (t_R=14.6min; 1.5 % NGS on Shimalite W, 4 mm×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 $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.34; H, 9.95. IR ν_{max}^{KBr} cm^{-1}: 3220, 2560, 1678, 1270.

Lactonization of 6α-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid (XVI)——A solution of 6α-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×2.0 m, 180°) of the crystals were identical with those of 6α-lactone (XV).

Methylation of 6α-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid (XVI). Methyl 6α-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oate (XVII)——Usual treatment of 6α-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 heating[13] to colorless plates XVII (80 mg), mp 110—111.5° (drying below 40°). *Anal.* Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.49; H, 10.12. IR ν_{max}^{KBr} cm^{-1}: 3430, 1695, 1237, 1165. NMR τ: 8.92 (s, 3H; C_{10}-Me), 8.73 (s, 3H; C_4-Me), 6.22 (s, 3H; $COOC\underline{H}_3$), *ca.* 5.45 (m (half band width=*ca.* 7.5 cps), 1H; $\underline{H}$-C_6-OH).

Alkaline Hydrolysis of Methyl 6α-Hydroxy-8βH,9βH-*enantio*-podocarpan-16-oate (XVII)——A reaction mixture of 6α-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 6α-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×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 6α-hydroxy acid (XVI).

Alumina Treatment of Methyl 6α-Hydroxy-8βH,9βH-*enantio*-podocarpan-16-oate (XVII)——Neutral alumina (2.5 g) was added to a ether solution of 6α-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 6α-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×2 m, 200°).

Dehydration of Methyl 6α-Hydroxy-8βH,9βH-*enantio*-podocarpan-16-oate (XVII). Methyl 8βH, 9βH-*enantio*-Podocarp-5-en-16-oate (XIX)——1) Dehydration by MsCl-Pyridine: A solution of 6α-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 6α-lactone (XV) by comparison of their IR spectra (CCl_4).

On the other way, the former oil was distilled at 80°/3×10^{-3} mmHg and then recrystallized from MeOH–H_2O to colorless needles XIX, mp 63—64°. *Anal.* Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.44; H, 10.19. IR ν_{max}^{KBr} cm^{-1}: 1729, 1650. NMR (100 Mc) τ: 9.13 (s, 3H; C_{10}-Me), 8.74 (s, 3H; C_4-Me),

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

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6.40 (s, 3H; $COOC\underline{H}_3$), 4.37 (q, 1H, $J=1.75$, 6.50 cps; $>=C\underline{H}-CH_2$). 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 $POCl_3$–Pyridine: To a solution of 6α-hydroxy ester (XVII) (100 mg) in dry pyridine (4 ml), $POCl_3$ (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 H_2O and dried over Na_2SO_4. 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–H_2O to colorless needles (45 mg), mp 63—64°, whose IR (CCl_4), NMR spectrum and gas–liquid chromatogram ($t_R=4.0$ min; 1.5% OV-17 on Gaschrom P, 4 mm × 2.0 m, 240°) were completely identical with those of Δ^5-ester (XIX).

Catalytic Hydrogenation of Methyl 8βH, 9βH-*enantio*-Podocarp-5-en-16-oate (XIX)——1) Hydrogenation (platinum catalyst) of Δ^5-Ester (XIX) to Methyl 8βH, 9βH-*enantio*-Podocarpan-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 PtO_2) under H_2-gas pressure (100 kg/cm²) for 2.5 hr. After absorption of H_2-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 H_2O and dried over Na_2SO_4. Removal of ether gave colorless oil, which was chtomatographed on alumina to give an oil (27 mg) in petr. ether elution. Distillate of the oil (XX) at $120°/2\times10^{-3}$ 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 $C_{18}H_{30}O_2$: 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; C_{10}-Me), 8.83 (s, 3H; C_4-Me), 6.37 (s, 3H; $COOC\underline{H}_3$). $t_R=15.0$ min (1.5% OV-17 on Gaschrom P, 4 mm × 2.0 m, 190°).

2) Hydrogenation (Palladium–Charcoal Catalyst) of Δ^5-Ester (XIX) to Methyl 8αH, 9βH-*enantio*-Podocarpan-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°/3×10^{-3} mmHg was slowly crystallized and recrystallized from MeOH–H_2O to colorless needles (XXI), mp 59—61°. *Anal.* Calcd. for $C_{18}H_{30}O_2$: 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; C_{10}-Me), 8.83 (s, 3H; C_4-Me), 6.37 (s, 3H; $COOC\underline{H}_3$). $t_R=11.15$ min (1.5% OV-17 on Shimalite W, 4 mm × 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 6β-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid (XIV). 6β-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6β-Lactone (XXVII)——1) Lactonization by Thermal Fusion: 6β-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 H_2O and dried over Na_2SO_4. Removal of solvent gave crude crystals (48 mg), which were recrystallized from MeOH–H_2O without heating to mp 120—150°. Its gas–liquid chromatogram and NMR (Table III) showed so-called 6β-lactone (XXVII) was contaminated with 6α-lactone (XV) in a proportion of 5/12. *Anal.* Calcd. for $C_{17}H_{26}O_2$: 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; C_{10}- or C_4-Me), *ca* 5.84 (m, 1H; $-C_6\underline{H}$–OH). $t_R=14.7$ min (*cf.* 6α-lactone (XV): 13.7 min; 1.5% OV-17 on Gaschrom P, 4 mm × 1.8 m, 200°).

2) Lactonization with *p*-TsOH: A solution of 6β-hydroxy acid (XIV)[1] (47 mg) and *p*-TsOH (19 mg) in dry benzene (47 ml) was distilled for 10 min under N_2-gas stream until the distillate was come up to *ca.* 15—20 ml. The residue was washed with 10% KOH aq., then with H_2O and dried over Na_2SO_4. Removal of the solvent gave crystals (48 mg), whose gas–liquid chromatogram (respective peak area) showed it consisted of 6β-(XXVII) and 6α-lactone (XV) in ratio of 7:3.

3) Lactonization by DCC-Pyridine: A reaction mixture of 6β-hydroxy acid (XIV)[1] (40 mg) and DCC (30 mg) in pyridine (3 ml) was heated at 100° for 1 hr under N_2-gas stream. After the solvent was removed, the resulted residue was dissolved in $CHCl_3$ and then was filtered. The filtrate was washed with 10% KOH aq., then with H_2O and dried over $CaCl_2$. Removal of $CHCl_3$ 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 (CCl_4) and NMR spectrum indicated it mainly consisted of 6β-hydroxy lactone (XXVII). However, it was difficult to separate the lactone (XXVII) off from DCC.

Epimerization of 6β-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6β-Lactone (XXVII). 6α-Hydroxy 8βH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6α-Lactone (XV)——1) Epimerization by Thermal Fusion: 6β-Lactone (XXVII) (50 mg) obtained from 6β-hydroxy acid (XIV) by thermal fusion method (a mixture of 6β-(XXVII) and 6α-lactone (XV) in ratio of 12:5), was heated at 250° for 4 hr 10 min (its IR spectrum (CCl_4) showed 6β-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 H_2O and dried over Na_2SO_4. Removal of the solvent gave crude crystals (40 mg), which were recrystallized from MeOH–H_2O to give colorless needles, mp 152—153°, whose IR spectrum (KBr) was identical with 6α-lactone (XV).

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2) Epimerization by Neutral Alumina: In the presence of neutral alumina (2 g), a solution of 6β-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 (CCl_4) indicated it mainly consisted of 6α-lactone (XV) together with a small amounts of 6β-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–H_2O to colorless needles, which were completely identical with 6α-lactone (XV) by comparison of IR spectrum (KBr).

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

$LiAlH_4$-reduction of 6α-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6α-Lactone (XV). 6α-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-ol (XXVIII)——6α-Lactone (XV) (32 mg) was reduced by reflux with $LiAlH_4$ (50 mg) in dry ether (10 ml) for 5 hr. The resulted mixture was diluted with H_2O, acidified with HCl aq., then extracted with ether and the ether extract was dried over Na_2SO_4. Removal of the solvent gave crude crystals (36 mg), which were recrystallized from MeOH–H_2O to colorless prisms (XXVIII) (21 mg), mp 208—209.5°. *Anal.* Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.51; H, 11.09. IR ν_{max}^{KBr} cm^{-1}: 3190, 1067, 1023. NMR τ: 9.02 (s, 3H; C_4-Me), 8.62 (s, 3H; C_{10}-Me), 6.89 (d, 1H, J=12.0 cps; $C\underline{H}_2OH$), 5.68 (d, 1H, J=12.0 cps; $C\underline{H}_2OH$). t_R=11.1 min (1.5% OV-17 on Shimalite W, 4 mm×2.0 m, 180°).

$LiAlH_4$-reduction of Methyl 6α-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oate (XVII)——6α-Hydroxy ester (XVII) (20 mg) was refluxed with $LiAlH_4$ (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–H_2O 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 6α-hydroxy alcohol (XXVIII) obtained from 6α-lactone (XV).

$LiAlH_4$-reduction of 6β-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6β-Lactone (XXVII)——6β-Lactone (XXVII) (50 mg) prepared by thermal fusion method (a mixture of 6β-(XXVII) and 6α-lactone (XV) in ratio of 12:5) was refluxed with $LiAlH_4$ (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×1.8 m, 230°) showed it consisted of 6β-hydroxy alcohol (XXIX) as main product together with 6α-hydroxy alcohol (XXVIII). The ratio (XXIX: XXVIII=*ca.* 2:1) of the product measured by NMR peak integral due to C_{10}- and C_4-methyl.

$LiAlH_4$-reduction of Methyl 6β-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-oate (XVIII). 6β-Hydroxy-8βH, 9βH-*enantio*-podocarpan-16-ol (XXIX)——6β-Hydroxy ester (XVIII)[1] (50 mg) was reduced by reflux with $LiAlH_4$ (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–H_2O to colorless needles (XXIX) (20 mg), mp 152.5—155°. *Anal.* Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.78; H, 11.57. IR ν_{max}^{KBr} cm^{-1}: 3310, 1087, 1058. NMR τ: 8.83, 8.78 (s, 3H; C_4- and C_{10}-Me), 6.62 (d, 1H, J=10.5 cps; $C\underline{H}_2OH$), 5.80 (d, 1H, J=10.5 cps; $C\underline{H}_2OH$).

Attempt on Lactonization of 6β-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid (XXX) under Acidic Condition——1) Lactonization in HCl aq.-*tert*-BuOH: A solution of 6β-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 H_2O and it was extracted with ether. The extract was washed with 10% KOH aq. (acidic part), then with H_2O and dried over Na_2SO_4 (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 Na_2SO_4. Removal of the ether gave an oil (23 mg), whose methyl ester (CH_2N_2-treatment) was identical with 6β-hydroxy ester (XXXI)[1] by comparison of IR spectrum (CCl_4) and gas–liquid chromatogram (t_R=5.8 min; 1.5% OV-17 on Gaschrom P, 4 mm×2 m, 200°). Accordingly, the lactonization did not occur, but only starting compound was recollected.

2) Lactonization in HCl aq.-MeOH: A solution of 6β-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 H_2O and dried over Na_2SO_4 (neutral part). a) Neutral Part: The solvent was evaporated to give an oil (37 mg), whose IR spectrum (CCl_4) and gas–liquid chromatogram (t_R=6.80 min; 1.5% OV-17 on Shimalite W, 4 mm×2 m, 200°) were identical with those of 6β-hydroxy ester (XXXI). b) Acidic Part: Alkaline extract was acidified and extracted with ether. After the extract was washed with H_2O and dried over Na_2SO_4, it was evaporated to give an oil (5.5 mg). The corresponding methyl ester (CH_2N_2 treatment), which was identical with 6β-hydroxy ester (XXXI) by comparison of their IR spectrum and gas–liquid chromatogram. Accordingly, HCl–MeOH treatment of 6β-hydroxy acid (XXX) gave the corresponding methyl ester (XXXI) and recollected acid (XXX).

Lactonization of 6β-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid (XXX). 6β-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6β-Lactone (XXXII)——A reaction mixture of 6β-hydroxy acid (XXIX)[1] (50 mg) and *p*-TsOH (20 mg) in dry benzene (50 ml) was distilled for 10 min under N_2-gas stream until

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the distillate reached to *ca.* 20 ml. The residue was washed with 10% KOH aq., then washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave crude crystals (47.5 mg), which were recrystallized from MeOH–H_2O to colorless needles (XXXII) (23 mg), mp 98—99.5°. *Anal.* Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.81; H, 9.71. IR ν_{max}^{film} cm^{-1}: 1773, 1103, 1045, 996. NMR τ: 9.125, 8.74 (s, 3H; C_{10}- and C_4-Me), *ca.* 5.92 (m, 1H; H–C_6–OH). t_R=7.5 min (1.5% OV-17 on Gaschrom P, 4 mm×1.8 m, 200°).

Alkaline Hydrolysis of 6β-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6β-Lactone (XXXII)——A solution of 6β-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 H_2O, then extracted with ether and the extract was washed with H_2O, then dried over Na_2SO_4. 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 H_2O, dried over Na_2SO_4. Removal of ether gave an oil (XXX) (36.5 mg), whose IR (KBr) and NMR spectrum were identical with those of 6β-hydroxy acid (XXX).

Attempt on Epimerization of 6β-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6β-Lactone (XXXII)——1) Thermal Fusion Treatment: 6β-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 H_2O, then dried over Na_2SO_4. Removal of the solvent gave colorless oil (38 mg), whose IR spectrum (CCl_4) was identical with that of starting 6β-lactone (XXXII).

2) Alumina Treatment: After neutral alumina (5 g) was added to a solution of 6β-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 (CH_2N_2 treatment) showed that the former one consisted of dehydrated product (Δ^5 and Δ^6) (t_R=3.35 min), unidentified product (t_R=8.00 min) and 6α-Lactone (XXXIII) (t_R=10.27 min) in ratio of 1.0:76.2:13.5 and the latter one consisted of 6β-hydroxy ester (XXXI) (t_R=7.00 min) and 6β-lactone (XXXII) in ratio of 26.5:1.0.

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

Catalytic Hydrogenation of Methyl 6α-Hydroxy-*enantio*-podocarpa-8-en-16-oate (IX). Methyl 6α-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oate (XXXIV)——A solution of 6α-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–H_2O 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 $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.49. IR ν_{max}^{KBr} cm^{-1}: 3440, 1696. NMR τ: 9.12 (s, 3H; C_{10}-Me), 8.71 (s, 3H; C_4-Me), 6.235 (s, 3H; $COOCH_3$), 5.58 (m, (half band width=6.6 cps), 1H; H–C_6–OH).

On the other way, the former oil was identical with deoxy ester (XXI) by comparison of their IR-spectra (CCl_4).

Lactonization of Methyl 6α-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oate (XXXIV). 6α-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6α-Lactone (XXXIII)——After neutral alumina (2.5 g) was added to an ether solution of 6α-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–H_2O to colorless needles (XXXIII) (11 mg), mp 78—80°. Sample for elemental analysis was mp 86—87°. *Anal.* Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.45; H, 9.56. IR ν_{max}^{KBr} cm^{-1}: 1758, 1202, 1153, 1096, 997. NMR τ: 9.06, 8.73 (s, 3H; C_{10}- and C_4-Me), *ca.* 5.25 (m, 1H; H–C_6–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 6β-hydroxy ester (XXXI).[1]

Alkaline Hydrolysis of 6α-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6α-Lactone (XXXIII). 6α-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid (XXXV)——After a solution of 6α-lactone (XXXIII) (48 mg) in KOH (220 mg)–H_2O (1.0 ml)–EtOH (9.0 ml) was refluxed for 2 hr, the solvent was evaporated and the resulted residue was diluted with H_2O, extracted with ether. The alkaline layer was acidified and the appeared precipitates were extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give white powder (46 mg), a part (20 mg) of which was recrystallized from MeOH–H_2O to colorless needles (XXXV) (15 mg), mp 227.5—228.5°. *Anal.* Calcd. for $C_{17}H_{18}O_3$: C, 72.82; H, 10.06. Found: C, 72.98; H, 10.30. IR ν_{max}^{KBr} cm^{-1}: 3260, 2425, 1694, 1682.

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

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solvent was evaporated under reduced pressure and the resulted residue was extracted with ether. The extract was washed with 10% KOH aq., then with H_2O and dried over Na_2SO_4. Removal of the solvent gave colorless needles (8.5 mg), which were recrystallized from MeOH–H_2O 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 6α-lactone (XXXIII) obtained by alumina-treatment of 6α-hydroxy ester (XXXIV).

Methylation of 6α-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid (XXXV)——6α-Hydroxy acid (XXXV) (40 mg) was methylated by CH_2N_2–treatment. Removal of the solvent gave white powder (45 mg), which was recrystallized from MeOH–H_2O 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 6α-hydroxy tetrahydro-ester (IX).

$LiAlH_4$-reduction of 6β-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6β-Lactone (XXXII).——6β-Lactone (XXXII) (19.5 mg) was reduced in dry ether (15 ml) by reflux with $LiAlH_4$ (40 mg) for 3 hr. The resulted mixture was diluted with H_2O, then acidified and extracted with ether. After the extract was dried over Na_2SO_4, it was evaporated to give white powder (21 mg), which was recrystallized from MeOH–H_2O to colorless prisms (10 mg), mp 135—137°. Mixed mp and IR spectrum (KBr) of the compound were identical with those of 6β-hydroxy alcohol (XXXVI) obtained by $LiAlH_4$–reduction of 6β-hydroxy ester (XXXI).

$LiAlH_4$-reduction of Methyl 6β-Hydroxy-8αH,9 βH-*enantio*-podocarpan-16-oate (XXXI). 6β-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-ol (XXXVI)——The reaction mixture of 6β-hydroxy ester (XXXI) (51 mg) and $LiAlH_4$ (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–H_2O to colorless prisms (XXXVI) (35 mg), mp 141.5—143°. *Anal.* Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.68; H, 11.11. IR ν_{max}^{KBr} cm^{-1}: 3270, 1452, 1035. NMR τ: 9.09 (s, 3H; C_{10}-Me), 8.78 (s, 3H; C_4-Me), 6.68, (d, 1H, J=10.5 cps; $C\underline{H}_2OH$), 5.84 (d, 1H, J=10.5 cps; $C\underline{H}_2OH$).

$LiAlH_4$-reduction of 6α-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oic Acid 16→6α-Lactone (XXXIII). 6α-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-ol (XXXVII)——To a solution of 6α-lactone (XXXIII) (20 mg) in dry ether (15 ml), $LiAlH_4$ (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–H_2O to colorless needles XXXVII (14 mg), mp 157.5—158.5°. *Anal.* Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.56; H, 11.23. IR ν_{max}^{KBr} cm^{-1}: 3150, 1077, 1016. NMR τ: 8.975 (s, 3H; C_4-Me), 8.83 (s, 3H; C_{10}-Me), 6.87 (d, 1H, J=10.5 cps; $C\underline{H}_2OH$), 5.72 (d, 1H, J=10.5 pcs; $C\underline{H}_2OH$).

$LiAlH_4$-reduction of Methyl 6α-Hydroxy-8αH, 9βH-*enantio*-podocarpan-16-oate (XXXIV)——To a solution of 6α-hydroxy ester (XXXIV) (11 mg) in dry ether (10 ml), $LiAlH_4$ (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–H_2O 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 6α-hydroxy alcohol (XXXVII) obtained by $LiAlH_4$–reduction of 6α-lactone (XXXIII).

C_6-Epimerization at Lactonization of 6β-Hydroxy acids (II, V, XIV, XXX), and at 16→6β-Lactones (III, X, XXVII, XXXII), by Acidic Treatment (Table IV)——1) General Procedure (Epimerization of XIV as Example): A solution of 6β-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 CH_2N_2–treatment was examined by gas–liquid chromatography (Shimazu 4A-PF, 1.5% OV-17 on Gaschrom P (80—100 mesh), 4 mm×2 m, 200°, N_2). The ratio of the resulted components was measured by ratio of peak area (height × 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 6β-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 6β-hydroxy acid (XIV).

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