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Diterpenoids. XXIV.[1] Transformation of Podocarpic Acid Type Diterpene to B-Homo-C-nor-5β,10α-podocarpan Skeleton

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A skeletal transformation of XI, drived from *l*-abietic acid (I), was tried by the cleavage of B/C-ring juncture and successive condensation. The ether bridge suppresses the condensation direction as in the synthesis (VII→VIIIa) previously reported, and then, the cyclization gives XVIa regarded as a mother skeleton of aconitine.

l-Abietic acid (I), major component of pine rosin, is readily available commercially. In our laboratory, new aspects on the utilization of rosin have been developed by chemical transformation of *l*-abietic acid (I) to the physiologically active compound. The natural diterpenoids such as gibberellin (*e.g.* A_3 (II)) and aconitine type alkaloids (*e.g.* aconitine (III)) with an unique activity have a different basic skeleton from that of *l*-abietic acid (I), though they have partially similar structures. Thus, skeletal transformation of *l*-abietic acid is one of the important synthetic problems in the chemical conversion.

The first attempt was accomplished by benzilic acid rearrangement of diketone (IV) to hydrofluorene (V),[3] which is regarded as the basic skeleton of gibberellin. Recently, *l*-abietic acid (I) was converted to methyl 5β,10α-podocarp-8-en-15-oate (VI). Its B/C ring juncture was oxidatively cleaved and the aldol condensation of the resulting dioxo ester

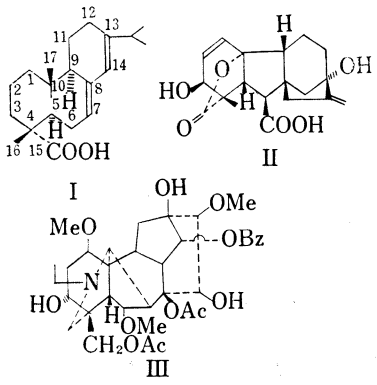


Chart 1

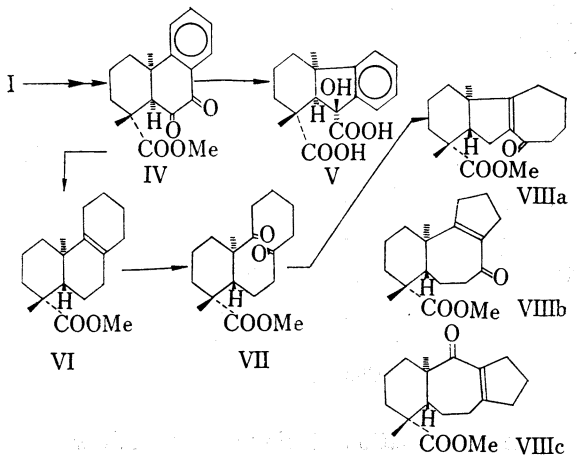


Chart 2

1) Preliminary Communication: A. Tahara and T. Ohsawa, *Tetrahedron Letters*, **1969**, 2469; Part XXIII: A. Tahara, T. Nakata, Y. Ohtsuka, S. Takada, and T. Tanabe, *Yakugaku Zasshi*, to be submitted. All melting points were measured on Kofler block and were not corrected. NMR spectra were usually measured at 60 MHz in $CDCl_3$ *vs.* Me_4Si as internal standard.

2) Location: *Wakō-shi, Saitama.*

3) A. Tahara, *Chem. Pharm. Bull.* (Tokyo), **9**, 252 (1961); A. Tahara and O. Hoshino, *Chem. Pharm. Bull.* (Tokyo), **9**, 655 (1961); J.F. Grove and B.J. Riley, *J. Chem. Soc.*, **1961**, 1105.

(VII) selectively gave the C-homohydrofluorene type compound (VIIIa).[4] Beside this B-nor -C-homo cyclization, two other possible B-homo-C-nor cyclizations (VIIIb and VIIIc) should be considered. One of these, VIIIb, is a skeleton of strongly poisonous diterpene alkaloids such as aconitine (III) and lycoctonine.

In order to synthesize this interesting type of the 6-7-5-membered fused ring system, the deoxopodocarpic acid type compound with a 6α,17-epoxy bridge (IX)[5] was considered to be suitable as the starting material because of the following reasons: *1*) The rigid epoxy brridge can stereochemically suppress the route to the C-homo-hydrofluorene skeleton as the molecular model examination suggests and *2*) the epoxy bridge can assure a foot-hold to make a nitrogen bridge characteristic for the structure of the diterpene alkaloid.

First, the benzene ring of epoxy acid (IX) was reduced by lithium metal in ethylamine in the presence of *tert*-amyl alcohol. The reaction proceeded to give quantitatively Δ^{8}-epoxy acid (X), mp 247—252°(decomp.), which was methylated to give the corresponding Δ^{8}-epoxy ester (XI), mp 112—113°. The ester (XI) was also obtained by lead tetraacetate-oxidation of 6α-hydroxy ester (XIII),[6] which was synthesized from XII, but the yield was not so high (40%).

Next, the $\Delta^{8,9}$-olefinic bond of XI was hydroxylated with osmium tetroxide in pyridine to give the dihydroxyl ester (XIV), mp 153—155°; its nuclear magnetic resonance (NMR) spectrum shows the absence of a signal due to the proton attached to the same carbon atom as the hydroxyl group. Considering the steric hindrance of the epoxy group, osmium tetroxide should attack from the β-side of the molecule to yield selectively *β-cis* configuration. The *vic*-glycol cleavage of XIV with lead tetraacetate gave dioxo ester (XV), mp 75—76.5°, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1705, in 82 % yield.

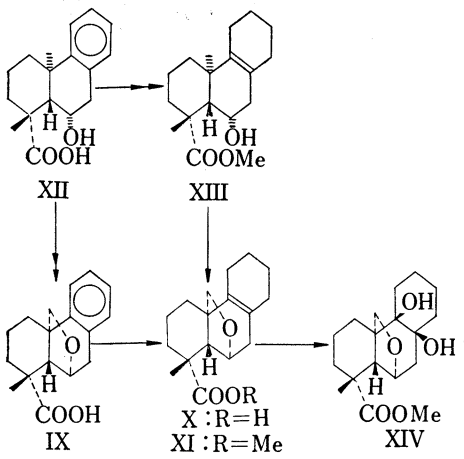


Chart 3

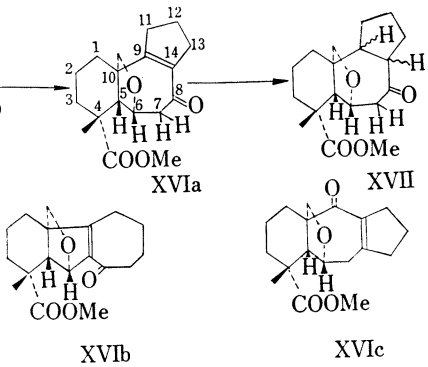


Chart 4

The condensation of dioxo ester (XV) was unsuccessful under basic condition as in the case of the synthesis of C-homohydrofluorene compound (VIII). Thus, the condensation was performed under acidic conditions. A solution of dioxo ester (XV) in methanol containing hydrochloric acid was refluxed to give a crystalline product. The crystals consisting

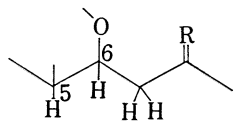
4) A. Tahara and O. Hoshino, *Tetrahedron Letters*, **1966**, 3825; A. Tahara, O. Hoshino, and T. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 54 (1969).
5) A. Tahara and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **12**, 984 (1964); A. Tahara, K. Hirao, and Y. Hamazaki, *Tetrahedron*, **21**, 2133 (1965).
6) A. Tahara and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **17**, 1529 (1969); **19**, 1768 (1971).

of two products in the ratio of 4:1 were chromatographed to separate the major one, mp 134—142°, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (COOMe), 1650 and 1610 (C=C-C=O).

Considering the molecular formula, $C_{18}H_{24}O_4$, and the infrared absorption, the compound can be assumed to be an unsaturated carbonyl product of normal aldol type condensation. Thus. the structure of the condensation product was restricted to three possible products (XVIa, XVIb and XVIc) as is illustrated in Chart 4.

In order to elucidate the structure, nuclear magnetic double resonance method was applied and the structure (XVIa) was finally determined. The NMR spectrum (field sweep) of XVIa showed a sextet due to the C_6-proton at 5.36 τ. When irradiated at 8.03 τ and 7.23 τ, the sextet changed to a triplet (J=3.6 Hz) ant a doublet (J=1.5 Hz), respectively. The signal appearing at the region of 8.03 τ can be assigned to the methine proton at the C_5-position. Irradiation at this point resulted in decoupling between C_5-H and C_6-H, and the resulting triplet suggests the presence of an active methylene group (7.23 τ) adjacent to a carbonyl group or its vinylogue. Consequently, the following partial structure can be given for the condensation product.

This conclusion excludes the structure (XVIb) among the possible three. Next, in order to decide which of the two structures (XVIa and XVIc) is correct, the oxo ester was reduced over 10 % palladium charcoal under a pressure of hydrogen gas (4.2 kg/cm^2). The gas-chromatogram of the product showed it consisted of two components. The mixture was refluxed with hydrochloric acid to give a homogeneous product; therefore the two components are assumed to be isomers at the active angular methine position.



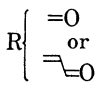


Chart 5

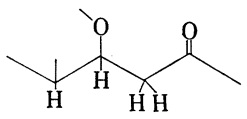


Chart 6

The structure of the homogeneous compound, mp 79°, can be discussed by analysis of its NMR spectrum (100 MHz, frequency sweep). The absorption due to the protons at 7.60 τ(1H, quartet (J=16 Hz, 4 Hz); C_7-H), 7.19 τ(1H, quartet (J=16 Hz, 3 Hz); C_7-H) and 5.49 τ(1H, sextet (J=3.3 Hz, 2 Hz); C_6-H)[7] are ABX system. Irradiation at 5.49 τ(X part) decouples to yield AB type doublet-doublets with J=16 Hz (geminal coupling). Therefore, the active methylene in the original enone compound still exists next to C_6-position. Thus, the partial structure should be elucidated as shown in Chart 6. This partial structure excludes XVIc, and so XVIa has been conclusively decided as the aldol condensation product of (XV).

This result indicated that the rigid ether bridge successfully suppresses the condensation direction as in the synthesis of C-homohydrofluorene (VII→VIIIa) and that the cyclization (XV→XVIa) gives a mother skeleton of aconitine as was postulated.

Experimental

6α,17-Epoxy-5β,10α-podocarp-8-en-15-oic Acid (X) and the Corresponding Ester (XI)——A mixture of epoxy acid (IX)[5] (200 mg), anhydrous *tert*-amyl alcohol (2 ml) and anhydrous ethylamine (20 ml) was stirred in a flask equipped with an ice-water condenser, and then Li metal (granule) (220 mg) was added to the mixture in one portion. Stirring for 10 min, *tert*-amyl alcohol (2 ml) was added slowly to decompose the residual Li metal. Removal of the solvent *in vacuo* yielded a residue in paste, which was diluted with NaCl aq., acidified with HCl aq. and extracted with ether. After the treatment in an usual manner, the organic layer gave colorless crystals (196 mg). Recrystallizations from MeOH gave colorless prisms (X), mp 247—252° (decomp.). *Anal.* Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.82; H, 8.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720(COOH). NMR τ: 8.79 (3H, singlet; C_4-Me), 6.29 and 5.92 (2H, AB doublet-doublets (J=7.8 Hz); C_{17}-H), 5.05 (1H, broad singlet; COOH).

7) Each peak, strictly speaking, is split to a doublet (J=1 Hz) possibly by a long range coupling.

The above epoxy acid (X) was methylated quantitatively with ether solution of diazomethane. Recrystallization from MeOH yielded (XI), colorless needles, mp 112—113°. *Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 74.74; H, 9.03. Found: C, 74.56; H, 9.29. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (COOMe). NMR τ: 8.74 (3H, singlet; C_4-Me), 6.37 (3H, singlet; COOMe), 5.33 (1H, multiplet; C_6-H).

Methyl 6α,17-Epoxy-5β,10α-podocarp-8-en-15-oate (XI)——A mixture of Δ^8-oxy ester (XIII)[6] (1.03 g), iodine (1.2 g) and $Pb(OAc)_4$ (3 g) in absolute benzene (100 ml) was refluxed for 105 min under the stream of nitrogen gas. After the removal of precipitate by filtration, the benzene solution was washed with 10% $Na_2S_2O_3$ aq., satd. Na_2CO_3 aq. and water successively and then dried over Na_2SO_4. Removal of the solvent yielded resinous substance (1.25 g). Purification by column chromatography over alumina (100 g) gave Δ^8-epoxy ester (XI) (381 mg, 37% yield) from petr. ether–ether (3: 1) elution. Recrystallization from MeOH yielded colorless prisms (XI), mp 114—115°, which were identified with the authentic sample of Δ^8-epoxy ester (XI) by mix. mp, IR spectrum and gas chromatography.

Methyl 6α,17-Epoxy-8β,9β-dihydroxy-5β,10α-podocarpan-15-oate (XIV)——To a solution of epoxy ester (XI) (560 mg) in absolute benzene (7 ml) and absolute pyridine (0.6 ml), OsO_4 (640 mg) was added under cooling with ice-water, and the mixture was left in the dark at room temperature for 5 days. After dilution with acetone ,H_2S gas was introduced. Black precipitate were filtered off with charcoal and the solvent was stripped out. Ether solution of the resulted residue was washed with water. Drying over Na_2SO_4, removal of the solvent yielded crystals (573 mg), which were recrystallized from petr. ether to give prisms (515 mg, 82% yield), mp 140—152°. Further recrystallization from MeOH yielded colorless prisms (XIV), mp 153—155°. *Anal.* Calcd. for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.27; H, 8.35. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 and 3500 (OH), 1730 (COOMe). NMR τ: 8.78 (3H, singlet; C_4-Me), 6.37 (3H, singlet; COOMe), 6.39 and 6.04 (2H, doublet–doublets (J=9.6 Hz); C_{17}-H), 5.50 (1H, broad triplet; C_6-H). Any proton attaching to a carbon having OH group cannot be found.

Cyclodeca-8,9-dioxo Ester (XV)——A mixture of diol (XIV) (510 mg), absolute benzene (175 ml) and $Pb(OAc)_4$ (1 g) was stirred at room temperature for 1 hr and the precipitates were filtered off. The filtrate was washed with water, Na_2CO_3 aq. and water successively. Drying over Na_2SO_4, removal of the solvent yielded dioxo ester (XV), (418 mg, 82% yield), mp 72—74°. Recrystallization from MeOH and then from benzene–petr. ether gave colorless prisms (XV), mp 75—76°. *Anal.* Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.26; H, 8.00. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (COOMe), 1705 (C=O).

Aldol Condensation of Cyclodeca-8,9-dioxo Ester (XV). Methyl 6α,17-Epoxy-8-oxo-B-homo-C-nor-5β,10α-podocarp-8-en-15-oate (XVIa)——Dioxo ester (XV) (415 mg) was refluxed with conc. HCl (4.5 ml) in MeOH (42 ml) for 40 min. After the removal of the solvent *in vacuo*, the residue was dissolved in ether and the solution was washed with $NaHCO_3$ aq. and then water. Drying over Na_2SO_4, removal of solvent gave crystals (365 mg), t_R min (2% OV-1, 4 mm×1.8 m, 80—100 mesh, 200°) 6.8, 8.7 (ratio 1: 4). This mixture was recrystallized from ether–petr. ether to give main product (145 mg, 37% yield) in pure state. While the same mixture (499 mg) yielded the main product (292 mg, 62% yield) after the purification by column chromatography over neutral alumina (50 g). Recrystallization from MeOH gave colorless prisms (XVIa), mp 134—142°. t_R min (1.5% OV-17, 4 mm×2 m, 80—100 mesh, 228°) 15.1. TLC (alumina, benzene: $CHCl_3$=5: 1): single spot. *Anal.* Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.92. Found: C, 70.66, H, 7.67. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (COOMe), 1650 and 1610 (C=C–C=O). NMR τ: 8.76 (3H, singlet; C_4-Me), 6.28 (3H, singlet; COOMe), 6.41 and 5.87 (2H, AB doublet–doublets, (J=8.4 Hz); C_{17}-H), 5.36 (1H, sextet; C_6-H). Mass Spectrum m/e: Calcd. for $C_{18}H_{24}O_4$ (M^+), 304, 16746. Found: 304. 16824.

Decoupling: Irradiation at 8.03 τ and 7.23 τ changed the sextet (5.36 τ) to triplet (J=3.6 Hz) and doublet (J=1.5 Hz) respectively.

Methyl 6α,17-Epoxy-8-oxo-B-homo-C-nor-5β,10α-podocarpan-15-oate (XVII)——Enone compound (XVIa) (90 mg) was hydrogenated over 10% Pd-C (40 mg) in EtOH (13 ml) at room temperature in the atmosphere of hydrogen gas (4.2 kg/cm^{-2}). After 5 hr the catalyst was filtered off and the solvent was stripped out. The resulting resinous substance was refluxed with conc. HCl (0.15 ml) in MeOH (8 ml) for 1 hr. Removal of the solvent gave a residue, which was dissolved in MeOH–ether and the solution was washed with $NaHCO_3$ aq. and NaCl aq. Drying over Na_2SO_4, evaporation of solvent yielded colorless resinous product (80 mg). Recrystallization from MeOH gave colorless prisms (XVII), mp 79°. *Anal.* Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.41; H, 8.41. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (COOMe), 1705 (C=O). NMR (100 MHz) τ: 8.78 (3H, singlet; C_4-Me), 6.31 (3H, singlet; COOMe), 7.60 and 7.19 (2H, AB part of ABX (J=16 Hz, J=4 Hz, J=3 Hz); C_7-H), 5.49 (1H, sextet, X part of ABX (J=3.3 Hz, J=2 Hz); C_6-H).

Decoupling: (100 MHz, frequency sweep). Irradiation at 5.49 τ (X part) decoupled the ABX coupling to leave AB-type doublet–doublets with J=16 Hz.

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