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Diterpenoids. X.[1] A Synthesis of c-Homohydrofluorene[2]

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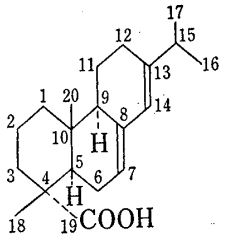
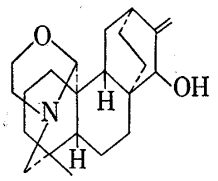
Previously, *l*-abietic acid (I) was transformed into hydrofluorene derivative, regarded as one of the basic structure of gibberellin, by application of the benzilic acid rearrangement. As successive transformation, a synthesis of c-homohydrofluorene (XX) has been realized by opening of B/C-ring juncture and successive ring closure of $\Delta^{8,9}$-unsaturated ester (X) prepared from (I).

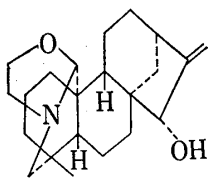
Since a few years ago, studies on chemical transformation of *l*-abietic acid (I)[4] to the other natural compounds have been undertaken in our laboratory. Although large amounts of *l*-abietic acid (I) are readily available from many kinds of common japanese pine trees, the acid itself has not remarkable physiological activities and, thus, is now limited in its utilization. However, many natural diterpenoids, such as gibberellin and diterpene alkaloid, closely related to *l*-abietic acid (I) have been widely known as noticeable substance. Project on syntheses of these useful products from *l*-abietic acid (I) would be expected to contribute to exploit new utilization of the resin acid.



I



II



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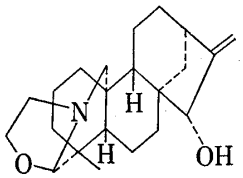
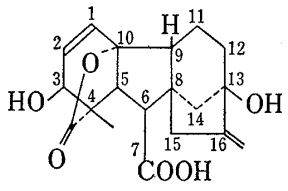
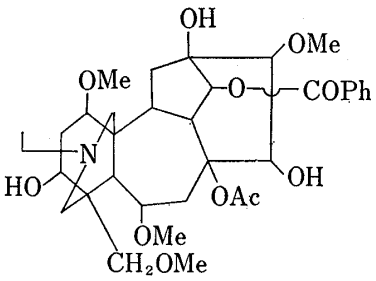
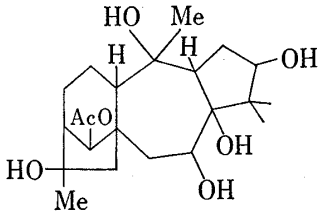


IV





VI



VII

Chart 1

1) Previous communication: A. Tahara, K. Hirao *Tetrahedron Letters*, **1966**, 3825; Part IX: *Chem. Pharm. Bull.* (Tokyo), **15**, 19 35 (1967).

2) All melting points (except mixed mp) were measured on koflar block and were uncorrected. Nuclear magnetic resonance (NMR) spectra were measured at 60 Mc in CCl_4 (5*s*10% solution) *vs.* Me_4Si as internal reference.

3) Location: *Yamato-machi, Kita-adachi-gun, Saitama.*

4) Numbering of the diterpenoid is used on the steroid convention (*cf* R. McCrindle and K. H. Overton, "Advances in Organic Chemistry," Vol. 5, ed. by R. A. Raphael, E. C. Taylor and H. Wynberg, Interscience, Inc., New York, N. Y., **1965**, p. 47) as shown in abietic acid (I) and gibberellin A_3 (V) (Chart 1).

Furthermore, *l*-abietic acid (I) has an undisputed structure with absolute configuration and its total synthesis has been accomplished.[5] Therefore, if a product is obtained from *l*-abietic acid (I) ,the conversion can be regarded as the completion of the formal total synthesis of the optically active one.

With this purpose, our total synthesis of natural diterpene alkaloid, such as atisine (II), veatchine (III) and garryine (IV), has been recently accomplished[6] in succession to the other elegant syntheses.[7] On the other hand, *l*-abietic acid (I) was also *trans*-formed into hexahydroflourene derivatives, basic skeleton of gibberellin (*e.g.* gibberellin A_3 (V)), by application of the benzilic acid rearrangement.[8] In amplification of this project, a preparation of *c*-homo-

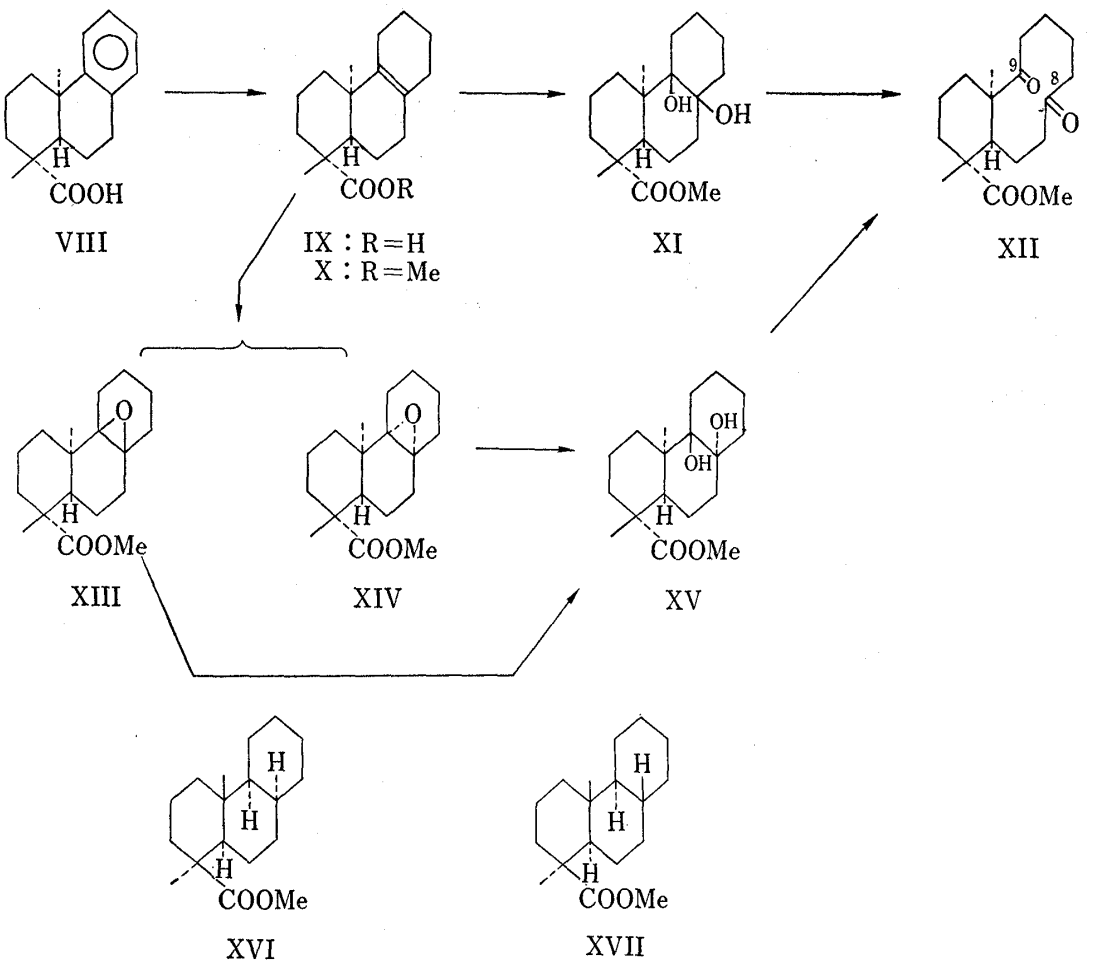


Chart 2

5) E. Wenkert, A. Afonso, J. B-son Bredenberg, C. Kaneko and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964).

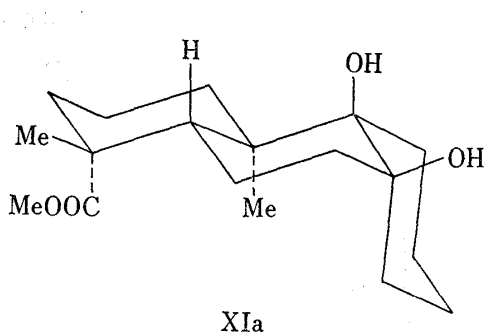
6) A. Tahara, K. Hirao and Y. Hamazaki, *Tetrahedron*, **21**, 2133 (1965); *Chem. Ind.* (London), **1965**, 850; *Chem. Pharm. Bull.* (Tokyo), **15**, 1785 (1967); A. Tahara and K. Hirao, *Tetrahedron Letters*, **1966**, 1453; *Chem. Pharm. Bull.* (Tokyo), **15**, 1934 (1967).

7) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963); **89**, 1483 (1967); W. Nagata, M. Narisada, T, Wakabayashi and T. Sugasawa, *ibid.*, **86**, 929 (1964); **89**, 1529 (1967); S. Masamune, *ibid.*, **86**, 290, 291 (1964); Z. Valenta, K. Wiesner and C. M. Wong, *Tetrahedron Letters*, **1964**, 2437. *cf* I. Iwai and A. Ogiso, *Chem. Ind.* (London), **1963**, 1084; T. Tsuchiya, Abstracts of Papers, 85th Annual Meeting of Pharmaceutical Society of Japan, Tokushima, Oct., 1965, p. 317.

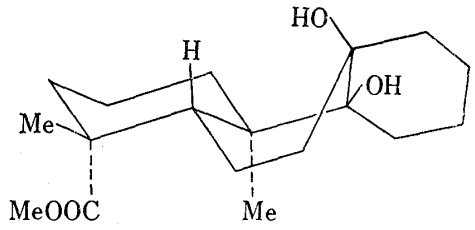
8) A. Tahara, *Chem. Pharm. Bull.* (Tokyo), **9**, 252 (1961); A. Tahara and O. Hoshino, *ibid.*, **9**, 655 (1961); *Sci. Papers Inst. Phys. Chem. Res.*, **56**, 84, 88 (1962), *cf* J.F. Grove and B. J. Riley, *J. Chem. Soc.*, **1961**, 1105.

hydrofluorene (XX) regarded as one of the basic structure of gibberellin, will be herein discussed.

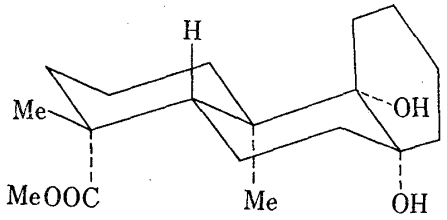
Deoxy-*enantio*-podocarpic acid (VIII)[9] prepared from *l*-abietic acid (I) through several steps, was chosen as the direct starting material for the present purpose. The acid (VIII) was reduced with lithium metal–ethylamine in the presence of *tert*-amyl alcohol as proton source[10] to give $\Delta^{8,9}$-unsaturated acid (IX), mp 143—146°, in satisfactory yield. Existence of a double bond at C_8–C_9 position was elucidated by the result of peracid or osmium tetroxide oxidations of the double bond as stated later and by disappearance of olefinic proton of the acid (IX) in the NMR spectrum. Fundamental idea for the synthesis of the aimed *c*-homofluorene (XX) was realized by opening of B/C-ring juncture and successive ring closure. Accordingly, at first, cleavage reaction of B/C-ring juncture of $\Delta^{8,9}$-unsaturated ester (X), mp 84—87°, to 8,9-dioxo ester (XII) was performed by the following two ways. In the first method, hydroxylation of the double bond of $\Delta^{8,9}$-unsaturated ester (X) with osmium tetroxide readily afforded dihydroxyl ester (XI), mp 157—160°, whose *vic.*-glycol bond was oxidatively cleaved with lead tetraacetate to give the aimed ester (XII), mp 102—104°, having two carbonyl



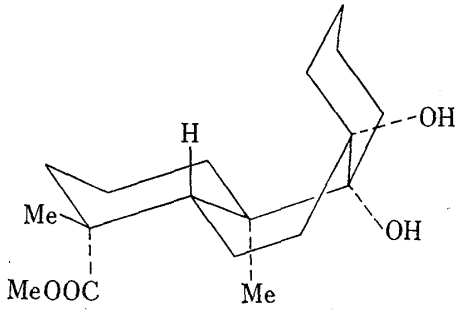
XIa



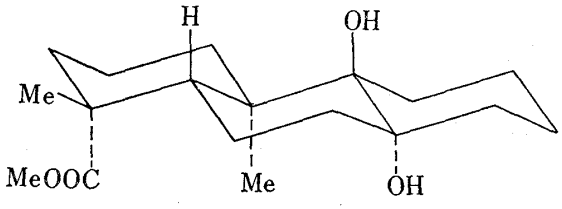
XIb



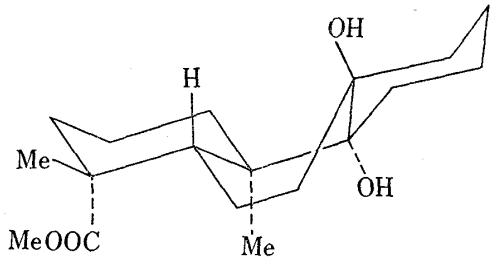
XIc



XId



XVa



XVb

Chart 3

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

10) *cf* R. A. Benkeser, R. E. Robinson, D. M. Sauve and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955); A. W. Burgstahler and L. R. Warden, *ibid.*, **86**, 96 (1964).

groups in ten membered ring, in good yield. While, the second way was a route through epoxide. Perphthalic acid oxidation of $\Delta^{8,9}$-unsaturated ester (X) gave stereoisomeric mixture of the corresponding epoxides (XIII and XIV), which was chromatographically separated to two epoxides, (XIII), mp 108—110°, as main product (72% yield) and (XIV), mp 147—151°, as by-product (7.6% yield). On the basis of the mechanism that an epoxide is preferentially prepared by attacking from less hindered side (β in this case), the epoxides (XIII and XIV) can be regarded as β- and α-epoxide respectively. The each epoxide (XIII and XIV) was left standing in 50% acetone aq. containing sulfuric acid to yield the same dihydroxyl ester (XV), mp 114—116°(mp 87—89° containing 1/3 mole of water of crystallization). Spectroscopic feature of the dihydroxyl ester (XV), IR ν_{max}^{KBr} cm^{-1}: 3582, 3510, 1705; NMR τ: 9.08, 8.85, 6.40, is similar to, but somewhat different from that of the other dihydroxyl ester (XI), IR ν_{max}^{KBr} cm^{-1}: 3480, 1725; NMR τ: 9.12, 8.84, 6.42 prepared by osmium tetroxide oxidation. The former dihydroxyl ester (XV) was cleaved by lead tetraacetate to afford dioxo ester, which was completely identical with the medium sized diketone (XII) obtained by the first method.

Successively, the stereochemistry of the isomeric dihydroxyl esters (XI and XV) will be discussed. From the general reaction mechanisms of osmium tetroxide–hydroxylation of a double bond (X→XI, in this case) and acidic cleavage of epoxide ring (XIII or XIV→XV, in this case), it is adequate to assume that the dihydroxyl products, mp 157—160°, and, mp 114—116°, have *cis*- and *trans*–dihydroxyl group respectively. Problem on their configuration was settled by NMR–analysis (chemical shift) of their methyl groups in comparison with those of both methyl hexahydropodocarpates having *anti–cis*-B/C-ring fusion (XVI)[11] and *anti–trans*-B/C-ring fusion (XVII)[11] as respective standard compound.

Firstly, on the stereochemistry of the *cis*-dihydroxyl compound (XI), possibility of four conformations (XIa, b,c,d) should be assumed. The chemical shift of the *cis*–dihydroxyl compound (XI; NMR τ: 9.12 (C_{10}-Me), 8.84 (C_4-Me)) is nearly equal to that of *anti–cis*–standard (XVI; NMR τ: 9.14 (C_{10}-Me), 8.83 (C_4-Me)). In general, NMR–signal of methyl group should shift 10 to 15 cps to lower magnetic field at 60 Mc[12] when hydroxyl group is located close to methyl group in 1,3-diaxial relationship as shown in (XIc). Therefore, a stereo–structure of the *cis*–compound (XI) is more reasonably assigned as *anti–cis*–type form (XIa or XIb) than as *syn–cis*–type form (XIc), in which C_8-hydroxyl group would exert influence upon C_{13}-methyl chemical shift. Furthermore, if the possibility of conformation (XIb and XId) can be canceled from a viewpoint of strong non–bonding interaction, the structure of the *cis*–dihydroxyl compound is most agreeable with (XIa).

Comparison of NMR-signals of methyl groups in *trans*-dihydroxyl compound (XV; NMR τ: 9.08 (C_{10}-Me), 8.85 (C_4-Me)) with those of the corresponding standard (XVII; NMR τ: 9.37 (C_{10}-Me), 8.83 (C_4-Me)), strongly supports an assignment that *anti–trans*–form (XVa) is more reasonable than the other *syn*–trans-form (XVb). Because the observation that τ–value (9.08) for C_{10}-methyl of (XV) is shifted 17.4 cps (in 60 Mc) to lower magnetic field from that (9.37) of the standard (XVII), shows that the C_{10}-methyl group in (XV) is observed to undergo a paramagnetic shift caused by C_8-hydroxyl group in 1,3-diaxial interrelation as expected in *anti–trans*-form (XVa). According to the experimental fact that both the α- (XIV) and β-epoxide (XIII) was hydrolyzed to give the same *anti-trans*–dihydroxyl compound (XV), it should be concluded that β-epoxide (XIII) was cleaved by α-side attack of hydroxy anion at C_8, while α-epoxide (XIV) was attacked from β-side at C_9 to give the same *trans*–dihydroxyl compound (XV).

11) Syntheses of these standard compounds (XVI and XVII) will be reported in near future. *cf* R. H. Bible, Jr. and R. R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961); J. W. ApSimon, O. E. Edwards and R. Howe, *Can. J. Chem.*, **40**, 632 (1962).

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

As to base catalysed intramolecular cyclization (aldol condensation) in medium sized ring, there existed in the literature several examples. Already, the first example was reported in 1933 on the condensation of cyclodeca-1,6-dione (XVIII) to cyclized compound (XIX).[13] In our case of the medium sized dioxo ester (XII) obtained from either *trans*- (XV) or *cis*-dihydroxyl ester (XII), three possible ways of the intramolecular cyclization were expected (*a*-route to XX, *b*-route to XXI and *c*-route to XXII). Since the line of condensation may depend to the same extent upon the operation of proximity effect, it is interesting for its conformational study to elucidate which condensation route is chosen in base catalysed reaction of diketo ester (XII). The condensed product (XX, XXI or XXII) expected by three possible ways, could be regarded as a basic skeleton of gibberellin group (*e.g.* gibberellin A_3 (V)), of toxic diterpene alkaloid (*e.g.* aconitine (VI)) or of grayanotoxin group (*e.g.* grayanotoxin I (VII)).

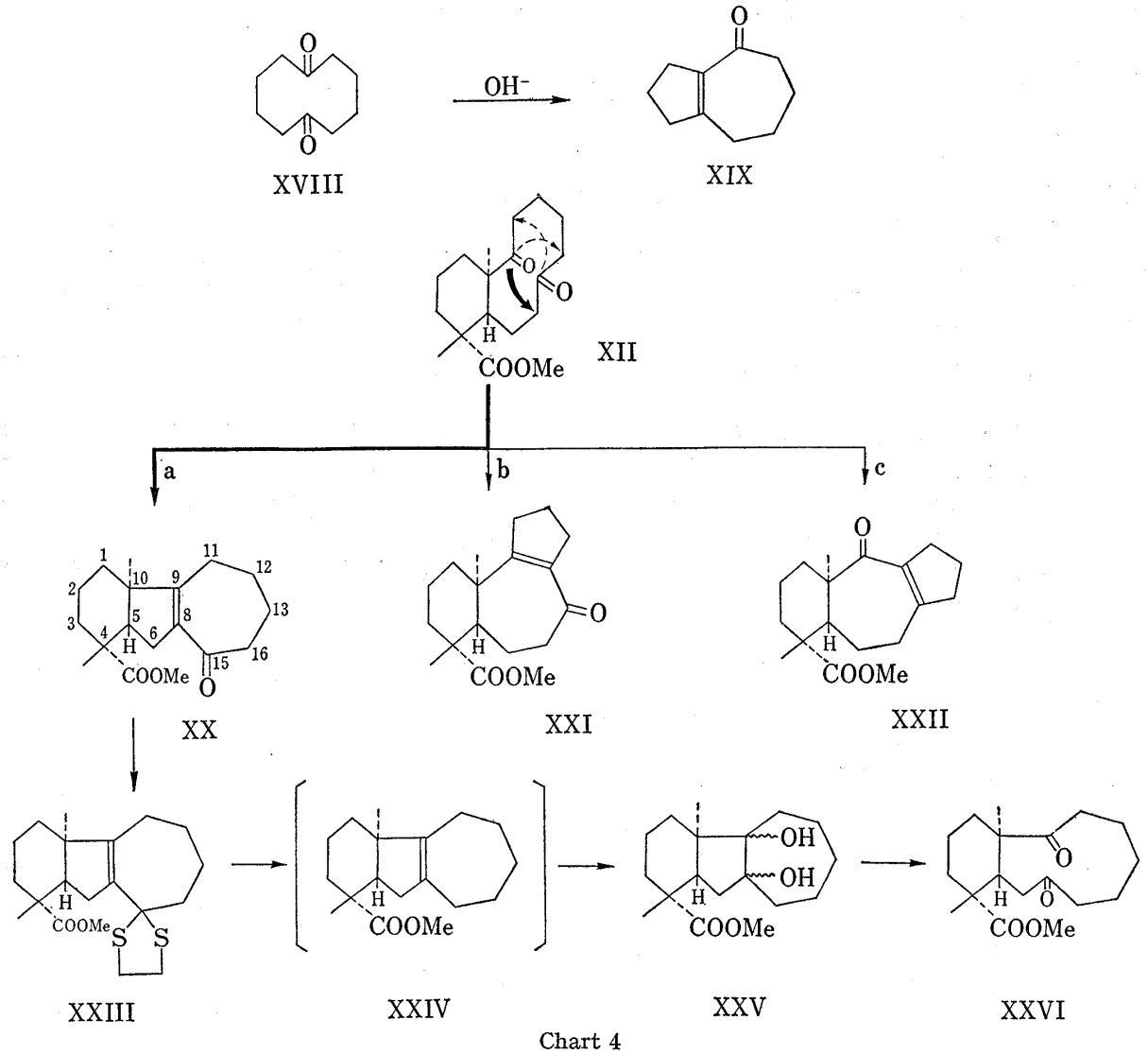


Chart 4

The condensation of dioxo ester (XII) was performed by treatment with methanolic potassium hydroxide. The resulted mixture was chromatographed on alumina to separate two colorless crystals, (XX), mp 92—94°, IR ν_{max}^{KBr} cm^{-1}: 1725, 1639 (α,β-unsaturated ketone in seven membered ring) in 71% yield and undetermined isomer, $C_{18}H_{26}O_3$, mp 112—114°, IR ν_{max}^{KBr} cm^{-1}: 1720, 1645 NMR τ: 9.03 (s, 3H), 8.78 (s, 3H), 6.39 (s, 3H)

13) W. Hückel and L. Schnitzspahn, *Ann. Chem.*, **505**, 274 (1933).

in 5.5% yield. In order to find a true structure for this major product among the three possible structures (XX, XXI and XXII), all cyclization modes of dioxo ester (XXVI, XXVII or XXVIII) expected from the possible condensation product (XX, XXI or XXII, respectively), were considered as shown in Chart 5. If the recyclized compound has perhydrophenanthrene skeleton, the position of carbonyl group in the α,β-unsaturated keto compound (XXIXa, XXXa or XXXIa) should indicate its mother compound (XXVI, XXVII or XXVIII, respectively).

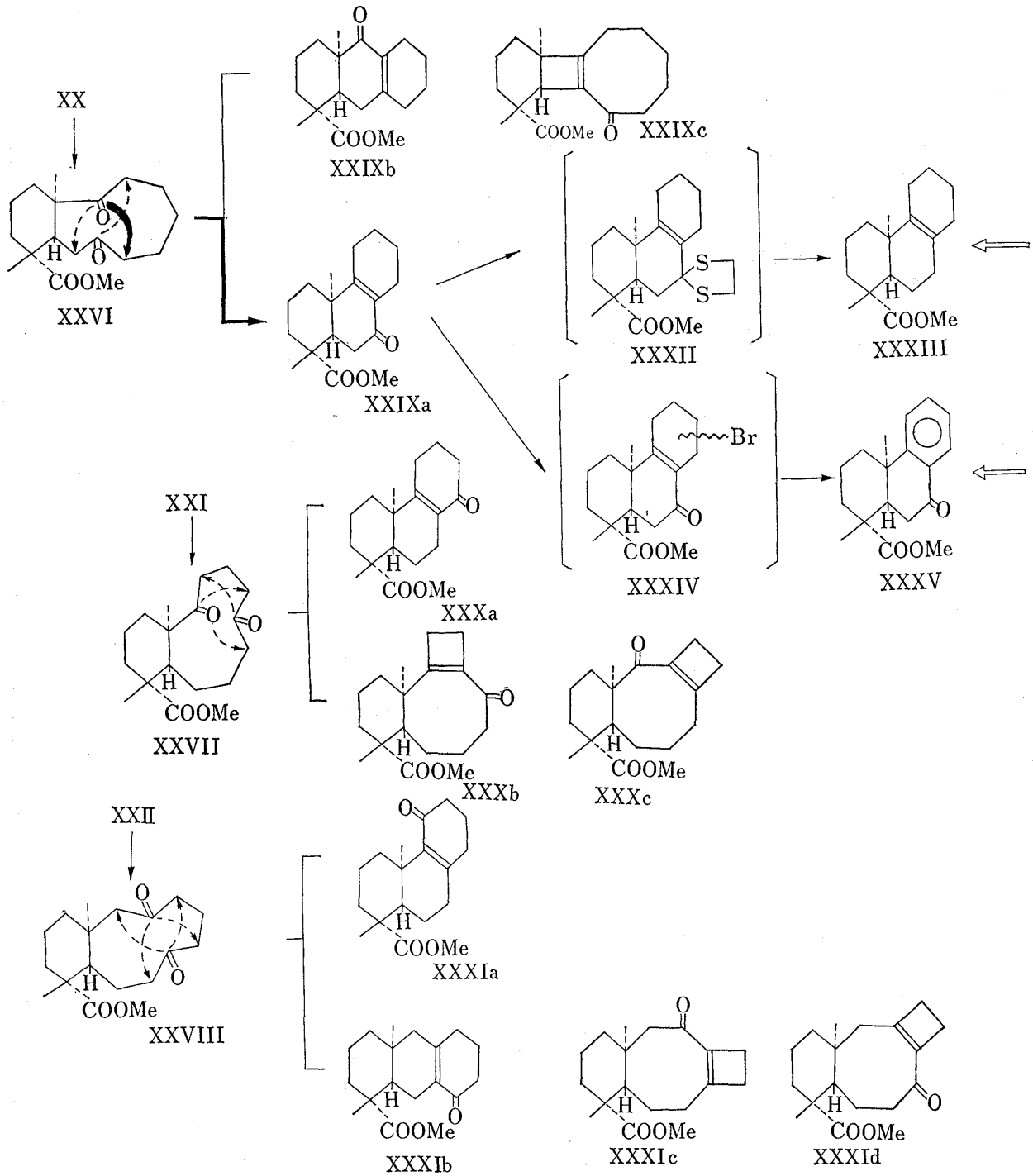
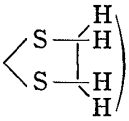
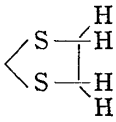
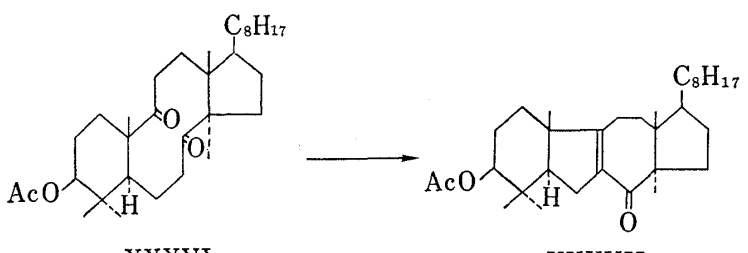


Chart 5

According to the above discussion, the problem of the structure of the major product (XX) was settled by the following examination. Removal of carbonyl group of XX was carried out, through thioketal (XXIII), mp 92—94°, by thioketal formation with ethane dithiol in the presence of *p*-toluenesulfonic acid or boron trifluoride–etherate, followed by successive reduction with Raney nickel (W–7) to give oily non–keto compound (XXIV). Spectroscopic data of thioketal (XXIII) (no IR–absorption due to α,β-unsaturated ketone in seven membered ring as in (XX), and NMR–absorption at 6.70 τ (s, 4H) due to ) and non–keto compound (XXIV) (no NMR–absorption due to ) were consistent with the respective structure. The non–keto compound (XXIV) was used in the next step without purification. Double bond of the compound (XXIV) was cleaved by usual method of osmium tetroxide treatment followed by lead tetraacetate oxidation through *cis*-8,9-dihydroxyl ester (XXV), mp 151—153°, IR ν_{max}^{KBr} cm^{-1}: 3450, 1730, 1700 to give oily 8,9-dioxo ester (XXVI), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735, 1700 in about 50% yield. The oily diketo ester (XXVI) without further purification was recyclized with methanolic potassium hydroxide as in the case of XII. Chromatographic purification of the resulted reaction mixture gave two isomers, $C_{18}H_{26}O_3$, mp 144—146°, in 55% yield and XXIXa, mp 102—104°, in 31% yield. Infrared and NMR spectra of the latter compound (XXIXa) show existence of α,β-unsaturated ketone in six membered ring (IR ν_{max}^{KBr} cm^{-1}: 1660) and nonexistence of olefinic proton.

The structure of the former product (mp 144—146°) still remains ambiguous, whereas that of the latter (mp 102—104°) was shown to be XXIXa by the following reaction: i) removal of carbonyl group and ii) aromatization of C-ring in XXIXa. Thereupon, the carbonyl group of XXIXa was removed by thioketalization and subsequent reduction with Raney nickel to give an oily compound, whose infrared spectrum (CCl_4) and retention time of gas liquid–chromatography were completely identical with those of $\Delta^{8,9}$-unsaturated ester (XXXIII). So, it was proved that XXIXa has a $\Delta^{8,9}$-perhydro phenanthrene skeleton. For the elucidation of its carbonyl location, bromination of XXIXa with N-bromosuccinimide in the presence of benzoyl peroxide, followed by dehydrobromination with boiling γ-collidine, was performed to give a compound having aromatic C-ring, whose physical constants (mp, mixed mp, infrared spectrum (CCl_4) and retention time of gas liquid–chromatography) were identical with those of authentic methyl 7-oxo-*enantio*-podocarpate (XXXV).[8] These experimental facts undeniably show that the structure of original compound (mp 102—104°) can be decided as 7-oxo-$\Delta^{8,9}$-unsaturated ester (XXIXa). The formation of the compound (XXIXa) can only be accounted for by the thought that the mother compound is *c*-homofluorene derivative (XX) (XX→XXVI→XXIXa).

Conclusively, it has been proved that the base catalyzed cyclization of 8,9-dioxo ester (XII) mainly proceeded by *a*-route within three possible ways and *c*-homohydrofluorene (XX), a basic skeleton of gibberellin, was synthesized. Furthermore, analogous cyclization mode (XXXVI→XXXVII) in steroid field[14] is also consistent with our present observation.



XXXVI XXXVII

Chart 6

14) G. Snatzke and A. Nisar, *Ann. Chem.*, **683**, 159 (1965).

Experimental

Reduction of *enantio*-Podocarpa-8,11,13-triene-19-oic Acid (VIII) with Lithium Metal. *enantio*-Podocarpa-8-monoene-19-oic Acid (IX)——Lithium metal (1.68 g) was added to a solution of acid (VIII) (518 mg) in ethylamine (40 ml) and *tert*-amyl alcohol (13.6 ml). The reaction mixture was stirred for 5 hr at room temperature and then was left standing overnight after *tert*-amyl alcohol (17 ml) was added. After sat. NaCl aq. was added to the reaction mixture, it was acidified with conc. HCl and extracted with ether. The ether extract was washed with sat. NaCl aq. and dried over Na_2SO_4. Removal of solvent gave crystals, mp 143—146° (510 mg, 99% yield), which were recrystallized from MeOH–H_2O to give colorless plates (IX), mp 143—146°. *Anal.* Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.58; H, 9.69. IR ν_{max}^{KBr} cm^{-1}: 1700 (COOH). NMR τ: 9.15 (s, 3H; C_{10}-Me), 8.75 (s, 3H; C_4-Me).

Methyl *enantio*-Podocarpa-8-monoene-19-oate (X)——Usual methylation of acid (IX) (410 mg) with excess diazomethane–ether gave crystals, mp 72—82° (417 mg, 97% yield), which were recrystallized from MeOH–H_2O, gave colorless prisms (X), mp 84—87°. *Anal.* Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.39; H, 10.23. IR ν_{max}^{KBr} cm^{-1}: 1720 (COOMe). NMR τ: 9.26 (s, 3H; C_{10}-Me), 8.84 (s, 3H, C_4-Me), 6.41 (s, 3H; COOMe).

Hydroxylation of Methyl *enatio*-Podocarpa-8-monoene-19-oate (X). Methyl 8β,9β-Dihydroxy-*enantio*-podocarpa-19-oate (XI)——Osmium tetroxide (500 mg) was added to a solution of ester (X) (500 mg) in ab. benzene (5 ml) and pyridine (0.5 ml) under ice-cooling. After the reaction mixture was left standing in the dark for 5 days at room temperature, the reaction mixture was treated with H_2S gas to give the precipitate. The precipitate was filtered off and washed with acetone. The solvent of combined filtrate was evaporated *in vacuo* and the resulted crystals (480 mg, 86% yield), mp 140—151°, were recrystallized from MeOH–H_2O to give colorless prisms (410 mg, 73% yield), mp 150—155°. Melting point of the analytical sample (XI) was 157—160°. *Anal.* Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.53; H, 9.30. IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1725 (COOMe). NMR τ: 9.12 (s, 3H; C_{10}-Me), 8.84 (s, 3H, C_4-Me), 6.42 (s, 3H; COOMe).

Oxidative Cleavage of Methyl 8β,9β-Dihydroxy-*enantio*-podocrpa-19-oate (XI). Cyclodeca-8,9-dione Ester (XII)——Lead tetraacetate (660 mg) was added to a solution of *cis*-dihydroxyl compound (XI) (400 mg) in AcOH (20 ml). The reaction mixture was left standing for 12 hr at room temperature and then for one more hour after H_2O was added. It was extracted with ether and the ether extract was washed with sat. $NaHCO_3$ aq. and then H_2O. After the extract was dried over Na_2SO_4, the solvent was evaporated to give crystals (390 mg, 98% yield), mp 80—90°, which were recrystallized from MeOH–H_2O to afford colorless needles (XII), mp 102—104°. *Anal.* Calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.81; H, 8.83. IR ν_{max}^{KBr} cm^{-1}: 1725 (COOMe), 1690 (sat. CO).

Epoxidation of Methyl *enantio*-Podocarpa-8-monoene-19-oate (X). Methyl 8β,9β-Epoxy-*enantio*-podocarpa-19-oate (XIII) and Methyl 8α,9α-Epoxy-*enantio*-podocarpa-19-oate (XIV)——Excess perphthalic acid (3.0 g) in ether (25 ml) was added to a solution of $\Delta^{8,9}$-unsaturated ester (X) (500 mg) in dioxane (15 ml) and it was left standing for 64 hr at room temperature. Then the organic solvent layer separated by addition of H_2O, was combined with ether extract from aq. layer. The combined extract was washed with sat. $NaHCO_3$ aq., sat. NaCl aq. and then dried over Na_2SO_4. Removal of the solvent gave crystals (550 mg), mp 60—105°, which were chromatographed on neut. Al_2O_3 (25 g) to give following crystals: a) Crystals (398 mg, 75% yield), mp 99—105°, obtained from petr. ether–benzene (20:1) elution were recrystallized from MeOH–H_2O to give colorless prisms (XIII), mp 108—110°. *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.02; H, 9.73. IR ν_{max}^{KBr} cm^{-1}: 1725 (COOMe). NMR τ: 9.23 (s, 3H; C_{10}-Me), 8.89 (s, 3H; C_4-Me), 6.44 (s, 3H; COOMe).

b) Crystals (48 mg, 9.1% yield), mp 139—150°, separated from petr. ether–benzene (1:1) elution were recrystallized from MeOH–H_2O to give colorless plates (XIV) (40 mg, 7.6% yield), mp 147—151°. *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.68; H, 9.26. IR ν_{max}^{KBr} cm^{-1}: 1720 (COOMe). NMR τ: 9.26 (s, 3H; C_{10}-Me), 8.92 (s, 3H; C_4-Me), 6.44 (s, 3H; COOMe). Mixed melting point of stereoisomeric epoxides (XIII) with (XIV) showed depressed melting point, 90—96°.

Methyl 8α,9β-Dihydroxy-*enantio*-podocarpa-19-oate (XV)——i) Epoxide Cleavage of Methyl 8β,9β-Epoxy-*enantio*-podocarpa-19-oate (XIII): A solution of β-epoxide (XIII) (50 mg) in acetone (1.0 ml), H_2O (1.0 ml) and conc. H_2SO_4 (15 mg) was left standing for 30 hr at room temperature. The reaction mixture was diluted with H_2O, then extracted with chloroform and the extract was washed with H_2O, and was dried over Na_2SO_4. Oily residue (51 mg) obtained by the solvent evaporation, was chromatographed on alumina (2.0 g) to separate crystals (5 mg) in petr. ether–benzene (10:1) elution, whose IR spectrum was identified with that of starting material (XIII), and crystals (30 mg, 57% yield), mp 95—105° in petr. ether-benzene (2:1) elution. The latter crystals were recrystallized from MeOH–H_2O to give colorless prisms (XV) (25 mg, 47% yield), mp 86—88°, whose analytical sample had mp 87—89°. *Anal.* Calcd. for $C_{18}H_{30}O_4 \cdot \frac{1}{3}H_2O$: C, 68.36; H, 9.70. Found: C, 68.24; H, 9.95. IR ν_{max}^{KBr} cm^{-1}: 3530, 3470 (OH), 1725, 1705 (COOMe).

Otherwise recrystallization of the crystals (XV) from petr. benzine gave colorless prisms, mp 114—116°. *Anal.* Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.85; H, 9.68. IR ν_{max}^{KBr} cm^{-1}: 3582, 3510 (OH),

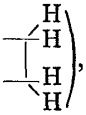
1705 (COOMe). NMR τ: 9.08 (s, 3H; C_{10}-Me), 8.85 (s, 3H; C_4-Me), 6.40 (s, 3H; COOMe). IR spectra (CCl_4) of the both crystal forms were identical with each other.

ii) Epoxide Cleavage of Methyl 8α,9α-Epoxy-*enantio*-podocarpa-19-oate (XIV): After a solution of α-epoxide (XIV) (50 mg) in acetone (1 ml), H_2O (1 ml) and conc. H_2SO_4 (15 mg) was left standing for 29 hr at room temperature, the reaction mixture was treated as in the case of β-epoxide (XIII). The obtained oil (50 mg) was chromatographed on alumina (2.0 g) to separate crystals (13 mg), in petr. ether elution, whose IR spectrum was identified with that of the starting material and crystals (XV) (22 mg) in petr. ether–benzene (2:1) elution. The latter crystals were recrystallized from MeOH–H_2O to give colorless prisms, mp 84—87°, whose physical constants (mp, mixed mp and IR spectrum (CCl_4)) were identical with those of *trans*-diol (XV) synthesized from β-epoxide (XIII).

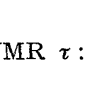
Oxidative Cleavage of Methyl 8α,9β-Dihydroxy-*enantio*-podocarpa-19-oate (XV). Cyclodeca-8,9-dioxo Ester (XII)——Lead tetraacetate (20 mg) was added to a solution of *trans*-dihydroxyl ester (XV) (11 mg) in AcOH (0.5 ml) and then it was left standing for 24 hr at room temperature. The reaction mixture was extracted with ether after H_2O was added. The extract was washed with sat. $NaHCO_3$ aq., H_2O and dried over Na_2SO_4. Removal of solvent gave crystals (10 mg, 92% yield), mp 90—99°, which was recrystallized from MeOH–H_2O several times to give colorless needles (XII), mp 101—103°. The crystals were identical (mp, mixed mp and IR spectrum) with dioxo ester (XII) obtained from *cis*-dihydroxyl ester (XI) through the above mentioned route.

Base catalyzed Cyclization of Cyclodeca-8,9-dioxo Ester (XII). Methyl 4β,10α-Dimethyl-15-oxo-c-homohydrofluore (5β-H)-8-monoene-4α-carboxylate (XX)——A solution of dioxo ester (XII)(600 mg) in MeOH (10 ml) and 10% KOH aq. (10 ml) was refluxed for 30 min under N_2-atmosphere. Residue obtained by removal of the solvent, was dissolved with ether and the ether solution was washed with H_2O, and dried over Na_2SO_4. Solvent evaporation gave oily crystals (540 mg), which were chromatographed on alumina (27 g) to separate crystals (31 mg, 5.5% yield), mp 109—112°, in petr. ether–ether (20:1) elution and the other crystals (402 mg, 71% yield), mp 82—89°, in petr. ether–ether ((20:1)–(10:1)) elution.

The former crystals, mp 109—112°, were recrystallized from MeOH–H_2O to give colorless prisms, mp 112—114°, whose structure had not been elucidated. *Anal.* Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.26; H, 8.98. IR ν_{max}^{KBr} cm^{-1}: 1720 (COOMe), 1645. NMR τ: 9.03 (s, 3H; C_{10}-Me), 8.78 (s, 3H: C_4-Me), 6.39 (s, 3H; COOMe). The latter crystals, mp 82—89°, were recrystallized from MeOH–H_2O to give colorless prisms (XX), mp 92—94°. *Anal.* Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.28; H, 8.70. IR ν_{max}^{KBr} cm^{-1}: 1725 (COOMe), 1639 (α,β-unsat. 7-membered ring CO), 1608 (C=C). NMR τ: 9.28 (s, 3H; C_{10}-Me), 8.80 (s, 3H; C_4-Me), 6.40 (s, 3H; COOMe). It was characterized as 2,4-dinitrophenylhydrazone, red needles, mp 227—230° (recrystallized from EtOH–H_2O). *Anal.* Calcd. for $C_{24}H_{30}O_6N$: C, 61.26; H, 6.43; N, 11.91. Found: C, 61.17; H, 6.43; N, 12.28. IR ν_{max}^{KBr} cm^{-1}: 1725 (COOMe), 1620–, 1595 (N=N, C=C).

Methyl 4β,10α-dimethyl-15-ethylenedithio-c-homohydrofluore(5β-H)-8-monoene-4α-carboxylate (XXIII)——i) A solution of oxo ester (XX) (50 mg), *p*-TsOH (30 mg) and ethane dithiol (0.03 ml) in AcOH (1 ml), was left standing for 3 hr at room temperature. After ether and H_2O were added to the reaction mixture, separated ether layer was washed with H_2O, 10% Na_2CO_3 aq., then H_2O successively and dried over Na_2SO_4. Removal of the solvent gave crystals (62 mg, 98% yield), mp 87—92°, which were recrystallized from MeOH–H_2O to give colorless prisms (XXIII), mp 92—94°. *Anal.* Calcd. for $C_{20}H_{30}O_2S_2$: C, 65.55; H, 8.25. Found: C, 65.62; H, 8.10. IR ν_{max}^{KBr} cm^{-1}: 1725 (COOMe). NMR τ: 9.38 (s, 3H; C_{10}-Me), 8.79 (s, 3H: C_4-Me), 6.70 (s, 4H; ), 6.37 (s, 3H; COOMe).

ii) A solution of oxo ester (XX) (50 mg) in AcOH (0.5 ml) containing BF_3-etherate (0.05 ml) and ethane dithiol (0.03 ml), was left standing for 35 min at room temperature. The reaction mixture was treated as in the case of i). The resulted colorless prisms (60 mg, 95% yield), mp 92—95°, were identical (mp and mixed mp) with the above mentioned thioketal (XXIII).

Methyl 4β,10α-Dimethyl-8,9-dihydroxy-c-homohydrofluore(5β-H)-4α-carboxylate (XXV) from Methyl 4β,10α-Dimethyl-15-ethylenedithio-c-homohydrofluore(5β-H)-8-monoene-4α-carboxylate (XXIII) *via* Methyl 4β,10α-Dimethyl-c-homohydrofluore(5β-H)-8-monoene-4α-carboxylate (XXIV)——A reaction mixture of thioketal (XXIII) (350 mg) and Raney Ni (W=7) (3.0 g) in ab. EtOH (15 ml), was refluxed for 10 hr and left standing overnight. After Raney Ni was filtered off, the solvent of the filtrate was evaporated in vacuum. The resulted oil (245 mg) was chromatographed on alumina (12.5 g) to give oil (XXIV) (227 mg, 86% yield), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735 (COOMe). NMR τ: Absorption due to  was disappeared, which was used without further purification in next step.

A reaction mixture of the obtained oily ester (XXIV) (225 mg) and OsO_4 (225 mg) in ab. benzene (3 ml) and pyridine (0.2 ml) was left standing in the dark for 4 days at room temperature. The reaction mixture was treated with H_2S gas to give precipitate. After the precipitate was filtered and then washed with

acetone, the combined filtrate was evaporated in vacuum. The resulted oily crystals (210 mg), mp 45—55°, was chromatographed on alumina (10 g) to give crystals (149 mg), mp 145—150°, in benzene and benzene–ether (1:1) elution. The crystals were recrystallized from MeOH–H_2O to give colorless needles (XXV) (133 mg, 53% yield), mp 150—153°, whose analytical sample has mp 151—153°. *Anal.* Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.28; H, 9.62. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1730, 1700 (COOMe). NMR τ: 9.38 (s, 3H, C_{10}-Me), 8.85 (s, 3H; C_4-Me), 6.39 (s, 3H; COOMe). No signal due to H–C–OH (5—5.2τ).

Methyl 7-Oxo-*enantio*-podocarpa-8-monoene-19-oate (XXIXa) and Its Isomer from Methyl 4β,10α-Dimethyl-8,9-dihydroxy-c-homohydrofluore(5β-H)-8-monoene-4α-carboxylate (XXV) *via* Cyclodeca-8,9-dioxo Ester (XXVI)——A reaction mixture of *cis*-diol (XXV) (114 mg) and Pb $(OAc)_4$ (185 mg) in AcOH (4 ml) was left standing at room temperature for 13 hr and then ether and H_2O were added. The ether solution was washed with H_2O, sat. $NaHCO_3$ aq., then H_2O successively and dried over Na_2SO_4. Removal of the solvent gave oil (XXVI) (110 mg, 97% yield), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735 (COOMe), 1700 (sat. CO), which was used without purification in the next step.

A solution of dioxo ester (XXVI) (106 mg) in MeOH (2 ml) and 10% KOH aq. (2 ml) was refluxed for 30 min and the solvent was evaporated under reduced pressure. Ether solution of the resulted residue was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave crystals (95 mg), which was chromatographed on alumina (4.7 g) to give the following fractions. From petr. ether–ether (50:1) elution crystals (58 mg, 58%, yield), mp 139—143°, were obtained and the crystals were recrystallized from MeOH–H_2O to give colorless prisms (55 mg), mp 140—144°, whose analytical sample has mp 144—146° and its structure is not yet elucidated. *Anal.* Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.68; H, 9.43. IR ν_{max}^{KBr} cm^{-1}: 1723 (COOMe), 1658 (α,β-unsat. CO), 1640 (C=C). NMR τ: 9.25 (s, 3H; C_{10}-Me), 8.82 (s, 3H; C_4-Me), 6.36 (s, 3H; COOMe).

While, the other crystals (34 mg, 34% yield), mp 97—100°, were obtained in successive petr. ether–ether ((50:1)–(25:1)) elution. The crystals were recrystallized from MeOH–H_2O to give colorless prisms (XXIXa) (30 mg), mp 99—102°, which is an isomer of the former compound, mp 144—146°. Its analytical sample had mp 102—104°. *Anal.* Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.67; H, 8.68. IR ν_{max}^{KBr} cm^{-1}: 1720 (COOMe), 1660 (α,β-unsat. CO), 1618 (C=C). NMR τ: 9.10 (s, 3H; C_{10}-Me), 8.81 (s, 3H; C_4-Me), 6.36 (s, 3H; COOMe).

Methyl *enantio*-podocarpa-8-monoene-19-oate (XXXIII) from Methyl 7-Oxo-*enantio*-podocarpa-8-monoene-19-oate (XXIXa) *via* the Corresponding Thioketal (XXXII)——A solution of α,β-unsaturated oxo ester (XXIXa) (15 mg), *p*-toluenesulfonic acid (10 mg) and ethane dithiol (0.01 ml) in AcOH (0.25 ml), was left standing for 20 hr at room temperature. After the reaction mixture was diluted with ether, the ether solution was washed with H_2O, 10% K_2CO_3 aq., H_2O successively and then dried over Na_2SO_4. Removal of the solvent gave oil (XXXII) (18 mg, 95% yield). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730 (COOMe), which was used in the next step without purification.

The mixture of the oil (XXXII) (18 mg) and Raney Ni (W=7) (0.25 g) in EtOH (3.0 ml), was refluxed for 10 hr. Raney Ni was filtered off and the filtrate was evaporated to give oil (8 mg). The oil was chromatographed on alumina (0.5 g) to separate crystals (4 mg, 29% yield). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730 (COOMe). t_R: 4.55 (2.0% QF-1 on Anakrom U, 1.75 m×4 mm, 169°), in petr. ether elution. Its physical constants (IR-spectrum and t_R) were identical with those of authentic sample (XXXIII) synthesized before.

Methyl 7-Oxo-*enantio*-podocarpa-8,11,13-triene-19-oate (XXXV) from Methyl 7-Oxo-*enantio*-podocarpa-8-monoene-19-oate (XXIXa) *via* the Corresponding Bromide) (XXXIV)——N-Bromosuccinimide (15 mg) and benzoyl peroxide (3 mg) were added to a solution of α,β-unsaturated oxo ester (XXIXa) (20 mg) in CCl_4 (3 ml). After the reaction mixture was refluxed for 30 min, floating matieral was filtered off and the filtrate was washed with sat. $NaHCO_3$ aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave viscous oil (XXXIV) (26 mg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (COOMe), 1680, 1610, which was used in the next step without further purification.

A solution of the resulted halo-oxo ester (23 mg) in freshly distilled γ-collidine (0.5 ml) was refluxed for 2.5 hr. The reaction mixture was diluted with ether and the ether solution was washed with 10% HCl aq., then H_2O and dried over Na_2SO_4. Removal of the solvent gave oil (13 mg), which was chromatographed on alumina (1 g) to separate crystals (5 mg, 28% yield) in petr. ether–ether (20:1) elution. The crystals were recrystallized from MeOH–H_2O to give colorless prisms (2 mg), mp 142—146°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730 (COOMe), 1690 (α,β-unsat. CO), 1600 (C=C). t_R: 10.80 (1.5% SE-30 on Anakrom U, 1.85 m×4 mm, 185°), whose physical constants (mp, mixed mp, IR and t_R) was identical with authentic methyl 7-oxo-deoxy-*enantio*- podocarpate (XXXV).[15]

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15) M. Ohta, *Chem. Pharm. Bull.* (Tokyo), **5**, 256 (1957).