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POTENTIAL INTERMEDIATES FOR SYNTHESES OF NATURAL DITERPENOIDS

SYNTHESES OF 10β, 15-EPOXY- AND 10α, 17-EPOXY-*ENANTIO*-PODOCARPA-5,7,13-TRIEN-16-OIC ACID DERIVATIVES[1,2]

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Abstract—Methyl 10β,15-epoxy-*enantio*podocarpa-5,7,13-trien-16-oate(XVIII), methyl 10α,17-epoxy-*enantio*podocarpa-5,7,13-trien-16-oate (XIX) and their derivatives were prepared as potential intermediates for syntheses of natural diterpenoids from abietic acid (I).

THE synthesis of naturally occurring diterpenoids, such as the gibberellin and the *aconitum* and *garrya alkaloid* types, from physiologically inactive resin acids is of obvious interest.

Abietic acid (I) may be regarded as a promising starting material for the above purpose, because it is readily available from natural sources, for example from many kinds of common Japanese pine trees and has a secure structure and absolute configuration. Moreover, the total synthesis of abietic acid has been accomplished,[3] therefore, the preparation of other natural diterpenes from abietic acid can be regarded as formal total synthesis.

The preceding papers have reported studies describing the transformations of abietic acid to hydrofluorene derivatives[4,5] which have a common skeleton with the plant growth-promoting substances, the gibberellins. Conversions of abietic acid to intermediates[6] having an antipodal *trans* A/B ring fusion (βC_{11}–H, αC_{12}–Me) with the

[1] Detailed report for the following preceding communications; Diterpenoids—V, *Chem. Pharm. Bull.* **12**, 984 (1964); Diterpenoids—VI, *Ibid.* **12**, 1121 (1964). This work was also presented at the *7th Symposium of Natural Organic Compounds* held at Fukuoka, Japan, on October 18 (1963) and at the *International Symposium on the Chemistry of Natural Products* held in Kyoto, Japan, on April 16 (1964). Symposium *Abstracts* pp. 41–42.

[2] All m.p.s (except mixed m.p.) were measured on the Kofler block and were uncorrected. All NMR spectra were measured at 60 MC in $CDCl_3$ (5–10% solution) vs. Me_4Si as internal reference (Authors thank Dr. K. Takeda and Dr. K. Tori, Shionogi and Co., Ltd., Osaka, and Prof. T. Okamoto, Tokyo University for the NMR measurements and Dr. Y. Kawazoe, National Cancer Center Research Institute, and Dr. N. Nakagawa, The University of Electron-communication, for their discussion.) All gas-liquid-chromatograms were measured by Dr. N. Ikekawa, this Institute, whom authors thank for his advice.

[3] E. Wenkert, A. Afonso, J. B-son Bredenberg, C. Kaneko and A. Tahara, *J. Amer. Chem. Soc.* **86**, 2038 (1964).

[4] A. Tahara, *Chem. Pharm. Bull.* **9**, 252 (1961); A. Tahara and O. Hoshino, *Sci. Papers Inst. Phys. Chem. Res.* **56**, 84 (1962).

[5] A. Tahara and O. Hoshino, *Chem. Pharm. Bull.* **9**, 655 (1961); *Sci. Papers Inst. Phys. Chem. Res.* **56**, 88 (1962).

[6] A. Tahara, O. Hoshino and Y. Hamazaki, *Chem. Pharm. Bull.* **11**, 1328 (1963); *Sci. Papers Inst. Phys. Chem. Res.* **58**, 15 (1964).

$\Delta^{8(14)}$-7-keto group suitable for construction of the bridge ($C_6 \rightarrow C_{14}$ or $C_7 \rightarrow C_{14}$) as in the *aconitum* and *garrya alkaloids* have been also given.

We now wish to report the selective oxidation of the 15- or 17-methyl group of the antipodal deoxypodocarpic acid type compounds. These compounds have the same absolute configuration as the basic skeleton of the *aconitum* and *garrya alkaloids*. The 15- or 17-oxidized compounds such as 10β, 15-epoxy ester (XVIII), 10α, 17-epoxy ester (XIX), could be important intermediates either in the syntheses of the bridge containing a nitrogen atom in the *aconitum* and *garrya alkaloids* or in the formation of the lactone ring in the gibberellins.

For the above purpose, methyl 9-oxo-10-acetoxy-*enantio*podocarpa-5,7,10,13-tetraen-16-oate (II)[5] prepared from abietic acid was chosen as a starting material. The ester (II) was readily catalytically hydrogenated (Pd—C, EtOAc, H_2SO_4) to give the 10β-acetoxy ester (III), m.p. 143–144·5° and the known ester (IV; the so-called methyl deoxypodocarpate enantiomer), m.p. 140–141°, in a ratio of 1·9:1. It is noted that the formation of our 10β-acetoxy ester (III) is in contrast with the view of Wenkert *et al.* who assigned an α-configuration to the C_{10}-acetoxy group of the acetoxy-nitrile (XVI) obtained by the same type of the hydrogenation of the nitrile (XV).[7]

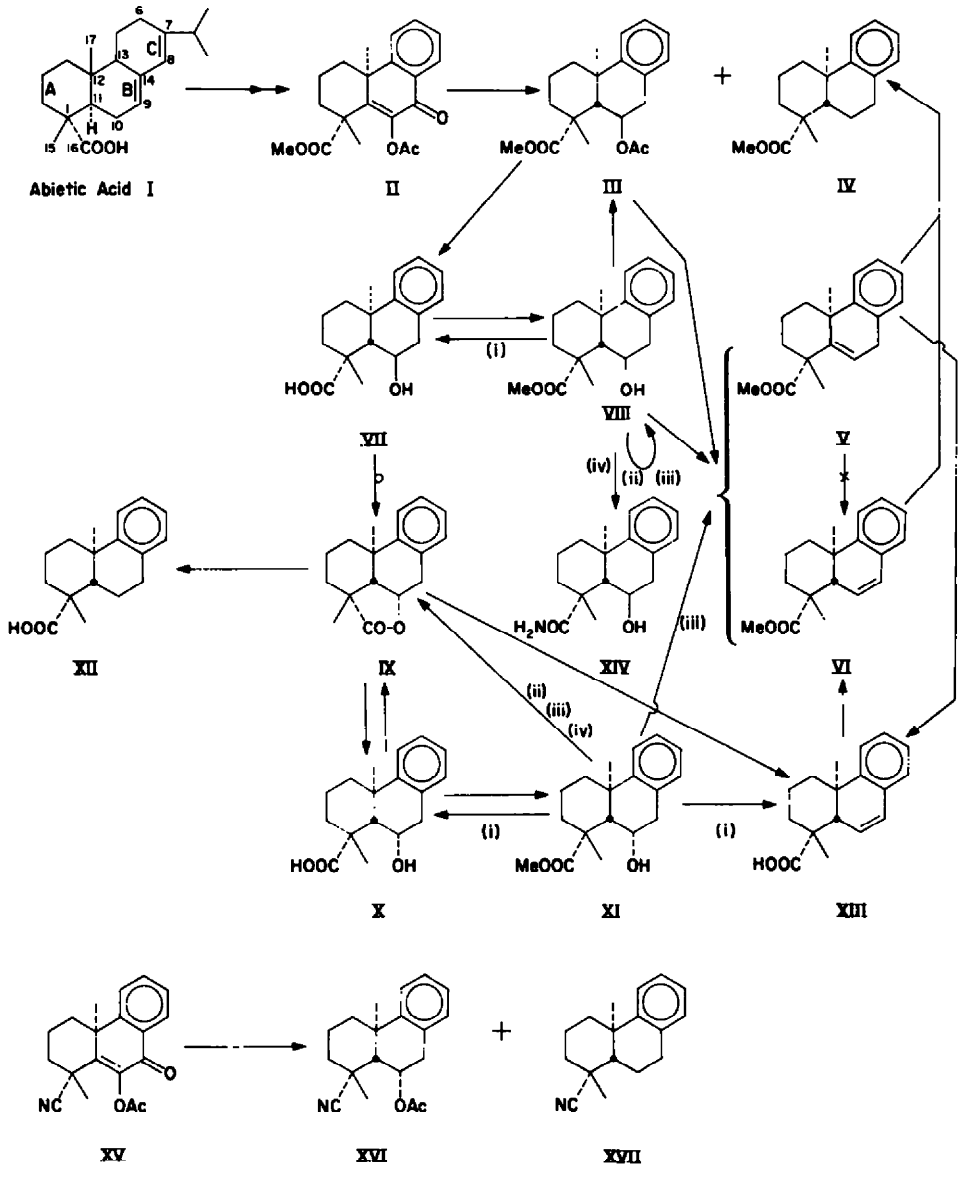
The evidence for the structure of the 10β-acetoxy ester (III), excepting the configuration at C_{10}, were obtained by a reaction involving loss of acetic acid. Pyrolysis of III at 290–300° or treatment of III with sulphuric acid–acetic acid at 80° afforded a mixture consisting of two isomeric unsaturated esters, m.p. 79° and m.p. 121°, in ratio of 1:3 by the pyrolysis reaction and 3:1 by the sulphuric acid reaction.

The two unsaturated esters (m.p. 79° and 121°) were catalytically hydrogenated to give the same ester (IV). Therefore, both esters must have the deoxypodocarpic acid enantiomer type skeleton (αC_1–COOH, βC_1–Me, βC_{11}–H and αC_{12}–Me). The location of double bond in these unsaturated esters follows from their UV and PMR spectra. The ester, (m.p. 79°) has a λ_{max}^{EtOH}: 264 mμ ($\varepsilon = 8600$) and a τ_{CDCl_3}: 3·57 (singlet (2H), Ph—CH=CH—C<), 7·60 (singlet (1H), >CH—CH=CH—) and the ester (m.p. 121°) has a λ_{max}^{EtOH}: 273, 267, 260 mμ ($\varepsilon = 600, 670, 580$) and a τ_{CDCl_3}: 4·02 (triplet (1H), Ph—CH_2—CH=C<), 6·49 (doublet (2H), Ph—CH_2—CH=C<). This indicates that the former (m.p. 79°) is VI with a double bond conjugated to the benzene ring and the latter (m.p. 121°) is V having a double bond nonconjugated to the benzene ring. Since an isomerization from the unconjugated ester (V) to the conjugated ester (VI) did not occur under the conditions of formation of the unsaturated esters, VI (having βC_{11}–H and αC_{12}–Me) is considered to be produced directly from the acetoxy ester (III) and not by isomerization of V. These experimental facts also established that the acetoxy ester (III) should have a methyl deoxypodocarpate enantiomer type skeleton with C_{10}–acetoxy group.

Alkaline hydrolysis (KOH–ethylene glycol, 180–200°, 15 min) of the 10β-acetoxy ester (III) yield the corresponding 10β-hydroxy acid (VII), which forms in two kinds of crystal form, m.p. 156–158° (containing no water of crystallization) and m.p. 156–158° (containing $\frac{1}{2}$ mols of water of crystallization). As evidence that the C_{10}–O configuration did not alter during the above alkaline hydrolysis (III $\rightarrow$ VII), the

[7] E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.* **80**, 211 (1958); In a personal communication from Prof. E. Wenkert, Indiana University, he has informed us that his recent work confirms the structure of XVI. (Authors wish to thank him for this information.)

corresponding ester (VIII), m.p. 78–80°, obtained from VII by diazomethane treatment, gave back the original 10β-acetoxy ester (III) by reaction with acetyl chloride and pyridine. Consequently, the compounds (VII and VIII) have the same skeleton and the same configuration at C_{10} as the starting compound (III).



By refluxing with 10% hydrochloric acid C_{10}–hydroxy group of the acid (VII) was readily lactonized with C_1–carboxylic acid to give IX, m.p. 174–176° (IR ν_{max}^{KBr}: 1758 cm^{-1}). Upon alkaline hydrolysis the lactone (IX) interestingly did not return to the original 10β-hydroxy acid (VII), but was converted to a new isomeric hydroxy

acid (X), m.p. 165–167°, whose physical constants (m.p., IR spectrum and NMR spectrum) were completely different from those of the original 10β-hydroxy acid (VII). The new isomeric hydroxy acid (X) was easily relactonized to the original lactone (IX). Also the lactone (IX) was hydrogenated (Pd—C, AcOH, H_2SO_4) to give only the known deoxypodocarpic acid enantiomer (XII). Since both isomeric hydroxy esters (VIII and XI), m.p. 144–147°, the latter obtained by methylation of the corresponding acid (X), were dehydrated by methanesulphonyl chloride to give the aforementioned unsaturated esters (V, VI) and the lactone (IX) in a ratio of 3:3:2 from VIII and 1:1:2 from XI and since no isomerization of V to VI occurred under the dehydration condition, these isomeric esters (VIII and XI) and also their corresponding acids (VII and X) have a common deoxypodocarpic acid enantiomer skeleton (αC_1–COOMe, βC_1–Me, βC_{11}–H and αC_{12}–Me). Therefore, these isomeric system are configurational isomers at C_{10}–hydroxy group and isomerization of the C_{10}–hydroxy group occurs during the lactonization of VII to IX.

Comparison of the IR spectra of the isomeric 10-hydroxy esters (VIII and XI) in ν_{OH} and $\nu_{C=O}$ region in CCl_4 showed the four absorption peaks ($\nu_{max}^{CCl_4}$ cm^{-1}: 3618 (ν free OH), 3548 (ν hydrogen bonded OH), 1732 (ν free C=O), 1713 (ν hydrogen bonded C=O)) for the ester (VIII) and two absorption peaks ($\nu_{max}^{CCl_4}$ cm^{-1}: 3485 (ν hydrogen bonded OH), 1715 (ν hydrogen bonded C=O) for the isomeric ester (XI). Since the IR absorptions corresponding to hydrogen bonded OH and C=O did not move with dilution of the sample concentration, as shown in the experimental part, these hydrogen bonds would be presumed as intramolecular and not intermolecular.

Chemical differences between the above two systems (VIII and XI) were observed in a number of reactions. (i) Although both esters (VIII and XI) were hydrolysed (KOH—MeOH—H_2O, reflux, 1·5 hr) to the respective original hydroxy acids (VII and X), a more drastic alkaline treatment (KOH–ethylene glycol–H_2O, 200°, 15 min) of the hydroxy ester (XI) and the lactone (IX) afforded an unsaturated acid (XIII), m.p. 145–148°, UV λ_{max}^{EtOH}: 265 mμ, which was methylated to the ester (VI) having a conjugated double bond, whereas the isomeric ester (VIII) only gave the corresponding 10β-hydroxy acid (VII). The isomerization (including hydrolysis of V to XIII) under the drastic alkaline hydrolysis conditions showed that the dehydration reaction of the hydroxy ester (XI) could include the double bond isomerization of Δ^{10} to Δ^{9}. However acidic (10% HCl—H_2O—MeOH, reflux, 2 hr) and mild alkaline (KOH—H_2O—MeOH, reflux, 1 hr) treatment of the unsaturated ester (V) resulted in the recovery of only the starting material (V) without the isomerization of V to VI. (ii) In treatment of both esters (VIII and XI) on alumina, only the former (VIII) was recovered, while the latter (XI) was quantitatively converted to the lactone (IX). (iii) In a thermal treatment (ethylene glycol, 200°), VIII was only recovered, while XI was converted to a mixture consisting of the lactone (IX) and the unsaturated esters (VI and V) in a ratio of 8:4:1. (iv) By heating (130–150°, 6 hr) with 28% ammonium hydroxide in a sealed tube, VIII was converted to the corresponding 10β-hydroxy amide (XIV), m.p. 170–171°, but XI was only lactonized to IX.

Usually, methyl podocarpate type compounds, in which C_1–COOMe is located

[8] These IR spectra were measured on a Perkin-Elmer 112G IR spectrometer (grating, single-beam system). (Authors thank Dr. J. Nakamura for the measurement.)

close to the C_{12}–Me in a 1,3-diaxial relationship, are very resistant to ester hydrolysis. In contrast, it is worth notice that the same type compounds with an acetoxy- or hydroxy group at C_{10}, as in the case of 10β-acetoxy- (III), 10β-hydroxy- (VIII), and 10α-hydroxy ester (XI), were very easily hydrolysed. Even 10β, 15-epoxy (XVIII) and 10α, 17-epoxy ester (XIX), *vide infra*, were hydrolysed more rapidly than methyl podocarpate type compounds, but more slowly than the compounds with substituted hydroxy group at C_{10}. This interesting observation could be readily explained by the intramolecular participation of the neighbouring oxygen group[9] in accord with similar previous suggestions.[10]

In order to prepare the compounds selectively oxidized at the 15- or 17-methyl group both isomeric 10-hydroxy esters (VIII and XI) were oxidized with lead tetra-acetate and iodine under UV illumination[11] to give the corresponding 10β, 15-epoxy ester (XVIII), m.p. 161–163°, and 10α, 17-epoxy ester (XIX),[12] m.p. 128–129°, in satisfactory yield.

A suitable oxidation for 10β-hydroxy ester (VIII) was achieved by treatment at 10° for 10 hr (XVIII; 95 w/w%), while for 10α-hydroxy ester (XI) the reaction condition was 60° for 18 hr (XIX; 74 w/w%). Furthermore, the yield of XVIII decreased as the reaction temperature was increased (50 w/w% at 23°, 27 w/w% at 56–59°). Upon maintaining VIII under the reaction condition (at 10° for 10 hr), but without iodine, only the starting material was recovered, while under refluxing condition also without iodine, the ester (XVIII; 17 w/w%) and the starting ester (59 w/w%) were produced. The evidence for stereochemical assignments of the two isomeric compounds will now be considered.

In this oxidation, the methyl group (15- or 17-Me) of the isomeric 10-hydroxy esters (VIII and XI) was bridged with the respective hydroxy group. This is supported by PMR analyses as shown below. Consideration of the chemical shift of 15- and 17-methyl groups of methyl O–methyl podocarpate (XXXIII), methyl deoxypodocarpate enantiomer (IV), and their corresponding alcohols (XXXIV and XXXV) with a study of molecular models indicates that the C_1–COOMe (axial) is oriented such that the 17-methyl group is in a conical region associated with positive shielding above the plane of the carbonyl double bond. Thus it is assumed that the τ-values, 8·96 and 8·97, for 17-methyl of the esters (XXXIII and IV) in 1,3-diaxial interaction with C_1–COOMe, show a diamagnetic shift as compared with τ-values, 8·82,[13] for 17-methyl of the corresponding alcohols (XXXIV and XXXV) in the same interaction with CH_2OH. In addition, the chemical shifts of τ-value, 8·73, for 15-methyl of the esters (XXXIII and IV) is observed to undergo a diamagnetic shift when the C_1–COOMe is converted to the C_1–CH_2OH of XXXIV and XXXV which show τ-values, 8·97 and 8·95 respectively, for 15-methyl group. More evidence for the above τ-value assignment in the esters is given by the fact that a NMR signal of the same type methyl as the 15-methyl of XXXIII and IV appeared in the range of 8·70 to 8·83 for

[9] The mechanism of these hydrolyses should be confirmed by kinetic analyses in the future.

[10] B. Capon: *Quart. Rev.* **18**, 58 (1964), and papers cited therein.

[11] Ch. Meystre, K. Heusler, J. Kalvoda, G. Anner and A. Wettstein, *Experientia* **17**, 475 (1961).

[12] Independently, Wenkert's group has also synthesized the same compound (XIX) from the nitrile XVI (private communication from Prof. E. Wenkert).

[13] It is still affected by paramagnetic effect of the benzene ring.

8 examples of sciadin derivatives,[14] sciadopate derivatives,[15] and 7-hydroxy-kaurenolide derivatives.[16]

Independently, Beak and Carney[17] have arrived at the same conclusions. A strong indication of the reliability of the aforementioned assignments for the methyl groups of the standards (XXXIII, XXXIV, IV and XXXV) is given by the following analyses of τ-value relationship for 15-methyl and 17-methyl of the 10β, 15-epoxy ester (XVIII), 10α, 17-epoxy ester (XIX) and the corresponding alcohols, (XX), m.p. 229–231°, and (XXI), m.p. 98–101°. The alcohols were prepared by reduction with $LiAlH_4$ of the esters (XVIII and XIX) respectively. By comparison of τ-values for the methyl group of the epoxy ester (XVIII) and the corresponding hydroxy ester (VIII) with those of the standards (XXXIII and IV), a τ-value for 17-methyl, 8·98, in the hydroxy ester (VIII), is not shifted from that of the standards (XXXIII and IV). However the τ-value for the 15-methyl, 8·51, is shifted 13·2 c/s to lower magnetic field than that of the standards (XXXIII and IV). In the corresponding epoxy ester (XVIII), the shifted signal for 15-methyl of VIII disappears, but the unshifted signal for 17-methyl of VIII remains. According to Kawazoe's observation[18] the NMR signal of methyl group shifted 10 to 15 c/s to lower magnetic field at 60 MC when a hydroxy group was located close to methyl group in steroid series (e.g. 1,3-diaxial relationship between hydroxy and methyl group in chair cyclohexane-like ring), and therefore, the C_{10}–hydroxy group of VIII is situated close to the 15-methyl and is combined with 15-methyl to give the epoxy bridge. By the same consideration, the fact that the τ-value for the 17-methyl, 8·63, in the other isomeric hydroxy ester (XI), is shifted 20·1 c/s to lower magnetic field from that of the standards (XXXIII and IV); whereas the τ-value for the 15-methyl, 8·70, is not shifted from that of the standards and that the shifted signal for 17-methyl disappears, but the unshifted signal for 15-methyl survives in the corresponding epoxy ester (XIX), lead to the conclusion that the C_{10}–hydroxy group is located close to 17-methyl of XI and is bridged to 17-methyl group in contrast with those in XVIII and VIII.

If the above τ-value assignments for the 15- and 17-methyl groups are consistent, it could be inferred that NMR signal for 17-methyl of the epoxy alcohol (XX) should appear at a lower magnetic field than that of the corresponding ester (XVIII) and that the signal for 15-methyl of the isomeric epoxy alcohol (XXI) should be present at a higher magnetic field than that of the corresponding ester (XIX). In accordance with the above expection the τ-value for the 17-methyl of XX is 8·85 and it is shifted 6·6 c/s lower than that (8·96) of the ester (XVIII); whereas the signal for the 15-methyl of the isomeric XXI is 8·91 and it is shifted 10·2 c/s higher than that (8·74) of the ester (XIX; cf. Table 1.).

In addition to the above NMR analyses, the following chemical proofs seem to support the correctness of the assigned structures for the two isomeric systems.

Indicative evidence for the above assignment of C_{10}–β-hydroxy group of the ester

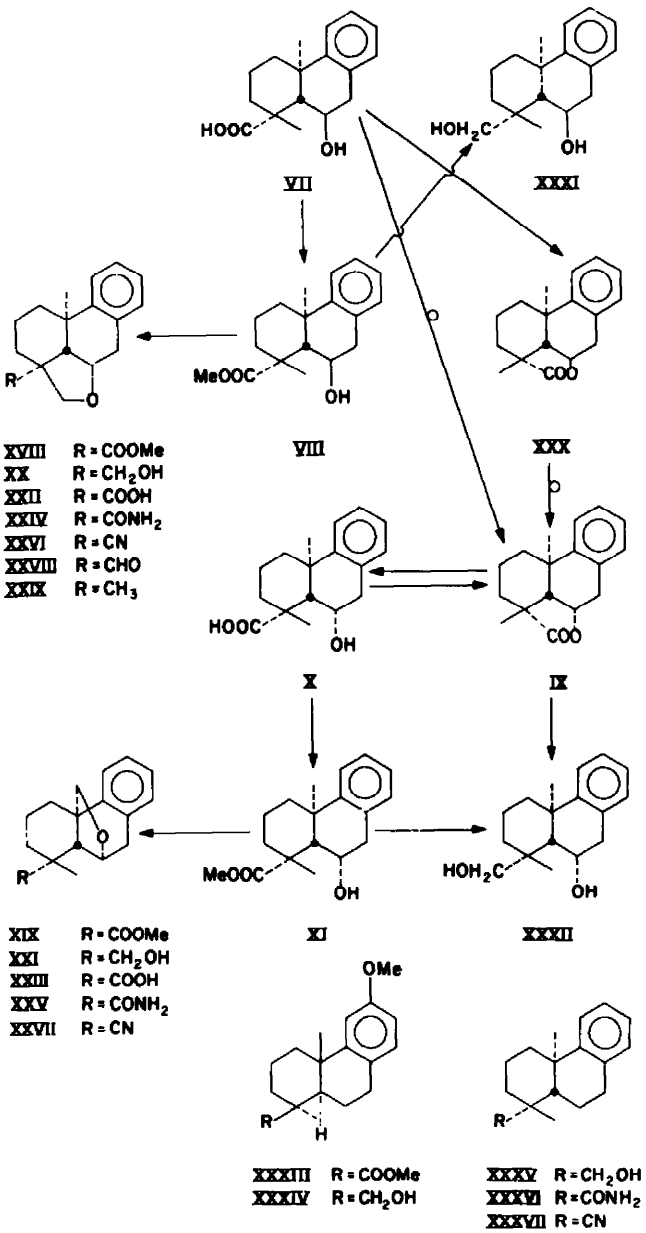
[14] C. Kaneko, T. Tsuchiya and M. Ishikawa, *Chem. Pharm. Bull.* **11**, 271 (1961).

[15] T. Miyasaka, *Chem. Pharm. Bull.* **12**, 744 (1964).

[16] B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 2944 (1963).

[17] P. Beak (Iowa State University, Ames) and R. W. J. Carney (Indiana University, Bloomington) in their theses under Prof. E. Wenkert's guidances. (The authors thank Prof. E. Wenkert and Dr. P. Beak for the informations on these data before publication.)

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



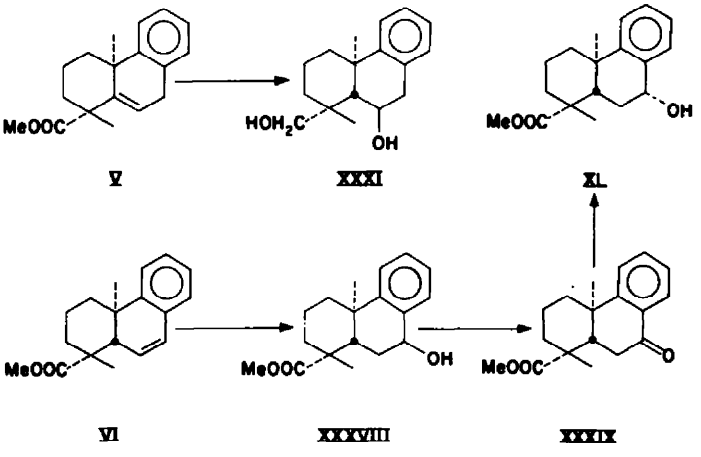
(VIII) is given by the fact that the Δ^{10}-ester (V) may be hydroborated ($NaBH_4$, BF_3–etherate) to give the aforementioned 10β-hydroxy alcohol (XXXI). Since the usual hydroboration to double bond is a *cis*-addition from the less-hindered side (β-side in case of V) and the alcohol (XXXI) doubtless has an antipodal *trans* A/B ring fusion (βC_{11}–H), it is clear that the C_{10}–hydroxy configuration should be β. In this connection, hydroboration ($NaBH_4$, BF_3–etherate) of Δ^9-ester (IV) also afforded the 9β-hydroxy ester (XXXVIII), which was oxidized to the authentic 9-oxo ester

TABLE 1. τ-VALUES FOR C_1–Me AND C_{13}–Me OF THE DERIVATIVES OF PODOCARPIC ACID (ENANTIOMER) TYPE COMPOUNDS

Ester ( ) shift (c/s) from that of XXXIII, IV			Acid ( ) shift (c/s) from that of XII			Alcohol ( ) shift (c/s) from that of XXXIV, XXXV			Alcohol-ester (c/s)	
	C_1–Me	C_{13}–Me		C_1–Me	C_{13}–Me		C_1–Me	C_{13}–Me	C_1–Me	Cl_3–Me
XXXIII	8·73	8·96				XXXIV	8·97	8·82	+14·4	−8·4
IV	8·73	8·97	XII	8·68	8·90	XXXV	8·95	8·82	+13·2	−9·0
III	8·73	8·98								
VIII	8·51 (−13·2)	8·98	VII	8·44 (−14·4)	8·88	XXXI	8·71 (−15·0)	8·71		
XI	8·70	8·63 (−20·1)	X	8·72	8·63 (−16·2)	XXXII	8·90	8·45 (−22·2)		
XVIII		8·96	XXII		8·82	XX		8·85		−6·6
XIX	8·74		XXIII	8·74		XXI	8·91		+10·2	

Amide			Nitrile		
	C_1–Me	C_{13}–Me		C_1–Me	C_{13}–Me
XXXVI	8·72 (or 8·82)	8·82 (or 8·72)	XXXVII	8·58 (or 8·63)	8·63 (or 8·58)
XXIV		8·83	XXVI		8·62
XXV	8·72		XXVII	8·56	

(XXXIX). This was different from the 9α-hydroxy ester (XL) obtained by $NaBH_4$ reduction of XXXIX. The C_9–hydroxy configuration for the esters (XXXVIII and XL) is supported by the consideration that the hydroxy group in the hydroboration and hydrogen atom in $NaBH_4$ reduction were supplied from the less-hindered side (β-side in case of XXXVIII and XL) of the molecule.

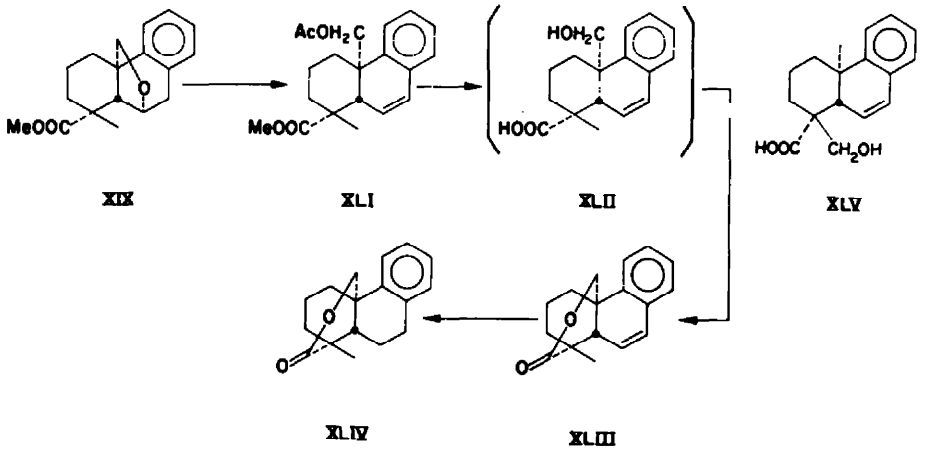


V XXXI XL

VI XXXVIII XXXIX

In another way, a chemical proof for the structure of 10α, 17-epoxy ester (XIX) was obtained as follows. The ether bridge of the epoxy ester (XIX) was cleaved by treatment of BF_3–etherate in acetic anhydride to give an unsaturated 17-acetoxy ester (XLI) as an oil. The UV spectra, λ_{max}^{EtOH} 262·5 mμ (ε = 7900), of this compound (XLI) showed that the oil consisted mainly of a compound having a double bond

conjugated to the benzene ring. Subsequently, alkaline hydrolysis following acidification of the Δ^9-17-acetoxy ester (XLI) afforded Δ^9-16 → 17 lactone (XLIII), m.p. 176·5–177·5°, IR ν_{max}^{KBr} 1730 cm^{-1}, which was readily catalytically hydrogenated to the corresponding saturated lactone (XLIV), m.p. 184–185°, IR ν_{max}^{KBr} 1730 cm^{-1}. The above behaviour of the acetoxy ester (XLI) on alkaline treatment is consistent with the view that lactonization of the 15-hydroxy acid (XLV) appeared to be almost impossible, whereas the 17-hydroxy acid (XLII; although it cannot be isolated) has a suitable structure for lactonization.



XIX XLI XLII XLV

XLIV XLIII

Consequently, it might be assumed that a configuration of C_{10}–hydroxy group of the ester (VIII; and therefore also its derivatives III, VII, XIV, XXXI, XVIII, XX, XXII, XXIV, XXVI, XXVIII and XXIX) should be assigned as β; whereas C_{10}–hydroxy group of the isomeric ester (XI; and hence its derivatives X, XXXII, XIX, XXI, XXIII, XXV and XXVII) should have an α-configuration.

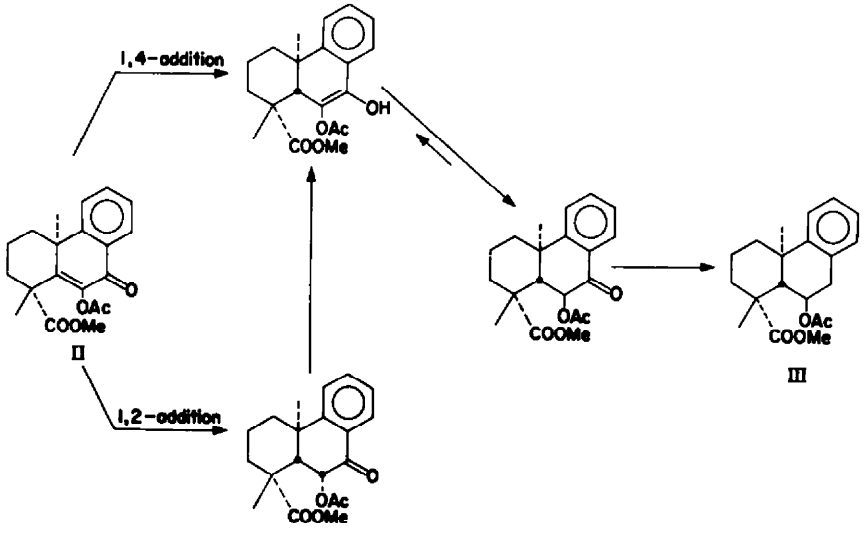
Next, consideration will be given to the stereochemistry of the lactone (IX) and isomeric unstable lactone (XXX).[19] As described above, the lactone (IX) was prepared from either 10β- (VII) or 10α-hydroxy acid (X), but could only be hydrolysed to 10α-hydroxy acid (X). Therefore it could be assumed that the C_{10}–configuration of the lactone (IX) belongs to 10α-hydroxy ester series. In comparison with the 16 → 10α lactone (IX), thermal treatment (200°, 3 hr, sealed tube) of 10β-hydroxy acid (VII) afforded an isomeric 16 → 10β lactone (XXX), whose IR absorption at 1774 and 1090 cm^{-1} are distinguishable from those at 1758, 1110 and 1040 cm^{-1} of the 16 → 10α lactone (IX). However the isomeric lactone (XXX) itself is so unstable that it was not possible to purify it from contaminated stable 16 → 10α lactone (IX). Even recrystallization of the unstable lactone (XXX) causes gradual isomerization to the lactone (IX), as detected by the fact that the m.p. and IR spectra steadily approach those of IX. Quantitative transformation of the unstable lactone (XXX) to the 16 → 10α lactone (IX) proceeded upon prolonged thermal reaction (240°, 5 hr, sealed tube) or aluminium oxide treatment (Al_2O_3, R.T., 2 days).

[19] Confirmation of the existence and possible conformation of the unstable lactone (XXX) by IR spectral analyses were first suggested to us by Dr. W. Nagata, Shionogi and Co., Osaka, to whom the authors are indebted for his valuable information.

Strong evidence for the structure of the unstable 16 → 10β lactone (XXX) was obtained from its reduction with $LiAlH_4$, which afforded the 10β-hydroxy alcohol (XXXI). In contrast, the same reduction of 16 → 10α lactone (IX) gave the corresponding 10α-hydroxy alcohol (XXXII). Owing to the lactonization of C_1–COOH in the A-ring with C_{10}–β-hydroxy group in B-ring of the 16 → 10β lactone (XXX), models indicate that conformation of A-ring should be a boat form.

On the basis of all the above observations, an isomerization ($\beta \rightarrow \alpha$) of C_{10}–hydroxy configuration should occur during the acid lactonization of 10β-hydroxy acid (VII) and the prolonged thermal treatment of the unstable lactone (XXX). Although the mechanism of this isomerization is not obvious, two possibilities may be assumed for this inversion; either an intramolecular S_{N_2}-substitution or an S_{N_1}-substitution, passing through carbonium ion at C_{10}.

In the catalytic hydrogenation (Pd—C, EtOAc, H_2SO_4) of II, the compound III having βC_{10}–OAc and βC_{11}–H was formed along with IV.[20] It is possible that III arises by either 1,4-addition or 1,2-addition of hydrogen[21] as shown in the following scheme.



Finally, syntheses of derivatives from the isomeric 10β, 15-epoxy (XVIII) and 10α, 17-epoxy ester (XIX) were undertaken in order to prepare some other potential synthetic intermediates. The 10β, 15-epoxy ester (XVIII) was converted by alkaline hydrolysis to 10β, 15-epoxy acid (XXII), m.p. 260–262°, from which the 10β, 15-epoxy amide (XXIV), m.p. 218–220°, was formed by ammonia gas treatment of the acid chloride. In addition, 10β, 15-epoxy-nitrile (XXIV), m.p. 147–149°, was produced by dehydration of XXIV with phosphorus oxychloride. Chromium trioxide oxidation

[20] Gas chromatographic analysis of the hydrogenated mixture gave only two peaks corresponding to III and IV appeared in the chromatogram (cf. A. Tahara, K. Hirao and Y. Hamazaki, *Chem. Pharm. Bull.* **12**, 1458 (1964)).

[21] Cf. R. L. Augustin, *J. Org. Chem.* **23**, 1853 (1958); R. L. Augustin and A. D. Broom, *Ibid*, **25**, 802 (1960).

followed by Wolff-Kishner reduction of 10β, 15-epoxy alcohol (XX) gave the corresponding hydrocarbon (XXIX), m.p. 76–77°,[22] via the respective aldehyde (XXVIII). By the same treatment as for 10β, 15-epoxy series the isomeric 10α, 17-epoxy acid (XXIII), m.p. 233–236°, 10α, 17-epoxy amide (XXV), m.p. 87–90° and 10α, 17-epoxy-nitrile (XXVII), m.p. 142–144°, were obtained from the 10α, 17-epoxy ester (XIX).

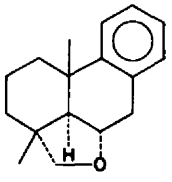
In the chemical shift for the methyl groups of these derivatives it is noticeable that τ-values for methyl of the isomeric acids (XXII), 8·82[23] (17-Me) and (XXIII). 8·74 (15-Me), of the isomeric amides (XXIV), 8·83 (17-Me) and (XXV), 8·72 (15-Me), and of the isomeric nitriles (XXVI), 8·62 (17-Me) and XXVII, 8·56 (15-Me), are in good agreement with τ-values for methyl of the respective standards, acid (XII), 8·90 (17-Me), 8·68 (15-Me), amide (XXXVI), 8·82, 8·72 and nitrile (XXXVII), 8·63, 8·58. However, NMR methyl signals of the amide (XXXVI) and the nitrile (XXXVII) are so close to each other that definite assignment to methyl group (15- or 17-Me) on the basis of τ-values for methyl of the epoxy amides (XXIV, XXV) and the epoxy nitriles (XXVI, XXVII), must be still left undecided (cf. Table 1.).

EXPERIMENTAL

Methyl 10β-*acetoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (III)

Catalytic hydrogenation of methyl 9-*oxo*-10-*acetoxy*-enantio*podocarpa*-5,7,10,13-*tetraen*-16-*oate* (II). A solution of II (9·5 g)[6] in EtOAc (100 ml) containing H_2SO_4 (1 ml) was shaken under H_2 atm. in presence of 10% Pd—C (2 g). After an absorption of H_2 had almost ceased, the catalyst was filtered off and the EtOAc solution washed with 10% Na_2CO_3 aq and H_2O successively, dried over Na_2SO_4 and evaporated. Chromatography of the residue, m.p. 105–115°, on neutral alumina (200 g) gave fractions (2 g) in pet. ether–ether (20:1) elution and (3·75 g) in pet. ether–ether (5:1) elution successively. The former fraction was recrystallized from MeOH—H_2O as colourless prisms of IV (1·76 g), m.p. 140–141°, IR ν_{max}^{KBr} cm^{-1}: 1727, NMR_{CDCl_3}(τ): 6·33 (—COOC$\underline{H}_3$), 8·73 (—CO—C—C$\underline{H}_3$), 8·97 (—C—C$\underline{H}_3$), GC_{min}[24]: 2·95 (1·5% SE-30 on Anakrom (mesh 80–100), 4 mm × 1·5 m, 182°), whose m.p. and IR spectrum were identical with those of the authentic methyl deoxypodocarpate (antipodal structure of IV). On the other hand, the latter fraction was recrystallized from MeOH—H_2O to colourless prisms of III (3·38 g), m.p. 140–142° and m.p. 143·5–144·5° as analytical sample. (Found: C, 72·69; H, 7·79. Calc. for $C_{20}H_{26}O_4$: C, 72·70; H, 7·93%), IR ν_{max}^{KBr} cm^{-1}: 1724, 1267, NMR_{CDCl_3} (τ): 6·31 (—COOC$\underline{H}_3$), 8·03 (—O—COC$\underline{H}_3$), 8·73 (—CO—C—C$\underline{H}_3$), 8·98 (—C—C$\underline{H}_3$) GC_{min}: 6·23 (1·5% SE-30 on Anakrom (mesh 80–100), 4 mm × 1·5 m, 182°). Mixed m.p. of III, with IV showed a depressed m.p.

[22] By comparison of m.p., optical rotation, IR spectrum and NMR spectrum, this hydrocarbon (XXIX) is shown as complete antipode of the hydrocarbon (XLVI), which was obtained by



XLVI

Wenkert' group. These results further confirm the structure of the 10β, 15-epoxy derivatives. (The authors gratefully thank Prof. E. Wenkert for donation of the valuable sample and for information from unpublished data.)

[23] Since XXII was not sufficiently soluble in $CDCl_3$, this chemical shift was measured in a very dilute solution.

[24] Abbreviation, GC_{min}, showed a retention time of the gas-liquid-chromatography.

Pyrolysis of methyl 10β-*acetoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (III) *to methyl* enantio-*podocarpa*-5,7,10,13-*tetraen*-16-*oate* (V) and *methyl* enantio*podocarpa*-5,7,9,13-*tetraen*-16-*oate* (VI)

Under N_2–stream III (100 mg) was heated for 3 min on a metal bath (bath temp was maintained at 290–300°) and the resulting oil (94 mg) was crystallized. Chromatography of the product on neutral alumina (6 g) gave two kinds of fractions (11 mg and 35 mg) in pet. ether elution successively. The latter (35 mg) was recrystallized twice from MeOH—H_2O as colourless needles of V, m.p. 121°, as analytical sample. (Found: C, 79·76; H, 7·93. Calc. for $C_{18}H_{22}O_2$: C, 79·96; H, 8·20%), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730, 1245, UV λ_{max}^{EtOH} mμ: 273 (ε = 600), 267 (ε = 670), 260 (ε = 580), NMR$_{CDCl_3}$ (τ): 4·02 (triplet (1H), Ph—CH_2—C$\underline{H}$=C), 6·35 (singlet (3H), —COOC$\underline{H}_3$), 6·49 (doublet (2H), Ph—C$\underline{H}_2$—CH=C), 8·59 (singlet (3H), —CO—C—C$\underline{H}_3$), 8·81 (singlet (3H), —C—C$\underline{H}_3$). The former (11 mg) was recrystallized twice from MeOH—H_2O as colourless needles of VI, m.p. 79°, as analytical sample. (Found: C, 79·63; H, 8·13. Calc. for $C_{18}H_{22}O_2$: C, 79·96; H, 8·20%), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730, 1218, UV λ_{max}^{EtOH} mμ: 264 (ε = 8600), NMR $_{CDCl_3}$(τ): 3·57 (singlet (2H), Ph—C$\underline{H}$=C$\underline{H}$—CH) 6·33 (singlet (3H), —COOC$\underline{H}_3$), 7·60 (singlet (1H), —C$\underline{H}$—CH=CH—), 8·67 (singlet (3H), —CO—C—C$\underline{H}_3$), 9·09 (singlet (3H), —C—C$\underline{H}_3$). Both V and VI had the same retention time of gas-chromatography. GC$_{min}$: 10·6 (2·0% XE-60 (G. E. Nitril Silicon) on Anakrom A (80–100 mesh), 1·5 m × 4 mm, 172°) and 4·0 (1·5% SE-30 on Anakrom A (80–100 mesh), 1·5 m × 4 mm, 182°). As described later an isomerization of the Δ^{10}-ester (V) to the Δ^9-ester (VI) did not occur during or after this pyrolysis.

Acetic acid elimination of methyl 10β-*acetoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (III) *to methyl* enantio*podocarpa*-5,7,10,13-*tetraen*-16-*oate* (V) and *methyl* enantio*podocarpa*-5,7,9,13-*tetraen*-16-*oate* (VI)

After a solution of III (90 mg) in AcOH (4 ml) containing H_2SO_4 (3 drops) was warmed at 80° for 30 min, it was diluted with H_2O and was extracted with ether. The ether extract was washed with 10% NaOH aq, then with H_2O, dried over Na_2SO_4 and evaporated. Chromatography of the oil (70 mg) on neutral alumina (10 g) gave two kinds of fractions (41 mg and 14 mg) in pet. ether–ether (20:1) elution successively. The former was identical with VI and the latter was identical with V by comparison of their IR spectra and of mixed m.p. with the respective authentic sample. As described below, an isomerization of V to VI did not occur during or after elimination.

Catalytic hydrogenation of methyl enantio*podocarpa*-5,7,9,13-*tetraen*-16-*oate* (VI) *and of methyl* enantio*podocarpa*-5,7,10,13-*tetraen*-16-*oate* (V) *to methyl* enantio*podocarpa*-5,7,13-*trien*-16-*oate* (IV)

(i). *Hydrogenation of* Δ^9-*ester* (VI). A solution of VI (15 mg) in MeOH (1·5 ml) in presence of 10% Pd—C (10 mg) was shaken under H_2 atm. After H_2 absorption had ceased, the catalyst was filtered off and the filtrate evaporated *in vacuo*. The residue (13 mg) was recrystallized from MeOH—H_2O as colourless prisms, m.p. 138–140°, which were identical with the authentic IV by no depression of mixed m.p. and coincidence of their IR spectra.

(ii). *Hydrogenation of* Δ^{10}-*ester* (V). A solution of V (30 mg) in MeOH (10 ml) in presence of 10% Pd—C (25 mg) was shaken under H_2 atm. It was treated as in (i). The residue (27 mg) was recrystallized twice from MeOH—H_2O as colourless prisms, m.p. 138–140°, which was identical with authentic IV by no depression of mixed m.p. and coincidence of their IR spectra.

10β-*Hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* (VII)

A solution of III (2 g) and KOH (700 mg) in ethylene glycol (50 ml) and H_2O (2·5 ml) was heated for 15 min on an oil bath (bath temp was maintained at 180–200°). After the reaction mixture was diluted with H_2O, it was carefully acidified with 10% HCl with ice cooling to prevent the formation of IX and then extracted with ether. The ether extract was washed with 10% NaOH aq.

(i). *Acidic part*. After the above alkaline (NaOH) extract was carefully acidified with 10% HCl with ice cooling, the precipitate (1·66 g) was collected and recrystallized from MeOH—H_2O to give colourless fine prisms of VII, which has two crystalline forms; (a). m.p. 156–158°. (Found: C, 74·32; H, 7·85. Calc. for $C_{17}H_{22}O_3$: C, 74·42; H, 8·08%), IR ν_{max}^{KBr} cm^{-1}: 3580, 3400, 1726, 1693, 1240, NMR$_{CDCl_3}$(τ): 8·44 (—CO—C—CH_3), 8·88 (—C—CH_3) and (b). m.p. 156–158° (once melted at about 80°). (Found: C, 72·08; H, 7·89. Calc. for $C_{17}H_{22}O_3 \cdot \frac{1}{2}H_2O$: C, 72·05; H, 8·18%), IR ν_{max}^{KBr} cm^{-1}: 3420, 3360, 1662, 1220. The latter was dried at 70° *in vacuo* for 2 days to give the

former crystalline form. Both crystalline forms were selectively obtained from their solution by seeding of either forms respectively. Mixed m.p. of both crystalline species showed no depression.

(ii). *Neutral part.* The above mentioned ether layer was washed with H_2O, then was dried over Na_2SO_4 and evaporated. The residue (200 mg) was recrystallized from MeOH—H_2O as colourless needles, m.p. 160–163°, whose IR spectrum was identical with that of IX.

Methyl 10*β-hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (VIII)

Compound VII (300 mg) was readily methylated with excess diazomethane in ether. An oil (slowly crystallized) was quantitatively obtained and it was twice recrystallized from pet. ether as colourless fine prisms of VIII, m.p. 79–80°, as analytical sample. (Found: C, 74·59; H, 8·10. Calc. for $C_{18}H_{24}O_3$: C, 74·97; H, 8·39%), NMR_{CDCl_3} (τ): 6·25 (—COOC$\underline{H}_3$), 8·54 (—CO—C—C$\underline{H}_3$), 8·98 (—C—C$\underline{H}_3$), GC_{min}: 4·0 (1·5% SE-30 on Anakrom A (80–100 mesh), 1·5 m × 3·0 mm, 180°).

Conversion of methyl 10*β-hydroxy* enantio*podocarpa*-5,7,13-*trien*-16-*oate* (VIII) *to methyl* 10*β-acetoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (III)

Acetyl chloride (0·5 ml) was added dropwise to a solution of VIII (49 mg) in anhydrous pyridine (2 ml) with ice cooling. After the reaction solution was left standing in a refrigerator for one day, it was diluted with H_2O and extracted with ether. The ether extract was washed with 10% HCl and H_2O successively and then dried over Na_2SO_4. After evaporating the solvent, the quantitative residue was twice recrystallized from MeOH—H_2O as colourless needles (35 mg), m.p. 132–141°, which were chromatographed on neutral alumina to give colourless needles (24 mg) in pet. ether–ether (5:1) elution. They were recrystallized again from MeOH—H_2O as colourless needles, m.p. 142–144°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of the aforementioned III.

10*α-Hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 10*α-lactone* (IX)

Lactonization of 10*β-hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* (VII). A solution of VII (200 mg) in 10% HCl (30 ml) and MeOH (added until complete dissolution) was refluxed for 30 min. After the MeOH was evaporated off, the residue was extracted with ether. The ether extract was washed with 10% Na_2CO_3 aq, and H_2O successively and then dried over Na_2SO_4. After evaporating the solvent, the residue (123 mg) was recrystallized twice from MeOH—H_2O yielding colourless fine prisms of IX (104 mg), m.p. 174–176° as analytical sample. (Found: C, 79·30; H, 7·71. Calc. for $C_{17}H_{20}O_2$: C, 79·65; H, 7·86%), IR ν_{max}^{KBr} cm^{-1}: 1758, GC_{min}: 4·5 (1·5% SE-30 on Anakrom A (80–100 mesh), 1·5 m × 3·0 mm, 182°), NMR_{CDCl_3}: 8·75 (—CO—C—C$\underline{H}_3$), 8·91 (—C—C$\underline{H}_3$).

10*α-Hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* (X). *Hydrolysis of* 10*α-hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 10*α-lactone* (IX)

A solution of IX (100 mg) in 10% KOH aq (3 ml) and MeOH (added until complete dissolution) was refluxed for 30 min. After the solvent was evaporated off and the residue diluted with H_2O, it was extracted with ether to separate alkaline H_2O-layer (acidic part) and ether extract (neutral part).

(i). *Acidic part.* After the alkaline H_2O-layer was acidified with ice cooling and extracted with ether, the ether extract was washed with H_2O and dried over Na_2SO_4. After evaporating the solvent, the residue (70 mg) was recrystallized from MeOH—H_2O as colourless fine prisms of X (35 mg), m.p. 163·5–165°, as analytical sample. (Found: C, 74·42; H, 7·92. Calc. for $C_{17}H_{22}O_3$: C, 74·42; H, 8·08%), IR ν_{max}^{KBr} cm^{-1}: 3210, 2360, 1935, 1675, 1270, NMR_{CDCl_3} (τ): 8·72 (—CO—C—C$\underline{H}_3$), 8·63 (—C—C$\underline{H}_3$). Mixed m.p. of this X with isomeric VII showed depressed m.p.

(ii). *Neutral part.* The ether extract was washed with H_2O and then dried over Na_2SO_4. After evaporating the solvent, the residue (23 mg) was recrystallized from MeOH—H_2O as colourless needles, m.p. 174–177°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of the starting IX.

Lactonization of 10*α-hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* (X) *to* 10*α-hydroxy*-enantio-*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 10*α-lactone* (IX)

A solution of X (50 mg) in 10% HCl (7·5 ml) and MeOH (10 ml) was refluxed for 30 min. After

the MeOH was evaporated, it was extracted with ether. The ether extract was washed with ether. The ether extract was washed with 10% NaOH aq and with H_2O successively and then dried over Na_2SO_4. After evaporating the solvent, the residue (43 mg) was recrystallized from MeOH—H_2O to colourless fine prisms, m.p. 174–176°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of IX.

Methyl 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XI)

Compound X (15 mg) was methylated with excess diazomethane–ether. The residue (15 mg) was recrystallized from MeOH—H_2O as colourless needles of XI, m.p. 144–147°, as analytical sample. (Found: C, 74·93; H, 8·27. Calc. for $C_{18}H_{24}O_2$: C, 74·97; H, 8·39%), NMR_{CDCl_3} (τ): 6·23 ($COOCH_3$), 8·70 (—CO—C—CH_3), 8·63 (—C—CH_3), GC_{min}: 6·4 (1·5% SE-30 on Anakrom A (80–100 mesh), 1·5 m × 3·0 mm, 181°).

Infra-red spectra analyses[8] *of methyl* 10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (VIII) *and methyl* 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XI)

IR absorption bands (in CCl_4) corresponding to hydroxy and carbonyl groups of VIII and XI were observed as follows:

(i). 10β-*Hydroxy ester* (VIII). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3618 (ν_{O-H}), 3548 (hydrogen bonded ν_{O-H}), 1732 ($\nu_{C=O}$), 1713 (hydrogen bonded $\nu_{C=O}$), which is constant in following concentration; (a). c = 0·140 M/L, l (cell length) = 0·1 mm for $\nu_{C=O}$, 0·5 mm for ν_{O-H}. (b). c = 0·014 /ML, l = 0·5 mm for $\nu_{C=O}$ and ν_{O-H}. (c). c = 0·005 M/L, l = 1·0 mm for $\nu_{C=O}$ 10·0 mm for ν_{O-H}.

(ii). 10α-*Hydroxy* ester (XI). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3485 (hydrogen bonded ν_{O-H}), 1715 (hydrogen bonded $\nu_{C=O}$), which is constant in following concentration; (a). c = 0·140 M/L, l = 0·1 mm for $\nu_{C=O}$ and ν_{O-H}. (b). c = 0·014 M/L, l = 0·5 mm for $\nu_{C=O}$ and ν_{O-H}. (c). c = 0·005 M/L, l = 1·0 mm for $\nu_{C=O}$ and ν_{O-H}.

Since the above hydrogen bonded absorptions were not shifted with dilution of the samples, these hydrogen bonds were not intermolecular, but intramolecular.

Catalytic hydrogenation of 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16→10α-*lactone* (IX) *to* enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* (l-*deoxypodocarpic acid* XII)

A solution of IX (42 mg) in AcOH (15 ml) containing H_2SO_4 (1 drop) was shaken under H_2 atm. in presence of 10% Pd—C (40 mg). After H_2 absorption ceased, the catalyst was filtered off and the filtrate evaporated *in vacuo*. The residue was diluted with H_2O and extracted with ether. The ether extract was washed with 10% NaOH aq and the alkaline extract acidified and then extracted again with ether. The ether extract was washed with H_2O, then dried over Na_2SO_4 and evaporated to give a residue (36 mg), m.p. 165–180°, which was chromatographed on silicic acid–celite (1:1; 6 g) to give colourless prisms, m.p. 192–197°, in pet. ether–ether (20:1) elution. Its physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of the authentic XII.

Dehydration of methyl 10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (VIII) *and methyl* 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XI) *by methanesulphonyl chloride*

(i). *In the case of* 10β-*hydroxy ester* (VIII). A solution of VIII (113 mg) and methanesulphonyl chloride (123 mg) in absolute pyridine (0·7 ml) was warmed for 100 min on a water bath maintained at 80 ± 5° and then was left standing overnight at room temp. After the reaction mixture was diluted with H_2O and then acidified with 10% HCl, the precipitate (95 mg) was collected, washed with H_2O and then chromatographed on neutral alumina (5 g) to give the following three fractions successively in pet. ether elution: Fraction a (21 mg) was recrystallized from MeOH—H_2O as colourless needles, m.p. 76–78°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of the authentic VI. Fraction b (18 mg) was recrystallized from MeOH—H_2O as colourless needles, m.p. 115–117°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of authentic V. Fraction c (13 mg) was recrystallized from MeOH—H_2O as colourless fine prisms, m.p. 162–170°, whose IR spectrum was identical with that of the authentic IX.

(ii). *In the case of* 10α-*hydroxy ester* (XI). A solution of XI (103 mg) and methanesulphonyl

chloride (120 mg) in absolute pyridine (0·7 ml) was treated as in (i). The precipitate was chromatographed on neutral alumina (10 g) to give successively the following three fractions: Fraction a (22 mg) appearing in pet. ether elution, was recrystallized twice from MeOH and then from pet. ether as colourless needles, m.p. 68–73°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of the authentic VI. Fraction b (22 mg) appearing in pet. ether–ether (10:1) elution, was recrystallized twice from MeOH and then from pet. ether as colourless needles, m.p. 114–117°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of the authentic V. Fraction c (52 mg) eluted in pet. ether–ether (5:1) portion, was recrystallized from MeOH—H_2O as colourless fine prisms, m.p. 162–170°, whose IR spectrum was identical with that of the authentic IX.[25]

An isomerization of V to VI did not occur under these dehydration conditions as described below.

Alkaline hydrolysis of methyl 10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (VIII) *and methyl* 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XI) *to the corresponding acids* (VII *and* X) *respectively*

(i). *In the case of* 10β-*hydroxy ester* (VIII). A solution of VIII (55 mg) and KOH (120 mg) in MeOH (15 ml) and H_2O (1 ml) was refluxed for 1·5 hr. After evaporating the MeOH, the mixture was diluted with H_2O and the neutral compound removed by ether extraction. The aqueous layer was, after acidification, extracted with ether and the ether extract washed with H_2O and dried over Na_2SO_4. After evaporating the ether, the residue (42 mg) was recrystallized from MeOH—H_2O as colourless fine prisms, whose IR spectrum was identical with that of the authentic VII. On the other hand, an oil (1–2 mg) was obtained as neutral compound.

(ii). *In the case of* 10α-*hydroxy ester* (XI). A solution of XI (50 mg) and KOH (100 mg) in MeOH (10 ml) and H_2O (1 ml) was treated as in (i). The acidic residue (37 mg) was recrystallized from MeOH—H_2O as colourless prisms, whose IR spectrum was identical with that of X. On the other hand, the IR spectrum of the neutral fraction (8 mg) showed that it consisted of IX and the starting XI.

Drastic alkaline hydrolysis of methyl 10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (VIII), *methyl* 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XI) *and* 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 10α-*lactone* (IX)

(i). *In the case of* 10β-*hydroxy ester* (VIII); *preparation of the corresponding acid* (VII). A solution of VIII (100 mg) and KOH (40 mg) in ethylene glycol (5 ml) and H_2O (0·5 ml) was refluxed for 15 min on an oil bath maintained at about 200°. The reaction mixture was diluted with H_2O, acidified and then extracted with ether. The ether extract was washed with 10% NaOH aq. (a). *Acidic part.* After the alkaline (NaOH) extract was acidified, then extracted with ether, the ether extract was washed with H_2O and was dried over Na_2SO_4. After evaporating the ether, the residue (102 mg), m.p. 150–153°, was identical with the authentic VII by comparison of their IR spectra. (b). *Neutral part.* The ether layer was washed with 10% NaOH aq and with H_2O successively and was dried over Na_2SO_4. After evaporating the ether, the resulting neutral part was undetectable.

(ii). *In the case of* 10α-*hydroxy ester* (XI); *preparation of* Δ⁹-*acid* (XIII). A solution of XI (39 mg) and KOH (20 mg) in ethylene glycol (2 ml) and H_2O (0·3 ml) was refluxed for 15 min on an oil bath maintained at about 185–200°. The reaction mixture was treated as in (i). (a). *Acidic part.* The residue (31 mg) was recrystallized from MeOH—H_2O as colourless cubes of XIII, m.p. 145–148°, as analytical sample. (Found: C, 79·79; H, 7·94. Calc. for $C_{17}H_{20}O_3$: C, 79·65; H, 7·86%), IR ν_{max}^{KBr} cm^{-1}: 1690, UV λ_{max}^{EtOH} mμ: 265. (b). *Neutral part.* This part (5 mg) was identical with IX by comparison of their IR spectra.

(iii). *In the case of* 10α-*lactone* (IX); *preparation of* Δ⁹-*acid* (XIII). A solution of IX (100 mg) and KOH (25 mg) in ethylene glycol (5 ml) and H_2O (0·25 ml) was refluxed for 15 min on an oil bath maintained at 190–200°. The reaction mixture was treated as in (i). (a). *Acidic part.* The residue (78 mg) was recrystallized from MeOH—H_2O as colourless cubes, m.p. 145–148°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with XIII. (b). *Neutral part.*

[25] Since the IR spectrum of the pre-chromatographic crystalline product showed no absorption corresponding to lactone, the lactone would be considered to arise from the unreacted 10α-hydroxy ester (XI) during chromatography on neutral alumina.

The residue (25 mg) was recrystallized from MeOH—H_2O as colourless fine prisms, m.p. 174–177°, whose physical constants (m.p., mixed m.p., and IR spectrum) were identical with those of IX.

Methylation of enantio*podocarpa-5,7,9,13-tetraen-16-oic acid* (XIII).

Compound XIII (31 mg) was methylated with excess diazomethane–ether. The resulting product (28 mg) was twice recrystallized from MeOH—H_2O as colourless needles (27 mg), m.p. 79°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of VI.

Treatment of methyl 10*β-hydroxy-*enantio*podocarpa-5,7,13-trien-16-oate* (VIII) *and methyl* 10*α-hydroxy-*enantio*podocarpa-5,7,13-trien-16-oate* (XI) *with aluminium oxide*

(i). *In the case of* 10*β-hydroxy ester* (VIII); *recovery of the starting material.* A solution of VIII (18 mg) in ether (0·5 ml) and pet. ether (5 ml) in presence of neutral alumina was left standing at room temp for 3 days. Alumina was filtered off and the filtrate evaporated. The residue was identical with the starting VIII by comparison of IR spectra.

(ii). *In the case of* 10*α-hydroxy ester* (XI) *and preparation of the lactone* (IX). Compound XI (30 mg) was treated at room temp overnight with neutral alumina (3 g) as in VIII. The residue (25 mg) was recrystallized from MeOH as colourless fine prisms, m.p. 170–173°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with IX.

Thermal treatment of methyl 10*β-hydroxy-*enantio*podocarpa-5,7,13-trien-16-oate* (VIII) *and methyl* 10*α-hydroxy-*enantio*podocarpa-5,7,13-trien-16-oate* (XI)

(i). *In the case of* 10*β-hydroxy ester* (VIII); *recovery of the starting material.* A solution of VIII (45 mg) in ethylene glycol (1 ml) was refluxed for 30 min on an oil bath maintained at 180–210°. The reaction mixture was diluted with H_2O and extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated to give an oil (41 mg), whose IR spectrum showed it mainly consisted of the starting VIII.

(ii). *In the case of* 10*α-hydroxy ester* (XI); *preparation of* Δ^9*-ester* (VI), Δ^{10}*-ester* (V) *and the lactone* (IX). A solution of XI (42 mg) in ethylene glycol (1 ml) was refluxed for 30 min on an oil bath maintained at 180–210°. After the reaction mixture was treated as in (i), the oil (37 mg) was chromatographed on neutral alumina (4 g) to give an oil (12 mg), whose IR spectrum was identical with that of VI, and an oil (3 mg), whose IR spectrum was identical with that of V, in pet. ether elution successively and then to give colourless prisms (24 mg), whose IR spectrum was identical with that of IX, in pet. ether–ether (5:1) elution.

Treatment of methyl 10*β-hydroxy-*enantio*podocarpa-5,7,13-trien-16-oate* (VIII) *and methyl* 10*α-hydroxy-*enantio*podocarpa-5,7,13-trien-16-oate* (XI) *with ammonia water*

(i). *In the case of* 10*β-hydroxy ester* (VIII); *preparation of* 10*β-hydroxy-*enantio*podocarpa-5,7,13-trien-16-amide* (XIV). A solution of VIII (100 mg) in 28% NH_4OH (2 ml) and dioxane (1 ml) was heated at 130–150° in a sealed tube for 6 hr. After the reaction mixture was diluted with H_2O, it was extracted with ether. The ether extract was washed with 10% HCl and H_2O successively and then dried over Na_2SO_4. After evaporating the ether, the resulting yellow oil (73 mg) was chromatographed on silicic acid–celite (1:1; 3 g) to give oil (45 mg), which was slowly crystallized, in pet. ether–ether (1:1) elution. The colourless fraction, m.p. 165–168°, was recrystallized from MeOH—H_2O as colourless fine prisms, m.p. 170–171°. (Found: C, 74·66; H, 8·22; N, 5·20. Calc. for $C_{17}H_{23}O_2N$: C, 74·69; H, 8·48; N, 5·12%), IR ν_{max}^{KBr} cm^{-1}: 3460, 3160, 1655.

(ii). *In the case of* 10*α-hydroxy ester* (XI); *preparation of the lactone* (IX). A solution of XI (50 mg) in 28% NH_4OH (4 ml) and dioxane (1 ml) was heated at 110–125° in a sealed tube for 4 hr. After the reaction mixture was diluted with H_2O, the resulting precipitate (37 mg) was collected and recrystallized from MeOH—H_2O as colourless fine prisms, m.p. 173–176°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of IX.

Isomerization of methyl enantio*podocarpa-5,7,10,13-tetraen-16-oate* (V) *to methyl* enantio*podocarpa-5,7,9,13-tetraen-16-oate* (VI) *by alkaline treatment following by methylation*

A solution of V (29 mg) and KOH (100 mg) in ethylene glycol (5 ml) containing H_2O (4 drops) was refluxed for 1 hr on an oil bath maintained at 190–205°. The reaction mixture was diluted with H_2O and then extracted with ether. (i). *Neutral part.* The ether extract was washed with H_2O,

dried over Na_2SO_4 and then evaporated to give an oil (9 mg), whose IR spectrum showed it consisted of VI and V. (ii). *Acidic part.* The aqueous layer of the ether extraction was acidified and then extracted with ether. After the ether extract was treated with excess diazomethane–ether solution and evaporating the ether and the resultant oil (19 mg) was chromatographed on neutral alumina (4 g) to give the following fractions in pet. ether elution successively: Fraction a (12 mg), which was recrystallized from MeOH—H_2O as colourless needles, m.p. 74–78°, whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of VI. Fraction b (5 mg), whose IR spectrum showed it consisted of VI and V.

Stabilities of methyl enantio*podocarpa*-5,7,10,13-*tetraen*-16-*oate* (V)

Compound V was not isomerized to VI or XIII and was quantitatively recovered under the following conditions:

(i). *Thermal treatment.* Under N_2-stream, V (33 mg) was heated for 3 min on a metal bath maintained at 290–300°.

(ii). *Treatment with* H_2SO_4 *in* AcOH. A solution of V (20 mg) in AcOH (0·5 ml) containing H_2SO_4 (1 drop) was warmed at 80° for 20 min.

(iii). *Treatment with methanesulphonyl chloride in pyridine.* A solution of V (35 mg) in pyridine (0·5 ml) containing MsCl (1 drop) was warmed at 80 ± 3° for 2 hr and then left standing at room temp for 3 hr.

(iv). *Acidic treatment.* A solution of V (12 mg) in MeOH (5 ml) and 10% HCl (2 ml) was refluxed for 2 hr.

(v). *Alkaline treatment.* A solution of V (20 mg) and KOH (20 mg) in MeOH (5 ml) and H_2O (1 ml) was refluxed for 1 hr.

Oxidation of C_1*-methyl group of methyl* 10*β-hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (VIII) *with lead tetraacetate. Methyl* 10*β*,15-*epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XVIII)

Under N_2-stream a solution of VIII (1053 mg) in absolute benzene (40 ml) was illuminated by UV lamp (penetrative type) in presence of $Pb(OAc)_4$ (2·3 g) and I_2 (1·3 g) at 10° for 10 hr. After filtering off the unsoluble precipitate, the benzene solution was washed with 10% $Na_2S_2O_3$ aq, sat. $NaHCO_3$ aq and H_2O successively and dried over Na_2SO_4. After evaporating the solvent, the residue (1138 mg) was chromatographed on neutral alumina (30 g) to give the following fractions in pet. ether–ether (10:1) elution successively; (i). Colourless needles (40 mg), whose physical constants (m.p., mixed m.p. and IR spectrum) were identical with those of IX. (ii). Colourless needles (1000 mg) which were recrystallized from pet. ether as colourless needles of XVIII, m.p. 161–163° as analytical sample. (Found: C, 75·36; H, 7·74. Calc. for $C_{18}H_{22}O_3$: C, 75·49; H, 7·74%), IR ν_{max}^{KBr} cm^{-1}: 1710, NMR_{CDCl_3} (τ): 6·28 (—COOC$\underline{H}_3$), 8·96 (—C—C$\underline{H}_3$), GC_{min}: 4·3 (1·5% SE-30 on Anakrom A (80–140 mesh), 1·5 m × 3·0 mm, 180°). (iii). An oily solid (15 mg), whose IR spectrum showed it consisted of XVIII and the starting VIII.

The same reaction of VIII (107 mg) at 23° gave IX (23 mg), XVIII (53 mg) and the starting VIII (7 mg). In another case, the same reaction of VIII (111 mg) at 56–59° gave IX (14 mg), XVIII (30 mg) and VIII (48 mg).

However, the same reactions of VIII without I_2 at 10° gave only recovered VIII and of VIII (100 mg) under reflux gave XVIII (17 mg) and VIII (59 mg).

Oxidation of C_{12}*-methyl group of methyl* 10*α-hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XI) *with lead tetraacetate. Methyl* 10*α*, 17-*epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XIX)

Under N_2-stream a solution of XI (323 mg) in absolute benzene (60 ml) was illuminated by UV lamp (penetrative type) in presence of $Pb(OAc)_4$ (500 mg) and I_2 (350 mg) at 60° for 18 hr. The reaction mixture was treated as in XVIII. The brown oil (302 mg), whose IR spectrum showed XIX was contaminated with IX and the starting XI, was refluxed with KOH (3 g) in MeOH (20 ml) and H_2O (0·5 ml) for 30 min. After evaporating the MeOH, the residue was diluted with H_2O and extracted with ether. The ether extract was washed with H_2O, then dried over Na_2SO_4 and evaporated. The resulting residue (265 mg) was chromatographed on neutral alumina (5 g) to give a fraction (240 mg) in pet. ether–ether (20:1) elution. It was recrystallized twice from MeOH—H_2O as colourless needles of XIX, m.p. 128–129°, as analytical sample. (Found: C, 75·43; H, 7·56. Calc. for

$C_{18}H_{22}O_3$: C, 75·49; H, 7·74%), IR ν_{max}^{KBr} cm^{-1}: 1715, NMR_{CDCl_3} (τ): 6·30 (—$COOCH_3$), 8·74 (—CO—C—CH_3), GC_{min}: 4·8 (1·0% SE-30 on Anakrom A (80–100 mesh), 1·5 m × 3·0 mm, 181°).

$LiAlH_4$ *reduction of methyl* 10β, 15-*epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XVIII) *and methyl* 10α, 17-*epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XIX)

(i). 10β, 15-*epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*ol* (XX). A solution of XVIII (50 mg) in tetrahydrofuran (1 ml) was treated with $LiAlH_4$ (10 mg) for 2 days. The reaction mixture, treated as usual, yielded a residue (46·5 mg), m.p. 220–227°, which recrystallized from MeOH—H_2O as colourless prisms of XX, m.p. 229–231°, as analytical sample. (Found: C, 78·92; H, 8·47. Calc. for $C_{17}H_{22}O_2$: C, 79·02; H, 8·58%), NMR_{CDCl_3} (τ): 8·85 (—C—CH_3).

(ii). 10α, 17-*epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*ol* (XXI). A solution of XIX (41 mg) in absolute ether (7 ml) was refluxed with $LiAlH_4$ (40 mg) for 3 hr and then left standing overnight at room temp. After treating the reaction mixture as usual, the quantitatively oil obtained (slowly crystallized) was recrystallized twice from MeOH—H_2O as colourless prisms of XXI, m.p. 98–101°, as analytical sample. (Found: C, 73·66; H, 8·69. Calc. for $C_{17}H_{22}O_2 \cdot H_2O$; C, 73·88; H, 8·75%), NMR_{CDC_3} (τ): 8·91 (—C—CH_3).

$LiAlH_4$ *reduction of methyl* 10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (VIII) *and methyl* 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XI)

(i). 10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*ol* (XXXI). A solution of VIII (60 mg) in absolute ether (20 ml) was refluxed with $LiAlH_4$ (55 mg) for 3 hr and then left standing at room temp overnight. After treating the reaction mixture as usual, the residue was recrystallized from MeOH—H_2O as colourless fine prisms of XXXI, m.p. 163–164·5, as analytical sample. (Found: C, 78·06; H, 9·17. Calc. for $C_{17}H_{24}O_3$: C, 78·42; H, 9·29%), IR ν_{max}^{KBr} cm^{-1}; 3310, NMR_{CDCl_3} (τ): 8·71 (6H)(HOH_2C—C—CH_3, —C—CH_3).

(ii). 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*ol* (XXXII). A solution of XI (10 mg) in absolute ether (4 ml) was refluxed with $LiAlH_4$ (22 mg) for 2 hr and then was left standing at room temp overnight. After the reaction mixture was treated as usual, the residue was recrystallized from MeOH—H_2O as colourless needles of XXXII, m.p. 176–177·5°, as analytical sample. (Found: C, 78·17; H, 9·07. Calc. for $C_{17}H_{24}O_2$: C, 78·42; H, 9·29%), IR ν_{max}^{KBr} cm^{-1}: 3310, NMR_{CDCl_3} (τ): 8·90 (HOH_2C—C—CH_3), 8·45 (—C—CH_3).

Hydroboration of methyl enantio*podocarpa*-5,7,10,13-*tetraen*-16-*oate* (V)

10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*ol* (XXXI). A solution of V (50 mg) in tetrahydrofuran (2 ml) was added dropwise to a mixture of $NaBH_4$ (40 mg) and BF_3–etherate (250 mg) in tetrahydrofuran (2 ml) at 4° during 10 min. The reaction mixture was left standing at 4° for 30 min, then at room temp for 30 min and finally warmed at 45° for 5 min. After adding 10% NaOH aq (2 ml) and then 30% H_2O_2 (3 ml) to the reaction mixture at 50°, it was left standing at room temp for 30 min and then extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The resulting oil (47 mg) was chromatographed on neutral alumina (3 g) to give successively fractions (7 mg) in pet. ether elution and (27 mg) in ether elution. IR spectrum of the former fraction was identical with that of the starting V. The latter fraction was recrystallized from MeOH—H_2O as colourless fine prisms (21 mg), m.p. 162–164°, whose physical constants (mixed m.p. and IR spectra in $CHCl_3$ and KBr) were identical with those of XXXI.

Hydroboration of methyl enantio*podocarpa*-5,7,9,13-*tetraen*-16-*oate* (VI)

Methyl 9β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XXXVIII). Under N_2-stream a solution of BF_3–etherate (180 mg) in diglyme (3 ml) added dropwise to a reaction mixture of VI (100 mg) and $NaBH_4$ (20 mg) in diglyme (3 ml) at 7° during 10 min and the reaction mixture left standing for 10 min at 7–10°. After adding 2 N NaOH aq (1 ml) and 28% H_2O_2 (2 ml) successively at 10°, it was extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and then evaporated. The residue (70 mg), m.p. 145–156°, was chromatographed on neutral alumina (4 g) to give a fraction (57 mg) from pet. ether–ether (5:1) elution which was recrystallized from MeOH—

H_2O to give colourless needles of XXXVIII, m.p. 165–168°, as analytical sample. (Found: C, 74·68; H, 7·90. Calc. for $C_{18}H_{24}O_3$: C, 74·97; H, 8·39%), IR ν_{max}^{KBr} cm^{-1}: 3530, 1708.

Chromium trioxide oxidation of methyl 9β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XXXVIII)

Methyl 9-*oxo*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XXXIX). A solution of CrO_3 (30 mg) in AcOH (0·4 ml) and H_2O (4 drops) was added to a solution of XXXVIII (20 mg) in AcOH (0·3 ml). After the reaction mixture was warmed at 75° for 30 min, MeOH (1 ml) was added to decompose excess CrO_3. After evaporating the AcOH and adding H_2O, it was extracted with ether. The ether extract was washed with sat. $NaHCO_3$ aq and with H_2O successively and then dried over Na_2SO_4. After evaporating the ether, the residue (15 mg) was recrystallized from MeOH—H_2O to give colourless prisms, m.p. 144–146°, whose physical constants (mixed m.p. and IR spectrum) were identical with those of authentic XXXIX.[6]

$NaBH_4$ *reduction of methyl* 9-*oxo*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XXXIX)

Methyl 9α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XL). $NaBH_4$ (50 mg) was added to a solution of XXXIX (55 mg) in MeOH (10 ml). After the reaction mixture was stirred at 25–28° for 2 hr, the MeOH was evaporated *in vacuo* and H_2O was added. The precipitate (55 mg) was collected and recrystallized from MeOH—H_2O as colourless needles of XL, m.p. 167–170°, as analytical sample. (Found: C, 74·51; H, 8·05. Calc. for $C_{18}H_{24}O_3$: C, 74·97; H, 8·39%), IR ν_{max}^{KBr} cm^{-1}: 3520, 1702. Mixed m.p. of this compound with XXXVIII showed a depressed m.p. and its IR spectrum was different from that of XXXVIII.

Reaction of methyl 10α, 17-*epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oate* (XIX) *with* BF_3-*etherate*

Methyl 17-*acetoxy*-enantio*podocarpa*-5,7,9,13-*tetraen*-16-*oate* (XLI). BF_3–etherate (0·5 ml) was added dropwise to a solution of XIX (100 mg) in Ac_2O (4 ml) with stirring. After the reaction mixture was left standing at room temp for 1·5 hr, H_2O and then K_2CO_3 powder was slowly added to neutralize with ice cooling. It was extracted with ether, the ether extract was washed with 10% $NaHCO_3$ aq and with H_2O successively and dried over Na_2SO_4. After evaporating the ether, a light yellow oil XLI (115 mg), b.p. 175–180° (bath temp)/1 mm Hg, gas-chromatographic pure, was obtained. (Found: C, 73·22; H, 7·19. Calc. for $C_{20}H_{24}O_4$: C, 73·14; H, 7·37%), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1230, UV λ_{max}^{EtOH}: 262·5 mμ (ε = 7900).

Alkaline hydrolysis of methyl 17-*acetoxy*-enantio*podocarpa*-5,7,9,13-*tetraen*-16-*oate* (XLI)

17-*Hydroxy*-enantio*podocarpa*-5,7,9,13-*tetraen*-16-*oic acid* 16 → 17-*lactone* (XLIII). A reaction solution of XLI (270 mg) and KOH (2·0 g) in diethylene glycol (10 ml) and H_2O (0·5 ml) was refluxed for 30 min on an oil bath (bath temp 200–210°). After the reaction mixture was diluted with H_2O, it was acidified with conc. HCl and extracted with ether. The ether extract was washed with 10% NaOH aq and with H_2O successively and dried over Na_2SO_4. After evaporating the ether, the colourless fine needles (177 mg), m.p. 176–177°, were recrystallized from MeOH—H_2O to m.p. 176·5–177·5° as analytical sample of XLIII. (Found: C, 80·07; H, 7·01. Calc. for $C_{17}H_{18}O_2$: C, 80·28; H, 7·13%), IR ν_{max}^{KBr} cm^{-1}: 1730.

Catalytic hydrogenation of 17-*hydroxy*-enantio*podocarpa*-5,7,9,13-*tetraen*-16-*oic acid* 16 → 17-*lactone* (XLIII)

17-*Hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 17-*lactone* (XLIV). Compound XLIII (30 mg) in MeOH (4 ml) was catalytically hydrogenated in H_2-atm. in the presence of the 10% Pd—C (15 mg). After treating as usual, the colourless needles (26 mg), m.p. 145–173°, were recrystallized three times from MeOH—H_2O to m.p. 184–185° as analytical sample of XLIV. (Found: C, 79·33; H, 8·21. Calc. for $C_{17}H_{20}O_2$: C, 79·65; H, 7·86%) IR ν_{max}^{KBr} cm^{-1}: 1730.

Thermal lactonization of 10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* (VII)

10β-*Hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 10β-*lactone* (XXX). Compound VII (150 mg) was heated at about 200° for 3 hr in a sealed tube. The resulting brown oil was dissolved in ether and the solution washed with 10% NaOH aq and H_2O successively and dried over Na_2SO_4.

After evaporating the ether, an oily product (A-crystals; 100 mg) was obtained. The IR spectra was distinguishable from that of the stable 16 → 10α-lactone (IX) as shown below.

Comparison of IR spectra (cm^{-1}) between both lactone (XXX and IX).[26]

17 → 10β-lactone (XXX)	16 → 10α-lactone (IX)
1774 (KBr)	1758 (KBr)
1090 (CCl_4)	1110 (CCl_4)
	1040 (CCl_4)

The A-crystals were recrystallized twice from MeOH as colourless fine needles (B-crystals), m.p. 130–142°, which were once more recrystallized from MeOH—H_2O to give colourless fine needles (C-crystals), m.p. 137–145°. (Found for B-crystals: C, 79·62; H, 7·92 and for C-crystals: C, 79·41; H, 7·71. Calc. for $C_{17}H_{30}O_2$: C, 79·65; H, 7·86%.) A comparison on the IR spectra of A-, B- and C-crystals showed that the typical absorptions for IX at 1110 and 1040 cm^{-1} were gradually increased by recrystallization in order of A-, B- and C-crystals. The 16 → 10β-lactone (XXX) is so unstable that it would be now impossible to purify and even A-crystals seem to be contaminated with small amounts of the stable 16 → 10α-lactone (IX). On the other hand, the alkaline extract (NaOH) was acidified and extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue (20 mg) was identical with the starting VII by comparison of IR spectra.

Isomerization of 10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 10β-*lactone* (XXX) *to* 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 10α-*lactone* (IX)

(i). *Thermal treatment.* Compound VII (100 mg) was heated at about 200° for 3 hr (the condition for the preparation of XXX) and then heated at about 240° for 5 hr in a sealed tube. The resulting product (87 mg), m.p. 152–160°, whose IR spectrum was very similar to that of IX, was heated again at 270° for 4 hr to give a product (80 mg), which was recrystallized twice from MeOH—H_2O as colourless fine prisms, m.p. 169–172°, whose physical constants (mixed m.p. and IR spectrum) were identical with those of IX.

(ii). *Treatment on* Al_2O_3. A mixture of the 16 → 10β-lactone (A-crystals; 10 mg) and neutral alumina (2 g) in ether (5 ml) was left standing at room temp for 2 days. After the alumina was filtered off and the ether evaporated, the residue (10 mg) was recrystallized from MeOH—H_2O as colourless fine prisms, m.p. 173–175°, which were identical with IX by comparison of their m.p. (mixed m.p.).

$LiAlH_4$ *reduction of* 10β-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 10β-*lactone*(XXX) *and* 10α-*hydroxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* 16 → 10α-*lactone* (IX)

(i). *In the case of the* 16 → 10β-*lactone.* $LiAlH_4$ (40 mg) was added to a solution of XXX (A-crystals whose IR spectrum showed it was contaminated with a small amount of IX; 34 mg) in absolute ether (10 ml) and the reaction mixture was refluxed for 7 hr. After H_2O was added, ether layer was washed with H_2O and dried over Na_2SO_4. After evaporating the ether, the residue (31 mg) was recrystallized from MeOH—H_2O as colourless fine prisms, m.p. 161–165°, whose physical constants (mixed m.p. and IR spectrum) were identical with those of XXXI.

(ii). *In the case of the* 16 → 10α-*lactone.* $LiAlH_4$ (50 mg) was added to a solution of IX (52 mg) in absolute ether (20 ml) and the reaction mixture refluxed for 8 hr. It was treated as in the case of XXX. The resulting product was recrystallized from MeOH—H_2O as colourless needles (36 mg), m.p. 176–177·5°, whose physical constants (mixed m.p. and IR spectrum) were identical with those of XXXII.

10β, 15-*Epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* (XXII)

A solution of XVIII (100 mg) and KOH (40 mg) in ethylene glycol (4 ml) and H_2O (0·3 ml) was refluxed for 20 min. The reaction solution was diluted with H_2O and then acidified. It was extracted with ether and the extract was washed with 10% NaOH aq (acidic part). The ether layer (neutral part) was washed with H_2O, then dried over Na_2SO_4 and evaporated. The residue (31 mg), m.p.

[26] These values were measured by kindness of Dr. W. Nagata, Shionogi and Co., Ltd., Osaka.

140–147°, had an IR spectrum, which was identical with that of the starting XVIII. On the other hand, the alkaline extract (NaOH) was acidified and was extracted with ether. The ether extract was washed with H^2O, then dried over Na_2SO_4 and evaporated. The residue (70 mg), m.p. 242–252°, was recrystallized twice from MeOH—H_2O as colourless fine prisms, m.p. 260–262°, as analytical sample of XXII. (Found: C, 74·84; H, 8·05. Calc. for $C_{17}H_{26}O_3$: C, 74·97; H, 7·40%) IR ν_{max}^{KBr} cm^{-1}: 3480, 1730, NMR_{CDCl_3} (τ): 8·82[22] (—C—C$\underline{H}_3$).

Compound XXII (2 mg) was treated as usual with excess diazomethane–ether solution to give a product (2 mg), m.p. 156–160°, whose physical constants (mixed m.p. and IR spectrum) were identical with those of XVIII.

10α, 17-*Epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*oic acid* (XXIII)

A solution of XIX (300 mg) and KOH (250 mg) in ethylene glycol (2 ml) and H_2O (0·5 ml) was heated at 185–200° in a sealed tube for 40 min. The reaction mixture was treated as in the case of XVIII. The acidic product (280 mg), m.p. 222–226°, was recrystallized twice from MeOH—H_2O as colourless needles, m.p. 233–236°—analytical sample of XXIII. (Found: C, 75·47; H, 7·98. Calc. for $C_{17}H_{20}O_3$: C, 74·97; H, 7·40%), IR ν_{max}^{KBr} cm^{-1}: 3420, 1725, NMR_{CDCl_3} (τ): 8·74 (HOOC—C—C$\underline{H}_3$.)

10β, 15-*Epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*amide* (XXIV)

Thionyl chloride (0·2 ml) and pyridine (1 drop) was successively added to a solution of XXII (57 mg) in absolute benzene (2 ml). The reaction solution was refluxed for 3 hr and then evaporated *in vacuo*. The resulting oil was dissolved in absolute ether, into which NH_3 gas was bubbled and the reaction mixture left standing overnight. After it was extracted with 10% NaOH aq, the alkaline extract (acidic part) was acidified and extracted with ether. The ether extract was washed with H_2O, then dried over Na_2SO_4 and evaporated. The acidic product (16·5 mg) was identical with the starting acid (XXII) by comparison of their IR spectra. On the other hand, the ether layer (neutral part) was washed with H_2O, dried over Na_2SO_4 and evaporated. The neutral residue (60 mg) was recrystallized from MeOH—H_2O as colourless prisms, m.p. 218–220°, as analytical sample of XXIV. (Found: C, 75·33; H, 7·78; N, 5·09. Calc. for $C_{17}H_{21}O_2N$: C, 75·24; H, 7·80; N, 5·16%), IR ν_{max}^{KBr} cm^{-1}: 3490, 3380, 3200, 3060, 1660, 1635, 1590, NMR_{CDCl_3} (τ): 8·83(—C—C$\underline{H}_3$).

10α, 17-*Epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*amide* (XXV)

Thionyl chloride (2 ml) and pyridine (1 ml) were successively added to a solution of XXIII (200 mg) in absolute benzene (20 ml) and the reaction mixture refluxed for 2 hr and treated as in the case of XXII. Negligible acidic and neutral fractions (210 mg), m.p. 89–130°, were obtained. A part (65 mg) of the neutral product was chromatographed on neutral alumina (3 g) in pet. ether–ether (1:1) to give a fraction (55 mg), which was recrystallized from MeOH—H_2O as colourless needles, m.p. 87–90°, as analytical sample of XXV. (Found: C, 70·30; H, 8·14; N, 4·78. Calc. for $C_{17}H_{21}O_2N{\cdot}H_2O$:C, 70·56; H, 8·01; N, 4·84%), IR ν_{max}^{KBr} cm^{-1}: 3530, 3410, 3210, 1670, 1645, 1610, NMR_{CDCl_3} (τ): 8·72 (H_2NOC—C—C$\underline{H}_3$), GC_{min}: 11·6 (1·5% SE-30 on Gaschrom (80–100 mesh), 1·5 m × 4·0 mm, 172°).

10β, 15-*Epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*nitrile* (XXVI)

A solution of XXIV (85 mg) and $POCl_3$ (5 drops) in pyridine (2 ml) was refluxed for 1 hr on an oil bath (bath temp, 120–140°). After ice water was added to the reaction mixture, it was acidified and extracted with ether. The ether extract was washed with 10% Na_2CO_3 aq and H_2O successively, then dried over Na_2SO_4 and evaporated. The residue (82 mg) was chromatographed on neutral alumina (5 g) in pet. ether–ether (10:1) to give a fraction (65 mg), which was recrystallized twice from MeOH—H_2O as colourless needles, m.p. 147–149°, as analytical sample of XXVI. (Found: C, 80·45; H, 7·64; N, 5·59. Calc. for $C_{17}H_{19}ON$: C, 80·57; H, 7·56; N, 5·53%), IR ν_{max}^{KBr} cm^{-1}: 2220, NMR_{CDCl_3} (τ): 8·62 (—C—C$\underline{H}_3$), GC_{min}: 8·1 (1·5% SE-30 on Gaschrom p. (80–100 mesh) 1·5 m × 4 mm, 170°).

10α, 17-*Epoxy*-enantio*podocarpa*-5,7,13-*trien*-16-*nitrile* (XXVII)

A solution of XXV (130 mg) and $POCl_3$ (5 drops) in pyridine (2 ml) was refluxed for 45 min on

an oil bath (bath temp 130–135°). The reaction mixture was treated as in the case of the dehydration of XXIV. The residue (107 mg), m.p. 139–145°, was chromatographed on neutral alumina (2 g) to give in pet. ether–ether (20:1) a crystalline fraction (85 mg), which was recrystallized twice from MeOH—H_2O as colourless prisms of XXVII, m.p. 142–144°, as analytical sample. (Found: C, 79·93; H, 7·44; N, 5·86. Calc. for $C_{17}H_{19}ON$: C, 80·57; H, 7·56; N, 5·53%), IR ν_{max}^{KBr} cm^{-1}: 2210, NMR_{CDCl_3} (τ): 8·56 (NC—C—CH_3).

10β,15-Epoxy-5,7,13-trien-*enantio*podocarpane (XXIX) from 10β,15-epoxy-*enantio*podocarpa-5,7,13-trien-16-ol (XX) *via* the corresponding aldehyde (XXVIII)

A solution of CrO_3 (40 mg) in 90% AcOH—H_2O (4 ml) was added to a solution of XX (150 mg) in AcOH (4 ml). After it was left standing for 3·5 hr at room temp, MeOH (to decompose excess CrO_3) and then H_2O were added to the reaction mixture, which was extracted with ether. The ether extract was washed with 10% NaOH aq and H_2O successively and then dried over Na_2SO_4. The extract was evaporated to give a colourless oil (95 mg), which was slowly crystallized to colourless plates, m.p. 157° (presumably XXVIII), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2750, 1725.

A reaction mixture of the above crude aldehyde (XXVIII), $NH_2NH_2 \cdot H_2O$ (5 ml), KOH (2 g) and diethylene glycol (10 ml) was added and the mixture heated to 145° during 30 min and at 145° for 2 hr. After the reaction mixture was heated to 200° for 4 hr in order to distill off excess $NH_2NH_2 \cdot H_2O$, it was diluted with H_2O, then acidified with conc. HCl and extracted with ether. The ether extract was washed with H_2O, then dried over Na_2SO_4 and evaporated to give an oily residue (70 mg), which was chromatographed on neutral alumina (2 g) to separate crystalline fractions (35 mg) in pet. ether elution and (13 mg) in ether elution successively. The latter fraction was identical with the starting XX by comparison of their IR spectra. The former fraction was recrystallized from MeOH—H_2O as colourless leaflets, m.p. 76–77°, as analytical sample of XXIX. (Found: C, 83·99; H, 9·46. Calc. for $C_{17}H_{22}O$: C, 84·25; H, 9·15%), NMR_{CDCl_3} (τ): 8·82 (6 protone), $[\alpha]_D^{23·5} = -136·5$ (EtOH, $c = 0·59$) (cf. Wenkert's sample (XLVI): $[\alpha]_D^{25·5} = -121·6$ (EtOH, $c = 0·63$)), whose IR and NMR spectra were identical with those of Wenkert's sample (XLVI).[22]

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